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Editorial:

- New challenges for lung transplantation in the era of COVID-19

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INDEX

Editorial

685 New challenges for lung transplantation in the era of COVID-19
Lucas Matos Fernandes, Paulo Manuel Pêgo-Fernandes

Original article

689 In search of disambiguation: development of eye drop bottle sleeves to aid in identification and survey among possible users. A cross-sectional study
Ana Luiza Fontes de Azevedo Costa, Thiago Gonçalves dos Santos Martins, Vagner Rogério dos Santos, Paulo Schor

696 Retrospective analysis on efficacy of convalescent plasma in acute respiratory distress syndrome due to COVID-19
Esma Eren, Ayşegül Ulu-Kılıç, Serdal Korkmaz, Merve Yıldız, Recep Civan Yüksel, Ayşin Kılınç-Toker, Emine Arman-Fırat, Zehra Bestepe-Dursun, Ilhami Çelik

701 Allergic rhinitis improvement after septorhinoplasty in a sample of allergic rhinitis patients with septal deviation: a quasi-experimental study
Vanesa García-Paz, Cintia Micaela Chamorro-Petronacci, Roi Painceira-Villar, Ricardo Becerro-de-Bengoa-Vallejo, Marta Elena Losa-Iglesias, Mario Pérez-Sayáns, Adolfo Sarandeses-Garcia, Daniel López-López

708 Multisite musculoskeletal pain in the general population: a cross-sectional survey
Alberto de Vitta, Nicoly Machado Maciel, Thiago Paulo Frascareli Bento, Caio Vitor dos Santos Genebra, Sandra Fiorelli Almeida Penteado Simeão

717 Recent dengue virus infection: epidemiological survey on risk factors associated with infection in a medium-sized city in Mato Grosso
Dandára Thaís de Oliveira Ferreira, Marina Atanaka, Mariano Martinez Espinosa, Lavinia Schuler-Faccini, Aline da Silva Caldeira, Juliana Herrero da Silva, Viviane Karolina Vivi-Oliveira, Rayana de Castro da Paz, Vagner Ferreira do Nascimento, Ana Cláudia Pereira Terças-Trettel

726 Could polyhexanide and chlorine dioxide be used as an alternative to chlorhexidine? A systematic review
Dayanne Simões Ferreira Santos, Mariela Peralta-Mamani, Felipe Suaki Brandão, Flaviana Bombarda Andrade, Thiago Cruvinel, Paulo Sérgio da Silva Santos

740 Indications for accurate and appropriate use of personal protective equipment for healthcare professionals. A systematic review
Maria Stella Peccin, Márcio Luís Duarte, Aline Mizusaki Imoto, Mônica Taminato, Humberto Saconato, Maria Eduarda Puga, Eduardo Signorini Bicas Franco, Erika Barbosa Camargo, Leila Bernarda Donato Gottems, Álvaro Nagib Atallah

755 Autonomic dysfunction is common in liver cirrhosis and is associated with cardiac dysfunction and mortality: prospective observational study
Carolina Frade Magalhães Girardin Pimentel, Ricardo Salvadori, Ana Cristina de Castro Amaral Feldner, Miguel Osman de Aguiar, Adriano Miziara Gonzalez, Gabriel Ribas Branco, Marcel Superbia, Michelle Lai, Daniel de Oliveira Mota, Maria Lucia Cardoso Gomes Ferraz, Wilson Mathias, Mario Kondo

765 Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of COVID-19 patients: a retrospective cohort study
Erdal Yılmaz, Rohat Ak, Fatih Doğanay

771 Mental disorders among pregnant women during the COVID-19 pandemic. A cross-sectional study
Deha Denizhan Keskin, Seda Keskin, Sedat Bostan

778 What anthropometric indicators are associated with insulin resistance? Cross-sectional study on children and adolescents with diagnosed human immunodeficiency virus
Carlos Alencar Souza Alves Junior, Priscila Custódio Martins, Luiz Rodrigo Augustemak de Lima, Diego Augusto Santos Silva

785 Burnout syndrome and workplace violence among nursing staff: a cross-sectional study
Sirlene Aparecida Scarpin Tsukamoto, Maria José Quina Galdino, Maynara Fernanda Carvalho Barreto, Júlia Trevisan Martins

792 Publicly versus privately funded cardiac rehabilitation: access and adherence barriers. A cross-sectional study
Giovanna Lombardi Bonini Borges, Mayara Moura Alves da Cruz, Ana Laura Ricci-Vitor, Paula Fernanda da Silva, Sherry Lynn Grace, Luiz Carlos Marques Vanderlei

799 Sociodemographic determinants of multimorbidity in Brazilian adults and older adults: a cross-sectional study
Marina Christofoletti, Giovani Firpo Del Duca, Tânia Rosane Bertoldo Benedetti, Deborah Carvalho Malta

807 Low molecular weight heparin is useful in adult COVID-19 inpatients. Experience during the first Spanish wave: observational study
Jose Ramon Gonzalez-Porras, Moncef Belhassen-Garcia, Amparo Lopez-Bernus, Luis Mario Vaquero-Roncero, Beatriz Rodriguez, Cristina Carbonell, Raul Azibeiro, Alberto Hernandez-Sanchez, Jose Ignacio Martin-Gonzalez, Juan Miguel Manrique, Gloria Alonso-Claudio, Felipe Alvarez-Navia, Jose Ignacio Madruga-Martin, Ronald Paul Macias-Casanova, Jorge García-Criado, Francisco Lozano, Jose Carlos Moyano, Miguel Vicente Sanchez-Hernandez, Víctor Sagredo-Meneses, Rafael Borras, Jose María Bastida, Guillermo Hernández-Pérez, Antonio Javier Chamorro, Miguel Marcos, Jose Angel Martin-Oterino

818 Patients' preferences regarding physicians' gender: a clinical center cross-sectional study
Carolina Matté Dagostini, Yan De Assunção Bicca, Miguel Bertelli Ramos, Sabrina Busnello, Murillo Cesar Gionedis, Natália Contini, Asdrubal Falavigna

828 Investigation of the effect of ultrasonography-guided bilateral erector spinae plane block on postoperative opioid consumption and pain scores in patients undergoing hepatectomy: a prospective, randomized, controlled study
Gülçin Hacıbeyoğlu, Ahmet Topal, Tevfik Küçükkartallar, Resul Yılmaz, Şule Arıcan, Sema Tuncer Uzun

837 Brazilian initial experience with lung transplantation due to irreversible lung fibrosis post-COVID-19 in a national reference center: a cohort study
Flavio Pola dos Reis, Lucas Matos Fernandes, Luis Gustavo Abdalla, Silvia Vidal Campos, Priscila Cilene Leon Bueno de Camargo, Samuel Lucas dos Santos, Ivana Teixeira de Aguiar, Juliana Patricia Pires, Andre Nathan Costa, Rafael Medeiros Carraro, Ricardo Henrique de Oliveira Braga Teixeira, Paulo Manuel Pêgo-Fernandes

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Correspondence to:

ASSOCIAÇÃO PAULISTA DE MEDICINA
Publicações Científicas
Av. Brig. Luís Antônio, 278 - 7º andar – São Paulo (SP) – Brasil – CEP 01318-901
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New challenges for lung transplantation in the era of COVID-19

Lucas Matos Fernandes[I], Paulo Manuel Pêgo-Fernandes[II]

Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[I]MD. Attending Physician, Thoracic Surgery Service, Lung Transplant Group, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.
https://orcid.org/0000-0001-9302-1035

[II]MD, PhD. Full Professor, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR; Director, Scientific Department, Associação Paulista de Medicina, São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7243-5343

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in late 2019 and has caused immense numbers of hospitalizations and deaths worldwide. There have now been more than 190 million diagnosed cases and more than 4 million deaths, according to the Johns Hopkins coronavirus center.[1] Organ transplantation, like most other surgical procedures, and especially lung transplantation, has been extensively affected by the pandemic,[2] due to high rates of hospital occupation and chances of infection, and to reallocation of healthcare professionals. Patients on waiting lists have faced not only the natural morbidity and mortality of their underlying diseases, but also an additional risk of complications due to COVID-19. Furthermore, the diminished supply of donors and difficulty in ensuring that these donors are negative for coronavirus infection have decreased the number of transplantations performed, thus increasing the mortality rate among waitlisted patients.

On the other hand, as already seen in other pandemics such as influenza, patients with severe acute respiratory syndromes due to current viral respiratory infections usually evolve without the need for lung transplantation, either because the catastrophic outcome of death occurs or because the pulmonary condition improves. However, during the COVID-19 pandemic, cases of chronification of acute lung transplantation cases have been reported worldwide. Most of these cases consisted of patients with lung disease for more than four to six weeks from which they had not recovered, but who did not have any other organic dysfunctions.

In mid-2020, after the first reports of transplantations in this type of patient were published, the Toronto group presented an article containing 10 guidelines to be considered in patients before indicating lung transplantation:[3] 1. Age (< 65 years); 2. Pulmonary dysfunction alone; 3. Long enough time for pulmonary recovery (something around four to six weeks at least); 4. Radiological evidence of irreversibility of the pulmonary condition; 5. The patient is awake and aware enough for discussion about transplantation; 6. Suitability for rehabilitation physiotherapy; 7. Meeting the usual criteria for lung transplantation (e.g. with regard to body mass index, drug addiction, smoking, etc.); 8. Polymerase chain reaction (PCR)-negative for SARS-CoV-2 in the lower respiratory tract; 9. The patient is at an experienced transplantation center; and 10. The center has extensive access to donors and there is low mortality on the waiting list.

In view of the low number of transplantations performed at the beginning of the pandemic, and the need for transplantations in this emerging population, the São Paulo State Technical Chamber for Thoracic Organs met to define criteria for patients to be evaluated and included in a list of those with severe acute insufficiency secondary to COVID-19 and, in April 2021, the criteria presented in **Annex 1** were agreed.

Based on this guidance, a series of evaluations was started, among patients institutionalized in the hospital complex of Hospital das Clínicas, Faculdade de Medicina, Universidade de Sao Paulo (HC-FMUSP), and among external patients (via telemedicine, who were then, if they fulfilled the minimum criteria, transferred to InCor/HC-FMUSP). Through this process, five institutionalized patients were analyzed: two were placed on the waiting list and then received transplants. Six external patients were evaluated: two were transferred, of whom one was waitlisted and received a transplant and the other, after evaluation and rehabilitation, presented clinical improvement and is on course for hospital discharge without the need for transplantation.

Much of this effort can be attributed to the intensive participation of the multidisciplinary team, with special mention for the physiotherapy, nutrition and intensive care unit (ICU) staff.[4]

Returning to surgical practice and the processes of donor selection, organ harvesting and operative tactics, to undertake transplantation in the midst of the pandemic, brought to light several points of note. In selecting recipients, in addition to the usual guidelines or ideal criteria, extended criteria were applied (**Table 1**).[5] Thus, a routine was created that included investigation of the clinical history of previous disease and exposure to contacts, a negative PCR test for SARS-CoV-2 and chest tomography without presentation of the infiltrates of ground-glass appearance that are characteristic of cases of COVID-19. In this manner, it was sought to ensure safety for the transplantation team, the recipient and the entire hospital to which the organ was sent, and thus to avoid occurrences of contamination of the team through inadvertent use of lungs infected with COVID-19, as in some published reports.[6] However, the procedure for extracting the lung block was done in the usual way, consisting of evaluation, perfusion and removal.

On the recipient side, there were also some points of note regarding the implantation surgery. Most patients who were awaiting lung transplantation due to severe acute respiratory syndrome consequent to COVID-19 were in situations of receiving circulatory extracorporeal membrane oxygenation (ECMO).[7-9] This was implemented initially for ventilatory disorders, but ultimately due to pulmonary hypertension associated with low compliance. These patients were monitored by means of invasive radial and femoral blood pressure measurements, bispectral index (BIS), Swan-Ganz, pulse oximeter, cardioscopy and transesophageal echocardiography.

In our experience, we chose to implement central venoarterial ECMO as intraoperative care, while maintaining peripheral venovenous ECMO, because the membranes had already been in use for more than three weeks. In this manner, contamination within the operative field was avoided, as described in an article published in this edition of the São Paulo Medical Journal.[10] Another complicating factor was that the patients very commonly presented pneumothorax and firm pleuro-pulmonary adhesions, and even drains were present. We chose to start the surgery on the side most affected by the disease, as is usually done, using the side with lower perfusion. Friable and hypervascularized lymph nodes of greater numbers and size were found in both hila. Reperfusion of the lungs was done slowly and gradually and the pressure of the pulmonary arteries was controlled by decreasing or increasing the circulatory assistance during the release of clamps from the pulmonary artery and left atrium. Throughout the transplantation, a cell saver was used. However, there was a need for blood transfusion and for replacement of fibrinogen and prothrombic factors. At the end of the transplantation, in the event of preserved biventricular function, we chose to remove the central venoarterial assistance and maintain the ECMO circuit circulating with saline solution, after total or partial return of the blood from the circuit. If it was not possible to fully return the blood, the rest was aspirated to the cell saver for reuse of the red blood cells. If, at the end of transplantation, there was a need for circulatory assistance due to ventricular dysfunction, we chose to switch to peripheral cannulation of the femoral artery using a thin cannula (15Fr), for partial assistance until recovery of cardiac function.

Before closing the chest wall, an extensive review of hemostasis was performed and pleural drains were placed in both pleurae, in line with the usual practice, one anteriorly and one posteriorly. During this period, tests on ventilatory autonomy and on shutdown of venovenous ECMO were performed, such that there was no entry of gas into the membrane via ECMO during this period. If the lungs maintained good oxygenation and exchange of carbon dioxide, the peripheral ECMO was also removed at the end of the surgery and the patient was sent to the intensive care unit for postoperative care.

Despite the replacement of the target organ of COVID-19, this type of patient remained critical. Early dialysis was necessary in operated cases, with maintenance of broad-spectrum antibiotics and antibiotics directed to germs previously identified and cultured from donor materials such as bronchoalveolar lavages. Tracheostomy was an important facilitator, with the aim of waking the patient and maintaining the rehabilitation that had been started preoperatively.

Lung transplantation in the midst of the pandemic proved to be a major challenge. This related both to searching for viable donors and to avoiding mortality among severely ill patients on the waiting list or among acute patients who progressed to a chronic form without other important organic dysfunctions, to allow them access to this type of treatment.

With the increase in mass vaccination and a better understanding of COVID-19, its treatments and cure, we believe that

Table 1. Ideal and extended criteria for donor selection

Ideal criteria	Extended criteria
Age < 55 years	Age > 55 years
Normal radiograph	Abnormal radiograph
PaO_2 > 300 (PEEP 5; FiO_2 100%)	PaO_2 < 300 (PEEP 5; FiO_2 100%)
Without thoracic trauma	With thoracic trauma
Sputum Gram stain: absence of organisms	Presence of microorganisms in tracheal secretions
No smoking	Smoking > 20 pack-years
Absence of purulent secretions at bronchoscopy	
No aspiration or sepsis	

Adapted from Orens JB et al.[5]

PaO_2 = arterial partial pressure of oxygen; PEEP = positive end-expiratory pressure; FiO_2 = fraction of inspired oxygen.

transplantation for acute patients due to this disease is a fleeting issue. Nevertheless, the lessons learned in the midst of this chaos will not be lost. The use of ECMO in patients with severe acute respiratory syndrome, which had already become part of the arsenal of large centers, will increasingly become used routinely. Although there is still a lack of exact criteria regarding which patients would have the best outcome from COVID-19 through use of this tactic, it has certainly marked its presence in relation to care for critical respiratory patient and for intraoperative support, as had already been seen in relation to patients with pulmonary hypertension.

We believe that transplantation plays a role in treatment for very well-selected acute lung patients who have evolved to chronic disease without presenting dysfunction of other organs. There is still a lack of studies and analyses on datasets larger than the case series seen over recent months, for enabling better definition of indications and outcomes. Until then, careful selection of patients and implementation of transplantation in large specialized centers and use of ECMO and rehabilitation are necessary in order to try to optimize the results and not waste lungs.

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Annex 1. Criteria established by the São Paulo State Technical Chamber for Thoracic Organs for inclusion in transplantation waiting lists of patients with severe acute insufficiency secondary to COVID-19, in April 2021

1. Polymerase chain reaction (PCR) negative for COVID-19 in samples, among which at least one should be from the lower respiratory tract;
2. Age less than 65 years (and ideally between 18 and 50 years);
3. Irreversibility of the clinical condition for more than six months;
4. Body mass index prior to hospitalization of between 17 and 27;
5. Hemodynamic stability;
6. Absence of active bacterial or fungal infections;
7. Patient awake and understanding that he or she will be evaluated for transplantation, and in agreement with undergoing this transplantation. Presence of an adequate caregiver who has been assessed by the nursing and psychology teams;
8. Approval from social services and absence of drug addiction, including smoking;
9. Suitable for active rehabilitation (minimum strength level of grade 3);
10. Ejection fraction greater than 50%. Transesophageal echocardiogram without showing any vegetations or anatomical or functional abnormalities;
11. Absence of coronary obstructions that cannot be treated percutaneously;
12. Absence of other organ dysfunctions;
13. Signing of a consent statement;
14. Autonomy is to be retained by the transplantation team for contraindicating the transplantation according to other clinical information that is collected and evaluated by the multiprofessional team.

In search of disambiguation: development of eye drop bottle sleeves to aid in identification and survey among possible users. A cross-sectional study

Ana Luiza Fontes de Azevedo Costa[I], Thiago Gonçalves dos Santos Martins[II], Vagner Rogério dos Santos[III], Paulo Schor[IV]

Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD, PhD. Pediatric Ophthalmology Fellow, UT Southwestern Dallas, Texas, United States.
orcid.org/0000-0002-6925-4207

[II]MD, PhD. Physician, Martins Clínica de Olhos, Rio de Janeiro (RJ), Brazil.
orcid.org/0000-0002-3878-8564

[III]PhD. Associate Professor, Department of Ophthalmology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0002-6034-6658

[IV]MD, PhD. Head, Department of Ophthalmology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
orcid.org/0000-0002-3999-4706

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ABSTRACT

BACKGROUND: Considerable numbers of individuals present low vision, blindness, illiteracy and other conditions that could possibly impair their identification of medications, such as eye drops. Through helping these individuals to identify their eye drops, they can achieve greater autonomy. Misidentification can be avoided through use of multisensory sleeves that can be adapted to most eye drop bottles. Correct use of eye drops is important for preventing progression of diseases like glaucoma that could potentially lead to blindness.

OBJECTIVE: To develop bottle sleeves to aid in identification of eye drops and then interview a group of possible users to evaluate the acceptance of the solution.

DESIGN AND SETTING: Cross-sectional survey performed at an ophthalmological clinic in São Paulo (SP), Brazil.

METHODS: We describe the development of multisensory sleeves to assist in identification of eye drops. To assess the acceptance of this solution, we interviewed 18 patients who were currently using three or more types of eye drops.

RESULTS: We developed four prototypes for eye drop bottle sleeves and conducted an acceptance test on them. Most of the patients who answered the survey about the sleeves were elderly. Most (95%) reported believing that the sleeves would help reduce the risk of mixing up eye drops with other medications that also dispense drops. They also believed that these would increase their autonomy in using eye drops.

CONCLUSION: The solution presented was well accepted and may help increase safety in using eye drops through preventing misidentification.

INTRODUCTION

Correct use of eye medications is very important for ensuring effective treatment of eye diseases. There is strong dependence on patient compliance and collaboration to ensure correct use. Incorrect use of these medications has already been demonstrated several times in the literature[1-5] and can be characterized in terms of several flaws in the process of eye drop use, such as inadequate hygiene, incorrect identification of which eye drop bottles to use, incorrect instillation technique and lack of adherence to treatment. Among the difficulties that may impede the use of eye drops, incorrect identification of the eye drops to be used can be highlighted. This misidentification can occur in a hospital environment, or at a pharmacy at the time of purchase or during daily use.

Occurrences of mix-ups of ocular medications with each other or with substances not suitable for ocular use can be very harmful. In such situations, individual end up using a substance that, in addition to not treating their eye problems, can worsen their clinical condition through causing several side effects both locally and systemically.[6,7-10] The similarities between bottles of eye medications and general substances can lead to an inadvertent misuse. Some substances are capable of causing severe eye burns since they do not have compatible pH.[11-13] The opposite situation can also occur, when eye drops are used via a pathway other than ocular, thereby increasing their absorption and possibly generating serious effects, especially in individuals who are more susceptible due to comorbidities.[14]

Incorrect use of eye drops at home is very common, since most users, even those with experience in using eye drops, have the perception that they are using these drops correctly and do not recognize that they are making mistakes during this process. Some groups of people are at greater risk of using medications incorrectly: not only ocular but also systemic medications. Among these groups, the following can be highlighted: visually impaired individuals,[15] users with low literacy,[16] users of multiple types of eye drops,[6,7] elderly people[17,18] and disabled people with cognitive impairments such as dementia.[19,20]

The sense of vision is the most common way to interact with the environment and, therefore, the most common means for guiding decision-making regarding the chosen medication. Temporary or permanent visual loss increases the risk of misidentification, due to difficulty in reading the labels of eye drop bottles.[6,7,21] According to the World Health Organization, there are 39 million blind people worldwide and 246 million people with low vision.[22]

Chronic eye conditions such as glaucoma may require the use of more than one type of eye drop for many years, or even for life. Glaucoma is the leading cause of irreversible blindness in the world, and its prevalence is increasing.[23] The use of multiple types of eye drops may indicate greater severity of the condition under treatment, and this is also common in postoperative states. In both scenarios, correct use is critical. However, there is a greater risk of mix-up between medications due to the possible temporary visual changes and the increased number of medications to be used.

All over the world, the elderly population is increasing, and the prevalence of ophthalmic diseases is higher in this group.[24] Advanced age is also usually accompanied by cognitive and visual impairment, which can affect the use of medications. One study showed that 66.3% of the individuals over 77 years old presented one or more limitations with regard to using their medications and, among these individuals, 31.8% were living alone and did not get help from others.[25]

Low literacy also limits the reading of labels and packaging.[16] According to the Brazilian Institute for Geography and Statistics, the percentage of illiterate people in Brazil in 2017 was 7%, which represents around 11.5 million people.[26] Worldwide, the United Nations Educational, Scientific and Cultural Organization (UNESCO) has estimated that in 2019, 100 million people between 15 and 24 years old were illiterate.[27]

Cognitive changes such as dementia create problems of adherence to treatment due to forgetfulness and altered perception of reality. The incidence of dementia increases significantly from the age of 65 years onwards.[28]

Some of these factors can overlap, and further increase the risk of misuse of eye medications. There are already some methods to help with identification of eye drops,[29,30] but most of them have limitations of dependence on visual acuity, literacy or color vision. In the United States, the Food and Drugs Administration (FDA), supported by the American Academy of Ophthalmology, approved the use of different colors for eye drop bottle caps in 1996. This color difference helps many patients and healthcare professionals to better identify eye drops, but it is not so useful for those who have impairment of color vision, such as individuals with glaucoma or optic nerve diseases.[30]

Artificial intelligence also has the potential to improve the identification of medications, for both ocular and systemic conditions. Applications such as MobileNet, which uses deep learning, can be trained to automatically recognize labels.[31] In addition, functions such as medication schedule reminders, with audible and visual alerts, can be added to show which medication should be used at a given time.

When there is a natural difference in the color of the ophthalmic solution, this becomes an additional factor to help differentiate between types of drops and prevent errors when there is no color vision deficiency. One study tested the impact of color differences to help in identifying eye drops and showed that there was a 64% improvement in correct identification of medications based only on analysis of the color of the substance of eye drops from identical bottles.[32]

In the present study, we detail the idealization and development of multisensory sleeves and evaluation of the acceptance of this new method to help reduce the risk of confusion between eye medications. Misuse of ocular medications is a subject that has only been poorly explored so far, but it is of great importance and needs to be addressed so that more solutions are proposed for increasing the safety of users. Specifically, we address eye drops that have extremely similar bottles and are, therefore, more prone to misidentification.

OBJECTIVE

To develop eye drop bottle sleeves to aid in identification of eye drops and prevent mix-ups and misuse, and to interview a group of possible users to evaluate their acceptance of the solution.

METHODS

Study setting and design

We describe the idealization and development of four multisensory bottle sleeve prototypes containing different textures and odors, using low-cost flexible materials that are adaptable to most eye drop bottles commercially available in Brazil. This was a cross-sectional survey.

The prototypes chosen for the tests were sleeves made from orange-colored silicone material of thickness 2 millimeters, with different textures. To add the four different odors that were used, we left the sleeves immersed in essences for 24 hours

before performing the test, to ensure that the odor would not dissipate before the test. The odors used were banana, chocolate, cinnamon and coffee, because these are well known by the Brazilian population.

After developing four sleeves with different textures and odors, we applied a verbal survey to a convenience sample of 18 adult individuals in an ophthalmological clinic in São Paulo (SP), Brazil. The investigator applied the survey to patients who had spontaneously sought emergency ophthalmological care for any eye problem and also to patients who were regularly scheduled for routine appointments at the ophthalmology service.

Data source and patient characteristics

The survey was applied to individuals who were using three or more types of eye drops, regardless of the length of time for which they had been using these medications. All the individuals surveyed had firstly agreed to participate by signing a consent form. This study was approved by a local public university ethics committee (approval number 1326/2016; date: November 30, 2017).

The following exclusion criteria were applied: refusal to participate, presence of dementia that could be observed in the initial conversation, or use of less than three types of eye drops. The survey is shown in **Table 1**.

The researcher gave the participants four bottles of eye drops produced by the same company, each with a different ophthalmological solution and wrapped in a sleeve with a different texture and odor (**Figure 1**). The participant was able to hold, test and analyze each eye drop bottle for as long as they wished, even during or after the questions in the survey.

RESULTS

Four prototypes were produced from the orange silicone rubber material. This material had a thickness of 2 millimeters and was cut into strips of different widths. The ends of these strips were sewn together to form rings of different widths that would fit snugly around the eye drop bottles (always with a height outwards from the cylinder of the bottle of 2 millimeters). The bottle sleeves thus set up were as follows: one bottle with two flat rings, each 5 millimeters in width (odor of banana); one bottle a single smooth and flat strip of 5 millimeters in width (odor of cinnamon); one bottle with a strip of 1.5 centimeters in width with embossed hearts (odor of coffee); and one bottle with a strip of 1.5 centimeters in width with vertical grooves (odor of chocolate) (**Figure 1**).

Eighteen individuals without any profile of dementia who were using three or more types of eye drops analyzed these eye drop bottles with the sleeves and answered the survey verbally. The demographic data on the interviewees are shown in **Table 2**, together with the pathological conditions that motivated the use of the drops. Out of the total of 18 patients who participated in the survey, 44% of them were female. The average age was 70.1 years (range 54-96), and 61% of the respondents were elderly. The most common ocular pathological condition that had led to use of eye drops was glaucoma (62%).

The answers to the questions in the survey are shown in **Table 3**. Only three individuals (17%) declared that they needed someone else to help them use eye drops, and all of these individuals

Table 1. Patient survey

1. What was the diagnosis that led to eye drop use?
2. Do you put in the drops yourself?
2a. If not you, who does this?
3. Have you ever used the wrong drop?
4. In your opinion, would the sleeves provide more autonomy?
5. In your opinion, would the sleeves reduce the risk of eye drop mix-up?
6. In your opinion, would the sleeves make it harder to squeeze the eye drop bottle to instill the drop?
7. In your opinion, which feature is more helpful? Texture, odors or both?

Figure 1. Prototype: the four types of sleeves produced and used in the survey.

Table 2. Demographic data on the questionnaire participants

Parameter	Number (%)
Sex	
Female	8 (44%)
Male	10 (56%)
Level of education	
Complete elementary school	2 (11%)
Incomplete elementary school	2 (11%)
Complete middle school	6 (33%)
Complete high school	4 (22%)
Higher education	4 (22%)
Age	
54-64 years	7 (39%)
≥ 65 years	11 (61%)
Ocular pathological condition that required eye drops	
Glaucoma	11 (62%)
Cataract, postoperative status	6 (33%)
Corneal ulcer	1 (5%)

Table 3. Answers obtained from the patients who were interviewed

Question	Yes	No
Do you put in the drops yourself?	15 (83%)	3 (17%)
Have you ever used the wrong drop?*	9 (50%)	8 (45%)
Would the sleeves provide more autonomy?	17 (95%)	1 (5%)
Would the sleeves reduce the risk of eye drop mix-up?	17 (95%)	1 (5%)
Would the sleeves make it harder to squeeze the eye drop bottle to instill the drop?	1 (5%)	17 (95%)
Which feature is more helpful?**		
- Texture alone	8 (45%)	
- Odor alone	2 (10%)	
- Both texture and odor together	7 (40%)	

*One patient (5%) could not remember whether the wrong drop had ever been used; **One patient (5%) said that neither feature was helpful.

appointed family members to do this. The other 83% said they did not depend on others to use drops. When asked if there was any confusion in choosing and using the correct medication, eight (45%) denied having this problem, one (5%) reported not remembering and nine (50%) said they had already mixed up bottles previously.

When asked if, in their opinion, the sleeve would provide them with more autonomy, 17 (95%) answered yes, while one (5%) answered no. When asked if the sleeve would interfere at the time of instillation, one (5%) answered yes because the bottle would be stiffer, and 17 (95%) answered no. Only one individual (5%) replied that the sleeves would not help to better differentiate the eye drops and reduce the risk of confusion, while the other 17 (95%) believed that the sleeves would help in this regard. When expressing an opinion on the preference for attributes on the sleeve, one individual (5%) stated that they did not prefer any, eight (45%) preferred only the texture, two (10%) preferred only the odor and seven (40%) preferred both the texture and the odor (**Table 3**).

DISCUSSION

The idealization and development of these prototypes for eye drop bottle sleeves was based on the observation that there was a need for assistance in identification of eye drops, especially among patients with visual problems, elderly people, illiterates and users of multiple types of eye drops.

The silicone material was chosen because it is inert, washable, safe and available at low cost. The choice of odors of banana, cinnamon, chocolate and coffee was intentional, as these odors form part of Brazilian culture and could thus further assist in the identification. The textures were chosen according to convenience, depending on the availability of the material used.

The acceptance test conducted was a type of usability test, which does not require a large sample to provide useful conclusions. The inclusion of individuals who were using three or more types of eye drops was essential, give that they are aware of the difficulties in dealing with multiple medications.

There have been reports in the literature regarding misidentification of ophthalmic medications in relation to substances that are not suitable for ocular use, even in the absence of use of multiple medications.[11-13] In addition to having an impact on quality of life,[33] use of multiple medications increases the risk of misidentification.[34] Incorrect identification of medications is an underestimated problem that is not clearly apparent, due to the subtle effects of most misused eye drops.

Personal factors can also contribute to increased risk of misidentification. Among these factors, low levels of literacy,[16] visual impairment,[15,21] advanced age[35,36] and cognitive changes[19,20] can be highlighted.

Most of the individuals interviewed (61%) were elderly. Half of the individuals acknowledged that they had mixed up their eye drops previously. In such cases, this may have been due to their use of multiple types of eye drops and to the limitations of advanced age. This finding is probably an underestimate, given that misidentification can go unnoticed if it does not cause significant consequences.

Although the majority of the respondents considered that the bottle sleeves could increase their autonomy, the majority were also responsible for their use of eye drops themselves. The gain in autonomy would probably be more impactful for users of eye drops with low vision or who are blind, and those who are illiterate and more dependent on the help of others.

One of the concerns in adding sleeves to the bottles is the possibility that this could make it difficult to squeeze the bottle to instill the drop. Users of eye drops who present pathological conditions that affect manual movement may already have difficulty with instillation, and possibly would have greater difficulty with the addition of the sleeves.

The preference for the sense of touch had also been observed in a previous study,[37] in which improved identification of eye drops when using sleeves was also demonstrated. The preference for touch can be explained by the ability to generate more effective memories than through the sense of smell. Smell-related memories are usually the result of memory about the feeling generated in response to the odor.[38] In addition, olfactory changes are common among the elderly, with a prevalence of 60-75% in those over 80 years old,[39,40] which may limit the utility of this characteristic for more advanced age groups.

Tactile acuity also suffers age-related decline, but it has been observed that this acuity is preserved in congenitally blind individuals and those undergoing intense tactile training.[41,42]

Healthcare professionals involved in patient care need to be able to identify which individuals are most at risk of using their

medications incorrectly and should seek solutions to assist them. A study showed that women over 75 years old and elderly people with diabetes, hypertension and sequelae of stroke are at greater risk of developing limitations in activities of daily living. These patients need to be carefully evaluated and assisted in their use of medication.[43]

It was important to do the acceptance test among potential users of this solution, so that problems could be identified and changes made in order to improve the sleeves in accordance with the needs of some of the possible users.

The use of identification aids is a creative way to reduce the risk of errors in using eye drops. This may also help in improving adherence to treatment and the safety of the treatment, especially among patients who are most susceptible to error, such as the elderly and people with visual impairments, who represent a considerable portion of the population.

Strengths and limitations of the study

Among the limitations of this study, we can mention the fact that a convenience sample was used and the fact that the component involving memory and cognition was not evaluated. More detailed studies with different populations of eye drop users could clarify which groups could gain greater benefit through use of these sleeves. Such studies could also promote greater adherence and enable assessment of possible clinical impacts.

Sleeves are a simple option that can be produced with flexible silicone material that is adaptable to most eye drop bottles. The idea of sleeves could be extrapolated to systemic medication bottles as well. In the United States, where prescription medication bottles are standardized, sleeves with a larger diameter could be useful for differentiating between bottles, especially in cases of polypharmacy, which is common in old age.

CONCLUSION

Most of the patients using three or more types of eye drops who we interviewed (95%) believed that the sleeves could improve their autonomy in using the drops, and that the sleeves could reduce the risk of misidentification between bottles.

These multisensory sleeves for helping in eye drop identification were a well-accepted solution and may help increase safety in using eye drops.

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review and editing (lead); Martins TGS: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Santos VR: conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), supervision (supporting) and writing-review and editing (equal); and Schor P: conceptualization (equal), supervision (supporting) and writing-review and editing (supporting)

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Address for correspondence:
Ana Luiza Fontes de Azevedo Costa
Universidade Federal de São Paulo (UNIFESP)
Rua Botucatu, 821
Vila Clementino — São Paulo (SP) — Brazil
CEP 04023-062
Tel. (+55 11) 5576-4981
E-mail: luizafacosta@hotmail.com

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Retrospective analysis on efficacy of convalescent plasma in acute respiratory distress syndrome due to COVID-19

Esma Eren[I], Ayşegül Ulu-Kılıç[II], Serdal Korkmaz[III], Merve Yıldız[IV], Recep Civan Yüksel[V], Ayşin Kılınç-Toker[VI], Emine Arman-Fırat[VII], Zehra Bestepe-Dursun[VIII], Ilhami Çelik[IX]

Kayseri City Education and Research Hospital, Kayseri, Turkey

[I]MD. Physician, Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-2712-9694

[II]MD, PhD. Professor, Department of Infectious Disease and Clinical Microbiology, Erciyes Üniversitesi Tıp Fakültesi, Kayseri, Turkey.
https://orcid.org/0000-0002-5105-1348

[III]MD, PhD. Assistant Professor, Department of Hematology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-5759-2735

[IV]MD. Physician, Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0003-1363-3993

[V]MD. Physician, Intensive Care Unit, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0003-4496-9473

[VI]MD. Physician, Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-6775-1234

[VII]MD. Physician, Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-7950-9509

[VIII]MD. Physician, Department of Infectious Disease and Clinical Microbiology, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-6736-0380

[IX]MD, PhD. Professor, Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey.
https://orcid.org/0000-0002-2604-3776.

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ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is an ongoing global health threat. However, currently, no standard therapy has been approved for the disease.

OBJECTIVES: To evaluate the clinical effectiveness of convalescent plasma (CP) in patients with acute respiratory distress syndrome (ARDS) due to COVID-19.

DESIGN AND SETTING: Retrospective study conducted at Kayseri City Education and Research Hospital, Kayseri, Turkey.

METHODS: The case group consisted of adult patients (> 18 years) with ARDS due to COVID-19 who received CP in combination with antiviral and supportive treatment. These patients were compared with others who only received antiviral and supportive treatment.

RESULTS: During the study period, a total of 30 patients with ARDS due to COVID-19 were included. Eleven patients (36%) received CP in combination with antiviral and supportive treatment, whereas nineteen patients (64%) in the control group only received antiviral and supportive treatment. On admission, the median age, demographic and clinical data and initial laboratory test results were similar between the groups ($P > 0.05$). On the 14th day of treatment, the laboratory values remained similar between the groups ($P > 0.05$). The mortality rates were not significantly different between the groups.

CONCLUSION: CP treatment did not affect mortality or lead to clinical improvement for COVID-19 patients with ARDS.

INTRODUCTION

At the end of 2019, a novel coronavirus was recognized as a cause of viral pneumonia cases in Wuhan, China. Since it had high genetic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV), the virus was officially named SARS-CoV-2 and the disease was named coronavirus disease 2019 (COVID-19).[1] The disease spread in a short time and was declared to be a pandemic by the World Health Organization (WHO) on March 11, 2020.[2] Globally, there have been 119,603,761 confirmed cases of COVID-19, including 2,649,722 deaths, reported to WHO, starting from the day on which it was first identified.[3]

Currently, there is no proven effective treatment for COVID-19.[4] Convalescent plasma (CP) treatment is one of the passive immunotherapy methods used. This is a very old procedure.[5] It was used successfully against SARS-CoV in 2003, the influenza A pandemic (H1N1) in 2009, Middle East respiratory syndrome coronavirus in 2012, and Ebola virus in 2015. Mair-Jenkins reviewed the experiences from all of these epidemics and reported that CP therapy was associated with reduced mortality.[6]

The use of CP for treating COVID-19 is highly controversial.[7] Ye et al. administered CP to six patients infected with SARS-CoV-2 and reported a rapid and dramatic improvement in patients who presented lung infiltration.[8] It was also reported that CP improved two patients with acute respiratory distress syndrome (ARDS) due to COVID-19.[9]

In a systematic review, CP was shown to have reduced the mortality rate among high-risk COVID-19 patients.[10] On the other hand, in another study, a meta-analysis comparing CP therapy with placebo did not demonstrate any evidence of benefit from use of CP compared with placebo or standard care, with regard to clinical improvement or reduction of all-cause mortality.[11]

OBJECTIVE

In this present study, we aimed to evaluate the effectiveness of CP for patients with ARDS due to COVID-19.

METHODS

Study design and patients

This retrospective study was carried out in a tertiary-level hospital with a total capacity of 1,600 beds, and 180 intensive care beds. Adult patients (> 18 years) who were treated in the intensive care unit (ICU) for ARDS due to COVID-19 were included to this study. The case group was defined as patients who received CP in addition to antiviral and supportive treatment. The control group only received antiviral and supportive treatment. The primary endpoint of the study was 14-day mortality; the secondary endpoints were improvement in respiratory function (PaO_2/FiO_2 ratio) and the laboratory findings on the 14th day of the disease.

Definitions

Presence of COVID-19 pneumonia was defined as either: I. SARS-CoV-2 PCR positivity in upper respiratory tract samples and bilateral peripheral ground-glass infiltration (typical for COVID-19) in thoracic computed tomography (CT) scans; or: II. Rapid antibody test positivity and typical infiltration for COVID-19 in thoracic CT.

ARDS was defined in accordance with the Berlin criteria: I. Respiratory distress that occurred or worsened in the last seven days; II. Radiologically detected pleural effusion, lung collapse or bilateral nodular opacities; III. Respiratory failure that cannot be explained by heart failure or volume; and IV. Hypoxemia. ARDS were classified according to the degree of hypoxemia, as mild ARDS ($200 < PaO_2/FiO_2 \leq 300$; positive end-expiratory pressure, PEEP ≥ 5 cmH_2O); moderate ARDS ($100 < PaO_2/FiO_2 \leq 200$; PEEP ≥ 5 cmH_2O); or severe ARDS ($PaO_2/FiO_2 \leq 100$; PEEP ≥ 5 cmH_2O), according to oxygenation.[12]

Patients who had a diagnosis of cancer, were receiving any immunosuppressive therapy or had serum IgA deficiency, and pregnant women, were excluded from the study.

Institutional protocol for treating COVID-19 patients

For COVID-19 patients who did not need hospitalization or had mild symptoms, oral hydroxychloroquine and oral azithromycin were prioritized. All critically ill patients were treated with favipiravir. ABO-compatible plasma was used for patients from eligible donors or if the blood type-compatible plasma was already available in the blood center of the hospital. Supportive therapy consisted of oxygen and fluid supplements, and also vasopressor agents if necessary. All patients received favipiravir (1600 mg loading dose and 800 mg/day maintenance dose, orally), methylprednisolone (40-80 mg/day parenterally) and enoxaparin (4,000-6,000 IU).

Selection of CP donors

The criteria for selecting individuals as donors were as follows: I. Evidence of COVID-19 documented by a laboratory test, consisting either of a diagnostic test (e.g. on a nasopharyngeal swab) at the time of illness, or of a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time when COVID-19 was suspected; II. Complete resolution of symptoms at least 14 days prior to donation and negative results for COVID-19 either from one or more nasopharyngeal swab specimens or from a molecular diagnostic test on a blood sample.[13]

Individuals who had recovered from SARS-CoV-2 infection were invited to donate CP. All donors were informed about the apheresis procedure, and their written consent was obtained. In addition to a RT-PCR assay for SARS-CoV-2 RNA, all potential donors were serologically screened for HBsAg, anti-HCV, anti-HIV 1-2 and anti-syphilis antibodies. The neutralizing antibody titer was not routinely obtained. The latest generation of cell separator apheresis device (Spectra Optia apheresis system; Terumo BCT, Lakewood, United States) was used to collect CP. 200-600 milliliters (ml) of plasma were collected using the apheresis device, depending on the total blood volume of the donor. Plasma components were labeled using the ISBT128 coding system and were stored below minus 18/25 °C, in storage cabinets at the blood center. No nucleic acid amplification tests or pathogen inactivation processes were routinely performed.

CP infusion

CP was delivered ready-for-use from the blood center to the pandemic intensive care units (ICUs) and each patient received two to three consecutive transfusions of 200 ml of A, B or O blood type (ABO)-compatible convalescent plasma (maximum of 600 ml of CP in total) over a period of 30 to 60 minutes, under supervision by the treating physician.

Statistical analysis

The information collected was processed using the Statistical Package for Social Sciences (SPSS) for Windows, version 22.0 (IBM, Chicago, United States). The Shapiro-Wilk test was performed to check the normality assumption of the data. Parametric data were presented as mean ± standard deviation (SD), and intergroup significance was determined using Student's t test. All the analyses were performed with the significance level set at $P < 0.05$.

Ethics statement

The clinical research was approved by the local ethics committee (date: October 1, 2020; number: 2020/10/196). This study was conducted in conformity with the principles outlined in the Helsinki Declaration.

RESULTS

A total of 30 patients with COVID-19-related ARDS were included in this study. The mean age of the patients was 62.16 ± 9.51 years and 73% of them were male. Hypertension (43.3%) was the most common comorbid disease. Sixty percent of the patients had previously received hydroxychloroquine. Two patients (6.7%) had severe ARDS. Four patients (13.3%) needed invasive mechanical ventilation.

Eleven patients (36%) were treated with CP in addition to antiviral therapy, and these were compared with nineteen patients (63%) who did not received CP. CP infusion was applied on a mean ± SD of 3.82 ± 3.68 days, and a median of three days (range: 1-14), after symptom onset. The mean age, gender, comorbidities and symptoms were similar between the two groups (P > 0.05). There was no significant difference between the groups regarding the severity of ARDS and need for respiratory support on admission (**Table 1**). Nasal oxygen was administered to eight patients (42%) in the control group and two patients (18%) in the CP group. On the 14th day of treatment, the mean values ± SD of the PaO_2/FiO_2 ratio were 227.94 ± 124.98 in the CP group and 294.34 ± 144.59 in the control group. There was no statistically significant difference between the groups (P = 0.722). The length of time taken for the CP group to be discharged from the ICU was statistically significantly longer than that of the control group.

The laboratory findings were not significantly different between the groups on the day of CP infusion (P > 0.05) (**Table 2**).

On the 14th day of treatment, the laboratory findings regarding leukocyte and lymphocyte counts and the levels of acute-phase reactants were similar between the two groups (P > 0.05) (**Table 3**). One intubated patient died on the 7th day after CP infusion. Three patients in the control group were intubated, of whom one became extubated on the 4th day.

None of the patients developed any side effects either during or after CP infusion.

DISCUSSION

In this study, we retrospectively evaluated the effect of CP on the survival of patients with ARDS due to COVID-19 pneumonia. We observed that CP treatment did not improve the clinical or laboratory findings. Also, it had no effect regarding improvement of survival, i.e. regarding lowering mortality. Also, the time taken to be discharged from intensive care was longer.

Table 1. Demographic and clinical characteristics of patients

Characteristics	Convalescent plasma group n = 11 (%)	Control group n = 19 (%)	Total n = 30 (%)	P
Age, mean (± SD)	59.81 (± 9.58)	63.52 (± 9.45)	62.16 (± 9.51)	0.312
Male	10 (90.9)	12 (63.2)	22 (73.3)	0.098
Symptoms				
Fever	8 (72.7)	10 (52.6)	18 (60.0)	0.279
Cough	5(45.5)	14 (73.7)	19 (63.3)	0.122
Dyspnea	8 (72.7)	13 (68.4)	21(70.0)	0.804
Duration of symptoms, mean (± SD)	3.82 (± 3.68)	4.68 (± 2.31)	4.37 (± 2.83)	0.430
Comorbidities				
Diabetes mellitus	2 (18.2)	8 (42.1)	10 (33.3)	0.180
Hypertension	3 (27.3)	10 (52.6)	13 (43.3)	0.177
Chronic obstructive pulmonary disease	2 (18.2)	3 (15.8)	5 (16.7)	0.865
Antiviral treatment before convalescent plasma				
Favipiravir	11 (100)	19 (100)	30 (100)	1.000
Hydroxychloroquine	9 (81.8)	9 (47.4)	18 (60.0)	0.143
Azithromycin	9 (81.8)	13 (68.4)	22 (73.3)	0.424
Severity of ARDS				
Mild	6 (54.5)	11 (57.9)	17 (56.7)	1.000
Moderate	4 (36.4)	7 (36.8)	11 (36.7)	1.000
Severe	1 (9.1)	1 (5.3)	2 (6.7)	0.552
PaO_2/FiO_2 on CP infusion day, mean (± SD)	205.34 (± 52.41)	212.04 (± 47.34)	209.59 (± 48.47)	0.214
Respiratory support				
Only nasal O_2	2 (18.2)	8 (42.1)	10 (33.3)	0.180
High-flow O_2	6 (54.5)	8 (42.1)	14 (46.7)	0.510
Invasive mechanical ventilation	1 (9.1)	3 (15.8)	4 (13.3)	0.603
Prognosis				
Discharge from intensive care unit up to 14th day after CP	4 (36.4)	15 (78.9)	19 (63.3)	0.027
PaO_2/FiO_2 on 14th day after CP, median (min-max)	227.94 (± 124.98)	294.34 (± 144.59)	269.99 (± 139.36)	0.722
Mortality up to 14th day	1 (9.1)	3 (15.8)	4 (13.3)	0.603

SD = standard deviation; ARDS = acute respiratory distress syndrome; CP = convalescent plasma; min-max = minimum-maximum.

On the 14th day, the PaO_2/FiO_2 ratio was lower in the CP group. Discharge from the intensive care unit may have been delayed due to the longer time taken for recovery of the oxygenation level.

The evidence of effectiveness of CP for treating COVID-19 is limited. There are quite a few different results regarding the effectiveness of CP. Firstly, Ye et al. observed that CP was effective in decreasing the viral load in non-severe cases. They also reported that patients with pneumonia had radiological improvements, but none of their cases were COVID-19-related ARDS.[8] In a retrospective propensity-score matched-control study, Liu et al. assessed the efficacy of CP among severe COVID-19 patients. A significant reduction in oxygen requirements (adjusted odds ratio [OR] 0.86; P = 0.025) and an improvement in survival (adjusted hazard ratio [HR] 0.34; P = 0.027) were observed among patients treated with CP, in comparison with controls.[14] In a one-arm multicenter interventional study, Perotti et al. observed the effects of CP infusion among 46 severe COVID-19 patients over a short period (seven days). Improvements in clinical and chest radiogram severity, laboratory test values (C-reactive protein, ferritin and lactate dehydrogenase) and functional respiratory parameters (PaO_2/FiO_2) were observed at the seven-day follow-up. A significant reduction in mortality rate (from 15% to 6.5%) was observed through comparing the mortality data of the present study with those of a historical cohort group.[15]

In contrast, in another study, the 28-day mortality rate among 52 critically ill patients with COVID-19 who were treated with CP in addition to standard therapy did not differ regarding clinical recovery, compared with the control group. However, patients with severe ARDS ($PaO_2/FiO_2 \leq 100$; PEEP ≥ 5 cmH_2O) were not included in that randomized study.[16] An open-label randomized clinical trial on CP versus standard care, named the ConCOVID study, was conducted in the Netherlands. The trial was halted prematurely, when the baseline SARS-CoV-2 neutralizing antibody titers of the participants and the CP units transfused were found to be comparable, thus challenging the potential benefit of CP among the patients included in that study. In any case, no differences in mortality (P = 0.95), time spent in hospital (P = 0.68) or disease severity at day 15 (P = 0.58) were observed between the study arms.[17]

However, it should be noted that those studies enrolled patients with severe COVID-19 but did not focus on the effectiveness of CP for treating ARDS.

There were some limitations to our study. Firstly, its retrospective design and small number of patients was an important limitation. In addition, the inability to measure neutralizing antibodies in this study, in which we evaluated patients who we followed up in the early period of the pandemic, was another limitation.

Table 2. Laboratory test results on the day of convalescent plasma infusion

Laboratory tests, mean (± SD)	Control group, n = 19	Convalescent plasma group, n = 11	Total, n = 30	P
White blood cell count × 10^9/l	7.52 (± 3.69)	8.21 (± 1.83)	7.77 (± 3.11)	0.504
Lymphocyte count × 10^9/l	0.76 (± 0.45)	0.82 (± 0.15)	0.78 (± 0.37)	0.620
Creatinine, mg/dl	0.83 (± 0.35)	1.50 (± 1.65)	1.07 (± 1.06)	0.213
Aspartate aminotransferase, U/l	32.26 (± 13.01)	38.81 (± 24.68)	34.66 (± 18.04)	0.346
Alanine aminotransferase, U/l	26.42 (± 11.95)	26.54 (± 7.00)	26.46 (± 10.27)	0.972
Lactate dehydrogenase, U/l	383.47 (± 118.36)	435.64 (± 159.80)	402.60 (± 134.74)	0.315
Procalcitonin, µg/ml	3.50 (± 10.00)	2.56 (± 1.18)	3.16 (± 7.92)	0.760
C-reactive protein, mg/dl	154.44 (± 105.81)	141.63 (± 80.92)	149.75 (± 96.16)	0.732
Ferritin, µg/ml	1377.36 (± 1639.60)	1140.72 (± 315.77)	1290.60 (± 1310.12)	0.642
D- dimer, µg/ml	2451.89 (± 2789.59)	2000.72 (± 562.63)	2286.46 (± 2240.40)	0.505
Fibrinogen, mg/l	6278.42 (± 1771.96)	6316.00 (± 454.12)	6292.20 (± 1421.38)	0.931

SD =standard deviation.

Table 3. Laboratory test results on the 14th day after convalescent plasma infusion

Laboratory tests, mean (± SD)	Control group, n = 19	Convalescent plasma group, n = 11	Total	P
White blood cell count ×10^9/l	7.75 (± 4.74)	8.30 (± 2.91)	7.95 (± 4.12)	0.735
Lymphocyte count ×10^9/l	0.92 (± 0.46)	0.87 (± 0.46)	0.90 (± 0.45)	0.784
Creatinine, mg/dl	1.55 (± 2.24)	1.40 (± 0.33)	1.50 (± 1.77)	0.819
Aspartate aminotransferase, U/l	32.94 (± 26.83)	26.90 (± 7.64)	30.73 (± 21.81)	0.475
Alanine aminotransferase, U/l	27.26 (± 19.29)	38.63 (± 21.98)	31.43 (± 20.70)	0.150
Lactate dehydrogenase, U/l	381.63 (± 134.83)	298.91 (± 127.38)	351.30 (± 136.10)	0.110
Procalcitonin, µg/ml	1.29 (± 1.80)	0.43 (± 0.83)	0.97 (± 1.56)	0.149
C-reactive protein, mg/dl	77.52 (± 75.76)	42.38 (± 31.01)	64.64 (± 64.73)	0.087
Ferritin, µg/ml	1760.15 (± 3716.18)	989.90 (± 1074.77)	1477.73 (± 3018.70)	0.510
D- dimer, µg/ml	3328.68 (± 4415.80)	2365.00 (± 1938.66)	2975.33(± 3690.81)	0.500
Fibrinogen, mg/l	5879.47 (± 1042.11)	5105.90 (± 1397.66)	5595.83 (± 1221.24)	0.095

SD = standard deviation.

CONCLUSION

In our study, in which we investigated the effectiveness of CP for treating patients with ARDS due to COVID-19, we found that CP was not effective with regard to decreasing mortality.

Further prospective controlled studies are needed in order to evaluate the effectiveness of CP for treating patients with COVID-19-related ARDS.

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Address for correspondence:
Esma Eren
Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kayseri City Education and Research Hospital, Kayseri, Turkey
Tel. +90 5545965092
E-mail: esmaereneryilmaz@gmail.com

Allergic rhinitis improvement after septorhinoplasty in a sample of allergic rhinitis patients with septal deviation: a quasi-experimental study

Vanesa García-Paz[I], Cintia Micaela Chamorro-Petronacci[II], Roi Painceira-Villar[III], Ricardo Becerro-de-Bengoa-Vallejo[IV], Marta Elena Losa-Iglesias[V], Mario Pérez-Sayáns [VI], Adolfo Sarandeses-Garcia[VII], Daniel López-López[VIII]

Hospital Universitario A Coruña, A Coruña, Spain

[I]MD. Research, Health and Podiatry Group, Department of Health Sciences, Faculty of Nursing and Podiatry, Universidade da Coruña, A Coruña, Spain; Area Specialist Physician, Department of Allergology, Complejo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain.
https://orcid.org/0000-0002-2671-3514

[II]PhD, DDS. Researcher, Instituto de Investigaciones Sanitarias de Santiago (IDIS), Santiago de Compostela, Spain; Researcher Fellow, MedOralRes (Grupo de Investigación en Patología Oral Médico Quirúrgica), Universidad de Santiago de Compostela, A Coruña, Spain.
https://orcid.org/0000-0002-5637-9908

[III]DP, MSc, PhD. Research, Health and Podiatry Group, Department of Health Sciences, Faculty of Nursing and Podiatry, Universidade da Coruña, Ferrol, Spain.
https://orcid.org/0000-0001-8943-1285

[IV]RN, BSc, MLIS, DPM, DHL, PhD. Full Professor, Facultad de Enfermería, Fisioterapia y Podología, Universidad Complutense de Madrid, Madrid, Spain.
https://orcid.org/0000-0003-1568-7602

[V]RN, DHL, BSc, MSc, PhD, DPM. Full Professor, Faculty of Health Sciences, Universidad Rey Juan Carlos, Alcorcón, Spain.
https://orcid.org/0000-0001-7588-2069

[VI]PhD, DDS. Researcher, Instituto de Investigaciones Sanitarias de Santiago (IDIS), Santiago de Compostela, Spain; Research Fellow, MedOralRes (Grupo de Investigación en Patología Oral Médico Quirúrgica), Universidad de Santiago de Compostela, A Coruña, Spain.
https://orcid.org/0000-0003-2196-9868

[VII]PhD, MD. Professor, Otorhinolaryngology, Escuela Universitaria (EU), Universidade da Coruña, A Coruña, Spain. Supervision
https://orcid.org/0000-0003-0159-4106

[VIII]MSc, BSc, PhD, DPM. Senior Lecturer and Researcher, Health and Podiatry Group, Department of Health Sciences, Faculty of Nursing and Podiatry, Universidade da Coruña, Ferrol, Spain.
https://orcid.org/0000-0002-9818-6290

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ABSTRACT

BACKGROUND: Allergic rhinitis (AR) is a chronic inflammatory disease that affects almost 30% of the adult population.

OBJECTIVE: To describe and compare the evolution of symptoms in patients diagnosed with AR and septal deviation prior to and following septoplasty (STP).

DESIGN AND SETTING: Quasi-experimental study developed in A Coruña University Hospital.

METHODS: Patients aged 18-65 years who had been diagnosed with AR and septal deviation were recruited. Obstruction airflow was evaluated before and after surgery, by means of anterior rhinomanometry (RNM). Severity symptoms and quality of life were assessed using a visual analogue scale (VAS) and the ESPRINT questionnaire, respectively.

RESULTS: A total of 50 subjects underwent STP and 42 were included in this study. Their mean age at the time of surgery was 34.16 ± 9.74 years (range 18-64). Significant reductions in mean VAS and ESPRINT were observed after surgery ($P < 0.01$). These outcomes were considered to represent an overall improvement in quality of life. The RNM results also improved significantly, from mean values of 478.07 ± 165.4 cm^3/s before STP to 826.4 ± 175.5 cm^3/s afterwards ($P < 0.01$).

CONCLUSIONS: The negative correlations of VAS and ESPRINT with RNM, from before and to after STP, demonstrate the efficacy of scales and questionnaires as objective methods for determining obstruction in the absence of rhinomanometry. Patients with allergic rhinitis and septal deviation showed improvements in obstruction severity and medication use after STP.

INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disease that affects almost 30% of the adult population and is associated with other inflammatory diseases.[1] In AR, the upper airway respiratory mucosa becomes inflamed in response to allergen exposure, mediated by the T helper 2 (Th2) immunological response. Common symptoms include sneezing, rhinorrhea, nasal congestion, nasal itching and nasal obstruction. Nasal obstruction is the symptom that is most refractory to medical treatment.[2]

The evolution of AR includes chronic rhinosinusitis, nasal polyposis or chronic rhinitis.[3] Despite the high prevalence of AR and the variety of medications for treating it, many patients still feel that their treatment has failed.[4] AR impairs quality of life (QoL) and work productivity, since it is an important cause of absence from work and school, and it generates huge costs in prescription medication.[5]

Deviation of the nasal septum is diagnosed in more than 70% of the general population to some degree.[6] It causes symptoms such as nasal obstruction, epistasis, snoring, anxiety, headaches, buccal breathing and sinusitis.[7,8] Septorhinoplasty (STP) is the most common treatment for patients with septal deviation and generally gives rise to satisfactory outcomes.[9]

The treatments for AR include avoidance of the causative allergen, a great variety of medications (such as antihistamines, anti-leukotrienes or corticoids) and specific allergen immunotherapy. These conservative methods lead to improvement of symptoms but, for some refractory patients, medication alone is not enough. The surgical procedures for treating AR include cryotherapy, laser cautery, sinus surgery or turbinate resection. AR guides do not nowadays include

STP as a therapeutic possibility, given that its outcomes are not as satisfactory as in patients who only show septal deviation.[10]

Kim et al. used two different AR groups to study how STP and turbinoplasty or turbinoplasty alone affected the evolution of their patients' disease.[11] They observed that the use of medication was diminished in both groups, with improvements in VAS (visual analogue scale (VAS) scores, although they did not measure airflow rates.

AR patients with septal deviation present a therapeutic challenge for physicians. The current guides for AR management underscore the need for research regarding the role of STP in the evolution of AR.[12]

OBJECTIVE

Our main objective was to describe and compare the impact of AR symptoms prior to and following STP. It was hypothesized that STP would modify the clinical course of AR in patients presenting an association between this entity and septal deviation, and that STP would reduce the use of medication.

METHODS

Design and sample

This was a prospective quasi-experimental non-randomized controlled pre and post-test study. Informed consent was obtained from all patients, in accordance with the Declaration of Helsinki of 1975, as revised in 2013. This study was approved by the Regional Research Ethics Committee of Galicia (Ref: 2015/280; June 30, 2015).

The sample size was determined as follows. We estimated in relation to "severity" that before the intervention, 60% of the patients presented moderate-severe rhinitis and that this percentage would be expected to be reduced to 30% after 12 months. Thus, 51 patients would be required to detect this difference as statistically significant with a safety of 95% and a statistical power of 80%, in a bilateral approach with paired data. Regarding the variable of VAS, we assumed from pilot experience that the mean score prior to surgery was around 7.5 and that the decrease could be to 7 with a standard deviation of 1.87. Thus, 46 patients would be required to detect this difference as significant with a safety of 95%, a statistical power of 80%, in a bilateral approach with paired data.

Patients aged 18-65 years who presented a diagnosis of AR and septal deviation were recruited through consecutive sampling. They underwent STP at the Allergology and Otorhinolaryngology service of A Coruña University Hospital (CHUAC).

The diagnosis of septal deviation was determined from rhinofibroscopy findings. The diagnosis of AR was established clinically, with testing for specific allergen sensitization, e.g. correlations with symptoms and skin prick test positivity > 3 mm. The allergens tested were all common aeroallergens in our environment, such as dust mites, pollens from grasses, weeds and trees, fungi (such as *Aspergillus*, *Alternaria* and *Cladosporium*), cat and dog epithelia, latex and panallergens such as profilin and lipid transporter protein (LTP), through commercial extracts from ALK Abello Laboratories (Madrid, Spain).

The patients needed to have had AR symptoms for at least one year. Their symptoms were classified in accordance with the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,[13] i.e. "intermittent AR" (symptoms on less than four days per week) or "persistent AR" (symptoms on more than four days per week).

The severity of the patient's symptoms was classified as "moderate-severe" if the patient reported having sleeping disorders, impairment of daily activity or absence from work or school, or "mild" if the patient had none of these.

Patients were excluded from the study in the following situations: less than one year of AR symptoms; already treated with specific immunotherapy against allergens; undergoing simultaneous surgical procedure (e.g. turbinate reduction); smokers; or presentation of chronic obstructive pulmonary disease, psychiatric disorders, malignant tumors, severe hepatopathy, obstructive sleep apnea or previous nasal surgery.[14,15]

Procedure

Patient enrolment, surgical procedures and parameter evaluation were performed by the same surgeon (VGP). Variables were collected from the patients' clinical history before and four weeks after surgery.

After screening, each patient's obstruction was evaluated by means of anterior rhinomanometry (RNM) (cm^3/s), using the Rhinospir Pro-165 device (Sibelmed, Barcelona, Spain). It was classified as mild, moderate, severe or very severe, according to the rhinomanometric grading.

QoL was scored through the ESPRINT scale. ESPRINT is a validated Spanish questionnaire on symptoms, activities of daily living, sleep disorders, psychology and overall health perception for AR patients.[16]

Symptoms like sneezing, itchy nose, ocular symptoms and nasal obstruction were evaluated using a visual analogue scale (VAS) and the clinical history. VAS scores were classified as mild (scores of 1-3), moderate (4-6) or severe (7-10).

Use of medications (intranasal corticosteroid, anti-leukotrienes, antihistamine eye drops or oral antihistamine) and their frequency of use were registered.

Statistical analysis

All data were collected in a database and were analyzed using the Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, Illinois, United States).

The standard deviation (SD) or interquartile range (IQR) were used to describe quantitative variables. For categorical variables, the frequency and percentage were used. Sample normality was assessed using the Kolmogorov-Smirnov test. Univariate analysis was used to compare measurements, with either Student`s t distribution or the Mann-Whitney U test, depending on the application conditions. To compare proportions, the chi-square test or Fisher`s exact test was used. A correlation analysis was carried out between quantitative variables using the Fisher or Spearman statistical test, according to the application conditions. Multiple regression models were applied, with percentage changes in airflow as the dependent variable, to assess whether these differed according to the severity of AR, with adjustments for age and sex. The significance level was set at $P < 0.05$.

RESULTS

A total of 50 patients underwent STP and 42 of them agreed to participate in this study, comprising 27 males (64.3%) and 15 females (35.7%). Their mean age at the time of the surgery was 34.16 ± 9.74 years (range 18-64). Among the age groups, the largest group was the patients who were younger than 30 years (37.2%) (**Table 1**).

All surgeries were conducted without complications and all patients were discharged in less than 24 hours. Follow-up was performed four weeks after surgery.

Allergies to beta lactamase (eleven patients) and non-steroidal anti-inflammatory drugs (NSAIDs) (two patients) allergic were the most common comorbidities (n = 13, 30.95%).

The allergen most recorded among the patients was dust mites (n = 33; 78.6%), followed by dust mites and pollen (n = 8; 19%) and pollen (n = 1; 2.4%).

The clinical data recorded prior to and following surgery are summarized in **Table 2**.

Regarding VAS scores before STP, most patients (97.6%) reported having severe symptoms (scores of 7-10) (**Figure 1**). After STP, most patients reported having mild symptoms (46.5%).

RNM measurements showed statistically different mean values among the operated patients, as can be seen in **Figure 2** (RNM evolution). Airflow changes were found to be correlated with sex and age ($P < 0.01$ and $P = 0.03$) and with previous RNM severity ($P = 0.01$), i.e. patients whose severity of symptoms before the surgery was worse underwent greater percentage improvements.

Among the operated women, 93% showed changes in temporality, from persistent to intermittent, while 59.2% of the men reported this evolution ($P = 0.019$).

Patients who were more than 40 years old reported worse outcomes regarding improvement of ocular symptoms ($P = 0.049$). Thus, 27% of these individuals continued to have these symptoms after surgery, while none of the patients aged between 30 and 40 years still had them.

Comorbidities, medication use, previous RNM severity or specific allergens were not associated with any improvement parameter ($P > 0.05$).

Correlation analysis

The correlations demonstrated the effectiveness of both self-assessment methods (VAS and ESPRINT tools) for evaluating symptoms and QoL before STP ($r = 0.32$; $P = 0.04$) and after STP ($r = 0.69$; $P < 0.01$).

The negative correlations of VAS and ESPRINT with RNM before STP ($r = -0.29$, $P = 0.05$; and $r = -0.31$, $P < 0.01$) and after

Table 1. Sociodemographic and clinical characteristics of the sample population

	Total group Mean ± SD Range n = 42	Male Mean ± SD Range n = 27	Female Mean ± SD Range n = 15	P-value Male versus female
Age	34.16 ± 9.7 (18-64)	31.63 ± 10.3 (18 -64)	38.73 ± 6.7 (29-50)	**0.04**
VAS score (prior to STP)	8.52 ± 1.1 (6-10)	8.56 ± 1 (7-10)	8.47 ± 1.3 (6-10)	0.8
VAS score (after STP)	3.74 ± 2.1 (1-8)	3.67 ± 2.2 (1-8)	3.87 ±1.8 (2-7)	0.77
ESPRINT score (prior to STP)	62.24 ± 14.84 (9 – 88)	60.89 ± 17.3 (9-88)	64.67 ± 8.93 (46-76)	0.43
ESPRINT score (after STP)	23.48 ± 18.8 (0-77)	21.93 ± 21.85 (0-77)	26.27 ± 11.74 (9-46)	0.48
Flow rate (prior to STP)	478.07 ± 165.4 (142-1242)	461.63 ± 123.7 (142-710)	507.67 ± 224.1 (287-1242)	0.39
Flow rate (after STP)	826.4 ± 175.5 (520-1340)	823.63 ± 178.2 (520-1265)	831.4 ± 176.46 (610-1340)	0.8

SD = standard deviation; VAS = visual analogue scale; STP = septoplasty.

Table 2. Clinical variables before and after surgery

Variable	Before surgery	After Surgery	P-value
Nasal obstruction	n = 42 (100%)	n = 21 (50%)	**< 0.01**
Sneezing	n = 42 (100%)	n = 42 (100%)	-
Rhinorrhea	n = 41 (97.60%)	n = 28 (68.3%)	**< 0.01**
Ocular symptoms	n = 23 (54.8%)	n = 4 (9.5%)	**< 0.01**
Nasal corticoid	n = 41 (97.6%)	n = 18 (42.9%)	**< 0.01**
Antihistamine	n = 41 (97.6%)	n = 28 (66.7%)	**< 0.01**
Anti-leukotriene	n = 15 (35.7%)	n = 1 (2.4%)	**< 0.01**
Intermittent AR	n = 2 (4.8%)	n = 2 (4.8%)	0.12
Persistent AR	n = 40 (95.2%)	n = 12 (28.6%)	**< 0.01**
Mean VAS score	8.52 ± 1.13	3.74 ± 2.1	**0.02**
Mean ESPRIT score	62.24 ± 14.84	23.48 ± 18.28	**< 0.01**
RNM (cm^3/s)	478.07 ± 165.4	826.4 ± 175.5	**< 0.01**
RNM classification			**0.037**
Normal	0	n = 14 (33%)	
Mild	n = 1 (2.4%)	n = 21 (50%)	
Moderate	n = 12 (28.6%)	n = 7 (16.7%)	
Severe	n = 18 (42.9)	0	
Very severe	n = 11 (23.8%)	0	
ARIA classification of severity			**0.04**
None	0	n = 34 (81%)	
Mild	n = 24 (57.1%)	n = 8 (19%)	
Moderate-severe	n = 18 (42.9%)	0	

AR = allergic rhinitis; VAS = visual analogue scale; RNM = anterior rhinomanometry; ARIA = allergic rhinitis and its impact on asthma.

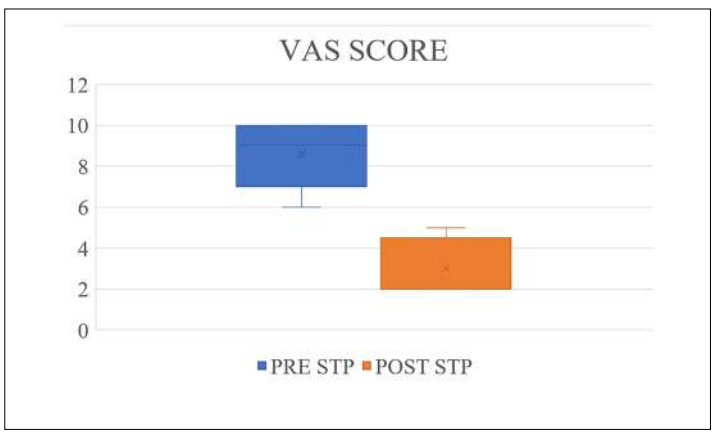
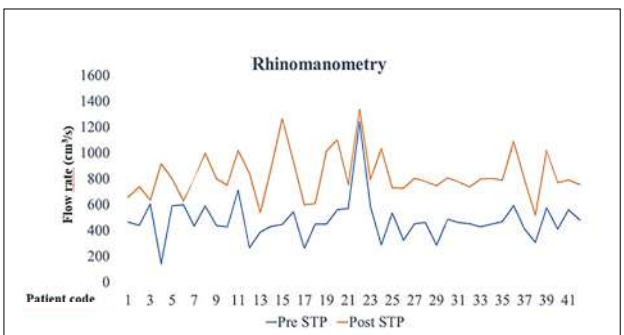


Figure 1. Evolution of visual analogue scale (VAS) results from before to after septoplasty (STP).



X-axis: patient code; y-axis: flow rate rhinomanometry, cm^3/seconds.

Figure 2. Evolution of anterior rhinomanometry on patients from before to after septoplasty (STP).

STP (r = -0.43, P < 0.01; and r = -0.43, P = 0.05) demonstrated the efficacy of the scales and questionnaires as objective methods for determining obstruction in the absence of rhinomanometry.

DISCUSSION

A total of 42 patients diagnosed with AR and septal deviation were included in this study. We analyzed STP outcomes through objective measurements of nasal patency, QoL and symptoms, using questionnaires, and most patients (n = 32; 76.1%) reported obtaining improvements in all these fields.

According to recent studies, patients with AR will feel less benefit and satisfaction after STP.[10,17,18] Physicians are usually faced with a dilemma when they have to decide how to manage nasal obstruction in AR patients, especially if this obstruction is incomplete. Two etiologies for the obstructive/congestive nasal symptoms of patients with allergic rhinitis and septal deviation are possible: one inflammatory and other structural. Accordingly, there should be distinct medical and surgical treatment considerations for each

of these.[18] For this reason, we decided to only include patients with more than one year of symptoms for whom medication treatment had already been established. Independently of the AR diagnosis, previous studies with different objective and subjective methods have demonstrated that a general improvement in nasal obstruction is achieved after STP.[8,9,11,18-20]

The results regarding determination of AR as a predictive factor for less improvement in STP have been contradictory in recent studies. Mondina et al. studied 100 patients after STP, among whom 28 presented AR, using the NOSE and RhinoQoL questionnaires before and after surgery. They concluded that AR was a predictive factor for less improvement,[21] as was also demonstrated by Kartzanis et al.[10] However, these outcomes are contradictory, considering that Stewart et al. could not prove this relationship.[22]

Confounding variables need to be considered cautiously. Improvements in AR symptoms could be due to use of topical antiallergic medication that can reach the nasal mucosa better after surgery. It is important to consider that there is some superposition of obstruction symptoms, given that they cannot be uniquely associated with any anatomical component or allergic component.[18]

Regarding sneezing, STP had no influence on sneezing frequency in our study, as none of our patients showed improvement in this symptom. Nevertheless, other authors have achieved significant changes in this symptom after STP.[9] Improvements in other symptoms such as rhinorrhea or ocular symptoms (i.e. itching or watery eyes) were reported by our patients, in the same way as shown by Faulcon et al.[23]

Recent classifications have used the frequency of symptoms (number of days per week) to determine the type of AR.[24] Most of our patients (95.1%) reported having persistent AR before surgery, and 71.4% of them improved to intermittent AR. It is important to underscore that complete resolution of AR was not registered in any patient, given that the original factor that generated AR, i.e. the allergen, was not eliminated.

Reductions in medication use (corticoids, antihistamines or anti-leukotrienes) were observed among the operated patients. Decreased need for corticoids was associated with improvement of obstruction symptoms ($P < 0.01$), although this relationship was not found with antihistamine or anti-leukotriene reduction. Improvement in rhinorrhea was associated with reduction of antihistamine use ($P = 0.019$). To the best of our knowledge, this was the first study to evaluate anti-leukotriene use among AR patients before and after STP.

AR impairs basic activities of daily life (BADL) in 81.8% of patients and affects their work capacity and social relationships.[25] The prevalence of AR is increasing around the whole world and is generating economic and social impairments, including medical expenditure and diminished work productivity. AR treatment aims to reduce symptoms and improve QoL. Although STP does not eliminate central inflammatory AR, the additional permeability obtained reduces edematous mucosa and can relieve symptoms.

The VAS results highlighted the improvement that patients experienced after surgery. This visual scale has also been used in other studies. Kim et al. conducted a study similar to ours, in which better VAS results after STP were found among AR patients.[11] ESPRINT is a validated questionnaire on quality of life, and its correlation with VAS indicates the relationship between patients' symptoms and their BADL ($r = 0.32$; $P = 0.043$). Both ESPRINT and VAS showed negative correlations with the RNM results. Demoly et al. validated the VAS scale as presenting high sensitivity, in a study on 100 patients, using RNM.[26] However, some other researchers such as Lara-Sánchez et al., in a prospective study on 102 patients, did not find any correlation with VAS and RNM.[27]

In some studies, the improvement obtained from before to after surgery was greater ten years after surgery (83%) than six months after it (69%).[28] The length of follow-up has usually ranged from one month to ten years, although most authors agree that one month provides enough time to judge the surgical outcome.[10,29] Since the level of patient satisfaction in our study was higher than 69%, our intention is to continue to make measurements annually over a five-year period.

The limitations of our study include its sample, given that the initial calculation for the sample size required for comparison of AR severity and VAS (assuming 95% certainty, 80% statistical power and 10% losses) indicated that sample required was 46 patients. Initially, 50 patients were included in this study but eight of them could not come to the post-test appointment, because of geographical and legal situations. Another possible limitation of this study was the lack of records regarding nasal decongestant use. Decongestants are medications that are used frequently through patients' own decisions, without medical indication. Use of this medication induces vasoconstriction and rapid symptom relief, but has no effect on other symptoms.[30]

STP has traditionally been discarded as a surgical modality for AR patients, given that they do not achieve improvement of their breathing, unlike patients who only present septal deviation.[10] However, some authors and current guidelines[11,12] agree that work in this field is still required. From our results, we recommend that STP should be used for patients with AR and septal deviation, particularly for refractory patients.

CONCLUSIONS

The negative correlation of VAS and ESPRINT with RNM from before to after STP demonstrates the efficacy of scales and questionnaires as objective methods for determining occurrences of obstruction in the absence of rhinomanometry. Patients with allergic rhinitis and septal deviation showed improvements in their severity of obstruction and reductions of their medication use after STP.

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Address for correspondence:
Cintia Micaela Chamorro Petronacci
Instituto de Investigaciones Sanitarias de Santiago (IDIS), MedOralRes (Grupo de Investigación en Patología Oral Médico Quirúrgica), Universidad de Santiago de Compostela
Travesía da Choupana, s/nº, 15706, Santiago de Compostela, A Coruña, Espanha
Tel. 0034 651011815
E-mail: cintiamica.chamo@yahoo.es

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Multisite musculoskeletal pain in the general population: a cross-sectional survey

Alberto de Vitta[I], Nicoly Machado Maciel[II], Thiago Paulo Frascareli Bento[III], Caio Vitor dos Santos Genebra[IV], Sandra Fiorelli Almeida Penteado Simeão[V]

Universidade do Sagrado Coração (UNISAGRADO), Bauru (SP), Brazil

[I]PT, PhD. Physiotherapist and Assistant Professor, Centro Universitário das Faculdades Integradas de Ourinhos, Ourinhos (SP), Brazil.
https://orcid.org/0000-0002-3248-456X

[II]PT, MSc. Doctoral Student, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0001-7558-239X

[III]PT, MSc. Physiotherapist, Department of Physiotherapy, Universidade do Sagrado Coração (UNISAGRADO), Bauru (SP), Brazil.
https://orcid.org/0000-0003-2394-8024

[IV]PT, MSc. Physiotherapist, Department of Physiotherapy, Universidade do Sagrado Coração (UNISAGRADO), Bauru (SP), Brazil.
https://orcid.org/0000-0001-5882-7025

[V]PT, PhD. Assistant Professor, Department of Mathematics, Universidade do Sagrado Coração (UNISAGRADO), Bauru (SP), Brazil.
https://orcid.org/0000-0002-3291-278X

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ABSTRACT

BACKGROUND: Epidemiological studies focusing on multisite musculoskeletal pain have revealed that the prevalence of multisite pain is high in general populations.

OBJECTIVE: To ascertain the prevalence of multisite musculoskeletal pain in the last 12 months and in the last seven days, in a population-based sample and investigate its association with demographic, socioeconomic, behavioral, reported morbidity and ergonomic variables.

DESIGN AND SETTING: Cross-sectional population-based survey in Bauru, São Paulo (Brazil).

METHODS: 600 individuals were interviewed. The following data were collected: participants' characteristics, through a precoded questionnaire; physical activity level, through the International Physical Activity Questionnaire; and musculoskeletal symptoms, through the Nordic questionnaire. Descriptive, bivariate and Poisson regression analyses were performed.

RESULTS: The prevalence of multisite musculoskeletal pain was 46.5% (confidence interval, CI 42.5 to 50.5) in the last 12 months and 26.1% (CI 22.8 to 29.8) in the last seven days. The variables associated with multisite pain in the last 12 months were female sex, presence of hypertension, diabetes mellitus or depression, watching TV more than three times a week and working in a seated position. Formerly smoking was a protection factor. The variables associated with multisite pain in the last seven days were female sex, age group 60 years and over, low income, presence of comorbidities of hypertension, diabetes mellitus or depression and working in a seated position.

CONCLUSION: There was high prevalence of multisite musculoskeletal pain, which was associated with demographic, socioeconomic, work-related, electronic device-related and reported morbidity variables.

INTRODUCTION

Musculoskeletal pain is a significant burden for the community in several countries, and is one of the main health problems around the world. Over recent decades, many epidemiological studies have focused on multisite musculoskeletal pain, and their findings have revealed that the prevalence of multisite pain is high, both in the general and in the working population.[1,2] The prevalence in the general population and among workers has been found to range from 2% to 60%,[1,3] depending on the definitions of the pain site and study population.[4,5]

Epidemiological studies have found that multisite pain is associated with female sex, advanced age, educational level, obesity, smoking, depressive and/or anxiety disorders, low self-rated health[3,6] and work-related factors: load handling, inadequate postures, repetitive movements, physical and mental stress, low support and job dissatisfaction.[4,7]

It has become important to obtain knowledge of the prevalence and factors associated with multisite pain in the general population, considering that, previously, a large number of studies focused on prevalence and risk factors in specific populations (workers) and single anatomical sites, such as the lumbar region.[8] Multisite pain can interfere with the ability to work, functionality, mobility, sleep quality, general health and quality of life of the population.[1] Therefore, studies on multisite pain are important. In addition, high public costs are generated through treatment of symptoms and the drop in productivity due to multisite pain.

The present study may contribute to knowledge of the current condition of musculoskeletal symptoms and to identifying possible associations between the presence of multisite pain and predictor variables, since population-based research studies on this outcome are scarce. It may

also assist other studies that have the aim of gaining greater understanding of the causes and thus creating interventions at various levels of healthcare.

OBJECTIVES

The objectives of the present study were to ascertain the prevalence of multisite pain in the last 12 months and in the last seven days, in a population-based sample of adults aged 20 years or over residing in the city of Bauru (São Paulo, Brazil) and to investigate the association of this multisite pain with demographic, socioeconomic, behavioral, reported morbidity and ergonomic variables.

METHODS

Study design and ethics

A cross-sectional study was carried out in the urban area of the city of Bauru, which is located in the center-west of the state of São Paulo, Brazil, with approximately 337,094 inhabitants, of whom 207,021 inhabitants are over 20 years of age. This project was approved by the Ethics Committee for Research on Human Beings, of Universidade do Sagrado Coração, Bauru, São Paulo, Brazil, under document no. 201/11, dated August 21, 2018.

Participants

This study was based on data that were collected through the project "Musculoskeletal symptoms, autonomy and quality of life in the population of Bauru, São Paulo", which was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), through procedural number 2011/20123-4, and by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), through procedural number 478188/2011-0.

Age and sex groups (called sample domains) were firstly defined with a minimum number of individuals per sample, in order to allow further analysis. Six sample domains were thus determined: 20 to 35-year-old men; 20 to 35-year-old women; 36 to 59-year-old men; 36 to 59-year-old women; 60-year-old and older men; and 60-year-old and older women.[9,10]

The sample size calculation was based on the following premises: an estimated proportion of 50% of the population subgroups, since this is the maximum variability that leads to obtaining conservative sample sizes; a 95% confidence level for estimation of confidence intervals; a 10% sampling error, indicating that the amplitude between the estimated sample and the population parameter should not exceed this value; and a design effect of 2. Through this calculation, the sample size for each age group (20 to 35 years, 36 to 59 years and 60 years or over) was determined to be a minimum of 200 individuals (100 males and 100 females). Thus, the total sample size was determined to be 600 participants living in the city of Bauru, SP, Brazil.[9,10]

The sample was randomly selected using a two-stage cluster design. The sampling units were obtained from the 2011 National Household Sample Survey, which provided a list of the private addresses in each census tract. Fifty urban census tracts were randomly selected from the 476 tracts identified. These census tracts constituted the primary sampling units (PSUs). The households were the secondary sampling units (SSUs). The PSUs were randomly selected by means of systematic sampling with a probability proportional to their sizes.[9,10]

For each census tract, the number of households to be randomly selected was determined according to the ratio of the average number of individuals per household in each sample domain.[9] It was estimated, therefore, that about 12 households per census tract should be visited. These households were randomly selected using a system that took into consideration all eligible individuals residing in the households. In households with more than one eligible subject, all subjects within the age range of each group were considered eligible for the interviews. In the event of refusal of one or all subjects, a new household was randomly selected.

Individuals who could not be located even after four visits were considered to be losses. In these cases, at least one visit was attempted in the evening and one on the weekend. Individuals who were unable to respond because of travel or who refused to answer the questionnaire through their personal choice were also considered to be losses.[9,10]

Data collection procedures

The interviews were conducted by trained interviewers and the fieldwork was supervised by the researchers involved in the study. Data collection took place between February and June 2012. The coding was performed by the interviewers and reviewed by the chief researcher. The supervisors also performed quality control, which consisted of applying a short version of the questionnaires to 10% of the respondents.[9,10]

Interviews were conducted with all residents aged twenty or over who were living in the selected households in the urban area of Bauru, excluding people with mental and physical disabilities. Older participants were asked to do the Mini-Mental State Examination at the beginning of the interview and those who scored below 27 were considered as having cognitive loss and therefore were excluded from the study.[9,10]

Instruments

The Nordic Pain Questionnaire, validated and adapted to Brazilian culture,[12] was used to collect data on pain in specific body regions (neck, shoulders, thoracic spine, elbows, wrists/hands, lumbar spine, hips/thighs, knees and ankles/feet). This questionnaire presents a drawing of the human body with the names of its different regions highlighted, so that interviewees

can better specify the region where their pain is. At the time of the interview, each subject answered the following questions: 1. have you felt any pain in this body region (e.g. shoulders) in the last twelve months? 2. have you felt any pain in this body region (e.g. shoulders) in the last seven days? This procedure was repeated for all regions, and all questions allowed only a yes or no answer. From these data, we created the variable "multisite pain", which was defined as pain in two or more sites (≥ 2 sites) in the last 12 months and in the last seven days.[1-3]

To characterize the subjects, the following data were collected, as previously reported.[9,10] The individual factors included sex, age (20-35, 36-59 or ≥ 60 years), body mass index (< 18.5; ≥ 18.5 and < 25; or ≥ 25 kg/m^2), marital status (single, married or widowed/separated), education (0-4, 5-8, 9-11 or 12 years or over), skin color or race (white, black, brown, indigenous or East Asian),[13] income (low: up to 3 times the minimum monthly wage (MW); medium: from 4 to 9 MW; or high: 10 or more MW).

The participants were asked the following questions regarding their use of electronic devices (time spent watching TV and on the computer and/or playing video games):[9,10] "Do you watch TV in a normal week?" (yes or no); "How many times do you watch TV in a normal week?" (up to two times; three to four times; or five times or more in the week); "How many hours do you watch TV on a normal day?" (up to 2 hours or 3 hours or more per day); "How often do you use a computer or play video games in a normal week?" (up to two times; three to four times; or five times or more per week); "For how many hours do you use a computer or play video games on a normal day?" (up to 2 hours or 3 hours or more per day).

The ergonomic variables were characterized in terms of the interviewee's perception of the frequency of exposure, which was identified from among the options of never, rarely, usually or always. The variables measured were physical effort, vibration and repetitiveness, and also any occurrence of an incorrect position, characterized by the frequencies with which the interviewee worked/studied in a sitting, standing, squatting, lying down or kneeling position. In the case of retired and unemployed individuals, they were asked to answer considering the activities that they habitually performed. In order to define the association between multisite pain and ergonomic variables, the frequencies obtained in the categories "never" and "rarely" were added together and categorized into a single group; the same was done for the categories "generally" and "always".[10,14]

Individuals who reported smoking every day (at least one cigarette per day) or occasionally (less than one cigarette per day) were considered to be smokers; and individuals who had stopped smoking at least six months before the interview were considered to be former smokers.[10,14]

Information on morbidity was collected through the interview, in which the subjects answered the question: "among the alternatives below (hypertension, osteoporosis, diabetes, osteoarthritis, respiratory, gastrointestinal diseases and urinary system diseases), choose the one/ones that matches/match a diagnosis that you received from a doctor in the last 12 months".[9]

The International Physical Activity Questionnaire (IPAQ), as validated for the Brazilian population, was used to check each subject's physical activity level. A threshold of 150 minutes of physical activity per week was established for classifying individuals as active (150 minutes per week or more) or insufficiently active (below 150 min per week).[15]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 18.0 (IBM Corp., Armonk, New York, United States) was used to analyze the data. The data were entered by an undergraduate student who did not participate in the study. 10% of the questionnaires were randomly chosen to test the accuracy of the data typing, and an error was found and corrected. Another 5% were then randomly chosen and no error was found.

The prevalence, confidence intervals and bivariate and Poisson regression analyses between multisite pain and all independent variables were calculated, to determine the significance level and estimated relative risk of the 95% confidence intervals.

Poisson regression analysis with robust variance was performed in accordance with a theoretical-conceptual hierarchical model. A reference category was established, for all variables, which was considered to present the lowest risk. The variables were organized into four levels according to their temporal and causal relationships to multisite pain. Adjustments to the first level were performed using all the variables that belonged to this level. Adjustments to the second level were performed using variables from the previous level that presented P-values < 0.10 and also the variables that belonged to the second level. Adjustments to the third level were performed using variables from the first and second levels with P-values < 0.10, and also the variables that belonged to the third level. The fourth level was controlled for the previous three levels. A regressive selection process was used to determine the variables that would remain in the regression model, such that all the variables with P-values < 0.05 were kept in the model.[16,17]

RESULTS

A total of 641 individuals from eligible households were considered for inclusion, and 600 of them were actually interviewed. There were 21 losses, for which the main reasons were: "participant absent from home" and "participant set a time with the interviewer but did not show". There were also 20 refusals, for

the following reasons: "participant did not respond to interview request" (n = 12) and "mental disability" (n = 8).

Among the interviewees, most had had between 9 and 11 years of formal education, were of white race, had married marital status, had low income, were non-smokers, were insufficiently active (physical activity level) and reported having diseases (hypertension, diabetes mellitus or depression).

Table 1 shows that women presented higher prevalence, independent of the sites, both in the last 12 months and in the last seven days. Low back pain was the most prevalent complaint among both men and women in both the past 12 months and the past seven days. Regarding the number of regions with pain, presentation of 1, 2 and up to 3 sites was more prevalent.

The prevalence of multisite pain in the last 12 months was 46.5% (confidence interval, CI 42.5 to 50.5), i.e. 38.3% (CI 33.0 to 43.9) in men and 54.6% (CI 49.0 to 60.2) in women, with a statistically significant difference (P < 0.0001). In the last seven days, the prevalence was 26.1% (CI 22.8 to 29.8), i.e. 19.3% (CI 15.2 to 24.1) in men and 33.0% (CI 27.9 to 38.5) in women, with a statistically significant difference (P < 0.0001).

Among the demographic variables, only female sex was associated with multisite pain in the last 12 months. On the other hand, multisite pain in the last seven days was associated with female sex, individuals with low income and individuals aged 60 years or over (**Table 2**).

Table 1. Prevalence of musculoskeletal pain at different sites, according to sex and time period

Musculoskeletal pain				
Parts of the body	Female		Male	
	12 months	7 days	12 months	7 days
	n (%)	n (%)	n (%)	n (%)
Neck	68 (22.7)	31 (10.3)	54 (18.0)	28 (9.3)
Shoulder	89 (29.7)	53 (17.7)	55 (18.6)	29 (9.7)
Thoracic back	84 (28.0)	51 (17.0)	51 (17.0)	34 (11.3)
Elbow	28 (9.3)	12 (4.0)	24 (8.0)	9 (3.0)
Wrist/hands	84 (28.0)	48 (16.0)	34 (11.3)	18 (6.0)
Low back	125 (41.7)	81 (27.0)	80 (26.7)	53 (17.7)
Hip/thighs	69 (23.0)	41 (13.7)	34 (11.3)	22 (7.3)
Knee	78 (26.0)	49 (16.3)	76 (25.3)	46 (15.3)
Ankle/foot	54 (18.0)	32 (10.7)	40 (13.3)	17 (5.7)
Number of pain sites				
None	75 (25.0)	138 (46.0)	106 (35.3)	181 (60.3)
1	61 (20.3)	63 (21.0)	79 (26.3)	61 (20.3)
2	56 (18.7)	40 (13.3)	51 (17.0)	30 (10.0)
3	38 (12.6)	27 (9.0)	33 (11.0)	12 (4.0)
4	28 (9.3)	16 (5.3)	15 (5.0)	4 (1.3)
5	13 (4.3)	4 (1.3)	3 (1.0)	1 (0.3)
6	11 (3.6)	3 (1.0)	5 (1.6)	5 (1.6)
7	3 (1.0)	4 (1.3)	3 (1.0)	2 (0.6)
8	7 (2.3)	1 (0.3)	3 (1.0)	2 (0.6)
9	8 (2.6)	4 (1.3)	2 (0.6)	2 (0.6)

It was noticed that smoking was a protective factor for individuals who reported being former smokers. Individuals who reported having hypertension, diabetes mellitus or depression presented an association with pain in the last 12 months and in the last seven days (**Table 3**).

Multisite pain in the last 12 months was associated with the variable of watching TV more than three times a week (**Table 4**).

Multisite pain was also significantly associated with use of a seated position in the last 12 months and in the last seven days (**Table 5**).

DISCUSSION

The variables associated with multisite pain in the last 12 months were female sex, presence of hypertension, diabetes mellitus or depression, watching TV more than three times a week and working in a seated position. On the other hand, formerly smoking was a protection factor. The associations in the last seven days were with female sex, age group 60 years or over, low income, presence of comorbidities of hypertension, diabetes mellitus or depression and working in a seated position. Multisite musculoskeletal pain had high prevalence in the population studied, like in other countries.[8,18,19]

Female sex was associated with multisite pain in the last 12 months and in the last seven days, thus corroborating the findings of other studies.[8,20] The difference between the sexes can be explained by the fact that women report and seek more support for musculoskeletal pain, are more exposed to physical factors, psychosocial factors and stress, have less strength than men and perform a double working day.[21]

In the present study, the age group above 60 years was associated with presence of multisite pain in the last seven days, unlike in studies in Estonia and Norway, where it was associated with multisite pain in the last 12 months.[3,20] Associations between aging and pain are multidimensional and, with advancing age, pain problems become highly complex due to multiple comorbidities.[22,23] Although multimorbidity becomes more common with age, more than half of the individuals with multimorbidity and nearly two-thirds of those with comorbidities relating to physical and mental health are under 65 years old.[23,24]

The outcome in the last seven days was associated with low income level., like in the study in Norway,[20,24] which highlighted that low education level and low income interfere to give rise to chronic pain.[24] The hypotheses that may explain this finding may include lack of access to healthcare services. In addition, individuals with low socioeconomic status do not take self-care actions, such as healthy lifestyle habits, and they work in occupations in which they are at risk of musculoskeletal injury.[24]

Regarding smoking, being a former smoker was a protective factor for multisite pain, thus contradicting other studies,[6,25] and this difference may be due to the methods used to evaluate cigarette

Table 2. Multivariate analysis on multisite pain and demographic and socioeconomic characteristics

Variables	Multisite pain							
	In last 12 months				In last 7 days			
	Total	n	%	PR (95% CI)	Total	n	%	PR (95% CI)
Sex								
Male	300	136	45.3	1.00	300	201	67.0	1.00
Female	300	164	54.7	1.59 (1.10-2.30)	300	99	33.0	1.84 (1.21-2.80)
Age groups								
20-35 years	200	71	25.4	1.00	200	34	21.7	1.00
36-59 years	200	100	35.8	1.49 (0.87-2.54)	200	45	28.7	1.32 (0.75-2.30)
60 or over	200	108	38.7	1.32 (0.70-2.48)	200	78	49.7	2.13 (1.21-3.75)
Schooling (years)								
12 or higher education	105	45	16.1	1.00	105	21	13.4	1.00
9-11	244	105	37.6	0.54 (0.24-1.23)	244	53	33.8	0.50 (0.21-1.19)
5-8	129	64	22.9	0.82 (0.40-1.67)	129	37	23.6	0.99 (0.45-2.18)
0-4	122	65	23.3	0.87 (0.49-1.52)	122	46	29.3	0.78 (0.40-1.53)
Race								
White	480	218	78.1	1.00	480	119	75.8	1.00
Black	38	24	8.6	1.52 (0.68-3.37)	38	17	10.8	2.00 (0.96-4.45)
Mixed	82	37	13.3	1.13 (0.64-1.99)	82	21	13.8	1.12 (0.60-2.10)
Marital status								
Married	345	147	52.7	1.00	345	85	54.1	1.00
Single	150	66	23.7	1.29 (0.81-2.05)	150	31	19.7	1.32 (0.70-2.49)
Widowed/divorced	105	66	23.7	1.40 (0.83-2.35)	105	41	26.1	1.03 (0.57-1.86)
Income								
High	71	30	10.8	1.00	71	9	5.7	1.00
Medium	140	58	20.8	1.52 (0.82-2.80)	140	31	19.7	2.01 (0.88-4.61)
Low	389	191	68.5	1.25 (0.64-2.47)	389	117	74.5	2.95 (1.34-6.26)

PR = prevalence ratio; CI = confidence interval.

use. However, a study conducted among former smokers with low back pain showed that they had lower risk of seeking therapeutic services than did current smokers, thus suggesting that the effects of smoking may be at least partially reversible.[6]

Multisite pain in the present investigation was associated with individuals who reported depression, thus corroborating the findings of other studies.[24,26] It had previously been reported that depression was associated with other factors (insomnia and social participation) and that, over the long term, it would contribute to the onset and increased symptoms of chronic musculoskeletal pain, probably due to central sensitization.[26]

In the present study, multisite pain was associated with hypertension, which corroborated the findings from some studies,[26,27] while this association was not noticed in other studies.[28,29] One possible explanation for this difference may have been the phenomenon of hyperalgesia in association with hypertension, caused by an interaction between cardiovascular and pain regulation systems.[28,29]

Multisite pain, in the present investigation, was associated with occurrences of individuals who reported diabetes, which corroborated the results from other studies.[16,17,30] Previous studies had indicated that pain and diabetes probably had relationships with vascular insufficiency, peripheral neuropathy, osteoporosis, obesity, sedentary lifestyle and other factors.[16] There is evidence suggesting that people with diabetes usually have other comorbidities (e.g. hypertension and dyslipidemia), thus resulting in a more severe clinical picture and consequently increased signs of musculoskeletal pain.[17]

Watching TV more than three times a week and working in a seated position were always associated with multisite pain in the last 12 months, thus corroborating one other investigation[31] but diverging from another study.[32] Moreover, it has been reported that the relationship between pain and a seated position would be due to the fact that this position immobilizes the skeletal structures, thereby increasing the demands of muscles, ligaments and other tissues (tissue stress), especially in unfavorable postures. The effect would be associated with the length of stay in the same position, together with low muscle activation, thus leading to pain.[33]

Carrying out occupational activities in seated positions was found in the present study to be associated with multisite pain in the last 12 months and seven days, similarly to the findings from previous studies conducted in Brazil and Finland.[8,34] Occupational activities that require physical demands cause individuals to use various body segments to perform this task, thus contributing to multisite musculoskeletal pain, and this has been found to be reported more frequently in the last seven days.[35]

Table 3. Multivariate analysis on multisite pain in relation to physical activity levels, reported diseases and smoking

Variables	Multisite pain							
	In last 12 months				In last 7 days			
	Total	n	%	PR (95% CI)	Total	n	%	PR (95% CI)
Smoking								
Nonsmokers	363	167	59.9	1.00	363	91	58.0	1.00
Former smoker	128	53	19.0	0.61 (0.38-0.99)	128	34	21.7	0.85 (0.48-1.50)
Smoker	109	59	21.1	1.20 (0.78-2.10)	109	32	20.4	1.33 (0.75-2.39)
Hypertension								
No	402	153	54.8	1.00	402	76	48.4	1.00
Yes	198	126	45.2	2.26 (1.53-3.33)	198	81	51.6	2.23 (1.47-3.38)
Diabetes mellitus								
No	531	232	82.3	1.00	531	124	79.0	1.00
Yes	69	47	16.8	2.75 (1.61-4.69)	69	33	21.0	1.79 (1.02-3.17)
Depression								
No	520	224	80.3	1.00	520	120	76.4	1.00
Yes	80	55	19.7	2.01 (1.17-3.45)	80	37	23.6	2.02 (1.20-3.42)
Gastrointestinal disease								
No	545	238	85.3	1.00	545	132	90.8	1.00
Yes	55	41	14.7	1.79 (0.93-3.33)	55	25	9.2	2.06 (0.97-3.72)
Renal disease								
No	568	255	91.4	1.00	568	141	94.7	1.00
Yes	32	24	8.6	2.11 (0.87-5.13)	32	16	5.3	1.79 (0.80-3.99)
Respiratory disease								
No	554	251	90.0	1.00	554	140	89.2	1.00
Yes	46	28	10.0	1.61 (0.84-3.10)	46	17	10.8	1.44 (0.73- 2.82)
Physical activity level								
Active	210	97	34,8	1.00	210	52	33.1	1
Sedentary	390	182	65.2	0.92 (0.62-1.38)	390	105	66.9	0.99 (0.62-1.57)

PR = prevalence ratio; CI = confidence interval.

Table 4. Multivariate analysis on multisite pain according to use of electronic devices

Variables	Multisite pain							
	In last 12 months				In last 7 days			
	Total	n	%	PR (95% CI)	Total	n	%	PR (95% CI)
Watching TV								
No	34	17	6.1	1.00	34	7	4.5	1.00
Yes	566	262	93.9	0.33 (0.91-1.23)	566	150	95.5	0.79 (0.16-3.80)
Number of times watching TV per week								
Up to 2	26	5	1.8	1.00	26	4	2.5	1.00
3 or over	540	257	47.6	3.56 (1.30-9.72)	540	146	27.0	1.50 (0.50-4.54)
Number of hours of TV per day								
Up to 2	303	137	49.1	1.00	303	75	47.8	1.00
3 or over	263	125	44.8	1.05 (0.70-1.58)	263	75	47.8	1.15 (0.74-1.80)
Use of computer/videogame								
No	314	162	58.1	1.00	314	106	67.5	1.00
Yes	286	117	41.9	1.42 (0.90-2.24)	286	51	32.5	0.20 (0.01-3.64)
Number of times using computer/videogame per week								
Up to 2	37	20	7.2	1.00	37	4	2.5	1.00
3 or over	249	98	39.4	0.51 (0.25-1.05)	249	48	19.3	1.97 (0.66-5.82)
Number of hours of computer/videogame per day								
Up to 2	159	76	27.2	1	159	31	19.7	1.00
3 or over	127	42	15.1	0.71 (0.44-1.14)	127	21	13.4	0.84 (0.40-1.79)

PR = prevalence ratio; CI = confidence interval.

Table 5. Multivariate analysis on multisite pain according to work-related variables

Variables	Multisite pain							
	In last 12 months				In last 7 days			
	Total	n	%	PR (95% CI)	Total	n	%	PR (95% CI)
Repetitive movements								
Never/rarely	240	104	37.3	1.00	240	55	35.0	1.00
Always/usually	360	175	62.7	1.00 (0.66-1.51)	360	102	65.0	1.49 (0.95-2.32)
Vibration/shaking								
Never/rarely	505	230	82.4	1.00	505	127	80.9	1.00
Always/usually	95	49	17.6	1.09 (0.60-1.98)	95	30	19.1	1.45 (0.79-2.65)
Loading and transporting weights								
Never/rarely	400	177	63.4	1.00	400	106	67.5	1.00
Always/usually	200	102	36.6	1.51 (0.99-2.30)	200	51	32.5	0.77 (0.45-1.31)
Kneeling								
Never/rarely	521	240	86.0	1.00	521	134	85.4	1.00
Always/usually	79	39	14.0	1.32 (0.72-2.40)	79	23	14.6	1.32 (0.67-2.59)
Lying down position								
Never/rarely	570	267	95.7	1.00	570	148	94.3	1.00
Always/usually	30	12	4.3	0.74 (0.30-1.82)	30	9	5.7	1.00 (0.35-2.85)
Seated position								
Never/rarely	223	100	35.8	1.00	551	134	85.4	1.00
Always/usually	377	179	64.2	1.73 (1.13-2.67)	49	23	14.6	4.10 (2.01-8.36)
Sitting and lifting loads								
Never/rarely	551	254	91.0	1.00	223	50	31.8	1.00
Always/usually	49	25	9.0	1.06 (0.48-2.31)	377	107	68.2	1.44 (0.86-2.40)
Sitting and leaning								
Never/rarely	444	198	71.0	1.00	444	107	68.2	1.00
Always/usually	156	81	29.0	0.99 (0.60-1.64)	156	50	31.8	1.21 (0.69-2.13)
Standing position								
Never/rarely	142	60	21.5	1.00	142	37	23.6	1.00
Always/usually	458	219	78.5	0.97 (0.59-6.85)	458	120	76.4	1.46 (0.83-2.56)
Standing and leaning								
Never/rarely	309	128	45.9	1.00	309	83	52.9	1.00
Always/usually	291	151	54.1	1.53 (0.99-2.35)	291	74	47.1	0.63 (0.41-0.97)

PR = prevalence ratio; CI = confidence interval.

This study has some limitations. We did not collect data on psychosocial factors, the frequency, severity, intensity and duration of multisite pain, or how multisite pain at multiple sites affected and/or limited the subjects' usual activities. The main contributions and strengths of the study are its use of validated questionnaires for the outcome studied and the large number of individuals interviewed. This study also indicated the factors associated with musculoskeletal pain in multi-site pain in a Brazilian population sample, which is an important contribution, given that in Brazil there is a scarcity of sources of data on multisite pain. Moreover, it has been emphasized in the literature that there is a the need to consider the number of regions with pain, together a need to collect data through interviews in order to reduce the information bias.[3,26] This study will make a contribution as a reference point for epidemiological investigations with a prospective design that aim to evaluate predictors, causality and clinical evolution, and possibly for systematic reviews and meta-analyses.

CONCLUSION

High prevalence of multisite pain was observed. It was greater in women, both in the last seven days and in the last 12 months, with a statistically significant difference. The variables associated with multisite pain in the last 12 months were female sex, presence of the comorbidities of hypertension, diabetes mellitus or depression, watching TV more than three times a week and working in a seated position, while formerly smoking was a protection factor. The associations in the last seven days were with female sex, age group 60 years or over, low income, presence of the comorbidities of hypertension, diabetes mellitus or depression and working in a seated position.

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Address for correspondence:
Alberto de Vitta
Centro Universitário das Faculdades Integradas de Ourinhos
Rodovia BR 153, Km 338 + 420 m
Água do Cateto — Ourinhos (SP) — Brasil
CEP 19909-100
Tel. (+55 14) 99717-6398/3302-6400
E-mail: alberto.vitta@unifio.edu.gov

Recent dengue virus infection: epidemiological survey on risk factors associated with infection in a medium-sized city in Mato Grosso

Dandára Thaís de Oliveira Ferreira[I], Marina Atanaka[II], Mariano Martinez Espinosa[III], Lavinia Schuler-Faccini[IV], Aline da Silva Caldeira[V], Juliana Herrero da Silva[VI], Viviane Karolina Vivi-Oliveira[VII], Rayana de Castro da Paz[VIII], Vagner Ferreira do Nascimento[IX], Ana Cláudia Pereira Terças-Trettel[X]

Universidade Federal de Mato Grosso (UFMT), Cuiabá campus, Cuiabá (MT), Brazil

[I]MSc. Nutritionist and Public Manager, Storage and Distribution Center for Medicines and Supplies of the Municipal Health Department, Várzea Grande (MT), Brazil.
https://orcid.org/0000-0001-5198-2997

[II]PhD. Nurse and Associate Professor IV, Postgraduate Program on Collective Health, Universidade Federal de Mato Grosso (UFMT), Cuiabá campus, Cuiabá (MT), Brazil.
https://orcid.org/0000-0003-3543-3837

[III]PhD. Statistician and Associate Professor IV, Postgraduate Program on Collective Health, Universidade Federal de Mato Grosso (UFMT), Cuiabá campus, Cuiabá (MT), Brazil.
https://orcid.org/0000-0002-0461-5673

[IV]MD, PhD. Full Professor, Department of Genetics, Universidade Federal do Rio Grande do Sul (UFRS), Porto Alegre (RS), Brazil.
https://orcid.org/0000-0002-2428-0460

[V]RN. Primary Healthcare Nurse, Municipal Health Department, Poconé (MT), Brazil.
https://orcid.org/0000-0002-3348-9178

[VI]MSc. Nurse and Technical Manager, Municipal Epidemiological Surveillance Department, Tangará da Serra (MT), Brazil.
https://orcid.org/0000-0002-5481-4603

[VII]MSc. Doctoral Student, Biologist and Professor, Department of Biomedicine, Universidade de Cuiabá, Cuiabá (MT), Brazil.
https://orcid.org/0000-0002-0639-7171

[VIII]Specialist. Pharmacist, Biochemist and Technical Consultant, General Coordination Office for Health Laboratories, Health Surveillance Department, Ministry of Health, Brasília (DF), Brazil.
https://orcid.org/0000-0002-7075-0865

[IX]PhD. Nurse and Adjunct Professor II, Universidade do Estado de Mato Grosso (UNEMAT), Tangará da Serra campus, Tangará da Serra (MT), Brazil.
https://orcid.org/0000-0002-3355-163X

[X]PhD. Nurse and Adjunct Professor, Universidade do Estado de Mato Grosso (UNEMAT), Tangará da Serra campus, Tangará da Serra (MT), Brazil; and Permanent Professor, Postgraduate Program on Collective Health, Universidade Federal de Mato Grosso (UFMT), Cuiabá campus, Cuiabá (MT), Brazil.
https://orcid.org/0000-0001-8761-3325

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ABSTRACT

BACKGROUND: Dengue is considered to be the most important arbovirus worldwide, with important complications that increase its lethality. In Brazil, an endemic country, the disease reaches significant incidence levels, with occurrences of serious cases and high costs of hospitalizations for its treatment.

OBJECTIVE: To analyze risk factors among individuals with recent histories of dengue infection in a medium-sized city in Mato Grosso.

DESIGN AND SETTING: Descriptive cross-sectional study, of epidemiological-survey type, conducted among the urban population of a city located in mid-northern Mato Grosso.

METHODS: A seroepidemiological survey using questionnaires and collection of biological material was conducted among 596 adults aged ≥ 18 years who had been selected through a cluster sampling process. Positive dengue cases were those with positive results from anti-dengue immunoassays (ELISA). Statistical analyses with descriptive and inferential techniques were used, with 95% confidence intervals and a 5% significance level.

RESULTS: The seroepidemiological profile of the study participants was predominantly female, with ages between 18 and 39 years, self-declared non-white race/color, not more than eight years of education and not living with a companion. Among the sanitary factors analyzed, the following were risk factors for dengue virus infection: no running water at home; no water supply from the public piped network; no waste from drains or toilets sent to the sewage network; endemic disease combat agents visiting the home; and presence of mosquito breeding sites at home.

CONCLUSION: Low schooling levels and previous dengue virus infection were associated with current dengue virus infection.

INTRODUCTION

Dengue has been shown to be one of the most important urban arboviruses. It is considered to constitute a reemerging infectious epidemic of great magnitude, responsible for morbidity and mortality among millions of people in more than 125 countries. In 2019, 2.7 million cases were recorded in the Americas, of which 22,127 were of great severity, and 1,206 deaths were reported. In Brazil, in the same year, there were 1,544,987 suspected cases of dengue and an incidence rate of 735.2 cases per 100,000 inhabitants. That year has been characterized as the one with the highest incidence in the history of this disease.[1-5]

Viral variations contribute to increased numbers of cases and especially to occurrences of severe forms of the disease. Four antigenically distinct serotypes of dengue are now circulating simultaneously, which enables infection by all variants. Thus, the clinical manifestations of this disease are diverse: it may be asymptomatic or may give rise to alterations in cell permeability, multiple organ failure and even death. Some complications may be present, such as neurological alterations, secondary bacterial infections, cardiac and respiratory dysfunctions and rhabdomyolysis.[6-9]

Knowing the incidence of the disease is essential for direct prevention and monitoring actions. As shown by the main population-based studies conducted in all regions of Brazil since 1999, the incidence of dengue virus infection has ranged from 4.0 to 90.1%.[10-18] This variation has mainly been due to the local circulating viral serotype and year of study. The central-western region of

Brazil is ranked second highest for dengue cases in this country, and the average incidence rate in the state of Mato Grosso is 30%.[19-21]

Mato Grosso has high temperatures and low humidity. It has a diversity of environments, comprising areas of the Cerrado, Pantanal and Amazon biomes, which are undergoing constant environmental transformation. These factors may favor occurrences of human infections caused by numerous pathogens.[21,22]

OBJECTIVE

In the light of this scenario, the aim of the present study was, through an epidemiological survey, to analyze risk factors among individuals with recent histories of dengue infection in a medium-sized city in Mato Grosso.

METHODS

This was a descriptive and cross-sectional study, of epidemiological-survey type, conducted among the urban population of a city located in mid-northern Mato Grosso. Data collection was performed between January and March 2018, by a previously trained team, and a pilot study was first conducted in a census tract that did not form part of the final sampling.

A cluster sampling process was carried out in two stages (census tracts and households). Initially, these tracts (delimited by the Brazilian Institute for Geography and Statistics) were assessed to identify inhabited homes (households), i.e. to determine whether these tracts contained households, shops, wasteland or other types of land use, as shown in **Figure 1**. From this, an updated listing of census tracts was obtained. Proportional numbers of households were then systematically intercalated for each census tract sampled.

To estimate the serological prevalence of dengue in the population, with a margin of error of five percentage points, a sample of 660 individuals was required. Thus, a standard error of 0.025 was adopted for a sample of 400 individuals, and 10% loss was added to this number, plus inflation of 1.5, to reach this total of 660 individuals.

The study included individuals aged 18 years or older who were already living in the urban area of this city before April 1, 2016, and who remained as residents until the time of data collection in 2018. Women of childbearing age and pregnant women were also included. Institutionalized individuals were excluded from the study. Among the 660 individuals drawn, 64 left the study due to refusal or absence. Thus, the final sample for the study comprised 596 individuals. Selection of these individuals was carried out by means of simple random sampling among the residents of the selected households. Data collection only began after the potential participants had signed an informed consent statement.

Data collection was performed in the households, and took approximately 40 minutes per household. The interview consisted of application of a structured questionnaire, composed of questions that addressed sociodemographic, health and sanitary factors.

The dependent variable of this study was recent seropositivity for dengue (immunoglobulin M, IgM). The independent variables analyzed were sex, age group, schooling, race/color, marital status, type of household, running water, main form of water supply, bathroom drain, garbage destination, use of mosquito nets, visits by endemic disease combat agents, presence of mosquito breeding sites and hospitalization due to dengue.

For serological analysis, peripheral venipuncture was performed in an antecubital region, to collect 6 ml of blood in a vacuum collection tube containing separator gel. These samples were then sent to the laboratory of the city's Epidemiological Surveillance Department. There, they were centrifuged and cryopreserved in order to transport them to the Virology Laboratory of the Medical School of the Federal University of Mato Grosso in Cuiabá, Mato Grosso, to be kept in an ultra-freezer (-80 °C).

Serological analyses were performed at the Central Public Health Laboratory of Mato Grosso, in Cuiabá. These were done in accordance with biosafety standards, through an immunoenzymatic

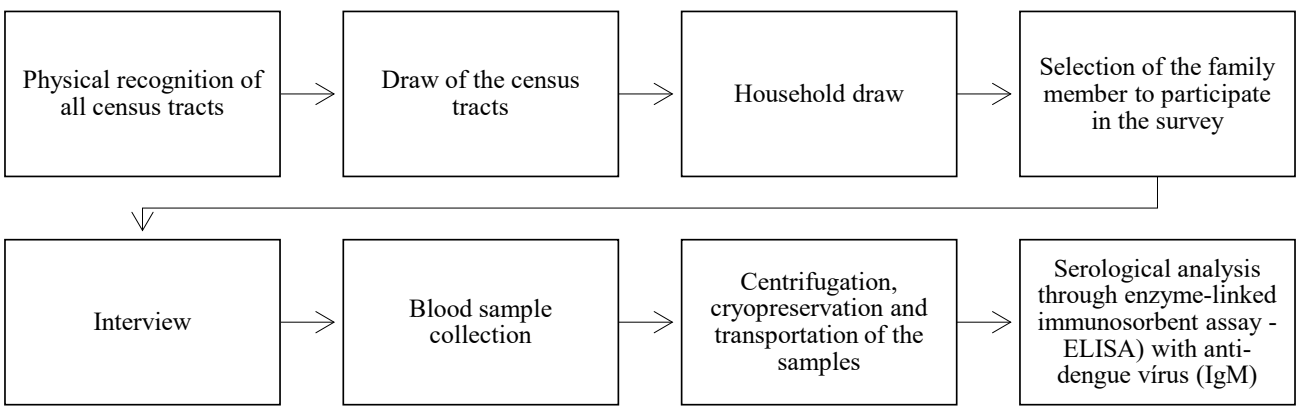

Figure 1. Sample selection from the dengue epidemiological survey.

assay (ELISA) using a IgM dengue virus kit (batch: ESR114M; Virion Serion, Wolfsburg, Germany).

The interview responses and laboratory results were double-entered, using a form constructed in the EpiInfo software, version 7 for Windows (CDC, Atlanta, Georgia, United States). Subsequently, the data were checked for any inconsistencies, using the Excel 365 software for Windows (Microsoft Corporation, Redmond, Washington, United States), thus originating the final database for analysis. For data processing, the IBM Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Armonk, New York, United States) was used.

Descriptive and inferential statistical techniques were used for the analyses. In the descriptive analyses, proportions and tables were used, while in the inferential analyses, chi-square tests, Fisher's exact test and crude prevalence ratios were obtained, with their respective 95% confidence intervals (CI). For all inferences, the significance level was taken to be 5%. For multiple analysis, the Poisson regression model was used, in which the independent variables were introduced into the method using a backward procedure. All variables that presented $P < 0.20$ in bivariate analyses were used in building the multiple model. For the final model, the variables that continued to present P-values below 0.05 ($P < 0.05$) were retained.

The confidentiality of the information provided by each participant was guaranteed. It was emphasized to the participants that all results would be handed over to them. Individuals whose results confirmed the presence of the disease were met by the municipal healthcare team, duly notified and brought into the flow of investigation and clinical management of dengue.

This study formed part of a matrix project that was approved by the Research Ethics Committee of the Clinical Hospital of Porto Alegre under opinion report no. 2.068.222, with Certificate of Presentation for Ethical Analysis no. 56176616.2.1001.5327, approved on May 17, 2017.

RESULTS

The sociodemographic profile of the 596 study participants was predominantly female (67.8%), of whom 45.5% were aged 18 to 39 years, 58.4% had had not more than eight years of schooling, 67.2% had non-white ethnicity/color and 51.1% said that they did not live with an affective companion.

Among those with recent infection detected through a serological test (IgM), the seroepidemiological profile of the study participants was composed of females (26.7%), aged between 18 and 39 years (28.2%), with not more than eight years of schooling (29.1%), non-white race/color (26.3%), who did not live with an affective companion (28.3%), as shown in **Table 1**.

The seroprevalence profile of dengue virus infection (DENV) according to sociosanitary characteristics and history of disease (**Table 2**), as constructed from bivariate analyses, had the following characteristics: individuals living in apartments (crude prevalence ratio, cPR: 0.77; 95% CI: 0.37-1.60; $P < 0.552$ from Fisher's exact test); without running water (cPR: 1.30; 95% CI: 0.42-4.06; $P < 0.650$ from Fisher's exact test); whose water supply did not

Table 1. Prevalences and 95% confidence intervals of dengue cases, according to sociodemographic variables in a city in Mato Grosso, Brazil, 2018

Variable	n (%)	Positive	Negative	cPR	95% CI	P-value
		n (%)	n (%)			
Sex						
Male	192 (32.2%)	47 (24.5%)	145 (75.5%)	0.92	(0.68-1.23)	0.558
Female	404 (67.8%)	108 (26.7%)	296 (73.3%)	1.00	-	-
Age group (years)						
18 to 39	271 (45.5%)	53 (28.2%)	135 (71.8%)	0.92	(0.50-1.67)	0.780
40 to 59	201 (33.7%)	66 (25.0%)	198 (75.0%)	1.13	(0.83-1.54)	0.451
≥ 60	124 (20.8%)	14 (12.0%)	103 (88.0%)	1.00	-	-
Schooling (years)						
Illiterate/≤ 8	247 (41.6%)	72 (29.1%)	175 (70.9%)	1.23	(0.94-1.62)	0.130
> 8	347 (58.4%)	82 (23.6%)	265 (76.4%)	1.00	-	-
Race/color						
Non-white	399 (67.2%)	105 (26.3%)	294 (73.7%)	1.07	(0.79-1.44)	0.656
White	195 (32.8%)	48 (24.6%)	147 (75.4%)	1.00	-	-
Living with a companion						
No	300 (51.1%)	85 (28.3%)	215 (71.7%)	1.23	(0.92-1.60)	0.168
Yes	287 (48.9%)	67 (23.3%)	220 (76.7%)	1.00	-	-

cPR = crude prevalence ratio; 95% CI = 95% confidence interval.
n: sample size according to variable; P: chi-square test.

Table 2. Prevalences and 95% confidence intervals of positive and negative dengue cases (immunoglobulin M, IgM), according to health variables and disease history in a city in Mato Grosso, Brazil, 2018

Variable	Positive	Negative	cPR	95% CI	P-value
	n (%)	n (%)			
Type of household					
House	148 (25.8%)	426 (74.2%)	0.77	(0.37-1.60)	0.552*
Apartment	5 (33.3%)	10 (66.7%)	1.00	-	-
Running water					
No	2 (33.3%)	4 (66.7%)	1.30	(0.42-4.06)	0.650*
Yes	150 (25.6%)	435 (74.4%)	1.00	-	-
Main form of water supply					
Other	15 (30.6%)	34 (69.4%)	1.21	(0.78-1.89)	0.413
General network	137 (25.3%)	405 (74.7%)	1.00	-	-
Bathroom drain					
Other	125 (27.1%)	337 (72.9%)	1.21	(0.85-1.73)	0.276
Sewage network	29 (22.3%)	101 (77.7%)	1.00	-	-
Destination of garbage					
Other	7 (15.6%)	38 (84.4%)	0.58	(0.29-1.16)	0.095
Public garbage collection service	148 (26.9%)	402 (73.1%)	1.00	-	-
Use of mosquito net					
No	143 (26.2%)	402 (73.8%)	1.05	(0.63-1.75)	0.851
Yes	12 (25.0%)	36 (75.0%)	1.00	-	-
Visit by endemic disease combat agents					
Every 2 to 4 months	50 (31.1%)	111 (68.9%)	1.22	(0.86-1.72)	0.257
Once	15 (20.8%)	57 (79.2%)	0.82	(0.49-1.38)	0.443
Don't remember/don't know	45(23.8%)	144 (76.2%)	0.94	(0.65-1.34)	0.720
Monthly	43 (25.4%)	126 (74.6%)	1.00	-	-
Breeding site for mosquitoes was found					
Yes	14 (28.0%)	36 (72.0%)	1.05	(0.65-1.69)	0.849
No	93 (26.7%)	255 (73.3%)	1.00	-	-
Unknown /not applicable	48(24.5%)	148 (75.5%)	0.92	(0.68-1.24)	0.568
Hospitalization due to dengue					
Yes	7 (12.5%)	49 (87.5%)	0.49	(0.20-1.19)	0.005
No	61 (31.6%)	132 (68.4%)	1.00	-	-

cPR = crude prevalence ratio; 95% CI = 95% confidence interval.
n: sample size according to variable; P: chi-square test; *Fisher's exact test.

come through the general [piped] distribution network (cPR: 1.21; 95% CI: 0.78-1.89; P < 0.413); whose wastewater disposal from the bathroom drain was to a destination other than the sewage network (cPR: 1.21; 95% CI: 0.85-1.73; P < 0.276); and whose garbage was removed by the public garbage collection service (cPR: 0.58; 95% CI: 0.29-1.16; P < 0.095).

Among the participants who were positive for DENV, 26.2% reported not using a mosquito net, 31.1% had had visits from endemic disease combat agents every two to four months and 28.0% had already found mosquito-breeding sites in their homes. Although all of these last variables mentioned were not statistically significant for DENV infection, they were shown to be risk factors for infection. Regarding the participants' self-reported histories of the disease, the variable of hospitalization due to dengue presented a statistically significant association with DENV infection. In this study, the overall prevalence of DENV infection (defined as IgM) in the population was 26.0%.

In the final model obtained through robust Poisson regression (rPR), the variable of hospitalization due to dengue (cPR: 1.30; 95% CI: 1.01-1.69; P < 0.014, i.e. significant at the 5% level) maintained statistical significance with DENV infection, whereas the variable of schooling (years of education) (cPR: 1.49; 95% CI: 1.04-1.49; P < 0.047, i.e. significant at the 5% level) became statistically significant only in this final model (**Table 3**).

Table 3. Variables in the final model and prevalence ratios adjusted using robust Poisson regression (rPR) that presented associations with positive and negative dengue cases (immunoglobulin M, IgM), with their respective 95% confidence intervals (CI) and P-values, in a city in Mato Grosso, Brazil, 2018

Variable	Category	rPR	95% CI	P-value
Hospitalization due to dengue	Yes	1.30	1.01-1.69	0.014*
	No	1.00	-	-
Schooling (years)	Illiterate/≤ 8	1.49	1.04-1.49	0.047*
	> 8	1.00	-	-

rPR = prevalence ratio adjusted using robust Poisson regression model with variable selection by means of backward method. CI: confidence interval; *Significant at the level of 5%.

Note: The garbage destination variable remained in the model as the adjustment variable, although the P-value was greater than 0.05.

DISCUSSION

In the city investigated, from 2008 to January 2020, according to the epidemiological bulletin of diseases transmitted by the vector *Aedes aegypti* that was issued by the city's Epidemiological Surveillance Department, 7,581 suspected cases of dengue were reported among residents. Of these, 5,933 cases were confirmed, with a higher average endemic index between January and May of each year. In the epidemiological survey conducted in 2018, which was conducted during this period of higher endemic index, in this city, 155 cases of dengue were confirmed by means of serological tests (IgM) among the 596 participants. Thus, the overall prevalence of DENV infection among the participants was 26.0%.

Regarding the seroprevalence found, similar studies have been conducted in several countries to test their populations for recent infection (IgM) by DENV. This was done among individuals over the age of 15 in a dengue hyperendemic area in Barranquilla, Colombia,[23] among children and adolescents under 18 years and adults of ages between 18 and 95 years old in seven municipalities of five provinces in Colombia,[24] among adults in Jamaica[25] and among individuals with suspected dengue fever in southern Odisha[26] in India and Khyber Pakhtunkhawa[27] in Pakistan, and the percentage prevalences found were 14.9%, 11.8%, 3.6%, 21.05% and 31.86%, respectively. The prevalence of DENV found in the population in southern Odisha, India (21.05%) was the closest to what was found in the present study (26.0%).

Regarding the percentages of seroprevalence, it is worth mentioning the possibility of occurrences of cross-reactivity in serological tests between DENV, Zika virus (ZIKV) and chikungunya virus (CHIKV). These arboviruses all circulate simultaneously in the city of the present study in Mato Grosso. DENV and ZIKV have already caused epidemics in previous years in this city (DENV in 2009, 2012 and 2013; ZIKV in 2016). CHIKV has circulated in this city since 2016 and had its peak of cases in 2018, i.e. before the time of data collection for the present survey.[28] In this context of cross-reactivity, there is protein homology between DENV and ZIKV, which are both flaviviruses and share all the essential structural characteristics, such as capsids, envelopes, membrane protein precursors and quaternary structures. This consequently enables considerable immunological cross-reactivity.[29-32] Simultaneous detection of antibodies to DENV and CHIKV is also observed, and these can respond either through cross-reactivity or through coinfection.[33]

Although the municipality studied here and Odisha, in India, had similar prevalences, which were both higher among women, the prevalences according to age groups were different: in Tangará, cases were concentrated between the ages of 18 and 39 years (28.2%), while in Odisha, the largest proportion was between 11 and 20 years of age (42.5%).

There were no statistically significant differences in any of the sociodemographic variables in the present study, except for schooling. Although schooling levels did not present any significant differences in the bivariate analysis (cPR: 1.23; 95% CI: 0.92-1.62; P < 0.130), it was found in the final model that being illiterate or having not more than eight years of education was correlated with a risk of DENV infection (rPR: 1.49; 95% CI: 1.04-1.49; P < 0.047, i.e. significant at the 5% level) (**Table 3**).

The association between low schooling level and occurrences of DENV infection that was observed in the city of the present study has also been one of the sociodemographic factors correlated with positive DENV cases elsewhere. However, this was not as an isolated factor, but as part of a larger set of sociodemographic, economic and poor health factors that influence occurrences of dengue cases. Schooling has been pointed out as an important aspect of overall awareness levels regarding dengue. This awareness includes knowing about the vectors that transmit the disease, identifying and implementing disease control and prevention methods within the population and recognizing the signs and symptoms of the disease process.[34-37]

Individuals with low levels of education were also among those with lower levels of knowledge about the disease. Their situation was the inverse of people who had attended college/university and who, therefore, formed part of the group with the highest percentage of seronegativity for DENV.[38] A study conducted in Sri Lanka

on the level of awareness of dengue among schoolchildren (13 to 15 years of age) recommended that educational programs aimed at raising awareness and knowledge of dengue prevention and control practices should be included within teaching of young populations, in order to contribute to transformation of knowledge into good practices against DENV in endemic areas and to help in controlling future epidemics.[37]

Investigations on the association of schooling levels with DENV infection have also portrayed how health and/or environmental factors can influence exposure to infection. Regarding these factors and the risk of DENV infection, scenarios that favor infection involve the type of housing of the population and the regularity and means of obtaining and using water. Thus, inadequate storage of water, inadequate sewage disposal and insufficient urban garbage collection, in addition to little or no practical action aimed at vector prevention, favor DENV transmission.[34,36,38-42] Nonetheless, in the present study, there were no statistically significant associations for any of the health variables analyzed, as was also previously observed in studies conducted in the city of Belo Horizonte (Minas Gerais) in 2008 and in the city of Caraguatatuba (São Paulo) in 2018.[40,43]

Directly associations with risks of DENV infection were observed with regard to nonuse of protective measures such as mosquito nets (26.2%), presence of mosquito breeding sites (28.0%) and visits by endemic disease combat agents (31.1%) to homes at intervals of two to four months. These would constitute preventive measures against the transmitting vectors.

One important part of the actions to combat the vectors that transmit DENV is health education actions. However, the dengue control model in Brazil remains political and case-anchored, which includes occasional investments in campaigns against mosquitoes and guidance on actions through the media, with little effective impact on the fight against the disease in general.[44,45] Traditionalism in the control model is characterized by lack of innovation in the strategies to cope with endemic disease, combined with little improvement in infrastructure and little investment in new means of empowering healthcare professionals or embracing the community.[3,44,46] A study conducted in Icaraí-Caucaia (Ceará) on health education for dengue prevention and control concluded that health education was delivered ineffectively, without dialogue between healthcare professionals and the population, and that generalist methods of knowledge transmission by healthcare professionals were fruitless in combating a disease such as dengue.[45]

Although dengue is a debilitating and self-limiting disease, most patients follow a benign clinical course and recover. However, some cases may evolve to severe forms and death. Dengue can present three clinical phases, i.e. febrile, critical and recovery, which highlights the need for attention to and monitoring of the appearance of warning signs. These may indicate evolution to the severe forms of the disease, which would usually appearing on the third to seventh day after the onset of the disease. Dengue with complications is characterized by severe bleeding, severe organ dysfunction or significant plasma extravasation, with additional severity in children and the elderly, because they present a faster disease course and are vulnerable to complications inherent to their ages.[2] Some studies have also indicated the possibility of mutual increment of infections between DENV and ZIKV from extrinsic improvement dependent on antibodies. This is a phenomenon that has been implicated in severe forms of dengue, such as dengue hemorrhagic fever and dengue shock syndrome, and in cases of increased severity of the disease through secondary infection by DENV.[29,30]

Hospitalization can be indicated for both forms, i.e. dengue hemorrhagic fever and dengue shock syndrome. The objective is to maintain hydration and hydroelectrolytic balance.[47,48] Hospitalization due to dengue was one of the variables that were statistically associated (cPR: 1.30; 95% CI: 1.01-1.69; $P < 0.014$, i.e. significant at the 5% level) (**Table 3**) with DENV infection and with serological tests (IgM) that identified recent infection in individuals. This may be a secondary response to previous infection by other flaviviruses or other DENV serotypes.[2,29,30,31,32,33,48] This highlights that the results from the present study may reflect cross-reactivity between DENV and ZIKV, since it was conducted two years after an epidemic of ZIKV.

Over the last decade, 546,939 hospitalizations due to dengue treatment were recorded in Brazil, with a total cost of 184 million reais. The central-western region occupied third place among the five geographical regions of Brazil, both in numbers of hospitalizations (91,540) and in hospitalization expenditure (30,366,167.67).[49] Dengue is known to be a serious public health problem that generates high costs for this country's population and economy. It negatively affects individuals, families and social productivity.[50-52] Therefore, putting health surveillance actions into practice, while considering the individual characteristics of each population, listening to the community and providing training for healthcare professionals, is an important form of contributing to coping with diseases of great magnitude such as dengue.

It is of paramount importance to know the factors that are associated with DENV infection, given its already-known association with social vulnerability, and also its impact on society as a whole. The present study is important insofar as it provides knowledge of yet another dengue distribution profile, in a medium-sized city in a state covering an immense area.

The following limitations of the present study need to be taken into consideration. Children (under the age of 18 years) were not included in this survey, given that children, along with the elderly, make up the risk group for dengue cases. The serotypes circulating among the participants were not identified, although this is necessary in order to ascertain how the disease is circulating in

the community. No other analyses such as the reverse transcriptase polymerase chain reaction (RT-PCR) were performed to confirm recent cases of dengue, although that could also have helped in identifying cross-reactivity between DENV and the Zika and chikungunya arboviruses that circulate simultaneously with dengue in this city.

CONCLUSIONS

In this cross-sectional study conducted in a city located in mid-northern Mato Grosso, the findings showed that there were no significant associations between DENV infection and the sanitary variables that characterized the population. However, some variables were risk factors for infection. The variables of hospitalization due to dengue and schooling level were statistically significant with regard to occurrences of DENV infection, in the final model. This may indicate the existence of a relationship between low schooling levels and lower awareness of how to protect oneself against the infection and how to prevent it.

The data from the present study allowed us to identify the profile of recent dengue infection in this city, thereby generating information about the population that provides an analysis on the population's health situation. The results obtained raise the possibility of conducting further studies to determine the serotypes of DENV, as well as to investigate occurrences of cross-reactivity with other arboviruses circulating in this city.

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Address for correspondence:
Ana Cláudia Pereira Terças-Trettel
Universidade do Estado de Mato Grosso (UNEMAT), Campus Universitário de Tangará da Serra
MT-358, s/nº
Jardim Aeroporto — Tangará da Serra (MT) — Brasil
CEP 78300-000
Tel. (+55 65) 99967-5203
E-mail: ana.claudia@unemat.br

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Could polyhexanide and chlorine dioxide be used as an alternative to chlorhexidine? A systematic review

Dayanne Simões Ferreira Santos[I], Mariela Peralta-Mamani[II], Felipe Suaki Brandão[III], Flaviana Bombarda Andrade[IV], Thiago Cruvinel[V], Paulo Sérgio da Silva Santos[VI]

Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil

[I]DDS. Dentist and Master's Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-1899-3499

[II]DDS, MSc. Dentist and Doctoral Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-0243-9194

[III]DDS, MSc. Dentist and Doctoral Student, Department of Dentistry, Dentistry School, Universidade Estadual de Maringá (UEM), Maringá (PR), Brazil.
https://orcid.org/0000-0003-1484-9964

[IV]DDS, PhD. Dentist and Associate Professor, Department of Dentistry, Endodontics and Dental Materials, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-1238-2160

[V]DDS, PhD. Dentist and Associate Professor, Department of Pediatric Dentistry, Orthodontics and Public Health, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7095-908X

[VI]DDS, PhD. Dentist and Associate Professor, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-0674-3759

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Adverse effects.
Dental management.

ABSTRACT

BACKGROUND: Maintenance of oral microbiota balance is the simplest way to prevent infectious oral diseases, through controlling dental biofilm. Combined use of mouthwash and mechanical removal has been shown to be a very effective way for this.

OBJECTIVES: To identify clinical studies comparing the antimicrobial effect and possible adverse effects and/or side effects of chlorhexidine-based mouthwashes with those of mouthwashes containing chlorine dioxide and/or polyhexanide, for controlling oral microbiota.

DESIGN AND SETTING: Systematic review designed by the stomatology sector of postgraduation in applied dental sciences of Bauru Dentistry School, University of São Paulo, Brazil.

METHODS: A systematic review was conducted using online databases (PubMed, Embase, Web of Science and Science Direct) up to April 8, 2020. The search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS: The studies included comprised eight articles published between 2001 and 2017. A total of 295 young adults, adults and elderly people were evaluated (males 44.75% and females 55.25%). Three articles compared polyhexanide with chlorhexidine and five articles compared chlorine dioxide with chlorhexidine. No studies comparing all three mouthwashes were found. The concentrations of the study solutions were quite varied, and all rinses had an antimicrobial effect. In four studies, it was stated that no side effects or adverse effects had been found. Three studies did not address these results and only one study addressed side effects and/or adverse effects.

CONCLUSION: Mouthwashes containing chlorine dioxide and polyhexanide are viable alternatives to chlorhexidine, since they reduce oral biofilm and have little or no reported side or adverse effects.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO - CRD42019115929 – Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019115929.

INTRODUCTION

Rationale

Control of dental biofilm and maintenance of the balance of the oral microbiota is the simplest way to prevent diseases such as periodontal disease and dental caries.[1] Combined use of mouthwash and mechanical removal has been shown to be a very effective way for controlling cariogenic and periodontogenic biofilms.[2] These biofilms may present a risk of systemic dissemination through microaspiration or the hematogenous route, with consequent secondary infections.

Among the various chemical agents used to control dental biofilms, chlorhexidine (CHX) is the gold standard because of its excellent bacteriostasis, substantivity, non-specificity and broad spectrum.[3,4] However, there is evidence that prolonged use of CHX has adverse effects, such as tooth and restoration staining, mucosal irritation, microbial resistance and changes to taste sensation, thus restricting its use to specific cases in dentistry.[3-6]

Polyhexamethylene biguanide or polyhexanide (PHMB) and chlorine dioxide (ClO_2) are alternatives to CHX. Studies have demonstrated that PHMB has a broad antimicrobial spectrum, low risk of contact hypersensitivity and good tolerability by cells and tissues, and that it also promotes wound healing.[7,8] Interestingly ClO_2 is not particularly influenced by variations in mouth pH after activation. ClO_2 has action against bacteria, viruses and fungi and high water solubility that provides it with the ability to penetrate the biofilm quickly to exert its action.[9,10] To our knowledge, there have not been any clinical or *in vitro* studies aimed at comparing the effects of these three solutions (CHX, PHMB and ClO_2).

OBJECTIVES

The aim of this systematic review was to identify clinical studies that compared the antimicrobial effect and possible adverse and/or side effects of CHX-based mouthwashes with those of mouthwashes containing ClO_2 and/or PHMB, for controlling dental biofilm.

Research question

Two research questions were formulated:

- Do mouthwashes containing PHMB and/or ClO_2 have antimicrobial efficacy in the oral microbiota comparable to that of CHX?
- Do studies with mouthwashes containing PHMB and/or ClO_2 show adverse and/or side effects, in comparison with to the effects associated with CHX?

METHODS

Study design

This systematic review was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items of Systematic Reviews and Meta-Analyses).[9]

Participants, interventions and comparators

All the studies selected met the criteria established through the PICO strategy: (1) Participants: oral microbiota; (2) Intervention: PHMB and/or ClO_2; (3) Control: CHX; and (4) Outcomes: antimicrobial efficacy of mouthwashes containing PHMB and/or ClO_2, compared with that of CHX.

Systematic review protocol

The protocol for this systematic review was registered in PROSPERO (CRD42019115929) and is available on the website www.crd.york.ac.uk/PROSPERO/.

Search strategy

A search of the literature was conducted to survey clinical studies that aimed to investigate the antimicrobial action of mouthwashes containing PHMB and ClO_2, compared with that of CHX. The studies included were identified based on a search strategy for each electronic database: PubMed, EMBASE, Web of Science and Science Direct. The search strategy was designed with Boolean operators (AND/OR) to identify all studies on this topic published in English, Portuguese or Spanish up to December 21, 2020. The descriptors used were "Chlorhexidine", "Polyhexanide", "Dioxide Chlorine" and "Mouthwash". The search strategies are detailed in **Table 1**.

In the Science Direct database, filters for research articles (31) and conference abstracts (2) were activated in order to exclude texts from encyclopedias, book chapters and other sources.

Eligibility criteria

This review included clinical studies that evaluated the effectiveness of mouthwashes and studies that compared the action of PHMB and/or ClO_2 in relation to CHX, regardless of the participants' age, sex, systemic changes or medication use.

The following types of studies were excluded: literature review articles, clinical cases or case series, studies that did not evaluate mouthwashes, studies not related to dentistry, *in vitro*, *in situ* and animal studies and studies published in other languages.

Data sources, study selection and data extraction

All records collected were moved to a folder of the reference manager EndNote Web (www.myendnoteweb.com). Any duplication of references was identified and then deleted.

Studies were identified independently by two reviewers (D.S.F.S. and F.S.B.) in two phases: 1. Reading the titles and summaries of each article; and 2. Reading the full text. Any discrepancies during either of these phases were resolved through discussion with a third reviewer (P.S.S.S.).

All studies included were independently examined by two reviewers (D.S.F.S. and F.S.B.) and their main characteristics were extracted in order to perform data synthesis and study quality assessment. Only the information described in the articles was considered.

Data analysis

A narrative data synthesis was carried out, structured around the characteristics of each study, i.e. the microbiological count, type of microorganism, characteristics of the population, parameters evaluated and results obtained.

Risk of bias

Two reviewers (D.S.F.S. and F.S.B.) independently assessed the risk of bias in the studies included through using the Cochrane risk of bias tool (RoB 2.0, 2008), which is available in the Cochrane manual for developing systematic intervention reviews, version 5.1.0 (Cochrane Handbook, Oxford, United Kingdom, and Melbourne, Australia).[10] Any discrepancies were resolved by a third reviewer (P.S.S.S.). This tool was chosen to assess the risk of bias in randomized clinical trials[10] in terms of seven domains: generation of random sequence, allocation concealment, blinding of participants and professionals, blinding of outcome evaluators, incomplete outcomes, selective outcome report and others. These were classified as presenting "low risk", "high risk" or "uncertain risk", in accordance with each criterion of the tool.[10] Afterwards, the data were inserted into the Review Manager (RevMan Version 5.3, Cochrane Manager Review Center, Oxford, United Kingdom) software, and a risk-of-bias graph was generated.

RESULTS

Study selection

A total of 245 studies were initially identified in the following databases: PubMed (n = 132), Embase (n = 41), Web of Science (n = 39) and Science Direct (n = 33). Thirty studies were excluded due to duplication. Among the remainder, 48 studies were selected for reading the title and abstract and 39 of these were excluded for the following reasons: they were *in vitro* or *in vivo* studies, did not use CHX as a control (comparison), did not use PHMB and/or ClO_2 as an intervention or did not use mouthwashes. Thus, the full texts of nine studies were read. From this, one further study were excluded because it did not meet the eligibility criteria (it was an *in vitro* and *in vivo* study about decolonization rates of *Staphylococcus aureus*). Hence, the final analysis was conducted on eight studies. The detailed sequence can be seen in the study selection flowchart[9] (**Figure 1**).

Study characteristics

Table 1 shows the general characteristics of the studies included, which were published between 2001 and 2017. The search was carried out without restriction on publication date. These studies were conducted in Europe and Asia (Germany, Switzerland, Turkey, India and Indonesia). All of them were randomized clinical studies, and microbiological analyses were performed.[8,11-17] In total, 295 individuals were evaluated and, in

Table 1. Databases and search strategy

Database	Search Strategy
PubMed	((((“chlorhexidine”[MeSH Terms] OR “chlorhexidine”[All Fields]) AND (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR “mouthwash”[All Fields])) OR (“chlorhexidine”[MeSH Terms] OR “chlorhexidine”[All Fields]) OR (“chlorhexidine gluconate”[Supplementary Concept] OR “chlorhexidine gluconate”[All Fields])) AND (phmb[All Fields] OR (“polihexanide”[Supplementary Concept] OR “polihexanide”[All Fields] OR “polyhexamethylene biguanide”[All Fields]) OR (“polihexanide”[Supplementary Concept] OR “polihexanide”[All Fields] OR “polyhexamethylenbiguanid”[All Fields]) OR (“polihexanide”[Supplementary Concept] OR “polihexanide”[All Fields]) OR (dioxide[All Fields] AND (“chlorine”[MeSH Terms] OR “chlorine”[All Fields])) OR (“chlorine dioxide”[Supplementary Concept] OR “chlorine dioxide”[All Fields])) AND (mouthrinse[All Fields] OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR “mouthwash”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“mouth”[All Fields] AND “bath”[All Fields]) OR “mouth bath”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“mouth”[All Fields] AND “rinse”[All Fields]) OR “mouth rinse”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“mouth”[All Fields] AND “wash”[All Fields]) OR “mouth wash”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“bath”[All Fields] AND “mouth”[All Fields])) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“baths”[All Fields] AND “mouth”[All Fields])) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“mouth”[All Fields] AND “baths”[All Fields]) OR “mouth baths”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“mouth”[All Fields] AND “rinses”[All Fields]) OR “mouth rinses”[All Fields]) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“rinse”[All Fields] AND “mouth”[All Fields])) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“rinses”[All Fields] AND “mouth”[All Fields])) OR (“mouthwashes”[Pharmacological Action] OR “mouthwashes”[MeSH Terms] OR “mouthwashes”[All Fields] OR (“wash”[All Fields] AND “mouth”[All Fields])))))
Embase	(('chlorhexidine mouthwash'/exp OR 'chlorhexidine mouthwash' OR (('chlorhexidine'/exp OR chlorhexidine) AND ('mouthwash'/exp OR mouthwash)) OR 'chlorhexidine'/exp OR chlorhexidine OR 'chlorhexidine gluconate'/exp OR 'chlorhexidine gluconate' OR (('chlorhexidine'/exp OR chlorhexidine) AND ('gluconate'/exp OR gluconate))) AND (phmb OR 'polyhexamethylene biguanide'/exp OR 'polyhexamethylene biguanide' OR (polyhexamethylene AND ('biguanide'/exp OR biguanide)) OR polyhexamethylenbiguanid OR 'polihexanide'/exp OR polihexanide OR 'dioxide chlorine' OR (('dioxide'/exp OR dioxide) AND ('chlorine'/exp OR chlorine)) OR 'chlorine dioxide'/exp OR 'chlorine dioxide' OR (('chlorine'/exp OR chlorine) AND ('dioxide'/exp OR dioxide))) AND ('mouthrinse'/exp OR mouthrinse OR 'mouthwash'/exp OR mouthwash OR 'mouthwashes'/exp OR mouthwashes OR 'mouth bath' OR (('mouth'/exp OR mouth) AND ('bath'/exp OR bath)) OR 'mouth rinse'/exp OR 'mouth rinse' OR (('mouth'/exp OR mouth) AND rinse) OR 'mouth wash'/exp OR 'mouth wash' OR (('mouth'/exp OR mouth) AND wash) OR 'bath, mouth' OR (bath, AND ('mouth'/exp OR mouth)) OR 'baths, mouth' OR (baths, AND ('mouth'/exp OR mouth)) OR 'mouth baths' OR (('mouth'/exp OR mouth) AND ('baths'/exp OR baths)) OR 'mouth rinses'/exp OR 'mouth rinses' OR (('mouth'/exp OR mouth) AND rinses) OR 'rinse, mouth' OR (rinse, AND ('mouth'/exp OR mouth)) OR 'rinses, mouth' OR (rinses, AND ('mouth'/exp OR mouth)) OR 'wash, mouth' OR (wash, AND ('mouth'/exp OR mouth))))
Web of Science	(((((Chlorhexidine mouthwash OR Chlorhexidine) OR Chlorhexidine gluconate) AND (((((phmb OR polyhexamethylene biguanide) OR polyhexamethylenbiguanide) OR polihexanide) OR dioxide chlorine) OR chlorine dioxide)) AND ((((((((((mouthrinse OR mouthwash) OR mouthwashes) OR Mouth Bath) OR Mouth Rinse) OR Mouth Wash) OR Bath, Mouth) OR Baths, Mouth) OR Mouth Baths) OR Mouth Rinses) OR Rinse, Mouth) OR Rinses, Mouth) OR Wash, Mouth)).
Science Direct	(Chlorhexidine OR Chlorhexidine gluconate) AND (phmb OR polyhexamethylene biguanide OR polyhexamethylen biguanid OR polihexanide OR chlorine dioxide) AND (mouthrinse OR mouthwash OR mouthwashes OR Mouth Bath OR Mouth Rinse OR Mouth Wash)

the studies in which the participants were separated according to sex,[8,11-17] 44.75% were men and 55.25% women. Six studies involved young adults with an average age between 18 and 25 years,[8,11-13,15,17,18] one involved adults and the elderly[14] with a mean age of 60.8 ± 15.0 years and one involved adolescents aged 11-16 years.[16]

Evaluation profile of the clinical trials

One study evaluated the antifungal effects of ClO_2 compared with those of CHX;[14] one compared ClO_2 with CHX, against the chromogenic bacterium species *Actinomyces*;[16] three evaluated the effect of PHMB compared with CHX, on oral biofilm;[11-13] and three compared the effects of ClO_2 with those of CHX, on oral biofilm.[8,15,17,18]

One study evaluated totally edentulous individuals and their dentures,[14] six evaluated the teeth and mucous membranes of young adults,[8,11-13,15,17] one evaluated the tongue coating,[8] one evaluated individuals who had undergone orthodontic treatment[17] and one evaluated molar dental sulcus pigmentation in children.[16]

Mouthwashes

Three studies compared PHMB with CHX[11-13] and the other five compared ClO_2 with CHX.[8,14-16,17] No studies comparing PHMB with ClO_2 or all three solutions simultaneously were found.

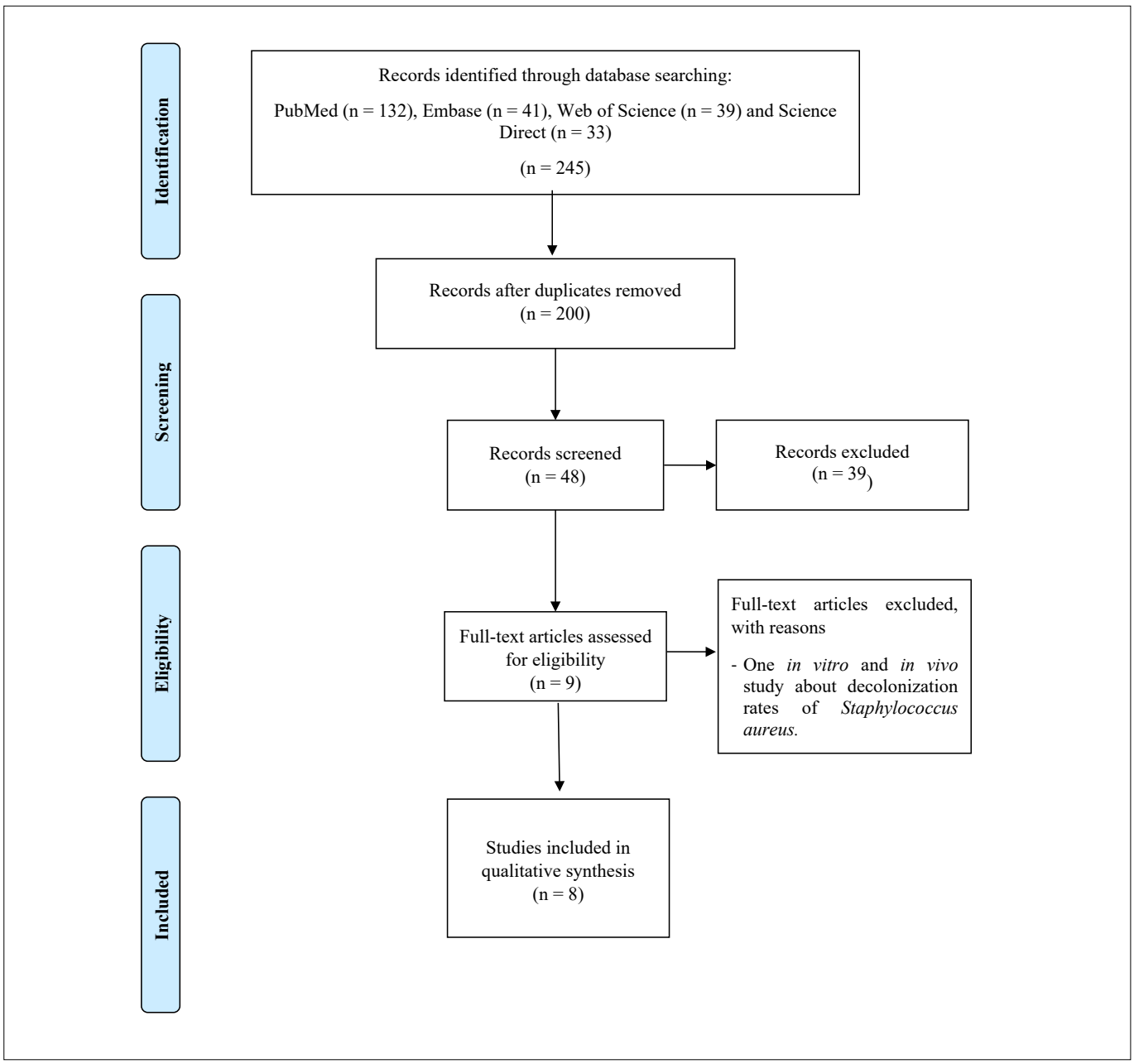

Figure 1. Flow diagram of the studies included for the review.

The CHX concentration that was most used was 0.20%,[8,14,15] followed by 0.12%[11,12] and 0.1%.[16] The PHMB concentrations used were 0.04%,[11] 0.12%[12] and 0.20%[13] and those of ClO_2 were 0.01%,[15] 0.80%[14] and 0.1%.[16]

In all studies,[8,11,16,20] the frequency of use was two washes per day, i.e. one in the morning and other at night, for each mouthwash. In addition to differences in concentrations, there were differences in quantity, duration of exposure to mouthwash solution and duration of the study (Table 2). The study that evaluated totally edentulous individuals[14] gave the recommendation that individuals should immerse their dentures in the mouthwash, overnight for 15 days.

Study outcomes

The primary outcome from this systematic review was to report on the antimicrobial efficacy of mouthwashes containing PHMB and/or ClO_2, compared with those containing CHX. The secondary outcome was to report on the adverse effects of mouthwashes.

Antimicrobial efficacy of mouthwashes

All three studies that compared PHMB with CHX used a concentration of 0.12% for CHX. These studies evaluated the action of mouthwashes on bacteria. Among their conclusions, one was that the substantivity of CHX was always 12 hours.[11-13]

Regarding the biofilm index, the studies showed that there were significantly lower rates with CHX than with PHMB 0.04% ($P = 0.038$).[11] There were no statistically significant differences between PHMB 0.12% and CHX ($P > 0.05$),[12] and PHMB 0.2% was significantly less effective on the biofilm index than CHX ($P = 0.016$).[13]

The bacterial count was investigated at two times: four hours after using the mouthwash and five days after this. Evaluation of the bacterial count of the dental surface showed that CHX was significantly more effective in reducing the bacterial count than PHMB 0.04%, at both times evaluated (four hours, $P = 0.003$; five days, $P = 0.030$).[11] There was no statistically significant difference between PHMB 0.12% and CHX ($P = 0.085$) after four hours, while after five days of use, PHMB 0.12% was significantly less effective than CHX ($P = 0.008$).[12] In the first four hours, with PHMB 0.20%, there was no significant difference compared with CHX ($P = 0.623$); after five days of use, PHMB 0.2% significantly inhibited bacterial growth, compared with CHX ($P = 0.029$).[13]

Evaluation of bacterial counts on the mucosal surface showed that CHX was significantly more effective than PHMB 0.04% ($P = 0.42$)[11] and PHMB 0.12% ($P = 0.013$)[12] after the first four hours and after five days of using PHMB 0.04% ($P = 0.007$)[11] and PHMB 0.12% ($P = 0.000$).[12] There were no significant differences between PHMB 0.2% and CHX four hours after use ($P = 0.738$) or five days afterwards: both solutions were equally effective ($P = 1.000$).[13]

Other studies compared ClO_2 with CHX[8,14-17] and found that CHX 0.2% inhibits biofilm more powerfully than ClO_2 0.01% ($P < 0.001$).[15] Four hours after use, CHX 0.2% was found to have been more efficient than ClO_2, such that there were fewer colony-forming units (CFUs) on the mucosa ($P < 0.001$) and on the dental surface ($P = 0.01$).[8] Regarding the biofilm index ($P = 0.05$), rate of accumulation of tongue biofilm ($P = 0.238$), presence of bacterial CFUs on the fifth day of mouthwash and application of mouthwashes for 15 days, use of ClO_2 was equal to use of CHX 0.2% ($P = 0.160$).[8] It was concluded that the reductions in the dental biofilm index (from 1.30 to 0.84; $P < 0.01$) and gingival index (from 1.43 to 1.23, $P < 0.01$) through use of ClO_2 were similar to what was seen regarding the dental biofilm index (from 1.27 to 0.83; $P < 0.01$) and gingival index (from 1.63 to 1.35; $P < 0.01$) in a mouthwash with CHX.[17] In evaluations on fungus, it was concluded that both rinses (ClO_2 0.80% and CHX 0.20%) eliminated *Candida albicans* hyphae (ClO_2, $P = 0.03$; and CHX, $P > 0.01$), decreased palatal inflammation (ClO_2, $P = 0.001$; and CHX, $P = 0.04$) and eliminated *Candida* colonization ($P = 0.001$ for both).[14] A single study showed that ClO_2 0.1% had a greater antibacterial effect ($P = 0.001$) than CHX 0.1% ($P = 0.01$).[16]

Adverse effects/side effects

The authors of seven studies[8,11-14,16,17] did not mention the expected adverse or side effects: among these, the authors of four studies reported that they did not observe any adverse effects and/or side effects during their investigations,[11-14] while such effects were not reported in the results from three studies.[8,16,17]

In one other study,[15] a questionnaire regarding the perception of mouthwashes was applied. The participants in that study preferred the taste of ClO_2 over that of CHX ($P < 0.001$) and reported that there was less change in taste when using ClO_2 than when using CHX ($P < 0.001$). The taste of CHX remained in the mouth longer than that of ClO_2 ($P < 0.001$), while use of CHX was more convenient than use of ClO_2 ($P < 0.001$) and the perception of plaque reduction through using CHX was greater than through using ClO_2 ($P < 0.001$).[15]

Risk of bias

In the present study, the Cochrane risk of bias (RoB) tool[10] was applied to assess the risk of bias in the eight randomized controlled trials that were included. The risk of bias was explored in seven domains.

Two studies were classified as presenting an uncertain risk of bias in three domains, specifically those relating to selection bias (random sequence generation and allocation concealment) and detection bias (blinding of outcome assessment),[14,16] given that in these studies the randomization and allocation methods were not mentioned and it was not reported whether the results were obtained through blind analysis. Six studies were classified as presenting an uncertain risk of bias in relation to detection bias (blinding

Table 2. Summary of information contained in the articles included in this review

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Rosin et al.,[11] Germany	16/12 men/4 women/23.4 years	**PHMB (0.04%) mouth rinse:** 0.2% Lavasept (Fresenius Kabi, Bad Homburg, Germany), 0.1% aromatic oil (Henkel, Düsseldorf, Germany), 0.1% Cremophor (Henkel, Düsseldorf, Germany), 10.4% ethanol (96%), 90.2% Ringer's solution. **Placebo mouth rinse:** 0.1% aromatic oil, 0.1% Cremophor, 10.4% ethanol (96%), 90.4% deionized water. **CHX mouth rinse (0.12%):** 6% chlorhexidine digluconate (20%) (Henkel, Düsseldorf, Germany), 94% deionized water. **Skinsept mucosa** (diluted in 0.12% chlorhexidine): 40% SkinseptA mucosa (Henkel, Düsseldorf, Germany), 6.24% ethanol (96%), 1% hydrogen peroxide (30.42%), 0.12% lactic acid, 52.64% deionized water.	**CHX** - 0.12%	**PHMB** - 0.04%	20/60	4	The effects on dental biofilm and oral bacterial count were compared.	Oral biofilm - Dental biofilm index and smears of dental surface and cheek mucosa (on days 1 and 5) and CFU count per sample. Four hours after the first use of mouthwashes, there was no statistical difference between PHMB, Skinsept and placebo, while CHX was superior for destruction of dental biofilm after 4 hours. In the mucosa, 4 hours after the first use of the mouthwashes, all mouthwashes were more effective than placebo for destroying oral biofilm. Twelve hours after the final use of mouthwashes, CHX was the most effective in destroying oral biofilm, PHMB was statistically more effective than placebo, while Skinsept did not show any difference in reducing biofilm, compared with placebo.	CHX 0.12% was more effective than PHMB 0.04% and placebo for destroying bacterial biofilm. The substantivity of CHX was always 12 hours. The substantivity of PHMB was 4 hours in the oral mucosa only. The antibacterial effect of PHMB was significantly greater than placebo on the mucosa alone.

Continue...

Table 2. Continuation.

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Rosin et al.,[12] Germany	16/ 6 men/ 10 women/ 23.4 years	**PHMB (0.12%) mouth rinse:** 0.6% LavaseptA (Fresenius Kabi, Bad Homburg, Germany), 0.1% aromatic oil (Henkel, Düsseldorf, Germany), 0.1% Cremophor (Henkel, Düsseldorf, Germany), 10.4% ethanol (96%), 88.8% Ringer's solution. **Placebo mouth rinse:** 0.1% aromatic oil (Henkel, Düsseldorf, Germany), 0.1% Cremophor (Henkel, Düsseldorf, Germany), 10.4% ethanol (96%), 89.4% deionized water. **CHX mouth rinse** (0.12%): 0.6% chlorhexidine digluconate (20%) (Henkel, Düsseldorf, Germany), 94% deionized water. **Essential oil mouth rinse:** Listerine antiseptic (Warner-Lambert, Consumer Healthcare Products, Freiburg, Germany).	**CHX** - 0.12%	**PHMB** - 0.12%	20/60	4	To increase the PHMB concentration from 0.04% to 0.12% and evaluate the effects on the biofilm formed and oral bacterial counts, compared with CHX 0.12%. To include an established commercial product (Listerine) available for another comparison.	Oral biofilm - Dental biofilm index and smears of the dental surface and cheek mucosa (on days 1 and 5) and CFU count per sample. Four hours after the first use of mouthwashes, no statistical difference was observed between PHMB and Listerine or PHMB and CHX regarding destruction of dental biofilm; and 12 hours after the final use of mouthwashes, PHMB was more effective for inhibiting bacterial growth than Listerine. In the mucosa, 4 hours after the first use of mouthwashes, CHX was the most effective for destruction of oral biofilm. Twelve hours after the final use of rinses, CHX was the most effective and PHMB was significantly better than placebo for destroying oral biofilm.	PHMB mouthwash showed significantly greater inhibition of bacterial biofilm growth than placebo. The bacterial count indicated persistence of PHMB antimicrobial activity 4 hours after use.

Continue...

Table 2. Continuation.

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Welk et al.,[13] Germany	16/ 6 men/ 10 women/ 21.1 years	**PHMB (0.2%) mouth rinse:** 1.0% Lavasept s containing 20% PHMB (Fresenius Kabi, Bad Homburg, Germany), 0.1% aromatic oil (Henkel, Düsseldorf, Germany), 0.1% Cremophor (Henkel), 10.4% ethanol (96%), 88.6% Ringer's solution. **CHX (0.12%) mouth rinse:** 6% solution of 20% chlorhexidine digluconate stock solution (Henkel), 94% deionized water. **Triclosan (0.3%)/ copolymer (2.0%) mouth rinse:** Commercially available Colgate Total Plax s mouth rinse (Colgate-Palmolive Company, New York, NY, United States) containing 0.3% 2,4,40-trichloro-20-hydroxydiphenyl ether/2.0% polyvinyl methyl ether maleic acid (PVM/MA) copolymer. **Placebo mouth rinse: 0.1%** aromatic oil (Henkel), 0.1% Cremophor (Henkel), 10.4% ethanol (96%), 89.4% deionized water.	**CHX -** 0.12%	**PHMB -** 0.20%	20/60	5	Comparison of mouthwash containing PHMB (0.2%) with mouthwash containing CHX (0.12%), to evaluate its effect on the growth of dental biofilm and on oral bacterial count.	Oral biofilm - Quigley & Hein[18] dental biofilm index (QHI), as modified by Turesky et al.[19] After the first use of mouthwashes, it was observed that CHX was statistically more effective in destroying dental biofilm than other mouthwashes and 8 hours after the final use of mouthwashes, PHMB inhibited bacterial growth more effectively compared with triclosan and placebo. In the mucosa, after the first use of mouthwashes, all mouthwashes were more effective than placebo in destroying oral biofilm, but there was no statistical difference between them. Eight hours after the final use of rinses, PHMB was equally effective in destroying oral biofilm, compared with CHX.	The mouthwash with 2.0% PHMB was significantly less effective in destroying bacterial biofilm than 0.12% aqueous CHX. After 8 hours of using PHMB, inhibition of bacterial growth was still observed.

Continue...

Table 2. Continuation.

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Paraskevas et al.,[15] Switzerland	77/ 34 men/ 43 women/ 23.2 years	**10 Quist-forte** (containing 100-ppm free **ClO_2**): The rinse was activated when 5 ml base solution was mixed with 5 ml activator solution. De Witte Tanden Winkel, Rotterdam, Netherlands. **Corsodyl (containing 0.20% CHX**, digluconate, ethanol, polyoxyl hydrogenated castor oil, sorbitol, E-125, purified water), GlaxoSmithKline, Zeist, Netherlands.	**CHX** - 0.20%	**ClO_2** - 0.01%	10/60	3	To evaluate inhibition of growth of dental biofilm through use of mouthwash containing ClO_2, compared with mouthwash with CHX, over the course of a 3-day dental biofilm growth model.	Dental biofilm - Dental biofilm index - In the control group (CHX), the overall average dental biofilm index was 1.39, compared with 1.96 in the test group (ClO_2), ($P < 0.001$).	The ClO_2 rinse was a less potent bacterial biofilm inhibitor than the CHX rinse.
Uludamar et al.,[14] Turkey	60/ 23 men/ 37 women/ 60.8 ± 15 years	Tissue conditioner material **Visco-gel**, Dentsply Detrey GmbH, Detrey-straße 1, D-78467 Konstanz, Germany **ClO_2 (0.8%) dioxidant**, Frontier Pharmaceutical, Inc., Melville, NY, United States). **Corsodyl (0.2% CHX gluconate)**, Group Laboratories SA (Pty) Ltd., Epping Industrial 1, Cape Town, South Africa.	**CHX** - 0.20%	**ClO_2** - 0.80%	30/60	15	The effect of tissue conditioning and two mouthwashes on resolution of clinical symptoms of prosthetic stomatitis and on reduction of *Candida albicans*.	*Candida albicans* - The method of Budtz-Jorgensen et al.[20] was used to classify the clinical effects of the treatment: Healing (without inflammation) - tissue conditioner: 40%; ClO_2: 60% and CHX: 70%. Improvement (decrease in inflammation) - tissue conditioner: 25%; ClO_2: 25% and CHX: 20%. Failure (no change in inflammation) - tissue conditioner: 35%; ClO_2: 15% and CHX: 10%. The UFC/ml count was used to assess the effect on fungal biofilm - before/after UFC treatment/ml (P-value): tissue conditioner: 208.35/196.15 ($P = 0.4$); ClO_2: 204.75/74.21 ($P = 0.001$) and CHX: 202.24/57.81 ($P = 0.001$).	Use of both mouthwashes (ClO_2 and CHX) eliminated hyphae, decreased palatal inflammation and eliminated Candida colonization.

Continue...

Table 2. Continuation.

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Yadav et al.,[8] India	25/ 11 men/ 14 women/ 19.8 years	Stabilized **ClO_2 mouth rinse** in aqueous vehicle **Fresh Chlor** (Rowpar Group Pharmaceuticals, Bangalore, India). **CHX (0.2%) gluconate mouth rinse** in aqueous vehicle **Hexedine** (ICPA, Bangalore, India).	**CHX** - 0.20%	**ClO_2** - ur	10/60	5	To evaluate the effectiveness of a mouthwash containing stabilized ClO_2 and a mouthwash containing CHX for inhibiting accumulation of biofilm on the tongue and formation of dental biofilm.	Oral biofilm - The marine dental biofilm index as modified by Rustogi was used to evaluate the teeth, the Winkel index and wet weight of the coating were used to evaluate the tongue and microbiological analysis was done using UFC. on samples collected from the dental and mucosal surfaces. The marine biofilm index as modified by Rustogi, the Winkel index and the wet weight of the tongue coating did not show any statistical difference between the groups. The biofilm collected after 4 hours demonstrated that use of CHX gave rise to UFC/sample smaller than what resulted from use of ClO_2 on the teeth: mean CHX 30.6800 and ClO_2: 35.8800 (P = 0.001); and on the mucosa: mean CHX: 37.6400 and ClO_2: 45.2800 (P = 0.00 (6.244E-5)).	The inhibitory properties against dental biofilm, the rate of accumulation of tongue biofilm and the antibacterial properties of the mouthwash with ClO_2 were comparable to those of the mouthwash with CHX.
Yeturu et al.,[17] India	85/ 40 men/ 45 women Aloe vera group (21.53 ± 3.41); CHX group (21.72 ± 4.67) and ClO_2 group (21.70 ± 3.01).	Aloe vera, **ClO_2** and **CHX**.	**CHX** - ur	**ClO_2** - ur	10/60	15	To evaluate the effect of mouthwashes containing Aloe vera, ClO_2 and CHX on biofilm and gingivitis during orthodontic treatment.	Dental biofilm - Dental biofilm index of Silness and Loe and gingival index. Average percentage reduction in the dental biofilm index: Aloe vera (20.38%), CHX (31.59%) and ClO_2 (30.29%), with P = 0.03. Average percentage reduction in the gingival index: Aloe vera (9.88%), CHX (16.30%) and ClO_2 (12.22%), with P = 0.04.	Aloe vera and ClO_2 showed reductions in dental and gingival biofilm rates that were almost the same as that of CHX over a period of 15 days. Therefore, ClO_2 and Aloe vera may be suitable and economical alternatives to CHX.

Continue...

Table 2. Continuation.

Author, country	Number of individuals/ sex/mean age	Mouthwash	Concentration		Quantity (ml)/ duration of exposure (s)	Duration of study (days)	What was studied	Microorganism - Microbiological count	Conclusion
Eunike et al.,[16] Indonesia	16/ ur/ 6-11 years (age variation)	Mouthwash containing ClO_2 **(0.1%)** and mouthwash containing **CHX (0.1%).**	**CHX -** 0.10%	**ClO_2 -** 0.10%	10/30	7	To evaluate the antibacterial effects of mouthwashes on the bacterial viability of *Actinomyces sp.* as a black spot agent.	*Actinomyces sp.* - Feasibility test with MTT test and culturing of black spot samples by means of visual inspection and Gram staining. Average viability (from optical density) of Actinomyces before/ after using rinses (P-value) was: CHX: 0.67/0.54 (P = 0.01) and ClO_2: 0.73/0.40 (P = 0.001).	Mouthwash containing 0.1% ClO_2 had greater antibacterial effect against *Actinomyces sp.* than rinse containing 0.1% CHX.

CHX = chlorhexidine; ClO_2 = chlorine dioxide; PHMB = polyhexanide; ur = unreported.

of outcome assessment),[8,11-13,15,17] given that it was not addressed whether blinding had been applied in order to obtain the results. The other domains of all studies were classified as having low risk of bias. No study was classified as having a high risk of bias in any domain (**Figure 2**). Therefore, overall, the studies included in this systematic review showed good methodological quality (**Figure 3**).

DISCUSSION

Finding a mouthwash that is as effective as CHX and which has fewer adverse effects has been a challenge for researchers. In this systematic review, it was seen that in a study that compared PHMB with CHX, the residual antimicrobial action (substantivity) of PHMB[12,13] and its antimicrobial activity were equal to those of CHX. These results make PHMB a viable alternative to CHX[12,13] for clinical practice, considering that substantivity is a characteristic that ensures that the product continues to act after its application. All the studies included in this review that compared PHMB with CHX stated the CHX showed substantivity of 12 hours.[11-13] Previous studies demonstrated that CHX showed substantivity for varying times,[21-25], *viz.* up to 7 hours in a 2010 *in vivo* study,[24] up to 24 hours in a 1974 study[22] and up to 12 weeks in a 2009 review.[23]

In biofilm collected from the mouths of individuals to compare ClO_2 with CHX, used twice a day for three days, it was found in one study[15] that there were significant reductions in the total biofilm index in both the test (ClO_2) and the control (CHX) groups, and that this reduction was observed in both groups in assessments on different surfaces, i.e. mucous membranes, teeth and upper and lower jaws. In another study,[8] it was demonstrated that after four days, there was no statistical difference in the degree of destruction of bacteria between the two rinses,[8] thus also showing that the antimicrobial action of ClO_2 was comparable to that of CHX. In an *in vitro* study[26] that was carried out to evaluate the action of ClO_2 on the dental canal compared with the action of CHX, it was demonstrated that ClO_2 was significantly more effective in reducing intracanal bacteria than CHX. In another randomized clinical study[27] comparing ClO_2 with sodium chloride to treat halitosis, ClO_2 reduced the amount of tongue coating and Gram-positive and Gram-negative bacteria in the saliva.[27] In dental black spots caused by *Actinomyces* sp., ClO_2 proved to be statistically more effective in reducing the bacterial viability of *Actinomyces* sp. than CHX, after seven days of use.[16] ClO_2 is believed to be an effective alternative for use among children, given that this solution is not carcinogenic or allergenic and does not cause any change in taste sensation. Moreover, there are studies that have suggested that it is less toxic to humans than CHX.[16,28] Therefore, although CHX is typically considered to be the gold standard, ClO_2 is also effective for biofilm control.

When rinses containing ClO_2 and CHX were applied to patients with orthodontic appliances, no statistical differences regarding reduction of the gingival index or total visible biofilm index were

observed.[17] Therefore, the effectiveness of these two solutions for controlling bacterial biofilms seems to be equal.

In a study that evaluated fungal biofilm,[14] a statistically significant reduction in the number of *C. albicans* hyphae (ClO_2, P = 0.03; and CHX, P > 0.01) was observed upon treatment with ClO_2 and CHX. Presence of *C. albicans* in hyphae in the oral mucosa indicated infection by this fungus.[29] The antifungal effects of these two solutions have already been proven.[30,31] In addition to reduction of hyphae, 60% of the patients treated with ClO_2 and 70% of the patients treated with CHX were found to have achieved a cure for inflammation,[14] which thus indicates the antifungal effects of ClO_2 compared with those of CHX.

Limitations

There were some limitations to this systematic review, given that in one study the concentrations of mouthwashes used in the experiment (CHX and ClO_2) were not reported[17] and in another the commercial name for the product (Fresh Chlor) was reported but the ClO_2 concentration was not reported.[8] In addition, no study addressed the expected adverse effects. Nor was it reported whether the results from each study were collected in a blinded manner. In this review, no meta-analysis could be performed, given the heterogeneity of purposes observed among the studies included. These conditions also make it difficult to generalize the conclusions, since the synthesis of the results was often based on a limited amount of evidence.

Recommendations

Because the results from the mouthwashes assessed in this systematic review were equal to or more significant than those from the gold standard CHX,[8,11-14,16,17] we recommend that future clinical and *in vitro* studies should be conducted; adverse effects should be considered at the time of evaluation in clinical studies;

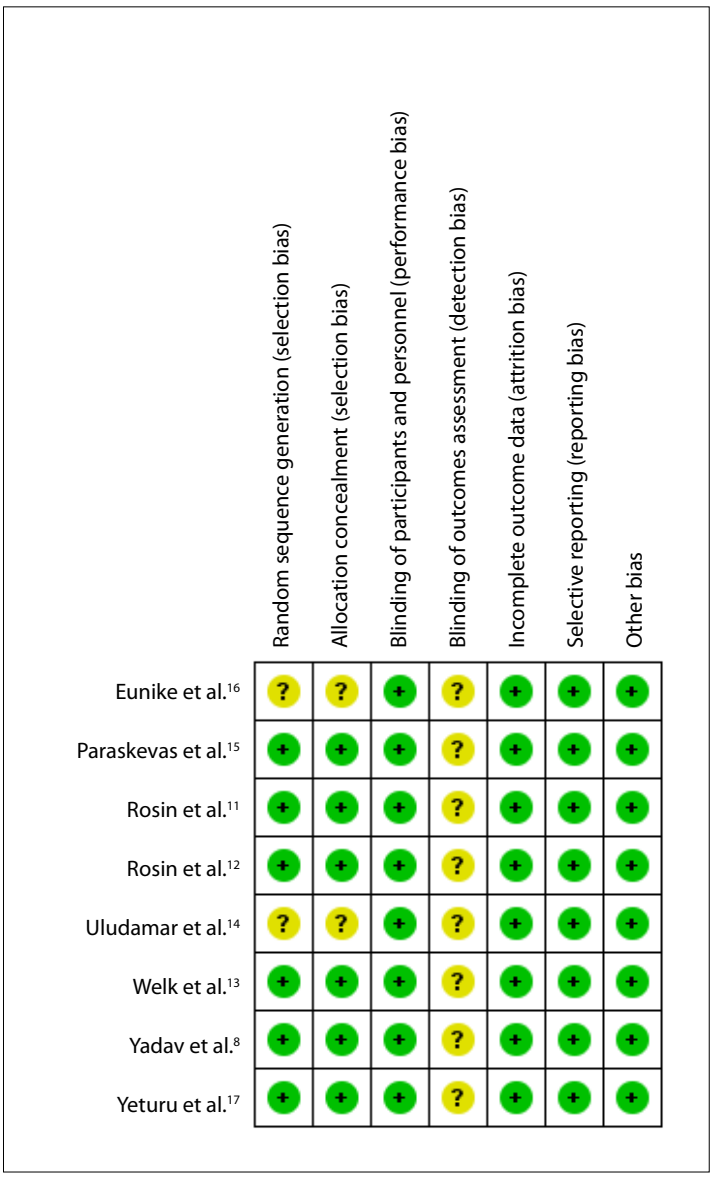

Figure 2. Assessment of the risk of bias in the included studies.

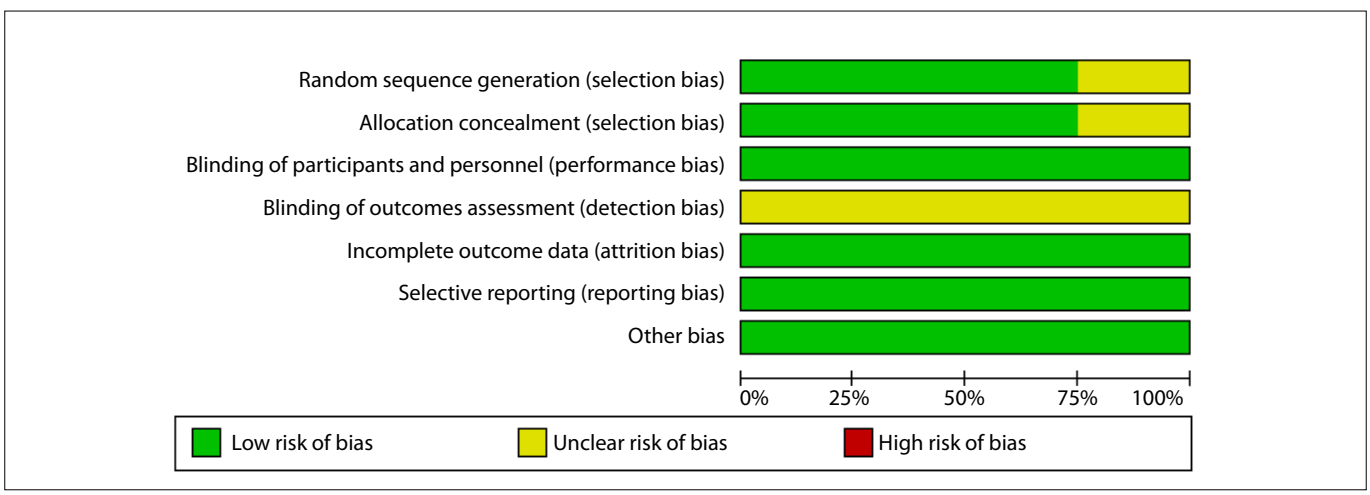

Figure 3. Percentages of risk of bias in studies included.

products should be specified; and blinding of results should be implemented and demonstrated.

CONCLUSIONS

Mouthwashes containing PHMB and ClO_2 are viable alternatives to CHX, since studies showed that the antimicrobial effects of PHMB were comparable with those of CHX and that the antimicrobial effects of ClO_2 were even greater than those of CHX. These alternative solutions have little or no reported side effects or adverse effects. No study compared both PHMB and ClO_2 with CHX.

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Authors' contributions: Santos DSF: conceptualization (lead), data curation (lead), investigation (lead), methodology (lead), project administration (lead), writing-original draft (lead) and writing-review and editing (lead); Peralta-Mamani M: data curation (supporting), formal analysis (supporting), methodology (supporting), software (equal) and writing-review and editing (supporting); Brandão FS: data curation (equal), formal analysis (equal), investigation (equal), resources (equal) and writing-review and editing (supporting); Andrade FB: formal analysis (supporting), methodology (supporting), supervision (supporting) and writing-review & editing (supporting); Cruvinel T: conceptualization (supporting), formal analysis (supporting), methodology (supporting), supervision (supporting) and writing-review and editing (supporting); and Santos PSS: conceptualization (supporting), data curation (supporting), formal analysis (supporting), methodology (supporting), project administration (lead), supervision (lead), validation (supporting) and writing-review and editing (supporting). All authors actively contributed to discussion of the results from the study, and reviewed and approved the final version to be released

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Address for correspondence:
Paulo Sérgio da Silva Santos
Departamento de Cirurgia, Estomatologia, Radiologia e Patologia, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP)
Al. Doutor Octávio Pinheiro Brisolla, 9-75
Bauru (SP) — Brasil
CEP 17012-901
Tel. (+55 14) 3226-6113
E-mail: paulosss@fob.usp.br

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Indications for accurate and appropriate use of personal protective equipment for healthcare professionals. A systematic review

Maria Stella Peccin[I], Márcio Luís Duarte[II], Aline Mizusaki Imoto[III], Mônica Taminato[IV], Humberto Saconato[V], Maria Eduarda Puga[VI], Eduardo Signorini Bicas Franco[VII], Erika Barbosa Camargo[VIII], Leila Bernarda Donato Gottems[IX], Álvaro Nagib Atallah[X]

Evidence-Based Health Department, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]PT, PhD. Associate Professor, Department of Human Movement Sciences, and Advisor, Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0329-4588

[II]MD, MSc. Musculoskeletal Radiologist, WEBIMAGEM Telerradiologia, São Paulo (SP), Brazil; and Doctoral Student in Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-7874-9332

[III]PT, PhD. Physiotherapist and Professor, Professional and Academic Master's Program, Laboratory for Evidence-Based Healthcare, Escola Superior de Ciências da Saúde, Hospital das Forças Armadas, Brasília (DF), Brazil.
https://orcid.org/0000-0001-8318-4658

[IV]PhD. Nurse and Associate Professor, Escola Paulista de Enfermagem, Universidade Federal de São Paulo, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-4075-2496

[V]MD, PhD. Adjunct Professor, Discipline of Emergency and Evidence-Based Medicine, Universidade Federal de São Paulo (UNIFESP), and Researcher, Cochrane Brazil, São Paulo (SP), Brazil.
https://orcid.org/0000-0002-0979-0286

[VI]MSc, PhD. Librarian, Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-8470-861X

[VII]PT, MSc. Doctoral Student in Evidence-Based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-2754-4369

[VIII]MD, PhD. Professor, Postgraduate Program on Public Health Policies, Escola de Governo em Saúde (EGS), Fundação Oswaldo Cruz (Fiocruz), Brasília (DF), Brazil.
https://orcid.org/0000-0003-1482-8282

[IX]PhD. Professor, Professional and Academic Master's Program, Laboratory for Evidence-Based Healthcare, Escola Superior em Ciências da Saúde (ESCS), Brasília (DF), Brazil.
http://orcid.org/0000-0002-2675-8085

[X]MD, PhD. Head of Evidence-Based Health Department, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0890-594X

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ABSTRACT

BACKGROUND: The speed of the spread of coronavirus disease 2019 (COVID-19) has put enormous pressure on hospitals and other healthcare facilities. This, together with blockages in several countries, has hindered the availability and accessibility of the necessary personal protective equipment (PPE).

OBJECTIVE: To identify, systematically evaluate and summarize the available scientific evidence on the efficacy, safety, safe use and reuse of PPE for healthcare professionals, for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DESIGN AND SETTING: Systematic review of studies analyzing products for disinfecting and enabling reuse of PPE for coronavirus within the evidence-based health program of a federal university in São Paulo (SP), Brazil.

METHODS: A systematic search of the relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL, SCOPUS, Web of Science and LILACS databases, for articles published up to November 30, 2020.

RESULTS: Ten studies were selected. These analyzed the use of N95, surgical and cotton masks, face shields, flexible enclosures with plastic covers or polycarbonate intubation boxes and plastic curtains; and also PPE disinfection using several substances.

CONCLUSION: Combined use of a face shield with a N95 mask proved to be superior to other associations for protecting healthcare workers. Some products are useful for disinfecting PPE, such as 70% ethanol, 0.1% sodium hypochlorite and a mixture of quaternary ammonium and H_2O_2, and hydrogen peroxide. Ultraviolet light and dry heat at 70 °C can be used to decontaminate N95 masks.

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INTRODUCTION

The pandemic caused by coronavirus disease 2019 (COVID-19) is severely affecting healthcare systems worldwide, including the care of several chronic diseases, such as cancer.[1-3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent that causes COVID-19, is a respiratory virus transmitted through droplets and by contact. It can be disseminated through aerosolization, swab collection, intubation, aspiration, noninvasive ventilation, high-flow nasal cannulas and bag-mask ventilation.[4,5] Prevention and control measures for the new coronavirus need to include hand hygiene, disinfection of surfaces (notably those frequently touched), avoidance of touching the face, respiratory manners (covering the mouth while coughing) and use of masks.[1,4,6]

The speed of the spread of COVID-19 has put enormous pressure on hospitals and other healthcare facilities.[7] This, together with blockages in several countries, has hindered availability and accessibility regarding the necessary personal protective equipment (PPE).[7] The Centers for Disease Control and Prevention (CDC) of the United States recommends the use of gloves, aprons, respiratory protection (e.g. disposable N95 respirators) and eye protection (e.g. goggles or face shields), without the use of shoe protectors (props).[8] According to a meta-analysis by Li et al.,[9] use of face masks decreased the risk of COVID-19 infection by 70%, for healthcare workers.

PPE in healthcare is generally considered to be part of what is called transmission-based precautions.[10] Standard precautions or universal precautions are based on the principle that all

blood, body fluids, secretions, excretions other than sweat, non-intact skin and mucous membranes can contain transmissible agents for infectious diseases.[10] Depending on the expected exposure, hand hygiene and the use of PPE, such as gloves, aprons, masks, caps or eye protection (i.e. goggles or face protection) should be implemented.[10] According to the World Health Organization, more than 59 million people work in the healthcare sector worldwide.[10] These healthcare professionals are at risk of developing life-threatening infectious diseases through contact with patients' blood or body fluids, such as mucus, vomit or exhaled drops.[10]

Sprays and splashes of fluids containing infectious microorganisms represent an occupational risk for healthcare professionals.[11] The droplets of these fluids can be inhaled, come into contact with damaged skin or be deposited on the mucous membranes of the mouth, nose or eyes.[11] Once in these structures, pathogens can infect workers and cause disease.[11] It should be considered that small aerosol droplets from a patient with a cough can remain in the air and spread throughout a room, and can easily be inhaled by a healthcare professional.[11,12]

The risk of infection and its consequences are variable but are well recognized as an occupational risk.[10] However, in epidemics, the risk of infection is higher because of the higher infection rate among healthcare professionals than among the general population.[5,10] The variable clinical spectrum of COVID-19 needs to be considered: given that the majority of cases are asymptomatic or oligosymptomatic,[2] infection can be passed from an asymptomatic healthcare professional to a patient with any other disease, or it can even be passed among the patients themselves.[10] Furthermore, if healthcare professionals become infected, this decreases the capacity of the healthcare system to provide care, particularly at times of epidemic, when it is overburdened.[10]

This situation was previously experienced in 2002 and 2003, during the epidemic of the severe acute respiratory syndrome (SARS), in which 20% of all patients were healthcare professionals and about 10% lost their lives.[10,13,14] The scarcity of PPE and its ineffective implementation were the main reasons behind the high number of healthcare professionals who became infected at the beginning of the COVID-19 pandemic.[7] In March 2020, Remuzzi et al. reported that a fifth of healthcare professionals working in intensive care units (ICUs) were infected with COVID-19.[15] Giwa et al. estimated that at least 10% of healthcare professionals in Italy would become infected with COVID-19 despite their use of PPE.[16] In a case series analyzed by Wang et al., out of 138 consecutive patients who were hospitalized due to COVID-19 in Wuhan, China, during January 2020, 30% were healthcare professionals.[17]

In January 2020, the CDC released guidelines on the decontamination process for reusing N95 masks.[18] A variety of procedures can be followed for reusing these masks, but none of the known methods completely remove the associated risks.[18] The existing systematic reviews refer only to use of masks in relation to the COVID-19 pandemic.[14] Concerning other types of PPE, such as gloves, glasses and face shields, the existing systematic reviews are not specific to COVID-19, and have included reference to several agents that cause respiratory infections.[6] Furthermore, we did not find any systematic reviews on the use of PPE such as gloves, glasses and face shields, for protection against COVID-19.

OBJECTIVES

The objective of the present study was to identify, systematically evaluate and summarize the available scientific evidence regarding the efficacy, safety, duration of use and reuse of personal protective equipment (masks, face shields and glasses) for healthcare professionals, for protection against infection by SARS-CoV-2.

METHODS

Study model

This study was a rapid systematic review. The research protocol was registered on the OPENSCIENCE Framework.

Inclusion criteria

The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Concerning the type of studies, given that only a limited number of studies have been published so far, the purpose of this review was to map the knowledge of the subject and identify the designs of these studies according to their level of evidence. There was no restriction on the origin, language or publication status of the study.

Phenomena of interest

Use of PPE (masks, face shields and goggles) for prevention of COVID-19 transmission among healthcare professionals and disinfection of PPE constituted the phenomena of interest.

Types of participants

Except for laboratory studies, the types of participants considered for this systematic review were healthcare professionals in a hospital environment or outpatient setting.

Types of intervention

Studies that evaluated the effectiveness and efficacy of several types of PPE, such as different types of masks, duration of use, use of goggles and face shield protectors, separately or in combination, and other techniques that helped to prevent contamination by COVID-19 among healthcare professionals, were assessed.

Types of outcome

Primary outcomes

The primary outcomes were interventions and disinfecting materials that were effective for preventing COVID-19 contamination.

Secondary outcomes

The secondary outcomes considered were the following:

- PPE durability
- User satisfaction
- Cost

The secondary outcomes were not considered as inclusion criteria for the studies.

Search methods for selecting studies

The search strategy was elaborated starting from the following research question: "What is the degree of effectiveness and safety of personal protective equipment (masks, face shields and glasses) for the protection of healthcare professionals against infection by SARS-CoV-2, and how can this equipment be safely used and reused?"

The searches were elaborated using Health Science Descriptors and were translated into each of the databases selected: Cochrane Library (Wiley); Embase (Elsevier); BVS Portal; Medical Literature Analysis and Retrieval System Online (MEDLINE, PubMed); CINAHL; Web of Science; Scopus; and Opengrey (https://opengrey.eu). The following descriptors were used: severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields] AND "Respiratory Protective Devices"[MeSH Terms] or "Masks"[MeSH Terms] AND "Face Shield"[MeSH Terms]

A manual search was also conducted in the reference lists of the primary and secondary studies identified in the electronic search. The search strategies developed and used for each electronic database were performed on November 30, 2020, and are presented in **Table 1**. There were no restrictions on languages or forms of publication.

Selection of studies and data extraction

Identification of eligible studies followed a two-stage process accomplished by two independent reviewers. Any disagreement was resolved by a third reviewer. In the first stage, after exclusion of duplications, the titles and abstracts of the references identified through the search strategy were evaluated, and the potentially eligible studies were preselected. In the second stage, a full-text evaluation on the studies preselected was carried out to confirm their eligibility. The selection process was performed through the Rayyan platform (https://rayyan.qcri.org).[19] The details of the ten studies that in the end were selected for evaluation are shown in **Table 2**.[7,8,20-27]

Evaluation of methodological quality

The critical appraisal tool of the Joanna Briggs Institute was applied to all eligible studies in order to evaluate the methodological quality of the studies.

RESULTS

Studies selected

The systematic review yielded 513 papers and a further three papers were identified through manual searches. After removing duplicates, we obtained 389 articles. After the titles and abstracts had been read by two independent evaluators through the Rayyan online platform, 13 articles were included for reading the full text. After the full texts had been read, another three studies were excluded. The PRISMA flowchart is shown in **Figure 1**. Thus, ten studies were included for analysis. Since these studies refer to COVID-19, all of them were from the year 2020: two were published in June, two in July and one in each of the following months: March, August, September, October, November and December.

Characteristics of studies included

The ten studies included all related to COVID-19 and were from the year 2020. Two of them were published in June, two in July and one in each of the following months: March, August, September, October, November and December. One article was produced in Brazil, three in the United States, one in France, one in China, three in India and one in Singapore.

Six studies were cross-sectional (Ong, Chaturvedi, Noguera, Sapoval, Fischer and Chow),[7,8,20-23] three studies had laboratory designs (Arumuru, Armijo and Saini)[24-26] and one study (Smith) was carried out on a simulation mannequin in an intensive care setting.[27]

Ong et al.[8] sampled the PPE used by healthcare professionals who cared for patients with COVID-19. Chaturvedi et al.[7] surveyed the opinions of 227 orthopedic surgeons and emergency medicine professionals who made use of 3D printed face shields. Noguera et al.[20] tested chemical disinfectants and autoclaving on 3D printed face shields, and also investigated the comfort, viability and visual integrity of the shields through a questionnaire that was applied to the healthcare professionals who were using them.

Sapoval et al.[21] conducted a study among 38 interventionist radiologists to assess the visual comfort of 3D printed face shields and these professionals' tolerance of them and ability to perform interventions normally while using them. Fischer et al.[22] analyzed decontamination of N95 masks and the possibility of their reuse. Chow et al.[23] used plastic curtains draped across the patients during tracheostomy and head and neck surgery, with the aim of minimizing the contamination of healthcare professionals from droplets

Table 1. Search strategy according to the corresponding database

Database	Search Strategy
Cochrane Library	#1 (COVID 19) OR (COVID-19) OR (2019 nCoV) OR (nCoV) OR (Covid19) OR (SARS CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID 19)) OR (2019 novel coronavirus disease) OR (COVID 19 pandemic) OR (COVID 19 virus infection) OR (coronavirus disease 19) OR (2019 novel coronavirus infection) OR (2019 nCoV infection) OR (coronavirus disease 2019) OR (2019 nCoV disease) OR (COVID 19 virus disease) #2 (Respiratory Protective Devices) OR (Device, Respiratory Protective) OR (Devices, Respiratory Protective) OR (Protective Device, Respiratory) OR (Protective Devices, Respiratory) OR (Respiratory Protective Device) OR (Respirators, Industrial) OR (Industrial Respirators) OR (Industrial Respirator) or (Respirator, Industrial) OR (Gas Masks) OR (Gas Mask) OR (Mask, Gas) OR (Masks, Gas) OR (Respirators, Air-Purifying) OR (Air-Purifying Respirator) OR (Air-Purifying Respirators) OR (Respirator, Air-Purifying) OR (Respirators, Air Purifying) OR Mask* #3 Face Shield* #4 #1 AND #2 AND #3
PubMed	#1 "COVID-19" [Supplementary Concept] OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (COVID-19 virus infection) #2 "Respiratory Protective Devices"[Mesh] OR (Device, Respiratory Protective) OR (Devices, Respiratory Protective) OR (Protective Device, Respiratory) OR (Protective Devices, Respiratory) OR (Respiratory Protective Device) OR (Respirators, Industrial) OR (Industrial Respirators) OR (Industrial Respirator) OR (Respirator, Industrial) OR (Gas Masks) OR (Gas Mask) OR (Mask, Gas) OR (Masks, Gas) OR (Respirators, Air-Purifying) OR (Air-Purifying Respirator) OR (Air-Purifying Respirators) OR (Respirator, Air-Purifying) OR (Respirators, Air Purifying) OR "Masks"[Mesh] OR (Mask*) #3 Face Shield* #4 #1 AND #2 AND #3
EMBASE	#1 'covid 19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) #2 'gas mask'/exp OR Gasmask OR (respiratory protective devices) OR 'mask'/exp OR mask* #3 Face Shield* #4 #1 AND #2 AND #3
LILACS	#1 MH:"Infecções por Coronavirus" OR (Infecções por Coronavirus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Doença pelo Novo Coronavírus (2019-nCoV)) OR (Doença por Coronavírus 2019-nCoV) OR (Doença por Novo Coronavírus (2019-nCoV)) OR (Epidemia de Pneumonia por Coronavirus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Coronavírus em Wuhan) OR (Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Novo Coronavírus de 2019-2020) OR (Epidemia pelo Coronavírus de Wuhan) OR (Epidemia pelo Coronavírus em Wuhan) OR (Epidemia pelo Novo Coronavírus (2019-nCoV)) OR (Epidemia pelo Novo Coronavírus 2019) OR (Epidemia por 2019-nCoV) OR (Epidemia por Coronavírus de Wuhan) OR (Epidemia por Coronavírus em Wuhan) OR (Epidemia por Novo Coronavírus (2019-nCoV)) OR (Epidemia por Novo Coronavírus 2019) OR (Febre de Pneumonia por Coronavírus de Wuhan) OR (Infecção pelo Coronavírus 2019-nCoV) OR (Infecção pelo Coronavírus de Wuhan) OR (Infecção por Coronavirus 2019-nCoV) OR (Infecção por Coronavírus 2019-nCoV) OR (Infecção por Coronavírus de Wuhan) OR (Infecções por Coronavírus) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia no Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavírus de 2019-2020) OR (Surto de Coronavírus de Wuhan) OR (Surto de Pneumonia da China 2019-2020) OR (Surto de Pneumonia na China 2019-2020) OR (Surto pelo Coronavírus 2019-nCoV) OR (Surto pelo Coronavírus de Wuhan) OR (Surto pelo Coronavírus de Wuhan de 2019-2020) OR (Surto pelo Novo Coronavírus (2019-nCoV)) OR (Surto pelo Novo Coronavírus 2019) OR (Surto por 2019-nCoV) OR (Surto por Coronavírus 2019-nCoV) OR (Surto por Coronavírus de Wuhan) OR (Surto por Coronavírus de Wuhan de 2019-2020) OR (Surto por Novo Coronavírus (2019-nCoV)) OR (Surto por Novo Coronavírus 2019) OR (Síndrome Respiratória do Oriente Médio) OR (Síndrome Respiratória do Oriente Médio (MERS)) OR (Síndrome Respiratória do Oriente Médio (MERS-CoV)) OR (Síndrome Respiratória do Oriente Médio por Coronavírus) OR MH:C01.925.782.600.550.200$ #2 (Respiratory Protective Devices) OR (Device, Respiratory Protective) OR (Devices, Respiratory Protective) OR (Protective Device, Respiratory) OR (Protective Devices, Respiratory) OR (Respiratory Protective Device) OR (Respirators, Industrial) OR (Industrial Respirators) OR (Industrial Respirator) or (Respirator, Industrial) OR (Gas Masks) OR (Gas Mask) OR (Mask, Gas) OR (Masks, Gas) OR (Respirators, Air-Purifying) OR (Air-Purifying Respirator) OR (Air-Purifying Respirators) OR (Respirator, Air-Purifying) OR (Respirators, Air Purifying) OR Mask* OR (MASCARAS) #3 Face Shield$ #4 #1 AND #2 AND #3

Continue...

Table 1. Continuation

Database	Search Strategy
SCOPUS	#1 (COVID 19) OR (2019 nCoV) OR (nCoV) OR (Covid19) OR (SARS CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) #2 (Respiratory Protective Devices) OR (Device Respiratory Protective) OR (Devices Respiratory Protective) OR (Protective Device* Respiratory) OR MASK* #3 Face Shield* #4 #1 AND #2 AND #3
Web of Science	#1 (COVID-19) OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (COVID-19 virus infection) #2 (Respiratory Protective Devices) OR (Device, Respiratory Protective) OR (Devices, Respiratory Protective) OR (Protective Device, Respiratory) OR (Protective Devices, Respiratory) OR (Respiratory Protective Device) OR (Respirators, Industrial) OR (Industrial Respirators) OR (Industrial Respirator) or (Respirator, Industrial) OR (Gas Masks) OR (Gas Mask) OR (Mask, Gas) OR (Masks, Gas) OR (Respirators, Air-Purifying) OR (Air-Purifying Respirator) OR (Air-Purifying Respirators) OR (Respirator, Air-Purifying) OR (Respirators, Air Purifying) OR Mask* #3 Face Shield* #4 #1 AND #2 AND #3
CINAHL	#1 (COVID-19) OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (COVID-19 virus infection) #2 (Respiratory Protective Devices) OR (Device, Respiratory Protective) OR (Devices, Respiratory Protective) OR (Protective Device, Respiratory) OR (Protective Devices, Respiratory) OR (Respiratory Protective Device) OR (Respirators, Industrial) OR (Industrial Respirators) OR (Industrial Respirator) or (Respirator, Industrial) OR (Gas Masks) OR (Gas Mask) OR (Mask, Gas) OR (Masks, Gas) OR (Respirators, Air-Purifying) OR (Air-Purifying Respirator) OR (Air-Purifying Respirators) OR (Respirator, Air-Purifying) OR (Respirators, Air Purifying) OR Mask* #3 Face Shield* #4 #1 AND #2 AND #3

and aerosols emanating from the patients, during the procedures. These authors analyzed the plastic sheets of the curtain and the face shields of the professionals to identify contamination.

Arumuru et al.[24] used a standard laboratory mannequin that simulated sneezing, in order to assess the effectiveness of masks for blocking the particles ejected during sneezing. Armijo et al.[25] analyzed protocols for decontaminating 112 face shields, in a laboratory. Saini et al.[26] evaluated the disinfection process for personal protective clothing, N95 masks and face shields, in a laboratory.

Smith et al.[27] conducted a simulation study in an ICU, among three healthcare professionals, to assess the risk of contamination of professionals and the use of PPE with three different protection strategies.

PPE analyzed

N95, surgical and cotton masks

Ong et al.[8] evaluated the front of the goggles and the front of the N95 masks of professionals who cared for 15 patients with COVID-19 in isolation rooms. These were each used during one day of activity and no contamination was found on these materials, thus confirming that prolonged use of N95 masks and goggles with adequate environmental and hand hygiene is a safe option. Arumuru et al.[24] evaluated the effectiveness of homemade cotton masks with three layers, N95 masks, standard three-layer surgical masks and face shields, using a sneeze simulator. They concluded that none of these measures effectively blocked the escape of particles ejected during sneezing. Protective measures effectively reduced leakage and shortened the sneeze range to between 30 and 90 cm. These authors stated that, without a mask, particles from a common sneeze can be projected for approximately 760 cm (25 ft) in almost 22 seconds. The N95 masks completely prevented the particles from leaking forwards, but leakage could still occur sideways and could move up to 60 cm backwards.

Face shields

Three studies on 3D-printed face shields and one study on N95 masks met our inclusion criteria for this investigation. Face shields produced through 3D printing were presented as an easy-to-implement economical alternative that would promote safety for users against infection by COVID-19 aerosols. One important point presented in these articles related to reducing the contamination and dirt of N95 masks, so as to favor longer-duration use and provide additional protection.

Chaturvedi et al.[7] evaluated 3D printed face shields in terms of cost-effectiveness, ergonomics, reuse and acceptance by orthopedic surgeons and emergency medical personnel. They reported that there was positive feedback regarding all variables.

Table 2. Analysis of the articles included in the study

Study and country	Study design	Sample	Material analyzed	Results and conclusion
Armijo et al.[25] United States	Laboratory.	The experiments were repeated five times on the face shield (headband, headpiece, facial shield) and organism (*Escherichia coli*, *Staphylococcus aureus*), thus making a total of 30 experiments, not including positive and negative controls.	In total, 112 face shields (the solid headband and the chin protector part of the face shield) were printed in 3D on the FDM platform because they were more accessible and easier to use for non-industrial applications. Diluted bleach solution was used for decontamination. *Escherichia coli* and *Staphylococcus aureus* were selected as Gram-negative and Gram-positive model organisms.	Face shields were useful and inexpensive. The efficacy of the decontamination protocol against *Escherichia coli* was greater than that of *Staphylococcus aureus*. *E. coli* was observed on facial protection, *Staphylococcus aureus* was detected on facial protection and on the chin. No organisms were recovered from the head bands. The decontamination protocol was highly effective against *Escherichia coli* and *Staphylococcus aureus*, achieving a reduction ≥ 4 log 10 (99.99%) in colony counts for each repeat. Face shields formed a barrier against soiling of N95 face masks and were more effective for eye protection from respiratory droplets than standard eye shields. Implementation of decontamination protocols successfully allowed face shield and N95 mask reuse, thus enabling a higher level of protection for anesthesiology providers at the onset of the COVID-19 pandemic.
Arumuru et al.[24] India	Laboratory, using a standard mannequin in a controlled environment.	Homemade cotton mask, surgical mask, N95 mask and a nostril of a mannequin.	Homemade masks, N95 masks and surgical masks, and a 30,000 Reynolds pulsed jet sneeze simulator. Trace particles were introduced into the stream to capture the emulated turbulent jet formed due to a sneeze. Compressed air and a solenoid valve were also used. A laser camera and lighting were set up.	A homemade three-layer mask was suitable for preventing penetration of fine-sized particles, but in a sneeze, these can travel up to 45.7 cm. With a surgical mask, the sneeze particles can travel up to approximately 76.2 cm and with a surgical mask plus a face shield the spread of the particles become greater, by traveling 12.2 cm. An N95 mask blocks sneezing in the forward direction; however, leakage from the sides and top spreads the sneeze backwards over a distance of up to approximately 60.9 cm. None of the measures adopted, such as homemade two- and three-layer masks, standard three-layer surgical masks and face shields effectively blocked the escape of particles ejected during sneezing. Protective measures effectively reduced leakage and diminished the sneeze range to between 30 and 90 cm.
Chaturvedi et al.[7] India	Cross-sectional study analyzing the characteristics of 3D printed face shields.	227 healthcare professionals.	Face shield produced by 3D printer.	Orthopedic surgeons reported that the face shield was useful during screening tasks, in which the interactions with patients involved wound care, immobilization and application of traction. In the wards and in the ICU, all groups of healthcare professionals found that face shields with soft PVC film were effective during airway management and other aerosol-generating procedures, as they could insert the PVC film visor into the PPE gown to provide complete closure of the facial region, although with an opening at the top for ventilation. Development of face shields with participation by healthcare professionals increased their acceptability and effectiveness. Use of face shields was effective in screening and treatment situations, with the ability to vary the configuration of the device. Cost-efficacy, ergonomics, reuse and acceptance were evaluated among orthopedic surgeons and emergency medicine personnel and positive feedback was obtained in relation to all variables considered.
Chow et al.[23] China	Cross-sectional study in a real environment.	Five patients without clinical evidence of COVID-19 underwent tracheostomy. Two horizontal anesthetic screens and a transparent sterile plastic sheet (plastic curtain) over a tracheostomy operative field were used.	Presence or absence of droplet contamination on the five plastic sheets used (plastic curtain) during the procedures and on the surgeon's face shield and instrumentation.	All five sheets were contaminated with droplets of 0.2 to 2.8 mm. Droplet contamination was most severe on the central surface at 91.5% (range: 86.7%-100.0%) followed by the left and right-side surfaces at 5.2% (6.7%-10.0%) and 3.3% (6.7%-10.0%), respectively. No droplet contamination was observed on the face shield. The droplet contamination count was greater in the upper central half of the plastic sheet that covered the surgical site in the lower part of the neck. Use of two horizontal anesthetic screens and a sterile plastic sheet over a tracheostomy operative field can effectively prevent droplet contamination, thus eliminating the need for a face shield with adequate eye protection and respirator. No droplet contamination was observed on the surgeon's face shield or on the instruments, thus showing that the plastic sheets (plastic curtain) were effective in preventing droplet and aerosol spillage.

Contine...

Table 2. Continuation

Study and country	Study design	Sample	Material analyzed	Results and conclusion
Fischer et al.[22] United States	Research letter citing a cross-sectional laboratory study.	N95 mask.	Ultraviolet light (260-285 nm) Dry heat at 70 °C. 70% alcohol. VHP.	The decontamination method against SARS-CoV-2 on N95 masks considered the time needed to reduce the virus viability within 1000 minutes. With ethanol, 99.56% was eliminated; with dry heat (70 °C), 93.89%; with UV light (260-285 nm), 91.84%; and with vaporized VHP, 99.36%. All the substances analyzed decontaminated the N95 masks. Decontamination by means of vaporization with hydrogen peroxide or ultraviolet light allowed N95 masks to be reused three times, while doing this with dry heat at 70 °C allowed it twice. Decontamination with 70% alcohol reduced the integrity of N95 masks and was not recommended.
Noguera et al.[20] Brazil	Cross-sectional study with evaluation questionnaire applied to users of the face shields that were developed.	3D printing face shield: the total number evaluated was not reported.	**Face shield after chemical disinfection:** [70% ethanol, H_2O_2-quaternary ammonium salt mixture, 0.1% sodium hypochlorite or water (negative control)] with different thicknesses and materials were tested: 0.5 mm and 0 mm polyethylene glycol, 75 mm, 0.75 mm polycarbonate, 0.5 mm PET and 0.5 mm glycol modified PETG. **Headbands for face shield after chemical disinfection and autoclaving (121 °C for 15 minutes):** Different materials (Tritan HT, PLA EasyFill, ASA WP, ABS PT and PETG XT) and different layer thicknesses (0.15 mm, 0.30 mm, 0.60 mm) were used. **3D printing questionnaire:** Online about the comfort, visual integrity and viability of the 3D face shield.	3,343 hospitalized COVID-19 patients, 2,778 trained health workers and 30,000 face shields were used. **Face shield visual integrity after chemical disinfection** None of the materials of the face shields or the layer thickness were damaged after a maximum of 40 disinfections with 70% ethanol, a mixture of quaternary ammonium salts and 0.1% sodium hypochlorite. To reduce the potential damage from steam, it is recommended to wait 3-5 minutes after each disinfection, given that at one minute after disinfection with 70% alcohol, vapors can cause eye redness. **Headbands for face shield after chemical disinfection and autoclaving** After chemical disinfection 30 times, none of the headbands had changes to their visible physical structure, as occurred with the mask visors. After decontamination in an autoclave, the PETG XT and TRITAN HT supports were found to have suffered considerable damage. There were reductions in size and material conditioning, and some cracks appeared, through the effect of the temperature and pressure of the autoclave; which led to a reduction in resistance through triggering of microfiber buckling. **3D printing questionnaire about face shields** In the questionnaire, most answers were very good, with regard to mobility, visual integrity, mask removal and disinfection. All projects were considered adequate, with no major differences between them. The GRU and INSPER projects received higher marks from users.
Ong et al.[8] Singapore	Cross-sectional study using a standardized technique with pre-moistened sterile smears.	Eyeglass protection, N95 respirators and shoe surfaces of 30 healthcare professionals who cared for 15 patients.	Sampling study on PPE used for one day by healthcare professionals who were taking care of confirmed COVID-19 patients over the previous 48 hours. All patients were in isolation rooms for airborne infections with 12 air changes per hour.	All 90 samples from 30 healthcare professionals (doctors, nurses and cleaning professionals) were negative. The average time spent in the patient's room in general was 6 minutes (range: 5-10): 8 minutes for doctors, 7 minutes for nurses and 3 minutes for cleaning professionals. The activities ranged from casual contact (e.g. medication administration or cleaning) to closer contact (e.g. physical examination or collection of respiratory samples). Prolonged use of N95 masks and eyeglass protection with strict adherence to environmental and hand hygiene when handling patients with SARS-CoV-2 may be a safe option. These results may not be generalizable to other room configurations.

Contine...

Table 2. Continuation

Study and country	Study design	Sample	Material analyzed	Results and conclusion
Saini et al.[26] India	Laboratory.	Personal protective clothing, N95 masks and face shields obtained in a biosafety level 3 laboratory and in a hospital.	**Biological indicators and culturing conditions** Biological indicator strips with *B. stearothermophilus* were used as the gold standard to confirm the integrity of the sterilization process. Recombinant laboratory strains of *E. coli* and *M. smegmatis* were incorporated into the study to assess their suitability as a biological indicator for disinfecting personal protective equipment. **Heat and alcohol treatment** 70 °C and 80 °C for 5 and 10 minutes each, 75% and 85% ethanol for 0.5 and 1 min each and propan-2-ol (75% and 85% for 0.5 and 1 minute each. **Disinfection using VHP** Run time of around 10 minutes with 200 ml hydrogen peroxide solution for a 1000 cubic foot room.	**Biological indicators for disinfection of PPE for SARS-CoV-2** *E. coli* was used as an indicator: it completely lost its viability at 70 °C and 85 °C. *Mycobacterium smegmatis* was more resistant to heat. *Escherichia coli* exhibited a low level of ethanol resistance, while *Mycobacterium smegmatis* was not viable. Use of propan-2-ol allowed viability of *Escherichia coli* and *Mycobacterium smegmatis*. Gold-standard *Bacillus stearothermophilus* spores exposed to aggressive treatments (heat 90 °C/30 minutes or alcohol 85%/1 minute) showed rebirth and growth. Only the *Bacillus stearothermophilus* standard remained viable under all conditions known to inactivate the SARS-CoV-2 virus, thus indicating its versatility as an ideal substitute or biological indicator for developing disinfection protocols for COVID-19. **Disinfection using vaporized hydrogen peroxide (VHP)** *Escherichia coli* was sterilized and there was a reduction greater than 7 $\log_{10}$ in *Mycobacterium smegmatis*. *Bacillus stearothermophilus* spores did not revive with VHP. A single VHP cycle (7%-8% hydrogen peroxide) was able to disinfect PPE in less than 10 min. Repetition of the procedure did not result in any physical break, deformity or other considerable change to the overalls and N95 masks.
Sapoval et al.[21] France	Cross-sectional study.	38 radiologists (21 attending physicians, 6 fellows and 11 residents) in 31 consecutive interventions, such as central venous access, percutaneous peripheral angioplasty, percutaneous urinary intervention, arterial embolization due to acute bleeding, radiofrequency ablation of lung tumor, transjugular liver biopsy and sampling of the adrenal vein.	Face shields consisting of a standard transparent polymerizable vinyl chloride sheet were built on a 3D printer. The 3D printed face shields were evaluated in 31 interventional procedures. The average duration of the interventions was 59 ± 58 (SD) minutes (range: 15-240 minutes). Each face shield was used 2 ± 1.7 (SD) times (range: 1-8 times).	In total, the average duration of the interventions was 59 ± 58 (SD) minutes (range 15-240 minutes); each face shield was used 2 ± 0.8 (SD) times (range 1-8 times). The average rating for the ability to perform the intervention assigned as usual was 1.7 ± 0.8 (SD) (range: 1- 4). The average visual tolerance rating was 1.6 ± 0.7 (SD) (range: 1-4). The average tolerability rating was 1.4 ± 0.7 (SD) (range: 1-3). Visual tolerance was satisfactory and no discomfort was observed, even during lengthy interventions. The study showed that 3D printed face shields were well accepted in several interventions in interventional radiology.

Contine...

Table 2. Continuation

Study and country	Study design	Sample	Material analyzed	Results and conclusion
Smith et al.[27] United States	Simulation study in an ICU environment.	A simulated patient in an ICU, with infection due to severe acute respiratory syndrome coronavirus-2 that involved endotracheal intubation, was used. A laryngoscopist, a nurse and a respiratory therapist assisted in laryngoscopy. Three different methods of intubation were used. Fluorescent marker was sprayed by means of an atomizer during the procedure. The three techniques included only PPE, a polycarbonate intubation box or a flexible coronavirus enclosure. Black light was used to evaluate the laryngoscopist and the respiratory therapist.	Contamination of the professional and personal protective equipment (gloves, apron, shoes and face shield) The PPE consisted of two masks (an N95 that was covered with a conventional surgical mask to protect the N95), a face shield, a cap, a long-sleeved waterproof plastic apron and gloves.	One person can install the coronavirus flexible casing in about two minutes. The intubation box can be unfolded in about two minutes, but it needs two people to position it properly. Use of PPE alone seriously contaminated the laryngoscopist and respiratory therapist. With the use of the intubation box, contamination of the laryngoscopist occurred only on the gloves, while the apron and face shield were not contaminated. The respiratory therapist showed great contamination on the gloves, the apron and the neck and face shield. The laryngoscopist reported that the arm holes restricted movement a little, without compromising intubation. With the coronavirus flexible closure system, the laryngoscopists and respiratory therapists were more protected. Only the gloves of both were contaminated. With all the three types, neither the nurse nor the surroundings were contaminated. The coronavirus flexible enclosure contained the fluorescent marker more effectively during endotracheal intubation than did personal protective equipment alone or the intubation box, based on the exposure of the laryngoscopist and respiratory support therapist.

ICU = intensive care unit; FDM = fused deposition modeling; VHP = vaporized hydrogen peroxide; PET = polyethylene terephthalate; PETG = polyethylene terephthalate glycol; SD = standard deviation; PPE = personal protective equipment; PVC = polyvinyl chloride; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UV = ultraviolet; HPV = human papillomavirus.

On the other hand, Noguera et al.[20] evaluated low-cost 3D-printed face shields for use by healthcare professionals during their shifts for treating patients with COVID-19. The disinfection protocols used on these shields were tested, and the comfort, visual integrity and viability of the protectors were evaluated by these professionals. These shields were found to be well accepted by the professionals. Chemical disinfection with 70% ethanol, 0.1% sodium hypochlorite and a mixture of quaternary ammonium and H_2O_2 was effective and did not cause changes to the materials of the face shields. Nonetheless, autoclaving has been shown to cause physical changes to face shields and should not be used.

The study carried out among interventional radiologists by Sapoval et al.[21] aimed to clinically evaluate face shields printed on a 3D printer with regard to protection against droplets from SARS-CoV-2, through 31 interventional procedures. Satisfactory results regarding visual comfort and tolerance were obtained.

Armijo et al.[25] aimed to meet the demands of anesthesiologists regarding the safety of masks to protect against COVID-19 infection. They also sought to minimize the contamination and dirt of N95 masks, so as to favor their reuse through an ultraviolet radiation sterilization protocol. Face shields were found to be useful, with low cost, and the decontamination protocol was highly effective against *Escherichia coli* and *Staphylococcus aureus* in the tests performed.

Protective goggles

No specific studies on goggles that met the inclusion criteria were identified.

Flexible enclosure with plastic cover or polycarbonate intubation box

A flexible enclosure with a plastic cover or polycarbonate intubation box was used in a study by Smith et al.,[27] with testing during an endotracheal intubation procedure in an intensive care unit. A simulated patient with COVID-19 was attended by a laryngoscopist, a respiratory therapist who assisted in the intubation and a nurse. Both the PPE used (gloves, apron, shoes and face shields) and the healthcare professionals themselves were evaluated for contamination, by means of fluorescent markers that

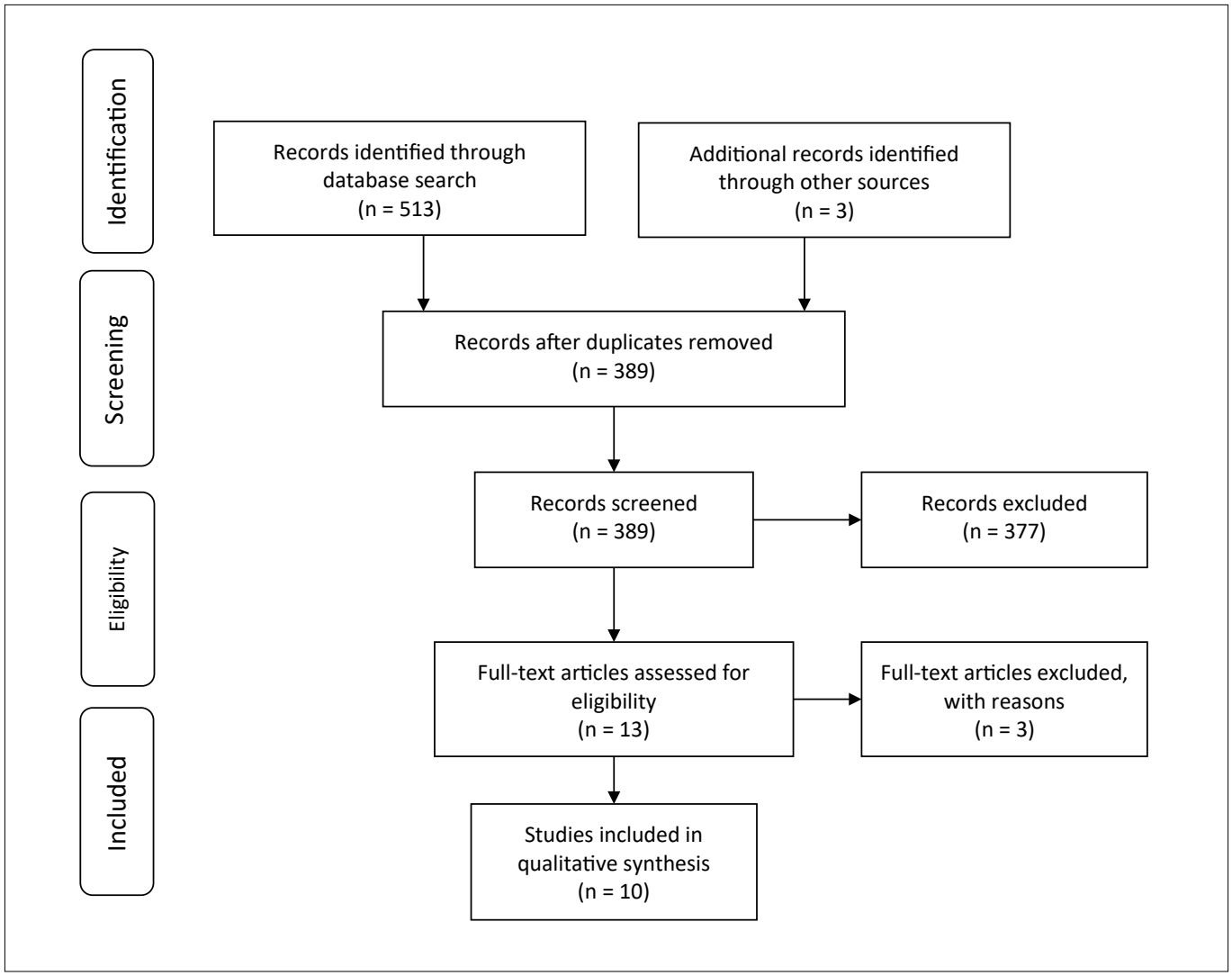

Figure 1. PRISMA flow diagram for study selection.

were sprayed out by an atomizer throughout the procedure. The flexible enclosure for coronavirus was found to contain the fluorescent marker more effectively during endotracheal intubation than PPE alone or the intubation box, based on the exposure of the laryngoscopist and respiratory support therapist.

Plastic curtains

Plastic curtains were tested in a study by Chow et al.[23] during five surgical procedures that involved tracheostomy and head and neck surgery. Droplet contamination was observed on all the plastic sheets that made up the curtain, such that this contamination was highest on the central surface, then on the left-side surface and then on the right. No contamination was seen on the face shields. Thus, this device can minimize transmission of the virus to healthcare professionals.

PPE disinfection and cleaning

Noguera et al.[20] aimed to evaluate the use of 3D printed face shields for comfort, durability, visual integrity and viability, and ways of disinfecting them. They observed that simple forms of disinfection, used conventionally, were safe and effective, except for autoclaving, which could cause significant damage to some materials used in making face shields.

Armijo et al.[25] aimed to provide additional protection for healthcare professionals, at low cost, that would reduce the potential contamination of N95 masks, thereby favoring longer duration of use with easy decontamination. They concluded that the use of N95 with face shields was useful and that the protocol for decontamination with a diluted bleach solution allowed penetration into any of the pores generated in the 3D printing process of the face shield, such that the decontamination process was highly effective.

Saini et al.[26] aimed to evaluate biological indicators as positive sterilization controls and to develop a method using vaporized hydrogen peroxide. They demonstrated that there was no impairment of the materials and no alteration of comfort perceived by the user.

Fischer et al.[22] aimed to compare methods for decontamination of N95 masks using ultraviolet light (260-285 nm), dry heat at 70 °C, 70% alcohol and vaporization with hydrogen peroxide. Vaporization with hydrogen peroxide showed the best results concerning SARS-CoV-2 and preservation of the integrity of N95 masks. Ultraviolet light eliminated SARS-CoV-2 more slowly and preserved the function of the N95 mask almost as well as vaporization with hydrogen peroxide. Both of these techniques allowed N95 masks to be reused three times.[22] Dry heat at 70 °C eliminated the virus with a speed similar to ultraviolet light, and was likely to maintain acceptable adjustment values for one or two decontaminations.[22] Decontamination with 70% alcohol reduced the integrity of N95 masks and was not recommended.[22]

Satisfaction of healthcare professionals in relation to PPE

Chaturvedi et al.[7] aimed to analyze the effectiveness of face shields made in a 3D printer that were used by orthopedists and emergency medical professionals. These professionals considered them to be satisfactory for use.

Sapoval et al.[21] aimed to evaluate the risk factors for COVID-19 among interventional anesthesiologists who used 3D-printed face shields during routine procedures in hospitals. It was concluded that 3D-printed face shields were well-accepted by anesthesiologists and fulfilled the proposed objectives.

DISCUSSION

The main contribution of this review was to synthesize the best available evidence about the use, reuse and disinfection of PPE as a non-pharmacological intervention, used in association with other measures for preventing contamination by COVID-19, such as cough etiquette (a common cough can travel at least 1.5-3 meters)[24] and hand hygiene, for healthcare professionals.

The main point for management of COVID-19 infection is to prevent in-hospital infection among healthcare professionals.[28] Coronavirus can spread through aerosols, droplets and contact contamination.[7] A droplet of 10 μm in diameter may persist suspended in the air for about 50 seconds when sneezing.[24] Since the half-life of the virus is approximately 6-7 hours, it is unlikely that there will be a viable amount of virus in the mask for three full days.[29] van Doremalen et al.[29] analyzed the survival of SARS-CoV-2 with 40% humidity at temperatures of 70-73 °F (21-22 °C), and concluded that it could survive as follows:

- Up to 3 hours after aerosolization, with an average half-life of 1.1 to 1.2 hours.
- Up to 4 hours on copper, with an average half-life of 1.1 to 1.2 hours.
- Up to 24 hours on cardboard, with an average half-life of approximately 3.5 hours.
- Up to 2 days on stainless steel, with an average half-life of 5.6 hours.
- Up to 3 days on plastic, with an average half-life of 6.8 hours.

Face shields have been classified as a form of PPE that protects the facial area and related mucous membranes (ear, nose and mouth) from splashes of body fluids.[7,30] Among the four types of PPE for the facial region, namely, face shields, face shields with N95 respirator, surgical masks with eye protector and safety glasses with N95 respirator, face shields with N95 respirator are the most effective.[7] The association of a face shield with N95 respirator and a flexible enclosure with a plastic cover or polycarbonate intubation box, as demonstrated by Smith et al.,[27] along with the plastic curtain that was used in the study by Chow et al.,[27] may be of special importance for protection of healthcare professionals during procedures such as orotracheal intubation and procedures involving tracheostomy.

Use of face shields can substantially reduce healthcare professionals' short-term exposure to larger particles of infectious aerosols and can reduce the contamination of their respirators.[11,31,32] They are less effective against smaller particles, which can remain in the air for long periods and easily flow around a face mask, for inhalation.[11] Thus, face shields can provide a useful complement to respiratory protection for workers who care for patients with respiratory infections but cannot be used as a substitute for respiratory protection.[11,32] Although face shields are bulkier than goggles or safety glasses, they offer the advantage of protecting the entire face from contamination.[11,30] Some professionals may also feel more comfortable with face shields or may find that they fit better than glasses or respirators.[11,30]

During the pandemic, cheaper solutions have emerged that can be developed locally, such as face shields, masks, etc.[7] These solutions are being widely propagated in urban areas with large-scale 3D printing facilities.[7] In the situation of lockdowns to which many regions have been subjected, domestic production becomes crucial for obtaining the best functional results regarding production of PPE.[7] Production of face shields is simple: they consist of three parts, i.e. the frame, an elastic cord for attachment and a transparent plastic visor.[7,32] When produced using a 3D printer, the total cost of one face shield is approximately one dollar, which makes it an economical device, considering its reusability.[7,32]

Before disinfecting face shields, they need to be disassembled.[7] Polyvinyl chloride (PVC) film visors should be discarded after use and replaced for the next cycle of use.[7] The disinfection procedures to be followed are as per the recommendations of the CDC, using

standard disinfection solutions such as isopropyl alcohol or sodium hypochlorite, and subsequently performing proper hand hygiene.[7] It is advisable to discard the paper clips or band after one cycle of use. Nonetheless, in situations that require reuse, they can be disinfected using a hospital disinfectant solution that has been registered with the Environmental Protection Agency (EPA).[7]

This information is decisive when thinking about mask reuse and the cost of masks. In March 2020, the U.S. Department of Health and Human Services announced that its national inventory strategy, i.e. the emergency stock of medicines and medical supplies, contained approximately 42 million masks, totaling both surgical and N95 masks.[14,33] This is equivalent to 1% of the estimated amount needed by United States healthcare professionals in a pandemic scenario (42 million stored compared with the estimated 3.5 billion needed).[14,33] In addition, use of face shields reduces mask contamination, when they are used together, thus extending their useful life.[25]

Although face shields do not offer absolute protection against contamination, they significantly decrease the chances of contracting the coronavirus.[7] One of the main problems with face shields and PPE hoods is the fogging of the visor, which impairs users' abilities during procedures and surgeries.[7] Discomfort due to lack of adequate ventilation is also a considerable concern.[7]

Li et al. analyzed masks after disinfection with 75% alcohol or soap and water at 60 °C and noted that the structure of the medical masks was damaged after treatment with these substances.[31] Use of water and soap or alcohol significantly reduces the filtering efficiency of N95 masks (54% and 67%, respectively).[34] Treating these masks with gamma radiation is also not recommended.[34] Autoclaving is not indicated for disinfection of face shields printed on 3D printers since it can cause significant damage to some materials used in their manufacture.[20] Chemical disinfection with 70% ethanol, 0.1% sodium hypochlorite and a mixture of quaternary ammonium and H_2O_2 is indicated.[20] Decontamination with diluted bleach solution is also an option.[25] Moreover, diluted bleach solution is useful for disinfection from some bacteria, such as *Staphylococcus aureus*.[25]

SARS-CoV-2 has been found to be highly stable at 4 °C but sensitive to heat.[35] According to the inventor of the N95 mask material, Dr. Peter Tsai, this material can be heated for 60 minutes, steamed at 125 °C for five minutes or boiled for five minutes, and then air-dried.[34] Most viruses are killed in less than two minutes when the water temperature reaches 70 °C (158 °F).[34,36] The rubber band must not be immersed in boiling water.[34] Through these methods, 92.4% and 91.7%-98.5% of mask filtration efficiency is retained and the criteria required by the Food and Drug Administration (FDA) and the CDC are met.[34] Nevertheless, if these methods are performed for more than five minutes, the efficiency of the filtration will drop further.[34]

Use of hydrogen peroxide was helpful in disinfecting PPE without damaging its material.[22,26] Decontamination through vaporization with hydrogen peroxide showed the best results concerning the speed of inactivation of SARS-CoV-2 and preservation of the integrity of N95 masks.[22] In the sequence, ultraviolet light eliminated SARS-CoV-2 more slowly and preserved the function of the N95 masks almost as well as vaporization with hydrogen peroxide, thus allowing the masks to be reused up to three times.[22] Although dry heat at 70 °C eliminate the virus at a speed similar to that of ultraviolet light, it damages the masks and thus only allows reuse twice.[22] Seventy percent alcohol impairs the integrity of N95 masks, and decontamination with this substance is not indicated.[22,37]

The ideal would be to use an N95 mask for one day and only use it again on the fifth day, which would therefore require at least four masks.[34] All copies of SARS-CoV-2 on the mask will be dead within three days even if no decontamination is performed.[29,34]

Although quaternary ammonium or bleach can also be used to disinfect gloves,[10] there is no evidence that they have any action on COVID-19. It should also be noted that there is little evidence that using two gloves on each hand as part of full-body PPE can reduce the risk of contamination and reduce the viral load on the hands without constant change of the gloves.[10]

None of the articles identified showed the ideal length of time for using the masks, or how to safely store them for reuse. However, the need to follow the recommendations of the company responsible for the product and those of the hospital's infection control commission were indicated.[22]

Implications for practice

The implications for practice of this review are that combined use of a face shield with a N95 mask among healthcare professionals may increase these professionals' protection. This would enable them to have a lower rate of infection and would thus reduce the pressure on the healthcare system.

Emphasis should also be given to the possible disinfection of these materials with 70% ethanol, 0.1% sodium hypochlorite, bleaches and a mixture of quaternary ammonium with H_2O_2. Disinfection, with the possibility of reuse, reduces the demand for these PPE materials, which may reduce the cost to institutions.

Disinfection of N95 masks by means of vaporization using hydrogen peroxide or ultraviolet light made it possible to reuse these masks three times, while use of dry heat at 70 °C allowed reuse twice. Decontamination with 70% alcohol would reduce the filtration efficiency of N95 masks and is not recommended. The main findings from the systematic review are summarized in Table 2.

Research implications

There is a need to assess the durability of PPE and how to store it properly after use and disinfection. It is also necessary to evaluate

disposable gloves and aprons, in order to reduce the demand for these items, given the large number of exchanges necessary during the work periods of healthcare professionals and their increasing market price, which is increasing the costs of professionals, institutions and governments.

We identified that there is a need for randomized controlled studies and observational studies with adequate designs, in order to better identify the risk factors, effectiveness, safety and cost of preventive measures for healthcare professionals who are faced with the challenge of COVID-19.

CONCLUSION

The studies identified so far provide low levels of evidence but consistently demonstrate that N95 masks, surgical masks and face shields, both those industrially manufactured and those produced through lower-cost 3D printers, are meaningful devices that act as a barrier to droplets and enable protection for healthcare professionals against COVID-19 infection. However, additional care regarding the length of time of use, disinfection and reuse is needed, along with hand hygiene and care regarding placement and removal of these devices. Combined use of a face shield and a N95 mask proved to be superior to separate use of each device or associations between face shields and surgical or cloth masks.

Auxiliary devices, such as flexible enclosures for coronavirus and plastic curtains, may be an additional alternative for protecting professionals who are directly involved in procedures with a higher risk of contamination, such as orotracheal intubation and tracheostomy. Some products are useful for disinfecting PPE, such as 70% ethanol, 0.1% sodium hypochlorite and a mixture of quaternary ammonium and hydrogen peroxide. Ultraviolet light and dry heat at 70 °C can be used to decontaminate N95 masks, while it needs to be borne in mind that dry heat at 70 °C reduces the integrity of N95 masks more dramatically.

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editing (equal); Puga ME: investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Franco ESF: methodology (equal), validation (equal), visualization (equal) and writing-review and editing (equal); Camargo EB: formal analysis (equal), funding acquisition (equal), resources (equal), software (equal) and writing-review and editing (equal); Gottems LBD: formal analysis (equal), funding acquisition (equal), resources (equal), software (equal) and writing-review and editing (equal); and Atallah AN: methodology (equal), validation (equal), visualization (equal) and writing-review and editing (equal). All authors actively contributed to discussion of the results from the study, and reviewed and approved the final version to be released

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Address for correspondence:
Márcio Luís Duarte
R. Napoleão de Barros, 865
Vila Clementino — São Paulo (SP) — Brasil
CEP 04024-002
Tel. (+55 11) 5576-4848
E-mail: marcioluisduarte@gmail.com

Autonomic dysfunction is common in liver cirrhosis and is associated with cardiac dysfunction and mortality: prospective observational study

Carolina Frade Magalhães Girardin Pimentel[I], Ricardo Salvadori[II], Ana Cristina de Castro Amaral Feldner[III], Miguel Osman de Aguiar[IV], Adriano Miziara Gonzalez[V], Gabriel Ribas Branco[VI], Marcel Superbia[VII], Michelle Lai[VIII], Daniel de Oliveira Mota[IX], Maria Lucia Cardoso Gomes Ferraz[X], Wilson Mathias[XI], Mario Kondo[XII]

Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD, PhD. Professor, Department of Medicine, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil. https://orcid.org/0000-0001-8092-1106

[II]MD. Physician, Department of Electrophysiology, Hospital São Luiz and Hospital e Maternidade São Luiz, Unidade Itaim, São Paulo (SP), Brazil. https://orcid.org/0000-0002-9202-1639

[III]MD, PhD. Physician, Department of Gastroenterology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil. https://orcid.org/0000-0002-8290-7073

[IV]MD. Physician, Department of Echocardiology, Hospital e Maternidade São Luiz, Unidade Itaim, São Paulo (SP), Brazil. https://orcid.org/0000-0001-9083-8269

[V]MD, PhD. Professor, Department of Surgery, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil. https://orcid.org/0000-0002-5425-7886

[VI]MD. Physician, Department of Echocardiology, Hospital e Maternidade São Luiz, Unidade Itaim, São Paulo (SP), Brazil. https://orcid.org/0000-0002-7206-4084

[VII]MD. Physician, Department of Echocardiology, Hospital e Maternidade São Luiz, Unidade Itaim, São Paulo (SP), Brazil. https://orcid.org/0000-0002-4321-889X

[VIII]MD. Physician, Liver Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States. https://orcid.org/0000-0002-1035-0659

[IX]PhD. Engineer and Professor, Department of Industrial Engineering, Universidade de São (USP), São Paulo (SP), Brazil. https://orcid.org/0000-0002-9629-8512

[X]MD, PhD. Professor, Department of Gastroenterology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil; and Research Coordinator, Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo (SP), Brazil. https://orcid.org/0000-0001-8992-8494

[XI]MD, PhD. Professor, Department of Cardiology, Instituto do Coração (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0003-0201-6754

[XII]MD, PhD. Professor, Department of Gastroenterology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil. https://orcid.org/0000-0002-0079-2955

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ABSTRACT

BACKGROUND: Although autonomic dysfunction has been shown to be associated with liver cirrhosis, the prevalence and prognostic implications are unclear. Abnormal heart rate variability (HRV), a measure of autonomic function, has not been well investigated in cirrhosis.

OBJECTIVE: To evaluate the prevalence of high-risk HRV parameters in a cohort of cirrhotic patients and their association with cardiac dysfunction and mortality.

DESIGN AND SETTING: Prospective observational study conducted in the Federal University of São Paulo.

METHOD: A cohort of 120 patients, comprising 17 healthy controls and 103 cirrhotic outpatients, was evaluated and followed for 10 months. HRV analysis was based on 24-hour Holter monitoring and defined using time-domain and frequency-domain parameters.

RESULTS: The HRV parameters were statistically lower in cirrhotic patients than in healthy subjects. High-risk HRV parameters were prevalent, such that 64% had at least one high-risk parameter. Time-domain parameters correlated with Child scores ($P < 0.0001$). In regression models, HRV parameters were independent predictors of diastolic dysfunction and mortality. During 10 months of follow-up, there were 11 deaths, all of patients with at least one high-risk HRV parameter. Kaplan-Meier analysis estimated low survival rates among patients with standard deviation of normal-to-normal RR intervals (SDNN) < 100.

CONCLUSION: Reduced HRV is prevalent in liver cirrhosis and is related to cardiac dysfunction, severity of liver disease and mortality. Abnormal high-risk HRV parameters are prevalent among cirrhotic patients and are also predictors of mortality. Our findings highlight the need for a more careful cardiac evaluation of cirrhotic patients.

INTRODUCTION

Liver cirrhosis has a wide spectrum of clinical extrahepatic organ manifestations. The heart is affected in the majority of patients, ranging from mild to severe impairment. The latter is more prevalent during end-stage liver disease.[1] Cirrhosis with portal hypertension is characterized by circulatory dysfunction with chronic peripheral vasodilation, leading to insufficient organ perfusion and a compensatory increase in cardiac output.[2] This hyperdynamic circulation requires an increase in heart rate (HR), which is dependent on the autonomic nervous system (ANS). Dysfunction of the ANS leads to an abnormal HR response, especially in situations when peripheral oxygen demand increases, as during hemodynamic stress or exercise.[3,4]

QT interval prolongation has been shown to correlate with cirrhotic cardiomyopathy,[1] representing one manifestation of electrophysiological abnormalities and autonomic dysfunction. However, few studies have demonstrated the relationship between these electrocardiographic abnormalities and outcomes in liver cirrhosis.[5-7]

Another way to access cardiac autonomic function is to measure heart rate variability (HRV), which involves analysis of consecutive normal R-R intervals (also called N-N) during a period of time. HRV reflects the heart's ability to adapt HR to changing circumstances by detecting and quickly responding to unpredictable and variable stimuli.[8] Sympathetic and parasympathetic system impairment leads to improper acceleration or insufficient increase in HR. A number of different measurements are used to analyze HRV during 24-hour Holter monitoring; these parameters

are classified into two distinct groups: time-domain and frequency-domain parameters. Time-domain parameters are most frequently used to diagnosis reduced HRV, while frequency-domain analysis estimates the amount and type of variance in this reduction, thus characterizing whether the autonomic dysfunction is due to an increased sympathetic tone or to parasympathetic impairment.

Autonomic dysfunction is considered to be a feature of liver cirrhosis, presented as autonomic imbalance secondary to relatively decreased parasympathetic activity and increased sympathetic tone.[9,10] Different factors seem to contribute to this dysfunction in cirrhosis, such as direct nerve injuries due to alcohol toxicity, alteration of lipid metabolism, vitamin E deficiency, immunological mechanisms and higher toxic metabolite concentrations.[10,11] In addition, elevated angiotensin II levels affect vagal function and elevated nitric oxide levels reduce the vascular response to norepinephrine. Cirrhotic patients with vagal neuropathy have fivefold higher mortality than those without this.[10,12]

The main use of HRV analysis has been in risk-stratifying patients with regard to malignant arrhythmias and death after myocardial infarction (MI).[8,13,14] Small studies have demonstrated that decreased HRV is present in liver cirrhosis, and that it may be an indicator of poor prognosis and mortality[5,15,16] Although autonomic dysfunction is a known complication in this group, these previous studies using HRV to diagnose autonomic dysfunction were based on short-time analysis, rather than continuous monitoring using 24 hour Holter electrocardiograms.[12,17,18] In addition, several of these study populations comprised patients with well-compensated liver disease, so the prevalence of autonomic dysfunction found were not reflective of the prevalence among patients with more advanced liver disease. While post-MI patients with ANS impairment have been found to be at higher risk of sudden cardiac death and malignant arrhythmias, it has not been demonstrated whether ANS impairment also confer the same risks among patients with cirrhosis.[19] There is no study in the literature comparing the relationship between decreased HRV and features of cirrhotic cardiomyopathy. Moreover, it is unclear whether autonomic cardiac dysfunction is the primary event or a consequence of cardiovascular dysfunction in liver cirrhosis.

OBJECTIVE

The aim of this study was to evaluated a large cohort of cirrhotic patients in order to detect the prevalence of autonomic dysfunction, as represented by decreased HRV and QT prolongation, and its relationships with advanced liver disease, clinical decompensation, mortality and underlying cardiac dysfunction.

METHODS

Patients and methods

A total of 120 subjects, comprising 103 outpatients with liver cirrhosis (57 male; 46 female; mean age 51.2 ± 12.9 years) and 17 healthy controls (6 male; 11 female; mean age 50 ± 13.4 years) were included in the present study. Cirrhosis was defined from the subjects' clinical histories (alcohol abuse, hepatitis infection, genetic disorder or metabolic syndrome), physical examinations, laboratory analyses (low albumin, high bilirubin, high prothrombin time and thrombocytopenia) and data from at least one imaging examination (nodularity and increased echogenicity, atrophy of the right lobe and hypertrophy of the left one, portal vein enlargement and splenomegaly). All patients underwent blood sample collection within one week of Holter analysis, in order to exclude patients with significant electrolyte disturbances. The exclusion criteria consisted of any previous cardiovascular disease, heart failure or diagnosis of hemochromatosis. Patients who had a history of alcohol abuse (more than 20 g of ethanol per day for women and more than 60 g for men)[20] would need to have abstained for at least six months prior to enrollment. Patients who presented a recent history (less than three months) of liver-related decompensation or hospitalizations were also excluded. Healthy controls were included if there was no previous diagnosis of liver disease and their echocardiograms showed normal systolic and diastolic functions.

A total of 164 patients at two liver transplantation centers were consecutively screened between October 2014 and December 2014. Among these, 61 were excluded based on the criteria listed above. The patients were followed up through clinical visits, hospital records or telephone calls to them. They were asked to provide their written informed consent on the day of enrollment. All patients underwent laboratory tests, electrocardiograms (ECG), transthoracic echocardiograms (ECO) and 24-hour Holter monitoring within one month of enrollment. This study was conducted in accordance with the Declaration of Helsinki (2000) and was approved by the ethics committee of our institution (CAAE: 30942714.8.0000.5505; dated: May 28, 2014).

QT interval and Holter monitoring

The QT interval (QT) was corrected for heart rate (QTc) using the Bazzett formula[21] and considered prolonged if greater than 440 ms. 24-hour Holter monitoring was obtained using a portable battery-operated three-channel Cardio-Light recorder and was processed using the Cardio Smart S-550 Cardio Sistemas Holter analysis software (CardioSmart, São Paulo, Brazil). After automatic QRS detection, the data were reviewed by an experienced Holter analyst. Patients without sinus rhythm were excluded. In the rhythm analysis, all parameters were calculated per hour, and were presented as 24-hour means for statistical analysis.

Abnormal HRV was analyzed as a marker of autonomic dysfunction and chronotropic incompetence, in accordance with current guideline recommendations.[22] Time and frequency-domain parameters were calculated. The time domain analyses were

reported as follows: the standard deviation of normal-to-normal RR intervals (SDNN-ms), representing overall autonomic dysfunction; the mean of the standard deviations of all NN intervals for all five- minute segments of the entire recording (SDNNIX); the standard deviation of the average N-N interval for each five-minute period over 24 hours (SDANN-ms), representing the sympathetic component of autonomic function; the square root of the mean of the squared differences between adjacent NN intervals (rMSSD-ms), which was correlated with parasympathetic activity; and the percentage of adjacent NN intervals that were > 50 msec (pNN50%), which was also correlated with the parasympathetic component. The data of the frequency domain were represented by total power (TP ≤ 0.4 Hz); very low-frequency power (VLF: 0.0033-0.04 Hz), which might represent the influence of the thermoregulatory, peripheral vasomotor or renin-angiotensin systems; low-frequency power (LF: 0.04-0.15 Hz), modulated by the sympathetic system; high-frequency power (HF: 0.15-0.49 Hz), modulated by the parasympathetic system; and the LF/HF ratio, which reflected the sympathetic-vagal balance.[22] The VLF, LF and HF components were expressed in ms^2 or nu (normalized units). The normal cutoff values described in the literature were considered to be standards.[22] The cutoffs for defining abnormal parameters associated with high risks of unfavorable outcomes (malignant arrhythmias and sudden cardiac deaths) were based on the European guidelines and on post-MI studies in the heart failure population.[13,22] The values reported in the literature are SDNN < 100 ms, 70 ms or 50 ms; SDANN < 100 ms or 55 ms; rMSSD < 15 ms; and pNN50 > 5%.[14]

Echocardiograms

Transthoracic echocardiogram studies was performed using Vivid E9 with the M5S transthoracic transducer from General Electric Medical Systems, Milwaukee, Wisconsin, United States. Left ventricular (LV) systolic function was represented by the ejection fraction (EF) (Simpson's biplanar method) and longitudinal global strain. Systolic dysfunction was defined as EF ≤ 55% or strain ≥ -18%. LV diastolic function was evaluated based on early and late peak diastolic velocities (E/A; estimated through Doppler analysis and considered normal if more than 1.0); the ratio between early diastolic transmitral flow velocity and lateral mitral annulus motion (E/e'; normal if less than 8.0);[23] and the deceleration time (DT; abnormal if greater than 240 ms). E/e' was considered to be the reference for diastolic dysfunction, given that this ratio is less influenced by preload and cardiac afterload.

Statistical analyses

The data were analyzed using a statistical software program (IBM SPSS Statistics, version 22.0) (IBM, Armonk, United States). Two-tailed Student's t tests and analysis of variance (ANOVA) were calculated for pairwise comparisons of continuous variables. Post-hoc testing was performed by using the Games-Howell test. Pearson's correlation test was performed to compare continuous variables. Categorical variables were expressed as percentages and analyzed using the chi-square test or Fisher's exact test, as applicable. Linear and logistic regressions were performed to evaluate associations between independent variables, HRV parameters or QTc intervals, and the presence of cardiac dysfunction and death. Receiver operating curves (ROC) and the area under this curve (AUROC) were computed to estimate sensitivity, specificity and cutoff points for the HRV parameters used in regression models. Kaplan-Meier curves were built and significant differences between them were assessed by means of the log-rank test. Statistical significance was considered present when P < 0.05, using two-tailed tests.

RESULTS

Patients' characteristics

The main demographic, clinical and laboratory characteristics of the patients are presented in **Table 1**. The healthy control patients had a mean age of 50 ± 3.8 years, and no statistical difference was found between this group and the cirrhotic patients. A total

Table 1. Patients' characteristics

Characteristic	
Gender M/F, n (%)	57/46 (55.3/44.7)
Age (years ± SD)	51 ± 13
Cirrhosis etiology, n (%)	
Virus	33 (35)
Alcohol	32 (31.1)
NASH	8 (7.8)
Others	30 (29)
Child-Pugh (mean ± SD)	7.1 ± 1.8
Child-Pugh class, n (%)	
A	23 (22.3)
B	68 (66)
C	12 (11.7)
MELD (mean ± SD)	11.1 ± 3.1
History of liver-related decompensation, n (%)	76 (73.8)
Hypertension, n (%)	19 (18.4)
Diabetes, n (%)	16 (15.5)
Beta-blocker in use, n (%)	34 (30.1)
Baseline laboratory tests (mean ± SD)	
Hemoglobin (mg/dl)	13.1 ± 1.9
Na (mmol/l)	137.8 ± 2.1
K (mmol/l)	4.1 ± 0.5
Mg (mg/dl)	1.8 ± 0.2
Ca^{2+} (mmol/l)	1.2 ± 0.1

Reference range values: Na (136-145); K (3.5-5.0); Mg (1.6-2.6) and Ca^{2+} (1.15-1.29). M/F = male/female; NASH = nonalcoholic steatohepatitis; MELD = model for end-stage liver disease; Na = sodium; K = potassium; Mg = magnesium; Ca = calcium.

of 106 patients were selected from two liver transplantation centers in São Paulo, Brazil. The majority of them were male (56%), and the etiology of the liver disease was most commonly non-alcoholic (69.8%). The mean model for end-stage liver disease (MELD) was 11.1, Child B was most common (66%) and 74% of the patients presented a history of at least one liver-related decompensation. Ascites was identified in 32.1% and hepatic encephalopathy in 10.4% of the patients on the day of the test.

All the patients were followed until death, time of transplantation or end of study follow-up (10 months). During the study period, 11 patients died and three underwent liver transplantation.

Echocardiograms

All the healthy patients presented normal echocardiographic values. More than half of this cohort (57%) had one or more features of diastolic dysfunction: 24% with E/e' > 8 (n = 25), 8.5% with E/A < 0.8 (n = 9) and 37% with DT > 240 ms (n = 38). Only 5 patients presented features of systolic dysfunction, as represented by EF ≤ 55% or strain ≥ -18%. The echocardiographic parameters, except for LA, did not differ between Child groups. Although 42% of Child C patients presented E/e' > 8.0, compared with 28% of Child A and B patients (n = 20), there were no statistically significant differences among Child groups (P = 0.18).

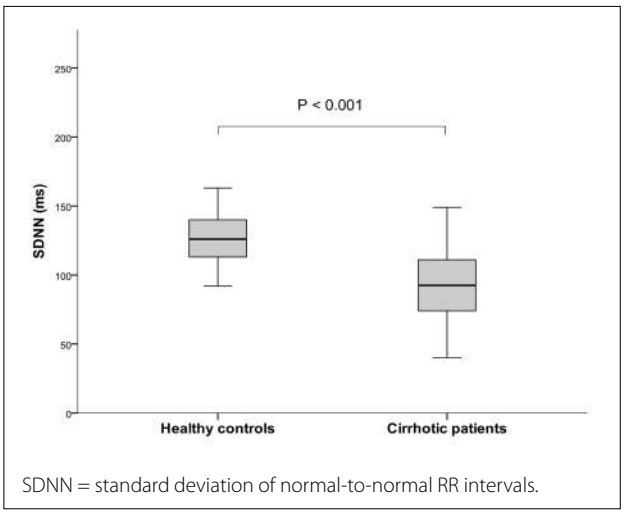
HRV and QTc analyses

QTc means were significant higher in cirrhotic patients (445 ± 29 ms) than in healthy controls (429 ± 19 ms) (P = 0.04). A prolonged QTc interval was frequent in this population (60.2%) and progressively longer among Child classes: Child A (428 ± 35 ms), Child B (449 ± 26 ms) and Child C (451 ± 25 ms). Statistical differences were demonstrated between Child A and B (P = 0.003) and between Child A and C (P = 0.02). Student's t test analyses did not show any differences between QTc means according to cardiac dysfunction, history of liver-related decompensations, alcohol consumption, use of beta blockers or death (P > 0.05). No electrolyte disturbance or anemia was present at the time of the evaluation.

Reduced HRV was frequently detected among cirrhotic patients. There were statistical differences in time-domain parameters, including SDNN, SDANN, SDNNIDX and rMSSD, between cirrhotic patients and healthy controls (**Figure 1**). In addition, TP, VLF and LF means were significant higher in controls than in cirrhotic patients (**Tables 2** and **3**).

Reduced HRV parameters were correlated with greater severity of liver disease. The time domain variables SDNN and SDANN correlated with Child scores (P < 0.0001; r = -0.406 and -0.407, respectively). In addition, the means were statistically different among Child stages (P = 0.002 for both), with a tendency to decrease as Child scores increased (for SDNN, Child A = 111 ms, Child B = 93 ms and Child C = 73 ms; P = 0.002). A weak negative correlation between Child scores and TP was also demonstrated (P = 0.033; r = -0.229). HRV parameters were also associated with MELD, albeit poorly correlated (SDNN, P = 0.008, r = -0.261; SDANN, P = 0.005, r = -0.277).

The majority of the cirrhotic patients presented with SDNN less than 100 ms (60%), while just 11.8% of the controls did (P = 0.002). **Table 4** shows the frequency of abnormal high risk HRV parameters, in accordance with the European guidelines[22] and with post-MI studies.[13] As demonstrated, several parameters were statistically different between the groups: parasympathetic impairment was noticeable through pNN50% > 5%, which was less frequent



SDNN = standard deviation of normal-to-normal RR intervals.

Figure 1. SDNN means are higher in the control group than in the cirrhotic patients.

Table 2. Heart rate variability (HRV) parameters

Parameter	Controls	Cirrhotic patients	P*
NN (ms)	810 ± 88	793 ± 110	0.27
SDNN (ms)	130 ± 29	94.8 ± 31	< 0.001
SDANN (ms)	110 ± 26	82.7 ± 29	< 0.001
SDNNIDX (ms)	60 ± 20	40.6 ± 16	< 0.001
rMSSD (ms)	36 ± 25	25.0 ± 13	0.051
pNN50 (%)	9.1 ± 9.7	4.4 ± 6	0.121
TP (ms^2)	2823 ± 2250	1438 ± 1611	0.002
VLF (ms^2)	1338 ± 932	823 ± 909	0.033
LF (ms^2)	969 ± 710	411 ± 539	< 0.001
HF (ms^2)	517 ± 779	206 ± 244	0.122
LF/HF ratio	3.7 ± 1.5	3.8 ± 2.4	0.991

*P (t tests comparing means between control and cirrhotic patients). NN = normal-to-normal; SDNN = standard deviation of normal-to-normal RR intervals; SDANN = standard deviation of the average of N-N intervals for each 5-minute period over 24 hours; SDNNIDX = the standard deviations of all NN intervals for all 5-minute segments of the entire recording; rMSSD = root mean square of successive differences between normal heartbeats; pNN50 = proportion of NN50 divided by the total number of NN (R-R) intervals; TP = total power; VLF = very low-frequency power; LF = low-frequency power; HF = high-frequency power.

in cirrhosis; and through reduced rMSSD, which was combined with sympathetic impairment characterized by lower SDANN and LF in cirrhosis.

No significant difference in HRV parameters was observed between patients with alcohol-related cirrhosis and those with other etiologies. The t test did not demonstrate any significant difference between these groups, according to the means for SDNN, SDANN, rMSSD, pNN > 50% and QTc.

HRV parameters were associated with Child classes independently of the presence of diabetes, hypertension or use of beta blockers. We analyzed the means for HRV parameters according to Child stages, using one-way ANOVA, in three different subgroups: 1) patients without diabetes; 2) those without hypertension; and 3) those not using beta blockers. We demonstrated that the presence of these factors did not affect the association between cirrhosis and autonomic dysfunction, as we found the same significant difference between classes as previously reported for the entire cohort (P < 0.001, P = 0.001 and P = 0.007, respectively). Therefore, the relationship between HRV parameters and Child groups was unaffected by the association of comorbidities or alcohol consumption in our study.

Table 3. Prevalence of abnormal high-risk heart rate variability parameters and QTc prolongation in cirrhotic and control groups

Parameter	Cirrhotic patients	Controls	P
SDNN < 100 ms	60%	12%	< 0.001
SDNN < 70 ms	20%	0%	0.04
SDNN < 50 ms	9%	0%	0.35
SDANN < 100 ms	77%	29%	< 0.001
SDANN < 55 ms	17%	0%	0.13
rMSSD < 15 ms	24%	6%	0.12
pNN50 > 5%	25%	60%	0.006
QTc > 440 ms	60%	0%	< 0.001

SDNN = standard deviation of normal-to-normal RR intervals; SDANN = standard deviation of the average of N-N intervals for each 5-minute period over 24 hours; rMSSD = root mean square of successive differences between normal heartbeats; pNN50 = proportion of NN50 divided by the total number of NN (R-R) intervals; QTc = QT interval corrected for heart rate.

Autonomic dysfunction and cardiac dysfunction

In cirrhotic patients, reduced HRV was more prevalent in those with features of diastolic dysfunction. The time-domain parameters SDNN and SDANN were significantly lower in patients with E/e' greater than 8.0 (81 ms versus 99 ms, P = 0.01; and 24 ms versus 78 ms, P = 0.01, respectively) (**Figure 2**). In addition, HF, LF and LF/HF ratio were significantly different between patients with or without diastolic dysfunction (59 versus 68 nu, 40 versus 32 nu and 2.6 versus 4.1; P = 0.005, P = 0.005 and P = 0.001, respectively).

Logistic regression was carried out to assess autonomic dysfunction parameters as predictors of diastolic cardiac dysfunction and mortality in our population (**Table 4**). Several time-domain and frequency-domain parameters were independent predictors of diastolic dysfunction. In addition, SDNN and SDANN were also reported as independent predictors of mortality according to the model. Also, we analyzed whether reduced HRV was associated with diastolic dysfunction and mortality. SDNN less than 100 ms and LF/HF more than 2 were considered to be independent variables for prediction of diastolic dysfunction (P = 0.018, b = 1.81, confidence interval (CI) for b = 0.213 to 2.57; and P = 0.002, b = -1.52, CI for b = -2.62 to -0.56, respectively). Regarding prediction of mortality, SDNN < 100 ms (P = 0.04, b = -1.94, CI for b = -20.0 to -0.36) and SDANN < 100 ms (P = 0.001, b = 19.25, CI for b = -19.86 to -18.3) were also related to deaths, while LF/HF ratio was not (P = 0.689).

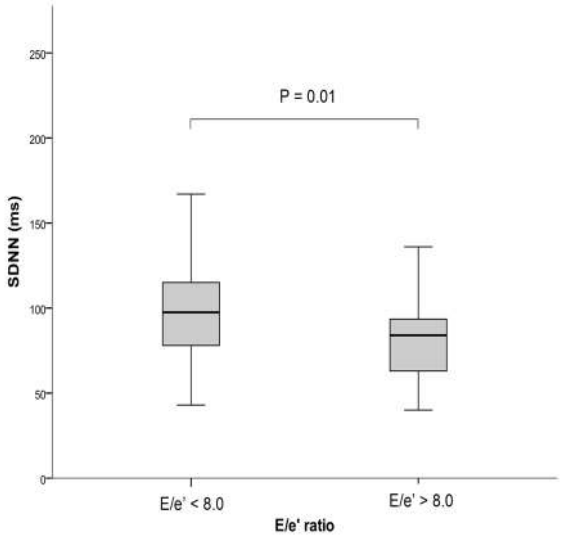
The predicted values from the regression model using SDNN were used to build the ROC curve and calculate the AUROC. For prediction of diastolic dysfunction, AUROC was 0.68 (P = 0.01, CI = 0.56-0.79) and for mortality, AUROC = 0.705 (P = 0.034, CI = 0.550-0.859). Sensitivity and specificity, computed using the Youden index, were 91.7% and 43.6% (for diastolic dysfunction) and 100% and 40% (for mortality). The SDNN cutoffs associated with diastolic dysfunction diagnosis and mortality in this model were 106 ms and 72 ms, respectively. The patients who died (11; 10.4%) had at least one high-risk HRV parameter. Ten patients had SDNN less than 100 ms (85.7%), while just one patient did not (SDNN = 103 ms). Kaplan-Meier survival analysis estimated significantly lower

Table 4. Logistic regression model for prediction of diastolic dysfunction and mortality using time and frequency-domain parameters

Predictor	Diastolic dysfunction			Mortality		
	b	P	CI for b	b	P	CI for b
SDNN	-0.31	0.005	-0.047/-0.009	-0.31	0.019	-0.071/-0.008
SDANN	-0.026	0.004	-0.049/-0.009	-0.36	0.01	-0.074/-0.012
rMSSD	-0.007	0.683	-0.052/0.029	-0.014	0.629	-0.012/-0.126
HF(nu)	-0.051	0.004	0.019/0.091	0.033	0.190	-0.027/0.092
LF(nu)	-0.051	0.002	-0.094/-0.016	-0.31	0.210	0.033/-0.091
LF/HF	-0.402	0.007	-0.821/-0.148	-0.291	0.072	-0.832/-0.026

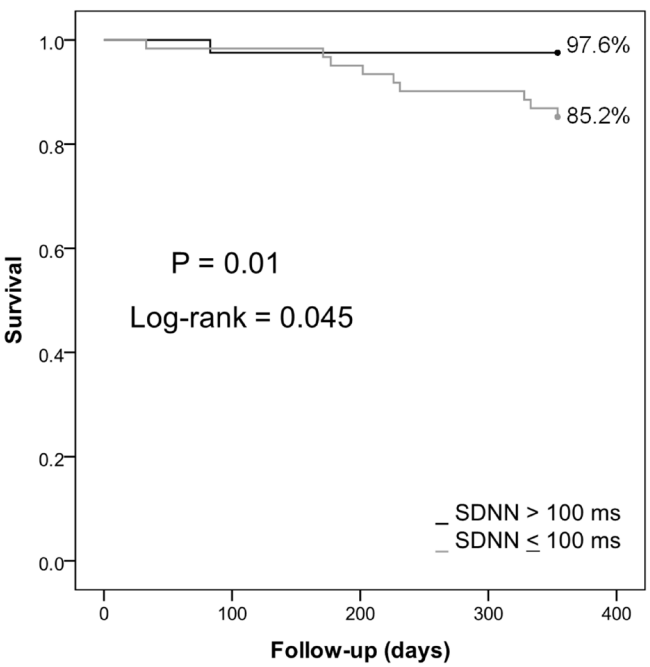
b = value of the model equation coefficient.

CI = confidence interval; SDNN = standard deviation of normal-to-normal RR intervals; SDANN = standard deviation of the average of N-N intervals for each 5-minute period over 24 hours; rMSSD = root mean square of successive differences between normal heartbeats; HF = high-frequency power; LF = low-frequency power.



SDNN = standard deviation of normal-to-normal RR intervals; E/e' = ratio between early diastolic transmitral flow velocity and lateral mitral annulus motion.

Figure 2. Lower SDNN means in patients with features of diastolic dysfunction, assessed by means of E/e' ratio.



SDNN = standard deviation of normal-to-normal RR intervals.

Figure 3. Mortality associated with SDNN less than 104 ms.

survival rates among patients with SDNN < 100 than among those with SDNN ≥ 100 (log-rank, P = 0.045) (**Figure 3**).

DISCUSSION

Autonomic dysfunction is a common finding among cirrhotic patients, documented through either QTc prolongation or reduced HRV.[5,18,24] This study hereby confirms these findings from previous study, and shows an association of QTc prolongation and HRV with increased mortality. We also found increasing prevalence and severity of autonomic dysfunction with increasing severity of liver disease, regardless of etiology, alcohol consumption or comorbidities. Moreover, this highlights the relationship between autonomic and cardiac dysfunctions, showing high prevalence of ANS impairment in patients with diastolic dysfunction. This relationship gives rise to potential use as a promising tool for cardiac evaluation in liver cirrhosis, as this is more likely to reflect the early changes of cirrhotic cardiomyopathy than are traditional echocardiographic measurements.

Patients with cirrhosis and portal hypertension have a progressively hyperdynamic circulatory state as liver function declines.[2] Maintenance of adequate peripheral organ perfusion depends on an increase in cardiac output, mainly through HR response to hemodynamic stress.[25] ANS is a key element in this delicate balance: when this does not work properly, the result is circulatory failure.

Previous studies have demonstrated common vagal neuropathy in cirrhosis, leading to progressive autonomic dysfunction due to parasympathetic impairment.[10,26] However, these were small studies,[12,27] mainly among patients without advanced liver disease,[17] and they were frequently related to alcohol consumption,[28] which itself causes cardiomyopathy. The study population characteristics of those studies prevented accurate evaluation of the real prevalence of this disorder in cirrhosis. Some studies based this diagnosis on peripheral neuropathy or on tests requiring patients' compliance (i.e. deep breathing and standing),[11,9,12] which may result in error if the patient is unable to perform the test correctly. In addition, given that ANS impairment is variable, presenting different patterns during the day and night,[29] use of 24-hour Holter monitoring seems to be more appropriate for assessing ANS impairment.

Our data from 24-hour Holter monitoring of a large cohort of 103 patients demonstrated a clear association between autonomic dysfunction (reduced HRV) and liver function severity (Child and MELD scores), regardless of previous alcohol consumption. Our cohort of patients had advanced liver disease, and the vast majority (almost 75%) had had at least one episode of liver-related clinical decompensation in the past (ascites, hepatic encephalopathy, variceal bleeding or hepatorenal syndrome). This is the biggest cohort of cirrhotic patients evaluated with regard to ANS impairment using HRV analysis that we are aware of.

The pathophysiology of heart failure in liver cirrhosis is not completely understood.[1] However, previous studies have suggested that decreased density of beta-adrenoceptors in cardiomyocytes may occur.[30] This could be responsible for the myocardial hyporesponsiveness to catecholamine, with progressive damage to myocardial tissue, thus leading to cardiac pump dysfunction. The hyperdynamic circulation that defines cirrhotic cardiomyopathy does

not present with traditional echocardiographic features of diastolic and systolic cardiac impairment until late in the disease process. In our cirrhosis cohort, we found that ANS imbalance was: 1) more prevalent than cardiac dysfunction; 2) associated with liver disease severity; and 3) predicted cardiac dysfunction. We suspect that ANS disorders may be the first event in cirrhotic cardiomyopathy. This suggests that screening for cirrhotic cardiomyopathy through testing for autonomic dysfunction would lead to earlier diagnosis, thus enabling possible earlier intervention or risk stratification for liver transplantation candidates. Further studies to test this specific hypothesis are required.

Although QTc is commonly prolonged in cirrhotic patients, we did not demonstrate any relationship between this parameter and cardiac dysfunction. Also, Qtc > 440 ms was more prevalent in the later stages of liver disease, but we could not identify any statistical association between this parameter and mortality risk. Genovesi et al.[5] demonstrated a significant correlation for QTc and hepatic vein pressure gradient (HVPG) in relation to Child scores, but no association with survival was demonstrated. Bernardi et al. suggested that QTc prolongation might have an important prognostic meaning,[31] but we, along with other studies, were unable to prove this association.[7] The high prevalence of QTc prolongation is clinically important in this patient population, in which some commonly used drugs (ciprofloxacin and furosemide) or associated electrolyte disturbances may increase the risk of arrhythmias by additionally prolonging the QT interval.

Although QTs is described as more frequently prolonged in patients with a history of alcohol intake who are not using beta-blockers,[32] we did not find any statistical differences based on histories of either alcohol use or beta-blocker use. Patients taking beta-blockers are likely to have more advanced disease (requiring prophylaxis for primary or secondary variceal bleeding). Because beta-blockers can decrease the QTc, the actual untreated mean QTc in this group of patients may be longer than what was observed. In the present study, reduced HRV was frequently detected in cirrhotic patients; also, time and frequency-domain parameters were significant lower in this group than in the healthy subjects. Our data confirm the results of previous studies that indicated a lack of cardiac chronotropic response in cirrhosis (reduced SDNN), as a consequence of parasympathetic impairment (reduced rMSSD) and sympathovagal imbalance (reduced LF/HF ratio).[12,15] Unlike the data in the literature, we also identified reduced sympathetic tone in our cohort (reduce SDANN and low LF). With the availability of modern electrocardiographic recorders and new software, 24-hour Holter monitoring enables a more comprehensive assessment of the pathophysiological pathways involved in autonomic dysfunction, and may help identify future treatment targets: for example, exercise training, which has previously been correlated with increased HRV in experimental studies.[33]

Baratta et al.[27] studied 30 cirrhotic patients waiting for liver transplants and did not find any relationship between cirrhosis severity (MELD) and the degree of autonomic dysfunction. On the contrary, in 30 another subjects, Ates et al.[15] demonstrated that there was a significant correlation between Child scores and time-domain parameters. The diversity of results found in the literature may be explained by the use of small cohorts, and by differing severities of liver disease in different subject populations. Here, we reported that there was quite a strong inverse correlation between SDNN and Child scores ($r = -0.4$; $P < 0.0001$) and a weak one with MELD ($r = -0.3$; $P = 0.008$), thus indicating more overall autonomic dysfunction with worsening liver function. The relationships between HRV parameters and Child groups were unaffected by the association of comorbidities (hypertension and diabetes) or alcohol intake, thus suggesting that liver function has a predominant influence on autonomic dysfunction.

In 1987, Kleiger et al. demonstrated that, post-MI, reduced HRV (defined as SDNN < 50 ms) was highly associated with sudden cardiac death and malignant arrhythmias.[13] Rovere et al. published the ATRAMI Study results, in which preserved HRV variability, defined as SDNN > 105 ms, gave rise to lower mortality rates than among patients with reduced HRV, thus reinforcing the value of HRV as a prognostic factor.[34] The European guidelines for HRV assessment define the cutoff value for highly depressed HRV as SDNN as < 50 ms, and for moderately depressed HRV as SDNN < 100 ms. In addition, no currently recognized HRV measurements provide better prognostic information, post-MI, than time-domain HRV measurements, in special SDNN and HRV triangular indexes.[22] Based on this, we decided to focus on SDNN analysis in our cohort.

Our data from this large cohort confirm the finding from some previous small studies that reduced HRV is an independent mortality risk factor in cirrhosis.[10,12,15] During the ten-month follow-up, 11 patients died, with lower SDNN means (75 ± 24 ms versus 96.9 ± 31.2 ms) and lower SDANN (64 ± 18.7 ms versus 84.8 ± 28.8 ms). We reported that were significant differences in Kaplan-Meier survival curves according to SDNN values ($P = 0.045$), and it was noticeable that longer follow-ups may better highlight this difference.

This is the first study in the literature to investigate the association between reduced HRV and cardiac dysfunction. We identified that 60% of our patients presented with SDNN < 100 ms, thus drawing attention to the arrhythmia risk in this population. Moreover, we reported that there was an independent association with SDNN for prediction of diastolic dysfunction when it was higher than 105 ms. We hypothesize that ANS disorder is the first event in cirrhotic cardiomyopathy, such that this would require careful attention during cirrhosis management. Currently, liver transplant evaluations rely on transthoracic echocardiograms to

diagnose cardiac dysfunction. Most of the current protocols do not routinely include autonomic dysfunction evaluation and therefore they may potentially miss the diagnosis of reduced HRV, which predisposes patients to poor outcomes during hemodynamic stress, as occurs during liver transplantation.

One potential limitation of the present study is that we did not exclude patients with diabetes, which is a known risk factor for autonomic dysfunction. For a more reliable interpretation, we carried out individual analyses comparing patients with and without this disorder, thus preventing bias in the interpretation, and no further difference between groups was detected. Another point to be noted is our inclusion of cases of alcoholic cirrhosis. However, all patients had been abstinent for at least six months, which will have decreased the direct alcohol neuropathy. We also compared patients with and without histories of alcohol intake, and the diagnoses of autonomic dysfunction were similar in both groups. Another weakness is that our evaluation was conducted among outpatients, although it is known that cardiac dysfunction in cirrhosis is more prone to be manifested during hemodynamic stress. Future protocols should be developed to evaluate cardiac function during cirrhosis decompensation; however, several confounders may prevent determination of causality related to liver disorders. Lastly, although our control group had more women than men, this difference was not statistically significant (P = 0.19). Moreover, no HRV differences between genders have been reported in the literature.

CONCLUSIONS

Our study shows that reduced HRV is prevalent in liver cirrhosis, and that this is related to cardiac dysfunction, severity of liver disease and mortality. We also report that abnormal high-risk HRV parameters, which had previously been defined in post-MI populations, are prevalent among cirrhotic patients and are a mortality risk factor in cirrhosis. We believe that careful assessment of autonomic function should be part of the liver transplantation evaluation, based on the high prevalence of this disorder and the risk of adverse events during hemodynamic stress.

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Address for correspondence:
Carolina Pimentel
Centro de Ensino e Pesquisa em Avaliações Tecnológicas e Inovações em Saúde (CEPATIS), Universidade Federal de São Paulo – Escola Paulista de Medicina (UNIFESP-EPM)
R. Botucatu, 740 — 3º andar
Vila Clementino —São Paulo (SP) — Brasil
CEP 04023-061
Tel. (+55 11) 99653-9040
E-mail: carolinapimentel.gastro@gmail.com

Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of COVID-19 patients: a retrospective cohort study

Erdal Yılmaz[I], Rohat Ak[II], Fatih Doğanay[III]

Department of Emergency Medicine, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Istanbul, Turkey

[I]MD. Specialist in Emergency Medicine, Department of Emergency Medicine, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Istanbul, Turkey.
https://orcid.org/0000-0001-6782-0087

[II]MD. Specialist in Emergency Medicine, Department of Emergency Medicine, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Istanbul, Turkey.
https://orcid.org/0000-0002-8324-3264

[III]MD. Specialist in Emergency Medicine, Department of Emergency Medicine, Edremit Devlet Hastanesi, Balıkesir, Turkey.
https://orcid.org/0000-0003-4720-787X

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NLR.
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Emergency.

ABSTRACT

BACKGROUND: Quick and accurate identification of critically ill patients ensures appropriate and correct use of medical resources. In situations that threaten public health, like pandemics, rapid and effective methods are needed for early disease detection among critically ill patients.

OBJECTIVE: To determine the relationship between the neutrophil-to-lymphocyte ratio (NLR) of coronavirus disease-19 (COVID-19) patients upon admission to the emergency department (ED) and these patients' prognosis.

DESIGN AND SETTING: Retrospective cohort study among COVID-19 patients in the ED of a tertiary-level hospital.

METHODS: Data on patients' age, gender, vital signs, chronic diseases, laboratory tests and clinical outcomes were collected from electronic medical records. Receiver operating characteristic (ROC) curve analysis was performed. The area under the curve (AUC) was used to assess the accuracy of NLR for predicting in-hospital mortality risk and intensive care unit (ICU) requirement. The Youden J index (YJI) was used to determine optimal threshold values.

RESULTS: 1,175 patients were included. Their median age was 63 years (IQR, 48-75). With an NLR cutoff value of 5.14, the sensitivity, specificity, PPV, AUC and YJI for ICU requirement were calculated as 77.87%, 74.08%, 92.4%, 0.811 and 0.5194, respectively. With the same cutoff value, the sensitivity, specificity, AUC and YJI for in-hospital mortality were 77.27%, 75.82%, 0.815 and 0.5309, respectively. In addition, advanced age, leukocytosis, anemia and lymphopenia were found to be associated with poor prognosis.

CONCLUSION: The NLR, which is a widely available simple parameter, can provide rapid insights regarding early recognition of critical illness and prognosis among COVID-19 patients.

INTRODUCTION

In December 2019, a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, China, and it spread rapidly all over the world.[1] The World Health Organization (WHO) gave the name coronavirus disease-19 (COVID-19) to the resultant disease and declared it to be an epidemic.[2] The first polymerase chain reaction (PCR)-positive COVID-19 case in Turkey was detected on March 11, 2020.[3]

In some studies in the literature, it was reported that 14% of COVID-19 patients developed severe pneumonia, one in 20 patients had an intensive care unit (ICU) requirement and approximately 66% of critically ill patients died.[4-6] High mortality rates among critically ill patients and rapidly spreading disease raise concerns about ICU requirements, which may place pressure on healthcare system resources.[7] In order to make optimal treatment decisions, prognostic predictors of mortality among COVID-19 patients need to be identified in order to help assess the severity of the condition.

Compared with the normal range, lower white blood cell (WBC) and lymphocyte counts but higher neutrophil counts have been found in COVID-19 patients.[8,9] In some recent studies, it has been reported that the neutrophil-to-lymphocyte ratio (NLR) is an independent prognostic factor for predicting outcomes of critical illness and in-hospital mortality among COVID-19 patients.[10,11]

OBJECTIVE

Our aim in this study was to determine the relationship between the prognosis and the NLR among COVID-19 patients.

METHODS

This retrospective cohort study was carried out in the emergency department (ED) of Kartal Dr. Lütfi Kırdar City Hospital between October 1, 2020, and March 1, 2021. The hospital's institutional review board approved the analysis and issued a waiver of consent (Ethics Committee Ruling number: 2021/514/198/30; date: March 29, 2021).

All COVID-19 patients over the age of 18 who were hospitalized between October 1, 2020, and March 1, 2021, were included in this study. The diagnosis of COVID-19 was determined based on the WHO guidelines. This study includes only patients who had positive results from a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test on nasal and pharyngeal swab samples.[12] A data form was used to collect patients' age, gender, vital signs, chronic diseases, laboratory tests and clinical outcome data from the electronic medical records.

Measurements

Chronic diseases presented by these patients, such as chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD), atrial fibrillation (AF), chronic renal failure (CRF), chronic neurological disease (CND), diabetes mellitus (DM) and hypertension (HT) were recorded by scanning digital file records stored in the hospital information management system (HIMS).

The following vital signs were assessed: systolic blood pressure (SBP), heart rate (HR) and blood oxygen saturation (SpO_2); along with the following laboratory parameters: white blood cells (WBC), neutrophils (Neu), lymphocytes (Lym), monocytes (Mon), hemoglobin (Hgb) and platelets (Plt). These were measured in the ED.

The NLR was calculated using the following simple formula: Absolute number of neutrophils/Absolute number of lymphocytes.

Outcomes

ED outcomes were determined as inpatient unit (IU) or ICU; and hospitalization outcomes as survivor or non-survivor.

Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (IBM Corp., released 2020; IBM SPSS Statistics for Windows, version 26.0; Armonk, NY, United States) and the MedCalc statistical software version 19.0.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

Continuous data did not meet the assumption of normality. The Mann-Whitney U test was used for analyses on continuous data and the chi-square test was used for analyses on categorical data. Continuous data were reported as medians and interquartile ranges (IQR; 25th to 75th percentile), while categorical data were reported as frequencies and percentages (**Tables 1** and **2**). A P-value of less than 0.05 was considered statistically significant.

Table 1. Gender and comorbidity data of the study population

		ICU requirement groups					Mortality groups				
	n = 1175	IU (n = 922)		ICU (n = 253)		Sig.	Survivor (n = 889)		Non-survivor (n = 286)		Sig.
Variables	Category	n	%	n	%	P	n	%	n	%	P
Sex	Male	483	79.6	124	20.4	0.341	469	77.3	138	22.7	0.185
	Female	439	77.3	129	22.7		420	73.9	148	26.1	
COPD	Absent	881	79.7	224	20.3	< 0.001	852	77.1	253	22.9	< 0.001
	Present	41	58.6	29	41.4		37	52.9	33	47.1	
DM	Absent	671	78.1	188	21.9	0.562	654	76.1	205	23.9	0.588
	Present	251	79.7	64	20.3		235	74.6	80	25.4	
HT	Absent	596	80	149	20	0.093	581	78.0	164	22.0	0.014
	Present	326	75.8	104	24.2		308	71.6	122	28.4	
CHF	Absent	883	81.2	204	18.8	< 0.001	856	78.7	231	21.3	< 0.001
	Present	39	44.3	49	55.7		33	37.5	55	62.5	
CAD	Absent	853	80.7	204	19.3	< 0.001	821	77.7	236	22.3	< 0.001
	Present	69	58.5	49	41.5		68	57.6	50	42.4	
AF	Absent	908	79.5	234	20.5	< 0.001	872	76.4	270	23.6	0.001
	Present	14	42.4	19	57.6		17	51.5	16	48.5	
CRF	Absent	865	79.5	223	20.5	0.002	848	77.9	240	22.1	< 0.001
	Present	57	65.5	30	34.5		41	47.1	46	52.9	
CND	Absent	888	79.3	232	20.7	0.002	865	77.2	255	22.8	< 0.001
	Present	34	61.8	21	38.2		24	43.6	31	56.4	

IU = inpatient unit; ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HT = hypertension; CHF = congestive heart failure; CAD = coronary artery disease; AF = atrial fibrillation; CRF = chronic renal failure; CND = chronic neurological disease; Sig. = significance.

Table 2. Descriptive statistics for age, vital parameters and laboratory measurements of the groups

		ICU requirement groups Median (IQR)			Mortality groups Median (IQR)		
Variables	**All Patients (n = 1175)**	**IU (n = 922)**	**ICU (n = 253)**	**P**	**Survivor (n = 889)**	**Non-survivor (n = 286)**	**P**
Age	63 (48-75)	59 (46-72)	74 (64-81)	< 0.001	58 (46-70)	75 (65-82)	< 0.001
Vital parameters							
SBP (mmHg)	120 (110-130)	120 (110-130)	120 (110-135)	0.278	120 (110-130)	120 (110-135)	0.256
HR (bpm)	85 (76-98)	83 (75-94)	98 (85-115)	< 0.001	83 (75-94)	96 (83-112)	< 0.001
SpO_2 (%)	96 (93-98)	96 (94-98)	90 (84-96)	< 0.001	96 (94-98)	92 (85-96)	< 0.001
Laboratory measurements							
WBC (10^3/ul)	6.3 (4.8-8.8)	5.9 (4.5-7.6)	9.6 (6.8-14)	< 0.001	5.8 (4.4-7.5)	9.4 (6.8-13.9)	< 0.001
Neu (10^3/ul)	4.3 (3.0-6.8)	3.8 (2.7-5.4)	8.2 (5.4-12.1)	< 0.001	3.8 (2.7-5.3)	7.95 (5.20-12.03)	< 0.001
Lym (10^3/ul)	1.1 (0.8-1.6)	1.2 (0.9-1.6)	0.8 (0.5-1.3)	< 0.001	1.2 (0.9-1.7)	0.8 (0.6-1.3)	< 0.001
Mon (10^3/ul)	0.43 (0.3-0.6)	0.5 (0.3-0.6)	0.4 (0.2-0.7)	0.509	0.43 (0.3-0.6)	0.45 (0.30-0.70)	0.788
Hgb (g/dl)	12.7 (11.3-13.9)	13 (11.8-14)	11.6 (9.9-13.1)	< 0.001	13 (11.9-14)	11.5 (9.5-13)	< 0.001
Plt (10^3/ul)	203 (158-255)	199 (157-199)	224 (163-288)	0.001	199 (156-248)	215 (161-277)	0.005
NLR	3.8 (2.2-7.8)	3.1 (1.9-5.5)	9.7 (5.7-16.9)	< 0.001	3.07 (1.93-5.03)	9.55 (5.58-15.63)	< 0.001

IU = inpatient unit; ICU = intensive care unit; IQR = interquartile range (25^{th} to 75^{th} percentile); SBP = systolic blood pressure; HR = heart rate; SpO_2 = blood oxygen saturation; WBC = white blood cells; Lym = lymphocytes; Neu = neutrophils; Mon = monocytes; Hgb; hemoglobin; Plt = platelets, NLR = neutrophil-to-lymphocyte ratio.

Receiver operating characteristic (ROC) analysis was performed, in which the area under the curve (AUC) was calculated to evaluate the predictive accuracy of the NLR values by means of the DeLong method.[13] The Youden J index (YJI) was used to calculate the highest threshold values for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).[14]

RESULTS

This study was conducted using data from 1,175 patients, among whom 439 were women and 483 were men. There were 889 patients in the survivor group and 286 patients in the non-survivor group; and there were 922 patients in the IU group and 253 patients in the ICU group (**Table 1**).

The median age of the population included in the study was 63 years (IQR: 48-75), with a minimum age of 19 and a maximum age of 98. The median ages in years (with IQR) of the groups were as follows: 58 (46-70) survivors and 75 (65-82) non-survivors; 59 (46-72) IU and 74 (64-81) ICU (**Table 2**).

Analysis on the effects of chronic diseases on the prognosis for COVID-19 showed that there were significant differences between the survivor and non-survivor groups and between the IU and ICU groups regarding COPD, CHF, CAD, AF, CRF and CND. While there was a significant difference between the survivor and non-survivor groups regarding hypertension (HT), there was no significant difference between the IU and ICU groups (**Table 1**). While there were statistically significant differences in both pairs of groups regarding HR and SpO_2, which are among the vital signs, there was no statistically significant difference regarding SBP (**Table 2**). While significant differences (P < 0.001) were detected in both pairs of groups regarding WBC, Neu, Lym, Hgb, Plt and NLR among the laboratory parameters, there was no significant difference in either pair of groups regarding monocytes (**Table 2**). The data on the study population are presented in **Tables 1** and **2**.

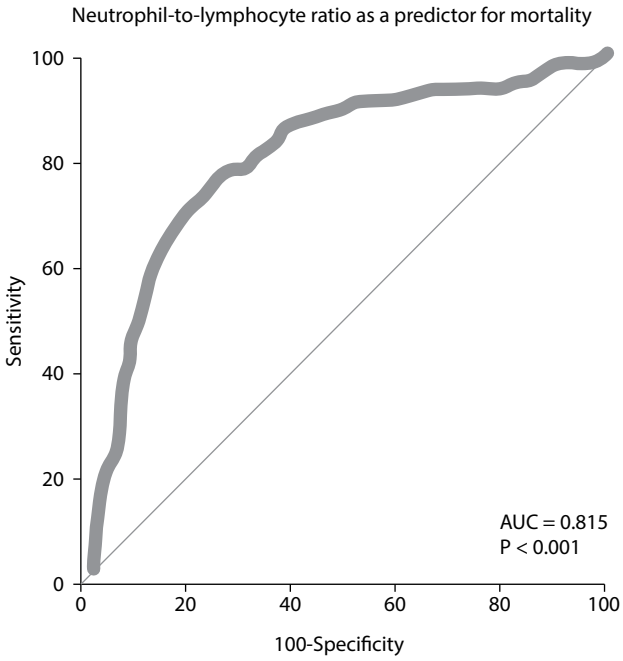
Predictive values for NLR, in relation to in-hospital mortality and ICU requirement, were analyzed by means of ROC analysis. With an NLR cutoff value of 5.14, the sensitivity, specificity, PPV, NPV, AUC and YJI values for in-hospital mortality were calculated as 77.27%, 75.82%, 50.7%, 91.2%, 0.815 and 0.5309, respectively (P < 0.001) (**Figure 1** and **Table 3**). With the same NLR cutoff value, the sensitivity, specificity, PPV, NPV, AUC and YJI values for ICU requirement were calculated as 77.87%, 74.08%, 45.2%, 92.4%, 0.811 and 0.5194, respectively (P < 0.001) (**Figure 2** and **Table 3**).

DISCUSSION

COVID-19 has a significant impact on the hematopoietic system. Dysregulation of the hematological and immunological systems plays a key role in the pathological process of this infection.[15]

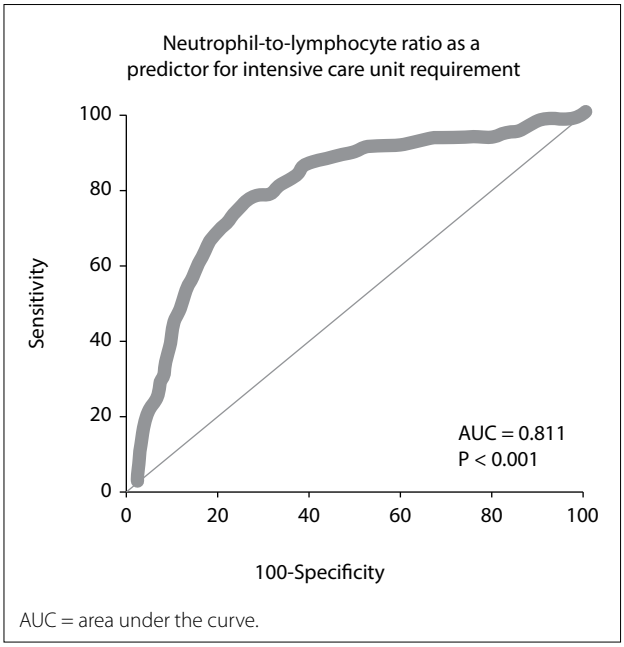
In this study, we concluded that the NLR values of COVID-19 patients at the time of admission to the ED can be used as a predictor for ICU requirement and mortality risk. In addition, advanced age, leukocytosis, anemia and lymphopenia were found to be associated with poor prognosis. Over recent years, the diagnostic and prognostic accuracy of various ratios such as neutrophil-to-lymphocyte, thrombocyte-to-lymphocyte and monocyte-to-lymphocyte have been studied in relation to many inflammatory conditions. Similar studies are ongoing in the COVID-19 pandemic.

In a study based on retrospective analysis of clinical data from 443 patients with COVID-19, Shang et al. reported that NLR,



AUC = area under the curve.

Figure 1. Neutrophil-to-lymphocyte ratio as a predictor for mortality.



AUC = area under the curve.

Figure 2. Neutrophil-to-lymphocyte ratio as a predictor for intensive care unit requirement.

Table 3. Predictive accuracy of neutrophil-to-lymphocyte ratio in terms of severity among COVID-19 patients

Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	YJI	Criterion for YJI	P
As a predictor for intensive care unit requirement							
77.87	74.08	45.2	92.4	0.811 (0.788 - 0.833)	0.5194	> 5.143	< 0.001
As a predictor for mortality							
77.27	75.82	50.7	91.2	0.815 (0.792 - 0.837)	0.5309	> 5.143	< 0.001

NLR = neutrophil-to-lymphocyte ratio; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; YJI = Youden J index; CI = confidence interval.

C-reactive protein (CRP) and platelet values can help determine the severity of the disease. They also reported that although all these parameters have prognostic significance, NLR had the best predictive performance.[16]

In a recent study conducted in Turkey, the relationship between ICU requirement for COVID-19 patients and their hemogram parameters at the time of initial admission was investigated. It was highlighted that high NLR and monocyte-to-lymphocyte and low platelet-to-lymphocyte ratios can be predictors for ICU requirement.[17]

In a prospective study conducted in Pakistan, it was reported that use of the NLR successfully enabled early recognition of severe conditions among patients with COVID-19 pneumonia.

In a study assessing the prognostic accuracy of the NLR, the AUC was calculated as 0.831 and the YJI was 0.589. In addition, it was reported that, for the optimum NLR threshold value of 4.795, the sensitivity was 83.9% and the specificity was 75%.[18] In our study, the best threshold value was found to be 5.14. In terms of ICU requirement, we calculated the sensitivity as 77.87%, specificity 74.08%, AUC 0.811 and YJI 0.519 for this NLR cutoff value of 5.14. Evaluation of the same cutoff value in terms of mortality prediction gave rise to sensitivity calculated as 72.27%, specificity 50.7%, AUC 0.815 and YJI 0.530.

The immune system is the system that is most affected by COVID-19 infection, after the respiratory system.[19] Therefore, it is not surprising that the NLR has high predictive accuracy. In assessing the pathogenesis of the disease, it is seen that necrosis, bleeding and atrophy occur in the spleen, and also that there are significant decreases in lymphocyte and neutrophil counts. In addition, in cases in which the inflammatory response increases, lymphocytes in lymph nodes are depleted and the numbers of CD4+ and CD8+ cells decrease.[20]

While neutrophils are vital in the innate immune response, lymphocytes also play an important role in the adaptive inflammatory response. Therefore, increased NLR reflects the imbalance of the inflammatory response and can be considered to be a possible indicator of disease severity in infectious diseases such as sepsis

and bacteremia.[21] In a meta-analysis examining 15 studies, it was reported that the neutrophil count and NLR were higher, but that the lymphocyte count was lower in severe COVID-19 cases, compared with non-severe cases.[22] Additionally, recent studies have reported that NLR can be a reliable predictor, not only for inflammatory diseases and infections, but also for other acute medical conditions, including cerebral hemorrhage, acute coronary syndrome and ischemic stroke.[23-25]

In general, elderly patients have been shown to be the "most vulnerable" group with regard to COVID-19 mortality.[26,27] In one study, COVID-19 patients aged 60 years and over were shown to have greater severity of clinical outcomes and higher mortality rates, compared with those who were under 60.[28] Similarly, in our study, we concluded that greater age was associated with increased risk of ICU requirement and mortality.

This study had certain limitations, such as having a relatively small sample size and being a single-center study. For more accurate and precise results, wider generalizability of the findings and validation of our results, multicenter clinical studies with larger sample sizes are required.

CONCLUSION

The NLR, which is a widely available simple parameter, can provide rapid insights regarding early recognition of critical illness and prognosis among COVID-19 patients.

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Address for correspondence:
Rohat Ak
Department of Emergency Medicine, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Şemsi Denizer Cad., E-5 Karayolu, Cevizli Mevkii
34890 Kartal/Istanbul, Turkey
Tel. + 90 506 821 31 36
E-mail: rohatakmd@gmail.com

Mental disorders among pregnant women during the COVID-19 pandemic. A cross-sectional study

Deha Denizhan Keskin[I], Seda Keskin[II], Sedat Bostan[III]

Ordu University, Faculty of Medicine, Training and Research Hospital, Ordu, Turkey

[I]MD. Assistant Professor, Department of Obstetrics and Gynecology, Faculty of Medicine, Ordu University, Ordu, Turkey.
https://orcid.org/0000-0002-6108-7619

[II]MD. Assistant Professor, Department of Obstetrics and Gynecology, Faculty of Medicine, Ordu University, Ordu, Turkey.
https://orcid.org/0000-0002-5640-4552

[III]MD. Professor, Department of Health Management, Faculty of Health Sciences, Ordu University, Ordu, Turkey.
https://orcid.org/0000-0002-9439-8448

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Anxiety.
Depression.
Sleepiness.

AUTHORS' KEY WORDS:
Psychiatric disorders.
Gestation.
Coronavirus disease-19.
Hopelessness.

ABSTRACT

BACKGROUND: Pregnancy is the most important event in women's lives and can lead to psychological lability. Several risk factors (such as disasters, events and pandemics) have been correlated with greater prevalence of mental disorders during pregnancy.

OBJECTIVES: To research how pregnant women have been affected by the coronavirus disease-19 (COVID-19) pandemic process, in order to contribute to the limited literature.

DESIGN AND SETTING: Cross-sectional survey study conducted at the Training and Research Hospital of the Faculty of Medicine, University of Ordu, Ordu, Turkey, from February 1 to March 1, 2021.

METHODS: In total, 356 pregnant women were enrolled and completed the survey. Intention of going to hospital and the Beck anxiety, Beck depression, Beck hopelessness and Epworth sleepiness scales were applied to detect mental disorders.

RESULTS: Among the participants, the anxiety, depression, hopelessness and sleepiness scores were 29.2%, 36.2%, 58.1% and 11.8%, respectively. The pregnant women stated that they avoided going to hospital in unnecessary situations by obeying the 'stay at home' calls, but also stated that they were afraid of the potential harmful effects of inadequate physician control. However, most of them stated that they would go to the hospital in emergencies.

CONCLUSIONS: This paper illustrated the effect of the COVID-19 pandemic on the mental health of pregnant women and emphasized their high rates of anxiety, depression, hopelessness and sleepiness. Since presence of mental disorders is indirectly related to poor pregnancy outcomes, preventive strategies should be developed, especially during this pandemic process.

INTRODUCTION

The coronavirus disease-19 (COVID-19) has spread rapidly throughout the world. After it was declared to be a pandemic by the World Health Organization (WHO) on March 11, 2020, the disease became a threat to global health.[1] In addition to the life-threatening situation of the virus, its economic, social and psychological effects have also been the subject of various studies.[2,3] Although vaccination continues rapidly, there is no indication that the COVID-19 pandemic will end soon, according to health authorities. And in this crisis environment, pregnant women still have to give birth during the pandemic.[4]

Pregnancy and childbearing are important events in women's lives, and both of these can lead to psychological lability. In addition to the anxiety caused by pregnancy itself, several other risk factors (such as disasters, events and pandemics) have been correlated with presence of high anxiety, depression and hopelessness during pregnancy.[5] Many pandemic-related factors, such as social/physical isolation, lockdown, physical inactivity and economic uncertainty have been causing mental disorders within society. Additional risks specific to pregnancy have made pregnant women more vulnerable to mental disorders than the general population.[6]

On the other hand, as shown in various studies, prenatal mental disorders are associated with miscarriage, preterm birth, low infant birth weight, gestational diabetes and gestational hypertension.[7-10]

Although many studies revealing the psychological effects of COVID-19 on society have been published, only a limited number of studies investigating the effects of the pandemic on the pregnant population are available in the literature.

OBJECTIVE

The aim of this study was to investigate how pregnant women have been affected by the pandemic process, in order to contribute to the limited literature on this subject.

METHODS

This descriptive cross-sectional survey study was conducted between February 1 and March 1, 2021. Over this period, the numbers of cases of COVID-19 infection were increasing rapidly in the city of Ordu, which is the third largest city by population in the Black Sea region of Turkey. Furthermore, also over the period of the survey, this city and its province (Altınordu) ranked highest in the weekly number of cases per 100,000 population in Turkey.[11]

The study population consisted of pregnant women who were followed up at the Ordu University Training and Research Hospital, in Ordu. Our study received ethical approval from the Ministry of Health of the Republic of Turkey, under the number 2020-05-11T18_34_16, dated May 27, 2020.

In our study, data from 356 pregnant women who completed the survey questionnaire were analyzed. Patients diagnosed with COVID-19 or with existing psychiatric diseases were excluded from the study.

The first part of the survey included ten questions that aimed to collect data about the participant's demographic characteristics and pregnancy conditions. These ten questions asked about their age, number of pregnancies, pregnancy trimester, work, body mass index, education, marital status, presence of chronic disease, smoking and any close contact with COVID-19-infected patients.

The second part of the survey consisted of the "intention of going to hospital" scale. This scale, consisting of nine questions, was developed by Bostan.[12] The questions in this part were as follows: Currently, while the coronavirus pandemic continues…? (a) I go to the hospital because I am curious about the condition of the patients; (b) I go to the hospital to visit my relatives or friends; (c) I go to the hospital to have my medicine prescribed; (d) I go to the hospital to have the routine tests that I have in mind; (e) I go to the hospital for the appointment that my physician has given me for a routine check; (f) I go to the hospital if I feel mild discomfort; (g) I go to the hospital if my current disease increases a little more; (h) I go to the hospital if my current illness becomes serious; (i) I go to the hospital if I have some trouble that I think is urgent; and (j) I would never go to the hospital. The participants were asked to answer these questions by selecting one of five options that were scored from zero to four. One of the questions on the intention of going to hospital scale was excluded from the analysis because it did not reach a sufficient factor load.

Lastly, in the third part of the survey, the participants answered questions on the Beck anxiety scale,[13] Beck depression scale,[14] Beck hopelessness scale,[15] and Epworth sleepiness scale.[16] Details of the questionnaire are presented in **Table 3**. The Beck anxiety scale was developed in 1988 and consists of 21 items on Likert scales ranging from zero to three, and with raw scores ranging from 0 to 63. The scores are classified as minimal anxiety (0 to 7), mild anxiety (8 to 15), moderate anxiety (16 to 25) and severe anxiety (26 to 63).

The Beck depression scale was first introduced in 1961 and contains questions on 21 symptoms and attitudes. The questions receive ratings from zero to three to reflect the intensity of symptoms or attitudes, and this gives rise to a score that can range from 0 to 63. A total score of less than 9 depicts minimal depression; a score of 10-18, mild depression; a score of 19-29, moderate depression; and a score of 30 or above, severe depression.

The Beck hopelessness scale was defined in 1974 and includes 10 questions. Its total score can range from 0 to 20. Scores from 0 to 3 are considered normal; 4 to 8, mild hopelessness; 9 to 14, moderate hopelessness; and greater than 15, severe hopelessness.

The Epworth sleepiness scale was initially reported in 1991 and is a self-administered questionnaire consisting of 8 questions. Respondents are asked to rate each item on a four-point scale (0 to 3). On this scale, scores of 0-9 are evaluated as mild sleepiness and scores of 10 and above are evaluated as severe sleepiness.

The Beck and Epworth scales are widely used within in healthcare. The validity of these scales has been tested by means of confirmatory factor analysis. The validity of the "intention of going to hospital" scale was tested by means of exploratory factor analysis. In addition, reliability analyses were performed on all the scales. The Kaiser-Meyer-Olkin (KMO) sampling coefficient was found to be greater than 0.80 for each scale, and this was accepted as very good.

The results from the Bartlett sphericity test, which was used to evaluate the appropriateness of the scales for factor analysis, were also found to be significant (P = 0.000). According to these evaluations, the scales were found to be suitable for factor analysis. It was understood that the factor loads of all the scales were generally high and their power to explain the total variance was sufficient.

To analyze the results from the study, the Statistical Package for the Social Sciences (SPSS) software, version 26, was used (IBM Statistics, Armonk, New York, United States). The analyses were carried out using a 95% confidence interval (P = 0.05). Descriptive statistical methods and correlation analyses were used in the study.

RESULTS

In total, 356 pregnant women in Ordu were enrolled in this study. Their demographic characteristics and pregnancy conditions are demonstrated in **Table 1**. The mean age of these pregnant women was 30.06 + 6.41 years. Among them, the majority were in the 20-25 age group (26.4%), married (92.7%), in the first trimester (39.3%) and primigravid (39.3%). Among all the participants, 65.7% were housewives or not working, 91.9% had a normal

Table 1. Demographic characteristics and pregnancy conditions

	n	%
Age		
18-24	79	22.2
25-29	94	26.4
30-34	80	22.5
35-39	74	20.8
40-44	29	8.1
No. of pregnancies		
1	140	39.3
2	95	26.7
3	72	20.2
4	23	6.5
> 5	26	7.2
Pregnancy trimester		
First	140	39.3
Second	95	26.7
Third	72	20.2
Work		
Housewife/not working	234	65.7
Working	122	34.3
Body mass index (BMI)		
Normal weight (BMI < 30)	327	91.9
Obese (BMI > 30)	29	8.1
Education		
Elementary school (eight years)	173	48.6
High school (four years)	125	35.1
University and above	58	16.3
Marital status		
Married	330	92.7
Single or divorced	26	7.3
Presence of chronic disease		
No	286	80.3
Yes	70	19.7
Smoking		
No	332	93.3
Yes	24	6.7
Any close contact with COVID-19 infected patients		
No	341	95.8
Yes	15	4.2

body mass index and 48.6% had completed their elementary education (total of eight years). In addition, 19.7% of the participants had a chronic disease and 6.7% were smokers. Only 4.2% of the pregnant women stated that they had had close contact with people diagnosed with COVID-19.

The second part of the survey consisted of eight questions on the "intention of going to hospital" scale, which are presented in **Table 2**. This scale was designed using a five-degree Likert scale. For as long as the pandemic continues, the participants declared that they would not go to the hospital to visit their relatives or friends, or to have their medicine prescribed, or to have the routine tests that they had in mind (96.6%, 50.8% and 57.3% respectively). The proportion of the patients who stated that they would not go to the hospital even when they felt mild discomfort was 60.7%. More than half of the participants (55.9%) declared that they would go to the hospital for routine checks, provided that an appointment had been made by their physician. About two thirds of the participants (68.8%) said that they would go to the hospital if their illness became serious, while four out of five (80.3%) said that they would go to the hospital if they thought their illness was urgent. 46.1% of the pregnant women showed uncertainty regarding their intention to go to the hospital if their current disease increased a little more.

The responses to the Beck anxiety, Beck depression, Beck hopelessness and Epworth sleepiness scales are presented in **Table 3**. Approximately one in three of the participants (29.2%) stated that they experienced anxiety. The rates of mild, moderate and severe anxiety were 18.3%, 8.1% and 2.8%, respectively. The depression rates were observed to be close to anxiety rates (36.2%). The rates of mild, moderate and severe depression were 25.5%, 7.6% and 3.1%, respectively. The hopelessness rates were higher than the anxiety and depression rates. While 44.3% of pregnant women reported having mild hopelessness, 11.8% experienced moderate and 2% experienced severe hopelessness. Lastly, mild sleepiness was found in 88.2% and severe sleepiness in 11.8% of the pregnant women.

Correlation analysis was done to understand the relationships between the research scales is presented in **Table 4**. It was observed that there was no statistically significant relationship between the intention of going to the hospital and the levels of anxiety, depression, hopelessness and sleepiness. On the other hand, a very strong linear relationship was found between the anxiety, depression, hopelessness and sleepiness levels of the pregnant women at the $P = 0.001$ error level.

DISCUSSION

More than one year has passed since COVID-19 was declared a pandemic. Despite this length of time, the effects of the pandemic are still felt all over the world.[17] Undoubtedly, healthcare professionals constitute the group most affected in this process. While the effect of pandemic on the healthcare sector and on healthcare workers has been the subject of many studies, the number of investigations in the literature, on its effects on the pregnant population, is limited.[18-20] The aim of this descriptive study was to contribute to this limited literature through investigating the effects of the pandemic process on pregnant women.

Pregnancy itself is already known to be a cause of psychological lability, and this has been shown in many studies.[5,21-23] Not surprisingly, pregnant women have relatively high prevalence rates of anxiety, depression, hopelessness and sleepiness. In three different meta-analyses that compiled data on the mental status of pregnant women, the prevalences of anxiety, depression and

Table 2. "Intention of going to hospital" scale

Question	I will definitely not go		I will not go		I may go		I will go		I will definitely go		$\bar{x}$	SD
	n	%	n	%	n	%	n	%	n	%		
a*											factor load was insufficient	
b*	198	55.6	146	41.0	6	1.7	6	1.7	0	0.0	0.49	0.62
c*	73	20.5	108	30.3	110	30.9	61	17.1	4	1.1	1.48	1.03
d*	80	22.5	124	34.8	94	26.4	53	14.9	5	1.4	1.37	1.03
e*	17	4.8	30	8.4	110	30.9	156	43.8	43	12.1	2.50	0.97
f*	54	15.2	162	45.5	87	24.4	47	13.2	6	1.7	1.40	0.95
g*	7	2.0	34	9.6	164	46.1	130	36.5	21	5.9	2.34	0.80
h*	0	0.0	12	3.4	99	27.8	182	51.1	63	17.7	2.83	0.75
i*	0	0.0	5	1.4	65	18.3	204	57.3	82	23.0	3.01	0.68
j*											factor load was insufficient	
										factor means	1.76	0.48

$\bar{x}$ = sample mean; SD = standard deviation.

*The questions of this scale were as follows: Currently, while the coronavirus pandemic continues…? (a) I go to the hospital because I am curious about the condition of the patients; (b) I go to the hospital to visit my relatives or friends; (c) I go to the hospital to have my medicine prescribed; (d) I go to the hospital to have the routine tests that I have in mind; (e) I go to the hospital for the appointment that my physician has given me for a routine check; (f) I go to the hospital if I feel mild discomfort; (g) I go to the hospital if my current disease increases a little more; (h) I go to the hospital if my current illness becomes serious; (i) I go to the hospital if I have some trouble that I think is urgent; and (j) I would never go to the hospital.

Table 3. Beck anxiety, Beck depression, Beck hopelessness and Epworth sleepiness scales

	n	%
Beck anxiety scale		
➢ Minimal anxiety (0-7)	252	70.8
➢ Mild anxiety (8-15)	65	18.3
➢ Moderate anxiety (16-25)	29	8.1
➢ Severe anxiety (26-63)	10	2.8
Beck depression scale		
➢ Minimal depression (0-9)	227	63.8
➢ Mild depression (10-18)	91	25.5
➢ Moderate depression (19-29)	27	7.6
➢ Severe depression (30-63)	11	3.1
Beck hopelessness scale		
➢ Normal (0-3)	149	41.9
➢ Mild hopelessness (4-8)	158	44.3
➢ Moderate hopelessness (9-14)	42	11.8
➢ Severe hopelessness (15-20)	7	2.0
Epworth sleepiness scale		
➢ Mild sleepiness (0-9)	314	88.2
➢ Severe sleepiness (10-24)	42	11.8

Table 4. Correlation analysis between the research scales

	Intention of going to hospital	Beck anxiety	Beck depression	Beck hopelessness
Intention of going to hospital	1			
Beck anxiety	-0.029	1		
Beck depression	-0.041	0.980**	1	
Beck hopelessness	-0.039	0.962**	0.990**	1
Epworth sleepiness	-0.038	0.970**	0.993**	0.992**

**Correlation is significant at the 0.01 level (two-tailed).

sleepiness were given as 15.2%, 11.9% and 45.7%, respectively.[24-26] The results from our study revealed that 29.2%, 36.2%, 58.1% and 11.8% of the participants had anxiety, depression, hopelessness and sleepiness, respectively, with levels varying from mild to severe. Thus, the pregnant women participating in our study reported that they experienced more anxiety, depression, hopelessness and sleepiness than in reports in the literature. We attributed this excess rate to the high prevalence of COVID-19 infection in Ordu province.

In addition, many studies have shown that events such as natural disasters, economic crisis and pandemics adversely affect the mental health of the community.[3,27,28] It is inevitable that such events will affect pregnant women worse than the general population.[22] It has been determined that the main factors adversely affecting pregnant women's mental health and causing anxiety in pandemics have been abstention from the daily routine, the need for social distancing and decreased social support. They also expressed fears about their babies', their families' and their own health, due to the uncertainties of the pandemic.[6] Studies on pregnancy in relation

to the COVID-19 pandemic have shown that the main factors that increased anxiety among pregnant women were lockdown measures and disruption to routine pregnancy follow-up.[6,24,25] Studies have shown that, in this pandemic situation, pregnant women prefer to have fewer checkups from doctors for fear of infection, but also worry that their pregnancy could be made more complicated through inadequate follow-up.[4,6,22,29]

Our findings showed that 29.2% of the pregnant women experienced anxiety. According to the "intention of going to hospital" scale, the pregnant women participating in this survey stated that they refrained from going to hospital in unnecessary situations such as visiting relatives/friends, having medications prescribed and having the routine tests that they had in mind. This result showed that the pregnant population had reached the required level of awareness regarding COVID-19 by following appeals to 'stay at home'. But at the same time, their preference to go to routine checks if they got an appointment showed their fear of the potential harmful effects of inadequate physician control. While their hesitation regarding going to hospital continued even if they felt mild discomfort, most of the pregnant women stated that they would go to the hospital in cases of emergency (such as if their current disease worsened or if they thought that their situation was urgent).

We observed that anxiety and depression rates have been found to be related to each other in many studies.[6,20,23] In our study, 36.2% of the participants presented depression (in 10.7%, it was moderate or severe). As expected, anxiety related to COVID-19 infection also led to depressive symptoms in the pregnant population.

In a cross-sectional study investigating sleep quality among pregnant women, sufficient sleep duration was defined as sleeping 7-9 h/day.[30] In some studies, it has been shown that the proportion of pregnant women with poor sleep quality (for a variety of reasons) was between 38.8% and 82.6%.[31-33] In our study, the rate of sleepiness was found to be lower than in the literature (11.8%). We attributed this low rate to the Epworth sleep scale that we used in the survey, because this scale evaluated sleepiness in only two stages, unlike the ones used in the literature. In studies on pregnant women, high anxiety level, low social support and insufficient partner support were found to be associated with low sleep quality. Therefore, it is very important to provide the necessary social and partner support in order to protect pregnant women from the psychologically destructive effects of the pandemic. With this support, situations such as social isolation and postpartum depression can be prevented, and a healthy partner relationship and adequate baby care can be provided after delivery.[34,35]

Studies conducting subgroup analysis have shown that multigravid pregnant women were more affected by the COVID-19 pandemic. Multigravid women have to struggle with several challenges, such as increased financial responsibilities and having an additional child. Moreover, in these studies, it was observed that greater anxiety was detected in the first and third trimesters, possibly due to hormonal changes and fear of delivery.[36,37]

Many studies have suggested that mental disorders have a more severe course in the prenatal and postnatal periods and that they have lasting negative effects on mothers, fetuses and children. The adverse prenatal outcomes include preeclampsia, gestational hypertension, gestational diabetes, miscarriage, intrauterine growth restriction and low birth weight.[7-10] Emotional, behavioral and cognitive problems have been found to be more common among postnatal mothers. Additionally, in further follow-up, changes to brain structures and functions were observed in their children.[38-39]

Some limitations of our study should be noted. Although we found high rates of anxiety, depression, hopelessness and sleepiness among pregnant women in the COVID-19 pandemic, we could not make any comparison with previous times since we did not have pre-pandemic data. In addition, we did not question the main reasons for increases in these parameters during the pandemic period in our survey. Our study provides information about the general population of pregnant woman because we were unable to clearly distinguish any group at higher risk among these pregnant women, through subgroup analyses, due to the limited number of patients and the cross-sectional structure of this survey.

CONCLUSION

This study revealed the effect of the COVID-19 pandemic on the mental health of pregnant women and highlighted the high prevalence rates of anxiety, depression, hopelessness and sleepiness among this population. Since the increased prevalence of mental disorders consequent to the pandemic is indirectly associated with poor pregnancy outcomes, the necessary support needs to be provided for this group of patients. This study has helped to emphasize the necessity of interventions that can be taken, especially during the pandemic process. Further studies could broaden the knowledge of the mental effects of COVID-19 among pregnant women.

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Address for correspondence:
Deha Denizhan Keskin
Department of Obstetrics and Gynecology, Medical Faculty, Ordu University
Cumhuriyet Ave., Mustafa Kemal Blvd., No: 478
52200 Altınordu/Ordu, Turkey
Tel. +905056273412
Fax. +904522265228
E-mail: dehadenizhankeskin@gmail.com

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What anthropometric indicators are associated with insulin resistance? Cross-sectional study on children and adolescents with diagnosed human immunodeficiency virus

Carlos Alencar Souza Alves Junior[I], Priscila Custódio Martins[II], Luiz Rodrigo Augustemak de Lima[III], Diego Augusto Santos Silva[IV]

Joana de Gusmão Children's Hospital, Florianópolis (SC), Brazil

[I]MSc. Doctoral Student, Postgraduate Program on Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil. https://orcid.org/0000-0002-5928-0567

[II]MSc. Doctoral Student, Postgraduate Program in Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil. https://orcid.org/0000-0002-6388-5550

[III]PhD. Adjunct Professor, Institute of Physical Education and Sport, Universidade Federal de Alagoas (UFAL), Maceió (AL), Brazil. https://orcid.org/0000-0003-0280-0151

[IV]PhD. Associate Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil. https://orcid.org/0000-0002-0489-7906

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ABSTRACT

BACKGROUND: Studies that test associations between anthropometric indicators and insulin resistance (IR) need to provide better evidence in the context of the pediatric population (children and adolescents) with human immunodeficiency virus (HIV), as anthropometric indicators present a better explanation of the distribution of body fat.

OBJECTIVE: To test the associations between anthropometric indicators and insulin resistance (IR) among children and adolescents diagnosed with HIV.

DESIGN AND SETTING: Cross-sectional study on 65 children and adolescents (8-15 years) infected with HIV through vertical transmission conducted at the Joana de Gusmão Children's Hospital, Florianópolis, Brazil.

METHODS: The anthropometric indicators measured were the abdominal (ASF), triceps (TSF), subscapular (SSF) and calf (CSF) skinfolds. The relaxed arm (RAC), waist (WC) and neck (NC) circumferences were also measured. Body mass index (BMI) was calculated from the relationship between body mass and height. IR was calculated through the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Simple and multiple linear regression analyses were used.

RESULTS: After adjustment for covariates (sex, bone age, CD4+ T lymphocytes, CD8+ T lymphocytes, viral load, and physical activity), associations between IR and models with SSF and CSF remained. Each of these explained 20% of IR variability. For females, in the adjusted analyses, direct associations between IR and models with ASF ($R^2 = 0.26$) and TSF ($R^2 = 0.31$) were observed.

CONCLUSIONS: SSF and CSF in males and ASF and TSF in females were associated with IR in HIV-infected children and adolescents.

INTRODUCTION

Antiretroviral treatment (ART) and human immunodeficiency virus (HIV) infection itself can cause side effects in individuals with HIV.[1] Among the adverse effects, visible changes in the body such as lipodystrophy syndrome[2] and metabolic changes such as dyslipidemia and insulin resistance (IR)[3] are among the most common adverse effects. IR is defined as lower capacity of insulin to instigate use of glucose by adipose tissue and muscles, or which leads to expansion of pancreatic insulin formation.[4]

HIV and continued use of ART are considered to be facilitators for development of IR in the pediatric population.[4] HIV infection, opportunistic infections and intestinal inflammation can culminate in changes to inflammatory cytokines, such as soluble tumor necrosis factor and hormones such as adiponectin and reduced leptin, which impairs glucose homeostasis.[5,6] In addition, changes to CD4+ and CD8+ T-cell functions may impair glycolysis, which may adversely influence glucose metabolism.[6] Specifically, ART protease inhibitors have been associated with hyperglycemia and glucose tolerance in adults diagnosed with HIV[7] and may inhibit the action of glucose transporter (GLUT4), thus resulting in decreased insulin-mediated glucose intake by muscle and adipose tissue.[1] In addition, changes to the body fat distribution pattern may result in changes to the hormonal secretory system of adipose tissue

and generate a chronic inflammatory profile, which facilitates IR development.[8]

Overweight is among the factors that contribute to the onset of IR in young people without HIV,[8] especially increased body fat. To assess body fat, anthropometric indicators are commonly used.[9] Different measurements have been directly associated with IR, such as neck circumference,[10] waist circumference (WC) and body mass index (BMI) in different populations.[11] In pediatric populations diagnosed with HIV, it has been reported that WC and BMI were directly associated with development of IR.[12,13] This underscores the relevance of easily and cheaply obtained anthropometric indicators for assessing associations with IR in HIV-infected children and adolescents.

Although a relationship between anthropometric indicators (WC and BMI) and IR in HIV-infected children and adolescents has been identified, the indicators used have not enabled analysis of fat distribution.[12,14,15] Skinfolds, which measure the thickness of the underlying layer of subcutaneous fat, are anthropometric indicators that have a direct association with reference methods for body fat assessment among young people diagnosed with HIV.[16] Furthermore, skinfolds are anthropometric markers that indicate accumulation of body fat in the peripheral region (i.e. triceps skinfold, TSF) and central region (i.e., subscapular skinfold, SSF; and abdominal skinfold, ASF).

Studies that test associations between skinfolds and IR need to provide better evidence in the context of the pediatric population (children and adolescents) with HIV, as anthropometric indicators present a better explanation of the distribution of body fat.

OBJECTIVE

The purpose of this study was to test associations between anthropometric indicators and IR in a pediatric population (eight to 15 years of age) with HIV.

METHODS

Population and sample

This was a cross-sectional study, conducted from 2015 to 2016 (November to June) in a city in southern Brazil. The research protocol was approval by the human research ethics committee of Universidade Federal de Santa Catarina (UFSC) (protocol number: 49691815.0.0000.0121; date of approval: February 15, 2016) and was also approved by the research ethics committee of Hospital Infantil Joana de Gusmão, Florianópolis, Santa Catarina (protocol number: 037/2015; date of approval: October 20, 2015).

Participants

Children and adolescents aged between eight and 15 years, with vertical transmission of HIV, were recruited for the study and were followed up clinically at the Hospital Infantil Joana de Gusmão, Florianópolis, Brazil. Eighty-three eligible patients were found. Three patients were excluded from the sample because they presented severe encephalopathy and because they were unable to walk. Three were excluded because we were unable to contact them, four because they had been transferred to another hospital and four because they refused to participate in the research; and another four were losses during the data collection. The final sample consisted of 65 subjects.

The inclusion criteria were the following: a) presence of information in the medical record to prove that HIV infection had been transmitted from mother to child; b) age between 8 and 15 years; c) ability to stand and communicate; and d) presence of laboratory and clinical information about the infection. The exclusion criteria were the following: a) presentation of contraindication against vigorous intensity exercises and existence of motor disability; b) problems that made speech, hearing and/or cognition impossible; c) presence of diseases that change body composition, except for HIV infection itself; and d) use of immunotherapies and regular use of diuretics. Individuals with any pathological condition other than HIV were excluded from the study.

The sample size was calculated *a posteriori*, taking into account the type I error ($\alpha = 0.05$) and type II error ($\beta = 0.80$) for testing associations between anthropometric indicators and IR, with an average effect size (0.50).[17] For simple and multiple linear regression analyses, the posterior analysis indicated that with $\alpha = 0.05$ and $\beta = 0.80$, a sample of 65 HIV+ children and adolescents would make it possible to find associations between anthropometric indicators and IR, with an effect size of 0.50.[17] All calculations were performed using the G* Power software version 3.1.9.2 (Universität Düsseldorf, Germany).

Dependent variable

To check IR, we used the Homeostasis Evaluation Model for Insulin Resistance Index (HOMA-IR), calculated through the mathematical model described by Matthews et al.[18] We applied the following equation: HOMA-IR = fasting blood glucose (mg/dl) x insulin (μIU/ml). In the mornings, fasting blood samples (15 ml) were collected to measure glucose and insulin concentrations. Glucose levels were determined using the oxidase method (Wiener CB 400i; Wiener Lab Group, Rosario, Argentina) and insulin levels were measured using the chemiluminescence method (Roche Diagnostics Elecsys, Indianapolis, United States).

The gold standard for IR evaluation is the hyperinsulinemic-euglycemic clamp.[4] However, this technique is expensive and invasive in the research context, and use of alternative methods for IR identification, such as HOMA-IR and the insulin sensitivity check index (QUICKI), is more frequent.[4,19] HOMA-IR has high correlation (r = 0.88) with the hyperinsulinemic-euglycemic clamp in the

pediatric population and demonstrates two evaluation parameters: plasma insulin and glucose.[19]

Independent variables

The anthropometric indicators measured were skinfolds: ASF, TSF, SSF and CSF; relaxed arm circumference (RAC); waist circumference (WC) and neck circumference (NC). Body mass index (BMI) was calculated from the relationship between body mass and square of height.

Standardization of measurements was performed in accordance with the guidelines of the International Society for the Advancement of Kinanthropometry (ISAK) by an ISAK level 1 certified anthropometrist. A sample of 32 children of the same age group was also measured to calculate the technical error of intra-rater measurement (TEM).[20]

To measure the skinfold thickness, a caliper plicometer (Cescorf, Porto Alegre, Brazil) with a resolution of 0.1 mm was used. Anthropometric tape without elasticity was used to measure body circumferences (Sanny, São Paulo, Brazil) with a unit of measurement of 0.1 cm. Portable digital scales (Tanita, 180 Tokyo, Japan) were used to measure body mass, with a total capacity of up to 150 kg, and with a resolution of 0.1 kg. A stadiometer (AlturaExata, Belo Horizonte, Brazil) was used for height verification, with a measuring capacity from 115 cm to 210 cm and a unit of measurement of 0.1 cm.

Control variables

Information on viral load, CD4+ T lymphocyte count (%) and CD8+ T lymphocyte count (%) was obtained from each participant's medical records. Bone age was assessed by means of wrist-carpal radiography, in the radiology sector of Joana de Gusmão Children's Hospital (JGCH). For this measurement, international standardization was used.[21] Bone age was treated as a continuous variable.

The GT3X-Plus Actigraph accelerometer (Manufacturing Technology Inc., Fort Walton Beach, United States) was used to measure moderate to vigorous-intensity physical activity (MVIPA), continuously over a seven to 14-day period that included weekend days. To ensure data reliability, the participants were asked to always use the accelerometer on the right side, located at the waist, throughout the day, and only to remove it for activities such as bathing, water activities and sleep. For data analysis, we considered records that extended across at least four days (three on weekdays and one on weekends) for a period of 10 hours or more, after removing times of non-use consisting of at least 60 one-minute records of successive zeros. The cutoff points proposed by Evenson[22] were used to quantify the MVIPA minutes, and these were adjusted according to the proportional time for which the youths remained awake (14 hours). Verbal and written instructions were made available to participants and guardians before the device was used.

Statistical treatment

Firstly, descriptive analyses were performed on the data (median and interquartile range). Kurtosis and asymmetry analyses were then used to verify data normality (range from -2 to + 2),[23] in addition to histogram analysis to identify data distribution normality. Student's t-test and the chi-square test were used to identify sex (male/female) differences. Simple and multiple linear regression were used to test associations between outcomes and exposures, respectively. For the multiple linear regressions, control variables (sex, bone age, CD4+ T lymphocytes, CD8+ T lymphocytes, viral load and physical activity) were used. Regression coefficients (β), 95% confidence intervals and determination coefficients (R^2) for each model analyzed and diagnoses of multicollinearity (VIF) were estimated. For descriptive analyses and simple and multiple linear regressions, the Statistical Package for the Social Sciences software (IBM SPSS Statistics, Chicago, United States), version 22.0, was used, with $P \leq 0.05$. All analyses were performed stratified according to sex (male/female), which can be justified through existence of sexual dimorphism, because as age increases, secretion of sex hormones can interfere with the amount of body fat.[24]

RESULTS

Sixty-five children and adolescents aged 8-15 years (30 males and 35 females), diagnosed with HIV, participated in the study. There were differences between the sexes, such that the females had higher SSF ($P < 0.001$) and CSF ($P = 0.050$) than the males. Regarding physical activity, the male adolescents did more minutes/day than the females ($P = 0.022$) **(Table 1)**.

Among the males, direct associations were observed in simple linear regressions between IR and SSF ($R^2 = 0.24$), CSF ($R^2 = 0.15$), WC ($R^2 = 0.15$), RAC ($R^2 = 0.11$), NC ($R^2 = 0.12$) and BMI ($R^2 = 0.15$). After adjustment for covariates (sex, bone age, CD4+ T lymphocytes, CD8+ T lymphocytes, viral load and physical activity), associations between IR and models with SSF and CSF remained, and each of these explained 20% of the IR variability **(Table 2)**.

For the females, direct associations were observed in simple analyses, such that ASF and TSF explained 20% and 18% of IR variability, respectively. In addition, direct associations with RAC ($R^2 = 0.10$) and NC ($R^2 = 0.25$) were observed. In the adjusted analyses, direct associations between IR and models with ASF ($R^2 = 0.26$) and TSF ($R^2 = 0.31$) were observed.

DISCUSSION

The main results from the present study add to the current literature to show that higher values for peripheral and central skin folds are associated with IR.

Table 1. Characteristics of children and adolescents diagnosed with human immunodeficiency virus (HIV), stratified according to sex (n = 65)

	Male (n = 30)		Female (n = 35)		
	Mean (SD)	**Min; Max**	**Mean (SD)**	**Min; Max**	**P-value**
Chronological age (years)	12.24 (2.19)	8.36; 14.79	12.16 (2.10)	8.01; 15.01	0.401
Bone age (years)	11.66 (2.83)	6.00; 17.00	12.31 (2.55)	5.75; 16.00	0.397
Height (cm)	147.72 (13.78)	116.80; 173.20	147.00 (12.63)	114.20; 167.00	0.694
Body mass (kg)	39.45 (12.24)	21.90; 72.40	40.38 (10.94)	18.70; 65.10	0.765
ASF (mm)	8.87 (4.07)	4.00; 18.00	10.74 (3.76)	5.00; 24.00	0.492
SSF (mm)	6.24 (2.00)	4.00; 13.00	8.23 (3.99)	4.00; 19.00	**< 0.001**
TSF (mm)	8.33 (2.38)	5.00; 13.00	10.74 (3.76)	6.00; 20.00	0.136
CSF (mm)	9.33 (2.84)	3.00; 16.00	11.06 (3.87)	6.00; 20.00	**0.050**
WC (cm)	63.59 (6.43)	53.00; 75.00	62.80 (6.72)	51.00; 82.00	0.870
RAC (cm)	20.97 (3.15)	16.00; 29.00	21.54 (3.03)	16.00; 27.00	0.880
NC (cm)	29.53 (3.41)	24.00; 38.00	28.34 (1.99)	23.00; 32.00	**< 0.001**
BMI (kg/cm^2)	17.69 (2.69)	12.62; 24.19	18.40 (2.74)	14.38; 24.80	0.671
Moderate-vigorous physical activity (minutes/day)	58.32 (31.90)	12.50; 141.80	39.51 (18.17)	10.50; 73.90	**0.022**
Viral load (log)	2.22 (1.03)	1.60; 5.04	2.11 (0.93)	1.60; 4.97	0.644
CD4+ T lymphocytes (cells/mm^3)	861.50 (364.55)	196.00; 1.811	854.31 (375.71)	135.00; 1731.00	0.552
CD8+ T lymphocytes (cells/mm^3)	44.27 (13.08)	405.00; 3.583	125.36 (508.49)	495.00 2.297	0.079
HOMA-IR	1.27 (0.83)	0.37; 3.79	1.56 (1.09)	0.27; 6.01	0.338
	n	**(%)**	**n**	**(%)**	
Current ART usage					0.846
Yes; with protease inhibitor	19	48.70	20	51.30	
Yes; without protease inhibitor	6	40.00	9	60.00	
Not used	5	45.50	6	54.50	
Sexual maturation					0.672
Prepubertal	8	53.30	7	46.70	
Pubertal	21	44.70	26	55.30	
Postpubertal	0	66.70	1	33.30	

ASF = abdominal skinfold; SSF = subscapular skinfold; TSF = triceps skinfold; CSF = calf skinfold; BMI = body mass index; RAC = relaxed arm circumference; WC = waist circumference; NC = neck circumference; IR = insulin resistance; cm = centimeters; mm = millimeters; SD = standard deviation; Min = minimum; Max = maximum; ART = antiretroviral drugs; HOMA-IR = Homeostasis Model Assessment for Insulin Resistance.

Table 2. Simple and multiple linear regressions between insulin resistance and anthropometric indicators among male and female children and adolescents diagnosed with HIV (n = 65)

	Male (n = 30)								
	Simple				Multiple*				
	β (95% CI)	**SE**	**R^2**	**P**	**β (95% CI)**	**SE**	**R^2**	**P**	**VIF**
ASF (mm)	0.06 (-0.02; 0.13)	0.04	0.42	0.12	0.05 (-0.04; 0.14)	0.04	0.08	0.28	1.30
SSF (mm)	0.21 (0.07; 0.35)	0.07	0.24	**< 0.01**	0.17 (0.01; 0.33)	0.07	0.20	**0.04**	1.34
TSF (mm)	0.09 (-0.03; 0.21)	0.06	0.03	0.16	0.05 (-0.09; 0.19)	0.07	0.05	0.47	1.22
CSF (mm)	0.12 (0.02; 0.23)	0.05	0.15	**0.02**	0.14 (0.01; 0.28)	0.06	0.20	**0.04**	1.34
WC (cm)	0.05 (0.01; 0.10)	0.02	0.16	**0.02**	0.03 (-0.04; 0.11)	0.03	0.07	0.33	2.64
RAC	0.09 (0.01; 0. 19)	0.05	0.11	**0.04**	-0.02 (-0.21; 0-16)	-0.08	0.03	0.82	3.54
NC	0.09 (0.01; 0.18)	0.04	0.12	**0.03**	0.02 (-0.13; -0.18)	0.07	0.04	0.72	3.16
BMI	0.13 (0.02; 0.24)	0.05	0.15	**0.01**	0.07 (-0.13; 0.28)	0.10	0.06	0.45	3.17
	Female (n = 35)								
ASF (mm)	0.10 (-0.57; 1.22)	0.44	0.20	< 0.01	0.11 (0.02; 0.20)	0.04	0.26	**0.01**	1.57
SSF (mm)	0.08 (-0.01; 0.17)	0.05	0.05	0.09	0.06 (-0.04; 0.17)	0.05	0.12	0.23	1.41
TSF (mm)	0.13 (0.04; 0.22)	0.04	0.18	**< 0.01**	0.14 (0.05; 0.24)	0.04	0.31	**< 0.01**	1.32
CSF (mm)	0.08 (-0.01; 0.18)	0.05	0.05	0.09	0.10 (-0.01; 0.22)	0.05	0.19	0.06	1.59
WC	0.05 (-0.01; 0.11)	0.03	0.07	0.07	0.02 (-0.05; 0.09)	0.03	0.09	0.55	1.61
RAC	0.13 (0.01; 0.25)	0.06	0.10	**0.04**	0.11 (-0.08; 0.29)	0.09	0.12	0.26	2.55
NC	0.28 (0.11; 0.44)	0.08	0.25	**< 0.01**	0.33 (-0.01; 0.69)	0.17	0.19	0.06	4.11
BMI	0.11 (-0.02; 0.25)	0.06	0.05	0.09	0.03 (-0.16; 0.22)	0.09	0.08	0.74	1.97

ASF = abdominal skinfold; SSF = subscapular skinfold; TSF = triceps skinfold; CSF = calf skinfold; WC = waist circumference; RAC = relaxed arm circumference; NP = neck circumference; BMI = body mass index; β = regression coefficient; CI = confidence interval; SE = standard error; VIF = multicollinearity diagnosis; *adjusted according to sex, bone age, CD4+ T lymphocytes, CD8+ T lymphocytes, viral load and physical activity.

SSF and CSF (males) and ASF and TSF (females) were directly associated with IR among these pediatric patients with HIV. Several studies have shown associations between different central and peripheral skinfolds and IR among HIV-infected children and adolescents,[25–28] based on the assumption that accumulation of subcutaneous adiposity is associated with IR due to increased lipotoxicity.[29] In this context, insulin favors entry of glucose into adipose tissue, which activates lipoprotein lipase, thus promoting storage of triglycerides and preventing the action of protein kinase, an intracellular enzyme that is capable of blocking insulin signaling pathways.[29] However, in the context of HIV infection, the complexity of the scenario increases due to the adverse effects both of the virus itself and of ART. This is concomitant with possible increases in body fat and, consequently, the lipotoxic effect of lipodystrophy.[4] Protease inhibitors (PIs) are believed to play an important role in the emergence of IR dyslipidemia and increased quantities of visceral adipose tissue.[1,4]

Specifically in relation to central skinfolds associated with IR, our data corroborate previous studies among children and adolescents of different ethnicities and without HIV diagnoses, regarding SSF[25,27] and ASF.[30,31] The android phenotype of body fat accumulation (more in the trunk) has been more associated with IR, which is explained by pancreatic β cell dysfunction due to formation of reactive oxygen species (ROS), which act on metabolic dysregulation to cause IR.[32] Regarding peripheral skinfolds (CSF [male] and TSF [(female]), which demonstrated associations with IR, our data are consistent with the findings from a systematic review that demonstrated that peripheral subcutaneous fat was associated with IR.[33]

HIV-infected individuals undergoing ART treatment with protease inhibitors are predisposed to lipodystrophy syndrome (fat loss or accumulation) in peripheral regions such as arms and legs.[2] Antiretroviral protease inhibitor treatment reduces the action of peroxisome proliferator-activated receptors (PPARy), thereby decreasing adiponectin levels and culminating in IR.[6] Although there is no consensus on the association between different lipodystrophy phenotypes and IR in pediatric patients diagnosed with HIV, high insulin concentrations were found previously in children with lipohypertrophy, and less consistently in children with lipoatrophy.[4]

The skinfolds associated with IR differed according to sex (male/female). This may be explained by the existence of sexual dimorphism. In girls, as their age increases, estradiol hormone secretion also increases, which leads to fat accumulation in the arms and consequently increases the amount of adipocytes in the tricipital region.[24] In boys, increasing secretion of testosterone hormone inhibits abdominal fat accumulation.[24]

Regarding the associations of anthropometric indicators with IR, the results from this study demonstrated the potential of skinfold analyses, such that associations were found with SSF and TSF among males, and with ASF and CSF among females. This is important from a practical point of view, for clinical use in monitoring the body composition and metabolic complications of HIV-infected children and adolescents, given that skinfold measurement is a low-cost alternative.

This study had some limitations, such as the fact that HOMA-IR was used as an indicator of glycemic homeostasis impairment. Nonetheless, this method is often used in clinical investigations. Other limitations related to the absence of any clinical diagnosis for lipodystrophy.

Among the strengths of this study, the analyses were controlled for potential confounders (sex, bone age, CD4+ T lymphocytes, CD8+ T lymphocytes, viral load and physical activity) in the multiple linear regression analyses, a strategy that had not previously been addressed in studies making correlations between anthropometric indicators and body fat among children and adolescents diagnosed with IR.

CONCLUSIONS

In conclusion, SSF and CSF in males and ASF and TSF in females were directly associated with IR. It can be suggested that use of these anthropometric indicators should form part of the routine clinical follow-up for HIV-infected children and adolescents. These low-cost anthropometric measurements can contribute to risk stratification among children and adolescents with IR, and consequently may prevent metabolic complications such as type 2 diabetes and other cardiovascular consequences.

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Address for correspondence:
Carlos Alencar Souza Alves Junior
Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Centro de Desportos (CDS), Universidade Federal de Santa Catarina (UFSC), Campus Universitário
Trindade — Florianópolis (SC) — Brasil
CEP 88010-970
Tel. (+55 73) 99151-7181
E-mail: alvesjunior.cas@gmail.com

Burnout syndrome and workplace violence among nursing staff: a cross-sectional study

Sirlene Aparecida Scarpin Tsukamoto[I], Maria José Quina Galdino[II], Maynara Fernanda Carvalho Barreto[III], Júlia Trevisan Martins[IV]

Universidade Estadual de Londrina (UEL), Londrina, Brazil

[I]MSc. Nurse, Hospital Evangélico de Londrina, Londrina (PR), Brazil; and Member of the Núcleo de Estudos da Saúde do Trabalhador, Universidade Estadual de Londrina (NUESTUEL), Londrina (PR), Brazil.
https://orcid.org/0000-0003-3610-7101

[II]PhD. Nurse and Adjunct Professor, Department of Nursing, Universidade Estadual do Norte do Paraná (UENP), Bandeirantes (PR), Brazil; and Coordinator, Study Group on Teaching, Health and Work, Universidade Estadual do Norte do Paraná (UENP), Bandeirantes (PR), Brazil.
https://orcid.org/0000-0001-6709-3502

[III]PhD. Nurse and Professor, Department of Nursing, Universidade Estadual do Norte do Paraná (UENP), Bandeirantes (PR), Brazil; and Member of the Study Group on Teaching, Health and Work, Universidade Estadual do Norte do Paraná (UENP), Bandeirantes (PR), Brazil.
https://orcid.org/0000-0002-3562-8477

[IV]PhD. Nurse and Associate Professor, Department of Nursing, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil; and Coordinator, Study Group on Occupational Health, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.
https://orcid.org/0000-0001-6383-7981

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ABSTRACT

BACKGROUND: Among healthcare professionals, nursing workers are the most prone to becoming victims of workplace violence and present the highest burnout levels.

OBJECTIVES: To investigate the association between burnout syndrome and workplace violence among nursing workers.

DESIGN AND SETTING: Cross-sectional study carried out at a teaching hospital in southern Brazil.

METHODS: This study involved 242 nursing workers. We collected data over a six-month period using a sociodemographic and occupational survey, the Survey Questionnaire Workplace Violence in the Health Sector and the Maslach Burnout Inventory – General Survey. For occupational violence, we selected the Survey Questionnaire Workplace Violence in the Health Sector. Burnout syndrome was evaluated using the Maslach Burnout Inventory – General Survey. The data were analyzed in the Statistical Package for the Social Sciences (SPSS). Categorical variables were described as absolute and relative frequencies and numerical variables in terms of central trend and dispersion measurements. For data analysis, we applied descriptive statistics and multiple logistic regression.

RESULTS: The multiple models indicated that the workers who had experienced verbal abuse, physical violence and concern about workplace violence over the past 12 months had significantly higher chances of presenting high emotional exhaustion ($P < 0.05$) and depersonalization ($P < 0.05$) and low professional accomplishment ($P < 0.05$).

CONCLUSION: Occurrence of violence significantly increased the chances of great emotional exhaustion and depersonalization and low professional achievement, within burnout syndrome. Therefore, workplace violence prevention strategies need to be put in place to provide workers with a safe workplace in which to conduct their activities.

INTRODUCTION

Workplace violence has become a worldwide public health problem.[1,2] All workers are exposed to violence, but healthcare professionals are at potential risk of experiencing physical or verbal abuse while performing their work activities.[3] Workplace violence is defined as any action, incident or behavior based on a voluntary procedure of the aggressor, as a result of which a professional is assaulted, threatened or suffers any damage or injury during the performance of his or her work, or as a direct result of the work.[4]

The harmful effects of violence on healthcare workers have been acknowledged in both developed and developing countries,[5] and have become a growing phenomenon.[6] In 2013, in the United States, there were around 24,000 cases of workplace violence per year, among which more than 70% occurred within healthcare services. This finding shows that workplace violence is almost four times more likely to be experienced by healthcare workers than by workers in other sectors.[7] Physical violence and sexual harassment are more prevalent in Anglo-Saxon countries, and verbal abuse in the Middle East.[1,8]

Workplace violence within healthcare comes from patients, caregivers, physicians and, co-workers and depends on the social characteristics of the subjects and the hospital environment.[9] Thus, nursing teams, which interact more closely with patients and caregivers and are present in hospitals 24 hours a day, end up being one of the main victims of violence.[10] In addition, nursing workers are the target of physical, verbal and psychological violent behavior, sexual harassment and lack of support and trust coming from colleagues, superiors and managers.[11,12]

When experiencing workplace violence, nursing professionals are predisposed to physical and psychological health-related injuries, which may affect the workers' ability to perform their daily activities.[13] Violence is related to occurrence of workplace accidents and absenteeism and negatively affects worker satisfaction and recognition.[14]

In addition, violence can affect the entire workforce and consequently impair the quality of care provided to patients and their families. The negative consequences of workplace violence for workers' health have been displayed through symptoms of stress, low self-esteem and discouragement among the victims. These are symptoms that trigger burnout syndrome.[15]

Burnout syndrome is manifested as a prolonged response to chronic interpersonal stressors. This process consists of three dimensions: emotional exhaustion, depersonalization and low professional accomplishment. The meaning of this three-dimensional model is that it clearly places the experience of individual stress within a social context and involves conceptions of oneself and others. As a consequence of the syndrome, work loses its meaning, thereby generating demotivation, negative attitudes and distancing, which cause losses within the health-work process.[16]

Investigating workplace violence and its association with burnout syndrome among nursing professionals is relevant due to the lack of studies on this subject in Latin America.[17] Thus, the results will enable further knowledge about workplace violence and its relationship with burnout syndrome and can contribute to development of improved violence prevention strategies and decreased workplace exhaustion, which will improve the quality of life in the workplace.

OBJECTIVE

The objective of this study was to investigate the association between burnout syndrome and workplace violence among nursing workers.

METHODS

This was a cross-sectional study carried out at a teaching hospital in southern Brazil that offers 313 beds through the Brazilian National Health System (Sistema Único de Saúde, SUS) and provides medium and high-complexity healthcare.

During the study period, the population was composed of 680 nursing workers. To calculate the sample size, a formula for finite populations was used, in which the outcome was taken to be 50% prevalence and a 95% confidence interval was assumed. Through this, the minimum number of workers to be included in the study was 242.

The inclusion criterion for this study was that the subjects needed to have been in their current job for at least one year, in order to avoid bias due to occupational adaptation. Workers who were on holiday or other leave during the data collection period were also excluded.

Data were collected from January to June 2018, through a sociodemographic and occupational survey, which evaluated workplace violence and burnout syndrome. The primary author clarified the purpose of the research and provided the workers with the instrument at the workplaces during their working hours. They were instructed to place the completed questionnaire in a sealed box that was available in all the places where data were collected.

This characterization questionnaire asked for the following sociodemographic data: age (in years), sex (female or male), marital status (single, married, divorced or cohabiting) and schooling (in number of years); and the following occupational data: professional category (nurse or auxiliary nurse/nursing technician), length of service at the institution (in years), weekly workload (in hours, dichotomized as ≤ 36 hours or ≥ 37 hours) and work shift (day or night).

To assess occupational violence, we selected the Survey Questionnaire Workplace Violence in the Health Sector, which was developed by the World Health Organization, International Labour and Public Service Organization and International Council of Nursing.[18] From this instrument, we used the questions about experiences of physical violence, verbal abuse, sexual harassment and other types of violence in the workplace over the previous 12 months. This questionnaire is not a construct that generates a score, which thus allowing analysis on different types of violence separately.

Burnout syndrome was evaluated using the Maslach Burnout Inventory - General Survey (MBI-GS). This is a scale elaborated by Maslach and Jackson, and the Brazilian version was translated by Tamayo in 1997 and validated by Schuster et al. in 2015. It presents good reliability, with Cronbach's alpha between 0.82 and 0.84.[19] It is a self-report questionnaire consisting of 16 assertions, accompanied by seven-point Likert-type responses (0-6). The dimension of emotional exhaustion is evaluated by means of six items, depersonalization is evaluated through four items, and low professional accomplishment is evaluated through six items.

The data were analyzed in the Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM, Chicago, Illinois, United States). The categorical variables were described in terms of absolute and relative frequencies and the numerical variables in terms of central trend and dispersion measurements.

The outcomes were the dimensions of the burnout syndrome: emotional exhaustion, depersonalization and professional accomplishment. These were classified as high or low, based on the median.[16] Associations between these dimensions and workplace violence were initially examined using univariate logistic regression and then unadjusted and adjusted multiple logistic regression. The multiple models were adjusted according to sex, age and work shift, which have been indicated in the literature to be

control variables.[20,21] The goodness of fit of the models thus elaborated was verified through the Hosmer-Lemeshow test, in which the higher the alpha value was, the better the fit also was. P-values < 0.05 were considered statistically significant.

Institutional review board approval was sought and obtained, in accordance with opinion report no. 2.386.855. Licenses to use the MBI-GS were purchased from Mind Garden, which manages the inventory's copyright.

This study was approved by our institution's ethics committee for research involving human subjects in November 2017. Its Brazilian certificate of presentation for ethics assessment (CAAE) number for public consultation is 78866017.1.0000.5231.

RESULTS

In total, 242 nursing workers aged between 20 and 68 years, and with an average age of 43 years, participated in this study. The majority of them were female (74.4%), worked as technicians and auxiliary nurses (71.9%) and developed their work activities during the day (60.7%) (**Table 1**).

Physical and verbal violence, sexual harassment and concern about workplace violence were significantly associated with all dimensions of burnout syndrome, except between sexual harassment and depersonalization. High emotional exhaustion was associated with physical violence (P < 0.001), verbal abuse (P < 0.001), sexual harassment (P = 0.002) and concern about workplace violence (P = 0.005). High depersonalization was associated with physical violence (P < 0.001), verbal abuse (P < 0.001) and concern about workplace violence (P = 0.002). Low professional accomplishment was associated with physical violence (P = 0.001), verbal abuse (P = 0.001), sexual harassment (P = 0.031) and concern about workplace violence (P = 0.002) (**Table 2**).

The multiple models indicated that the workers who had experienced verbal abuse, physical violence and concerns about workplace violence in the past 12 months presented significantly higher chances (P < 0.034) of high emotional exhaustion, high depersonalization and low professional accomplishment. Conversely, sexual harassment was not significantly associated (P > 0.05) with the dimensions of burnout syndrome when the other types of violence were included in the model (**Table 3**).

Table 1. Characteristics of study participants

Variables (n = 242)	Mean (standard deviation)	n (%)
Age (in years)	43.4 (9.4)	
Sex		
Male		62 (25.6)
Female		180 (74.4)
Marital status		
Single		117 (48.3)
Married		125 (51.7)
Education (in years of schooling)	15.4 (3.3)	
Professional category		
Nurse		68 (28.1)
Auxiliary nurse/nursing technician		174 (71.9)
Length of service at the institution (in years)	12.9 (9.7)	
Weekly workload in hours		
≤ 36 hours		122 (50.4)
≥ 37 hours		120 (49.6)
Work shift		
Day		147 (60.7)
Night		95 (39.3)

Table 2. Association between workplace violence and the dimensions of burnout syndrome among nursing workers

Variables (n = 242)	Emotional exhaustion		Depersonalization		Professional accomplishment	
	high	P-value	high	P-value	low	P-value
	n (%)		n (%)		n (%)	
Physical violence						
No	75 (38.9)	< 0.001	84 (43.5)	< 0.001	97 (50.3)	0.001
Yes	37 (75.5)		37 (75.5)		38 (77.6)	
Verbal abuse						
No	26 (26.3)	< 0.001	35 (35.4)	< 0.001	42 (42.4)	0.001
Yes	86 (60.1)		86 (60.1)		93 (65.0)	
Sexual harassment						
No	89 (42.2)	0.002	101 (47.9)	0.088	112 (53.1)	0.031
Yes	23 (74.2)		20 (64.5)		23 (74.2)	
Concern about workplace violence						
No	53 (38.4)	0.005	57 (41.3)	0.002	65 (47.1)	0.002
Yes	59 (56.7)		64 (61.5)		70 (67.3)	

DISCUSSION

The predominance of women in this study was in accordance with data from research carried out in other countries.[22,23] These data are culturally confirmed in nursing, as women have a series of experiences aimed at the construction of female abilities and skills, one of which is taking care of people;[24] and the most characteristic and defining attribute of nursing is care.

In relation to female gender and burnout, women may have higher levels of stress and depersonalization in the work environment due to their personal characteristics and functions outside of work, such as domestic work.[25] Regarding the professional category, most participants in the present study were nursing technicians or auxiliary nurses, which is common in the Brazil reality, as these categories represent 80% of nursing professionals.[26] In other countries, however, most of them are nurses.[27,28,29]

Currently, many healthcare professionals worldwide report having experienced workplace violence[27,30] and are consequently presenting psychological illness due to these experiences, such as the burnout syndrome.[31] These data were verified in this study, in

Table 3. Influence of workplace violence on the dimensions of burnout syndrome among nursing workers

Multiple models (n = 242)	Odds ratio – unadjusted (95% confidence interval)	P-value	Odds ratio – adjusted (95% confidence interval)*†	P-value
Emotional exhaustion				
Verbal abuse	3.419 (1.876-6.231)	< 0.001	3.520 (1.916-6.468)	< 0.001
Physical violence	3.716 (1.748-7.900)	0.001	3.653 (1.697-7.861)	0.001
Sexual harassment	2.383 (0.964-5.891)	0.060	2.305 (0.898-5.914)	0.082
Concern about violence at work	1.885 (1.062-3.348)	0.030	1.874 (1.049-3.347)	0.034
Depersonalization				
Verbal abuse	2.378 (1.342-4.211)	0.003	2.479 (1.387-4.432)	0.002
Physical violence	3.308 (1.577-6.936)	0.002	3.158 (1.490-6.691)	0.003
Sexual harassment	1.192 (0.512-2.774)	0.684	1.314 (0.544-3.174)	0.543
Concern about violence at work	2.213 (1.270-3.857)	0.005	2.253 (1.285-3.951)	0.005
Low professional accomplishment				
Verbal abuse	2.010 (1.146-3.525)	0.010	2.684 (1.250-5.763)	0.011
Physical violence	2.701 (1.267-5.757)	0.015	2.031 (1.153-3.578)	0.014
Sexual harassment	1.615 (0.659-3.957)	0.294	1.533 (0.607-3.873)	0.366
Concern about violence at work	2.115 (1.214-3.684)	0.008	2.105 (1.205-3.675)	0.009

*Adjustment variables: sex, age and work shift; †Hosmer-Lemeshow test on adjusted models: P = 0.712, P = 0.304 and P = 0.980, respectively.

which professionals' experiences of physical and verbal violence were associated with burnout syndrome.

In the United Kingdom, burnout and occupational violence are significant problems, as it has been estimated that 42% of nurses in that country are considered burned out.[32] More than 55,000 physical assaults against National Health Service (NHS) teams have been reported, which has led many hospitals to conduct risk assessment actions for service users, educate staff and use safety teams,[33] which are considered to be effective preventive measures.[34]

Becoming a target of workplace violence has a negative effect on workers' wellbeing[35] and causes psychological and physical harm, as well as extreme insecurity. These factors contribute to negative sentiments about work.[36] The ensuing feeling of low personal valuation makes workers experience high levels of stress,[37] which affect their interpersonal relationships, quality of life and ability to perform daily activities".[13] This also harms the victims in other regards: spiritually, morally and socially.[38]

In a study among nurses at 11 public hospitals in Spain, greater exposure to workplace violence was associated with greater emotional exhaustion and depersonalization, as well as with lower levels of psychological wellbeing.[39] Studies conducted in Brazil and Turkey identified that healthcare workers who experienced or were exposed to workplace violence showed high levels of emotional exhaustion and depersonalization and low levels of professional accomplishment, and that workers who were victims of various forms of violence experienced this harm even more strongly.[14,40] Similar findings were obtained among nurses in Lebanon and Palestine.[41,42] These results are consistent with the findings obtained from the present study, in which nursing workers who had experienced physical violence and verbal abuse in the previous 12 months showed higher chances of presenting high exhaustion, depersonalization and low professional accomplishment.

Verbal aggression has been found to be the most prevalent among the types of violence that nursing professionals experience. It entails emotional exhaustion that activates a cycle of losses that can lead to dissipation of these individuals' mental and physical resources. Moreover, as a result of perceiving this violence as a threat, workers may adopt an attitude of disengagement, such as depersonalization.[43]

Nursing professionals' exposure to violence tends to contribute to development of a negative and demotivated response to work, which negatively affects their mental health.[44] This exposure gives rise to feelings of hopelessness, disappointment, fear and anxiety.[42]

A study conducted in 23 hospitals in Guangdong province, in China, among 1,502 nurses, showed that violence in the workplace was directly associated with higher incidence of burnout, lower job satisfaction, lower patient safety and adverse events. Burnout was directly associated with lower patient safety and more adverse events.[45]

Studies in Turkey and Switzerland have shown that nurses who experienced verbal and physical abuse felt a strong desire to leave the profession. The fear that workplace violence will recur makes many of its victims more disposed to breaking their institutional bonds.[9,46]

In the present study, sexual harassment was only a statistically significant correlate when analyzed in isolation from other types of violence. Nonetheless, this link is a cause for concern, given that it did occur among the workers in this analysis. A previous study showed weak correlations between sexual harassment and the dimensions of burnout syndrome.[47]

It is a fact that sexual harassment often remains unreported because of its stigmatization.[48] The traditional nature of hospital environment hierarchies can lead the victims of sexual harassment to ignore it due to shame and the assumption that reporting it will make no difference, especially if the perpetrator is a physician or a boss.[49] Moreover, in Brazil, the media still attaches a negative stereotype to nursing by presenting the nurse's body as a sexual object. Thus, professional organizations need to mobilize to link the image of nursing to excellent human care delivery and management.

Furthermore, in the present study, concern about workplace violence was associated with high emotional exhaustion, high depersonalization, and low professional accomplishment. According to research conducted in another Brazilian state, only 17.8% of the interviewees said that they were not worried about violence.[50]

Nursing professionals who have been victims of workplace violence, as well as those who believe that there is a possibility of violence, are worried. Feelings of distress can emerge. Consequently, physical or mental illness may occur.[51]

Thus, it is imperative to ensure the safety of healthcare workers in order to prevent health problems, sick leave and dropout from the job, along with social isolation and the intention to quit this work.[14,52]

There were limitation to this study that related to the self-assessment method used. This may have led to responses that were tailored in accordance with socially acceptable standards. This study was conducted at a public teaching hospital that is rated outstanding because of the high level of medical and nursing care that it makes available in this state in Brazil. Nevertheless, the sample may not have been representative given that convenience sampling was used, which prevents generalization of the results. Additional research is recommended at philanthropic and private hospitals, also focusing on the use of prevention strategies.

Despite these limitations, this study has contributed to advancement of scientific knowledge through revealing information about the different forms of violence that nursing professionals experienced in their workplace and how this problem was associated with burnout syndrome. Thus, it is essential that joint actions in this field should be planned and implemented by nursing workers and managers, in order to promote health and prevent injuries. Such measures should seek to enhance a safe working environment for all parties, and organizational support for these measures should act as a mediator between workplace violence, job satisfaction and burnout levels.[53,54]

CONCLUSION

Workers who experienced verbal abuse, physical violence and concern about workplace violence in the previous 12 months showed significantly higher chances of high emotional exhaustion, depersonalization and low professional accomplishment.

Workplace violence prevention strategies need to be put in place, including workplace monitoring, so as to stimulate the reporting of violence, promote victim support networks and implement specific pre and post-intervention protocols for the different types of workplace violence, in order provide nursing workers with a safe workplace for development of their activities.

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Address for correspondence:
Maynara Fernanda Carvalho Barreto
Rodovia BR-369 Km 54, Vila Maria, CP 261
Bandeirantes (PR) — Brasil
CEP 86360-000
Tel. (+55 43) 99613-2264
E-mail: maynara_barreto@hotmail.com

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Publicly versus privately funded cardiac rehabilitation: access and adherence barriers. A cross-sectional study

Giovanna Lombardi Bonini Borges[I], Mayara Moura Alves da Cruz[II], Ana Laura Ricci-Vitor[III], Paula Fernanda da Silva[IV], Sherry Lynn Grace[V], Luiz Carlos Marques Vanderlei[VI]

Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil

[I]PT. Physiotherapist, Department of Physiotherapy, School of Technology and Sciences, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0002-8188-5300

[II]PT, MSc. Physiotherapist and Doctoral Student, Department of Physiotherapy, School of Technology and Sciences, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0002-3955-9149

[III]PT, PhD. Professor, Escola Superior de Saúde Egas Moniz (ESSEM), Egas Moniz - Cooperativa de Ensino Superior (CRL), Almada, Setúbal, Portugal.
https://orcid.org/0000-0002-3654-8532

[IV]PT. Physiotherapist and Master's Student, Department of Physiotherapy, School of Technology and Sciences, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0003-0769-4490

[V]PhD, CRFC. Professor, Faculty of Health, York University, Toronto, Ontario, Canada; and Senior Scientist, KITE & Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada.
https://orcid.org/0000-0001-7063-3610

[VI]PhD. Professor, Department of Physiotherapy, School of Technology and Sciences, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0002-1891-3153

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ABSTRACT

BACKGROUND: Cardiac rehabilitation (CR) barriers are well-understood in high-resource settings. However, they are under-studied in low-resource settings, where access is even poorer and the context is significantly different, including two-tiered healthcare systems and greater socioeconomic challenges.

OBJECTIVE: To investigate differences in characteristics of patients attending publicly versus privately funded CR and their barriers to adherence.

DESIGN AND SETTING: Observational, cross-sectional study in public and private CR programs offered in Brazil.

METHODS: Patients who had been attending CR for ≥ 3 months were recruited from one publicly and one privately funded CR program. They completed assessments regarding sociodemographic and clinical characteristics and the CR Barriers Scale.

RESULTS: From the public program, 74 patients were recruited, and from the private, 100. Participants in the public program had significantly lower educational attainment ($P < 0.001$) and lower socioeconomic status ($P < 0.001$). Participants in the private program had more cognitive impairment ($P = 0.015$), and in the public program more anxiety ($P = 0.001$) and depressive symptoms ($P = 0.008$) than their counterparts. Total barriers among public CR participants were significantly higher than those among private CR participants (1.34 ± 0.26 versus $1.23 \pm 0.15/5$]; $P = 0.003$), as were scores on 3 out of 5 subscales, namely: comorbidities/functional status ($P = 0.027$), perceived need ($P < 0.001$) and access ($P = 0.012$).

CONCLUSION: Publicly funded programs need to be tailored to meet their patients' requirements, through consideration of educational and psychosocial matters, and be amenable to mitigation of patient barriers relating to presence of comorbidities and poorer health status.

INTRODUCTION

Cardiovascular rehabilitation (CR) programs are recommended in clinical guidelines,[1,2] because participation results in significantly lower mortality and morbidity,[3] including in low and middle-income countries (LMICs).[4] However, CR participation remains low, at around 20%-30% in high-income countries,[5-7] and 14% in LMICs such as Brazil.[8]

The reasons for underuse of CR have been well-characterized in high-resource settings[7,9,10] and include factors at the healthcare system, provider and patient levels. However, barriers in lower-resource settings have not been well-studied. A recent review identified only 13 studies globally,[11] and there are also few studies in South America[12] or Brazil to date.[13-16] This is problematic, given the different contexts in these settings. Firstly, patients would be more socioeconomically disadvantaged, and hence face different barriers. Secondly, healthcare systems are more often two-tier.[17] So, for example, half of CR programs in Brazil are solely publicly-funded (53.3%), a third privately-funded, and the remainder a mixture.[18] It has been established that CR funding sources affect program characteristics, such as scale, healthcare providers on the team and component comprehensiveness.[17] However, to our knowledge, it has yet to be investigated how barriers might differ for patients accessing privately and publicly-funded programs in any country worldwide.[19]

OBJECTIVES

Therefore, the objectives of this study were to compare: (1) the sociodemographic and clinical characteristics of patients accessing publicly versus privately funded CR programs; and (2)

multi-level barriers to adherence in each of these types of programs. While the world needs more CR,[20] and offering privately funded programs may enable greater availability, the CR community needs to consider the inequities that this might raise.

METHODS

Design and procedure

This was an observational cross-sectional study. Participants signed an informed consent statement. The local ethics committee approved all procedures on June 28, 2018 (CAAE number: 88504718.0.0000.5402).

A convenience sample was recruited between March and August 2019. Participants in the public or private CR programs offered in the city of Presidente Prudente, São Paulo, Brazil, were approached with a view to inviting them to take part in this study and undergo assessments. These assessments were administered by physiotherapists who were not part of the programs.

Setting

The publicly funded CR program for this study is offered by the Cardiology Division of the Center for Studies and Attendance in Physiotherapy and Rehabilitation, School of Technology and Sciences, Universidade Estadual Paulista (UNESP), Presidente Prudente, São Paulo, Brazil. The CR program is funded by the Brazilian National Health System and is delivered through the physiotherapy program. The program is indefinite in length (i.e. phase II and maintenance).

The privately funded CR program is offered through the city's Heart Institute. The program is funded by the patient or through medical health insurance (25.9% of Brazilians have health insurance).[21] Most patients who use the private program have a health plan, for which they pay a monthly fee. This health plan covers 36 sessions, after which it is necessary to request coverage of further sessions if the doctor perceives more are required. When the patient does not have a health plan, they pay out-of-pocket monthly (R$ 390.00).

To start either program, patients require a written medical referral. The public program offers sessions three times/week, while the private program offers two to three per week, depending on the patient. In both programs, exercises are performed in groups; the public program serves on average 18 patients/session and the private one, 12 patients/session. With regard to staffing, in the private program, care is delivered by physiotherapy cardiology specialists; in the public program, care is provided by physiotherapy students supervised by professors.

The programs are primarily centered on structured exercises, and the exercise prescriptions are quite consistent between programs: they are based on heart rate reserve, and are re-evaluated each month. Exercises in the public program are done on treadmills and stationary bikes. In the private program, there are also resistance exercises. In addition, in the public program, there are group educational lectures and patients are provided with written materials. In the private program, there is informal counselling regarding risk factor control during the one-to-one sessions only.

Participants

The inclusion criteria were that the participants needed to be aged over 18 years, with a diagnosis of cardiovascular disease or with cardiovascular risk factors (as per the program inclusion criteria), and needed to have been in the CR program for ≥ 3 months (frequency of attendance was not considered). There were no exclusion criteria.

Measurements

The independent variable of interest was CR program funding type (public or private), which was coded based on the program attended. For objective one, the participants' sociodemographic characteristics (e.g. age, sex, education and work status) and clinical characteristics (e.g. body mass index, CR indication/cardiac diagnosis and number of months in CR) were first assessed. The participants then completed psychometrically-validated scales assessing factors that are known to impact CR access and which may be particularly important in lower-resource settings, along with the CR Barriers Scale (CRBS; https://sgrace.info.yorku.ca/cr-barriers-scale/crbs-instructions-and-languages-translations/).

To quantify the participants' socioeconomic level, a questionnaire from the Brazilian Association of Market Research Companies (ABEP) was administered. This asks about education level, family income, possession of certain items (e.g. number of televisions) and services offered in patients' homes.[22]

To evaluate cognitive function, the psychometrically validated Brazilian-Portuguese version of the Mini-Mental State Examination (MMSE)[23] was used. The test scores were adjusted based on level of education[24] and categorized based on the presence of any cognitive impairment (e.g. participants who had four years of education and scored less than 25 were considered at least mildly cognitively impaired).

To quantify mental health symptoms, the psychometrically validated Brazilian-Portuguese version of the Hospital Anxiety and Depression Scale (HADS)[25] was administered.

Lastly, CR barriers were assessed in relation to the second objective. The psychometrically validated Brazilian-Portuguese version of the Cardiac Rehabilitation Barriers Scale (CRBS) was administered.[13] This assesses patient perceptions of 21 barriers at the healthcare system, healthcare provider and patient levels on a scale from 1 ("strongly disagree") to 5 ("strongly agree"). Higher scores indicate higher barriers to CR adherence.[26] A total mean

score is computed, and there are five subscales: comorbidities/functional status, perceived need, personal/family issues, travel/work conflicts and access.

Statistical analysis

To investigate differences in patient characteristics and barriers between participants attending public versus private programs, Fisher's exact tests or independent-sample t tests were used (or the Mann-Whitney U test if the variables were not normally distributed, as per the Kolmogorov-Smirnov test), as appropriate. Statistical significance was set at 5%. The analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, Illinois, United States).

RESULTS

During the period of this study, 178 patients were approached, of whom 174 (97.75%) participated; 57.5% were from the private program. The sample characteristics are shown in **Table 1**.

With regard to sociodemographic characteristics, the participants in the public program had significantly lower educational attainment and lower socioeconomic status (plus a trend regarding work status). With regard to clinical characteristics, the participants in the private program had more cognitive impairment, and in the public program more anxiety and depressive symptoms than their counterparts. Participants were in the public program for significantly longer durations than those in the private program. Moreover, the total barriers were higher, the longer the participants were in the program ($r = 0.244$; $P < 0.05$).

As shown in **Table 2**, the total barrier scores in this sample of participants attending CR for ≥ 3 months were quite low. Regardless of the program accessed, travel/work conflicts were the greatest barrier, followed by personal/family issues and comorbidities/functional status. There was an open-ended question about any other barriers; no unique barriers were raised by participants.

As also shown in **Table 2**, the barriers were significantly higher among participants accessing the public program than among those accessing the private program. Moreover, scores on three of the five subscales were significantly higher among participants accessing the public program than among those accessing the privately funded program.

DISCUSSION

There have been few studies on CR barriers outside of Western, high-income settings.[11] In many of these countries, the healthcare systems are two-tier. It is known that there may be differences in program quality, and that there are significant differences in cost according to funding source,[17] yet to our knowledge there has been no investigation of how this impacts patients. In this study, we began to investigate differences in the nature of patients

Table 1. Sociodemographic and clinical characteristics of the participants, according to cardiac rehabilitation program funding type

Characteristics	Type of CR program		P
	Public (n = 74)	Private (n = 100)	
Sociodemographic			
Age (years)	65.61 ± 11.01	65.24 ± 14.22	0.315
Sex (male)	43 (58.11%)	65 (65.00%)	0.430
City (same as CR location)	68 (91.89%)	93 (93.00%)	0.779
Work status (working)	20 (27.03%)	40 (40.00%)	0.079
Highest education level			
Completed high school	32 (43.24%)	29 (29.00%)	< 0.001
Completed more than high school	42 (56.76%)	71 (71.00%)	
Socioeconomic level*			
A	15 (20.27%)	55 (55.00%)	**< 0.001**
B1	17 (22.97%)	21 (21.00%)	
B2	27 (36.49%)	19 (19.00%)	
C1	11 (14.86%)	2 (2.00%)	
C2	4 (5.40%)	3 (3.00%)	
D or E	0	0	
Clinical			
Duration of CR (months)	**77.38 ± 76.98**	**29.78 ± 21.68**	**< 0.001**
Diagnoses/indications for CR			
CVD	62 (83.78%)	90 (90.00%)	0.253
Ischemic heart disease	42 (67.74%)	68 (75.55%)	0.153
Heart failure	13 (20.97%)	8 (8.89%)	0.063
Valve diseases	2 (3.23%)	7 (7.78%)	0.304
Rhythm disorders	2 (3.23%)	6 (6.67%)	0.469
Other	3 (4.05%)	1 (1.00%)	0.041
Risk factors	**12 (16.22%)**	**10 (10.00%)**	**0.253**
Arterial hypertension	11 (91.67%)	9 (90.00%)	0.241
Family history	1 (8.33%)	1 (10.00%)	1.000
BMI (kg/m^2)	29.16 ± 4.71	28.81 ± 4.57	0.592
Cognitive impairment (MMSE)			
Subthreshold	45 (60.81%)	48 (48.00%)	0.015
At least mild	29 (39.19%)	52 (52.00%)	
Mean ± SD	26.54 ± 3.00	27.66 ± 2.09	
HADS - anxiety			
Unlikely anxiety	59 (79.73%)	89 (89.00%)	0.001
Possible anxiety	12 (16.22%)	8 (8.00%)	
Probable anxiety	3 (4.05%)	3 (3.00%)	
Mean ± SD†	5.00 ± 3.38	3.43 ± 3.43	
HADS - depressive symptoms			
Unlikely depression	64 (86.49%)	94 (94.00%)	0.008
Possible depression	8 (10.81%)	4 (4.00%)	
Probable depression	2 (2.70%)	2 (2.00%)	
Mean ± SD†	4.05 ± 3.03	2.93 ± 2.62	

Note: The results are expressed as percentages and absolute numbers or as means and standard deviations (e.g. age and BMI).
*For socioeconomic level, A: 45-100 points; B1: 38-44 points; B2: 29-37 points; C1: 23-28 points; C2: 17-22 points; and D and E: 0-16 points.
†Scores ranged from 0 to 7, and higher scores indicated greater symptom burden.
MMSE = Mini-Mental State Examination; HADS = Hospital Anxiety and Depression Scale; BMI: body mass index; CVD = cardiovascular diseases; CR = cardiac rehabilitation; kg = kilograms; m = meters.
*Differences tested using t tests (or Mann-Whitney U test when data were not normally distributed) or Fisher's exact tests, as applicable.

accessing these programs, and how their barriers to adherence might differ, and indeed some important differences emerged.

It was promising to observe fewer differences than expected, in the characteristics of those accessing a publicly funded program rather than a privately funded program. For instance, there were no differences with regard to sex, age or diagnostic indication. As expected, the chief differences were socioeconomic, which are likely to explain the differences in mental health as well as cognition.[27]

The differences in the nature of patients accessing public or private programs, if replicated, hold implications for program delivery. Public programs would need to consider the health literacy of their patients, and tailor their educational programming accordingly.[28] They would also want to ensure that they have staff who can assess and treat mental health issues, or have a close relationship with a referral source that does not have a long waitlist. Private programs could serve as important settings where patients who need more staff time could safely receive CR. If so, staff would need to have specialized training to successfully work with these patient groups.

The top barriers observed here were consistent with those reported in other studies, in Brazil, South America and beyond.[12,14,29-32] Overall, the barriers were low, which was consistent with other CRBS studies in enrollees.[33] This was to be expected, given the sample was composed of patients who had already completed ≥ 3 months of CR. Still, the patients accessing public programs did report significantly more barriers to adherence than did their counterparts in private programs. Socioeconomic differences in the cohorts do seem to explain the differences; for example, factors such as transportation costs, distance, time constraints and not getting support from healthcare providers to attend were more strongly endorsed by patients in the public than in the private system. Efforts to tackle the social determinants of health continue to be needed.

Study limitations

Caution is warranted when interpreting these results. Their generalizability is limited, particularly given that we sampled from only one public and one private program. Moreover, the programs were of long duration, compared with other programs internationally.[34] This study was also limited to participants who had been able to access CR and had adhered to the program for ≥

Table 2. Cardiac rehabilitation barriers according to program funding type

Barriers	Public (n = 74)	Private (n = 100)	Total (n = 174)	P
10…travel	2.77 ± 1.94	2.63 ± 1.94	2.69 ± 1.93	0.600
14…other health problems prevent me from going	2.56 ± 1.95	2.20 ± 1.81	2.35 ± 1.88	0.168
4…of family responsibilities	1.93 ± 1.63	1.69 ± 1.49	1.79 ± 1.55	0.290
12…of work responsibilities	1.83 ± 1.61	1.71 ± 1.53	1.76 ± 1.56	0.475
8…severe weather	1.67 ± 1.70	1.21 ± 0.84	1.41 ± 1.30	0.029
11…of time constraints	1.44 ± 1.21	1.07 ± 0.50	1.23 ± 0.89	0.003
3…of transportation problems	1.29 ± 0.88	1.11 ± 0.63	1.19 ± 0.75	0.012
13…I don't have the energy	1.12 ± 0.75	1.06 ± 0.42	1.11 ± 0.59	0.120
1…of distance	1.23 ± 0.76	1.00 ± 0.00	1.10 ± 0.51	< 0.001
2…of cost	1.07 ± 0.25	1.04 ± 0.40	1.05 ± 0.34	0.045
20…it took too long to get referred and into the program	1.00 ± 0.00	1.06 ± 0.42	1.03 ± 0.32	0.214
15…I am too old	1.00 ± 0.00	1.04 ± 0.40	1.02 ± 0.30	0.386
9…I find exercise tiring or painful	1.04 ± 0.26	1.01 ± 0.00	1.02 ± 0.17	0.101
6…I don't need cardiac rehab	1.03 ± 0.16	1.00 ± 0.00	1.01 ± 0.11	0.101
7…I already exercise at home, or in my community	1.03 ± 0.16	1.00 ± 0.00	1.01 ± 0.11	0.101
5…I didn't know about cardiac rehab	1.01 ± 0.12	1.00 ± 0.00	1.01 ± 0.08	0.248
21…I prefer to take care of my health alone, not in a group	1.01 ± 0.12	1.00 ± 0.00	1.01 ± 0.08	0.248
16…my doctor did not feel it was necessary	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.999
17… many people with heart problems don't go, and they are fine	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.999
18… I can manage my heart problem on my own	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.999
19… I think I was referred, but the rehab program didn't contact me	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.999
Total mean barrier	**1.34 ± 0.26**	**1.23 ± 0.15**	**1.28 ± 0.21**	**0.003**
F1- Comorbidities/functional status	1.33 ± 0.43	1.21 ± 0.30	1.28 ± 0.37	0.027
F2- Perceived need	1.15 ± 0.29	1.03 ± 0.16	1.09 ± 0.23	< 0.001
F3- Personal/family issues	1.34 ± 0.56	1.23 ± 0.50	1.28 ± 0.53	0.131
F4- Travel/work conflicts	2.29 ± 1.40	2.17 ± 1.29	2.22 ± 1.33	0.630
F4- Access	1.06 ± 0.18	1.02 ± 0.14	1.04 ± 0.16	0.012

Mann-Whitney U test for differences between groups; F = factors/subscales.
In the "Barriers" column, the questions are presented in order from highest to lowest average score, as the question number and the summarized wording of the question.

3 months. Arguably these participants were among the few who had been able to successfully access and adhere to CR, even in a low-resource setting. In future studies, the barriers among participants should be investigated at the time of diagnosis (considering that referral is perceived as the main barrier in Brazil),[18] as well as very early in their program. Lastly, the sample size was modest, and this was the first study examining these differences. Therefore, replication is warranted prior to implementing any changes based on these preliminary findings.

CONCLUSIONS

In summary, as expected, but for the first time, we have shown that within a two-tier healthcare system in a lower-resource setting, patients accessing publicly funded CR programs are of significantly lower socioeconomic status and have poorer mental health and cognitive ability than those accessing privately funded programs. Publicly funded programs will need to tailor their delivery to meet the needs of their patients through educational and psychosocial programming. While referral and time conflicts remain key barriers in these settings, once patients do access CR, the barriers are greater for those in publicly funded programs than in privately funded ones, particularly with regard to comorbidities/functional status, perceived need and access.

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Address for correspondence:
Mayara Moura Alves da Cruz
Departamento de Fisioterapia, Faculdade de Ciências e Tecnologia,
Universidade Estadual Paulista (UNESP)
R. Roberto Simonsen, 305
Centro Educacional — Presidente Prudente (SP) — Brasil
CEP 19060-900
Tel. (+55 18) 3229-5388
E-mail: maya_bilac@hotmail.com

Sociodemographic determinants of multimorbidity in Brazilian adults and older adults: a cross-sectional study

Marina Christofoletti[I], Giovani Firpo Del Duca[II], Tânia Rosane Bertoldo Benedetti[III], Deborah Carvalho Malta[IV]

Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil

[I]MSc. Doctoral Student, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
https://orcid.org/0000-0002-5672-6869

[II]PhD. Full Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
https://orcid.org/0000-0003-0893-2032

[III]PhD. Full Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
https://orcid.org/0000-0002-2035-5082

[IV]PhD. Full Professor, Department of Maternal and Child Nursing and Public Health, Universidade Federal de Minas Gerais, Minas Gerais (MG), Brazil.
https://orcid.org/0000-0002-8214-5734

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ABSTRACT

BACKGROUND: Multimorbidity due to non-communicable chronic diseases (NCDs) constitutes a significant challenge for healthcare systems. To attenuate its impacts, it is essential to identify the sociodemographic determinants of this condition, which can discriminate against population segments that are more exposed.

OBJECTIVE: To identify associations between multimorbidity conditions and sociodemographic indicators among Brazilian adults and older adults.

DESIGN AND SETTING: Cross-sectional telephone-based survey in 26 Brazilian state capitals and the federal district.

METHODS: The Vigitel 2013 survey was used, with data collected via a questionnaire. The outcome was multimorbidity (2, 3 or 4 NCDs), and the exposures were sociodemographic indicators (age, sex, skin color, marital status and education). The analysis consisted of multinomial logistic regression (odds ratio), stratified by age.

RESULTS: Among adults, multimorbidity comprising two, three or four diseases was associated with advancing age ($P < 0.001$); two and three diseases, with having a partner ($P = 0.004$ and $P < 0.001$, respectively); and two, three or four diseases, with lower education ($P < 0.001$). Among older adults, two, three or four diseases were associated with female sex ($P < 0.001$); three diseases, with living with a partner ($P = 0.018$); two diseases, with black skin color ($P = 0.016$); and two or three diseases, with lower education ($P < 0.001$).

CONCLUSIONS: To control and prevent multimorbidity, strategies for individuals with existing chronic diseases, with partners and with lower education levels are needed. Particularly for adults, advancing age should be considered; and for older adults, being a woman and having black skin color.

INTRODUCTION

Multimorbidity due to non-communicable chronic diseases (NCDs) constitutes a significant challenges for healthcare systems.[1] It is reflected in increased health problems, financial expenditure and decreased quality of life.[2] Over 95% of the population over 65 years of age is estimated to present more than one disease diagnosed in primary healthcare.[3] Middle-income countries such as China,[4] Serbia, Mexico, Russia, South Africa and India[5] present alarming multimorbidity results, but knowledge about simultaneous diseases in Latin American countries is limited. Specifically in Brazil,[6] studies have emphasized occurrences in subgroups of the population comprising older adults.[7-9]

Investigation of the determinants of multimorbidity, especially the sociodemographic aspects, is crucial for planning preventive public policies.[10] Some important variables need to be included in these investigations, in order to identify the population segment that is more exposed to NCD multimorbidity. These variables may include sex, age, marital status, skin color and educational level. The locality is also important. It can also be considered that population density, seasonal patterns, urbanization, economy[11] and cultural contextualization may influence inequalities and health disparities.

Separately, each NCD has important sociodemographic determinants, which reflect health inequalities and the populations most affected. In the case of multimorbidity, identifying the inherent indicators of the population is of considerable importance, in order to reflect on phenomena of disability and mortality, which are strongly related to diagnoses of multiple chronic diseases.[2] Therefore, recognition of sociodemographic determinants enables knowledge of the population subgroups that are most vulnerable to the aggravation of presenting interactions of multiple diseases.

OBJECTIVE

The aim of the present study was to identify the sociodemographic factors associated with multimorbidity due to non-communicable chronic diseases among adults and older adults in Brazil.

METHODS

Design and sample

The data for this cross-sectional study came from the annual national survey "Surveillance of Risk Factors and Protection Against Chronic Diseases by Telephone Inquiry" (Vigitel in the Portuguese-language acronym), conducted between February and December 2013. The sampling process was performed in three steps.[12] Weighting factors were used to compensate for nonuniversal fixed-line coverage bias, adjusted for the adult Brazilian population. This was based on each individual's weight in the sample, calculated via the ranking method. Details about the methodology, including the sampling process, weighting factors and ethics procedures are provided in the official report.[12]

Sample

The participants were a representative sample of adults (≥ 18 years old) living in all 27 Brazilian state capitals. To be eligible, the requirement was that the participant needed to have a residential landline telephone.

Data collection

Data were collected by means of telephone interviews simultaneously using a computer, and all the calls were recorded in case any queries arose. The instrument used was a validated questionnaire, and it was applied via telephone calls by trained staff. The questionnaire asked about sociodemographic, behavioral, nutritional and health factors.

Measurements

The outcome variable was multimorbidity due to non-communicable diseases (NCDs). The concept investigated was co-occurrence of multiple chronic or acute diseases and medical conditions within a single person, without an index condition, giving equal attention to all diagnoses.[13] The four categories proposed were: no occurrence (zero or one disease), and multimorbidity as occurrences of two diseases, three diseases or four diseases. The diseases considered were the four most prevalent NCDs in Brazil (diabetes, dyslipidemia, arterial hypertension and obesity). Occurrences were considered to consist of affirmative self-reports of diabetes, dyslipidemia or arterial hypertension; and for obesity, body mass index (BMI) of 30 kg/m² or higher (calculated based on self-reported weight and height). For BMI, hot-deck imputation of the data was used. The exposure variables used were sex (male or female), age groups (adult categories: 18 to 29, 30 to 39, 40 to 49 or 50 to 59 years old; older adult categories: 60 to 69, 70 to 79 or 80 years old and over), marital status (living without a partner or living with a partner), ethnicity (white or black) and education level (less than eight, nine to eleven or twelve years and over) and demographic macroregion (center-west, northeast, north, southeast and south).

Analyses

The analysis, conducted in 2016, was stratified according to age group (adults: 18 to 59 years; and older adults: ≥ 60 years). The descriptive analyses comprised absolute and relative frequencies, considering prevalence estimates and 95% confidence intervals (95% CI). Multinomial logistic regression (odds ratio [OR]) formed the inferential analysis that was used to investigate associations of sociodemographic indicators with each multimorbidity category (taking zero or one disease as the reference category). The first-level variables were sex, age, marital status, ethnicity and demographic macroregion; and the second level was education level. Backward selection was adopted for statistical modeling, with a critical level of $P \leq 0.20$ for each variable to remain in the hierarchical regression model, so as to minimize the confounding control. The significance level was 5% for all tests. All analyses considered sample weighting obtained through the inverse of the number of telephone lines existing in the household that was interviewed and the number of adults living in the interviewee's home.

Ethics

The Brazilian Ministry of Health's National Ethics Committee for Research on Human Beings approved this study under registration number 355.590/2013, on June 26, 2013.

RESULTS

Within the response rate of 71.5%, the total number of participants was 52,929 (37,947 adults and 14,982 older adults). Among the adults, the following were predominant: females (52.9%), individuals living without a partner (52.0%), blacks (55.1%), individuals with nine to eleven years of schooling (41.1%) and those living in the southeastern region (44.1%). Among the older adults, the following were predominant: females (59.5%), individuals living with a partner (56.9%), those of white non-Hispanic ethnicity (61.3%), those eight or fewer years of schooling (69.3%) and those living in the southeastern region (51.8%) (**Table 1**).

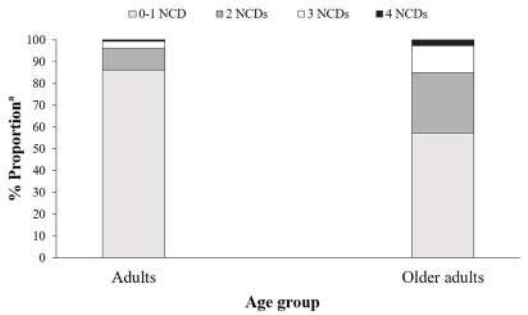
The frequency of multimorbidity in adults was 13.7% (9.8% with two, 3.3% with three and 0.6% with four NCDs), and 42.9% among old adults (27.9% with two, 12.4% with three and 2.7% with four NCDs) (**Figure 1**).

Table 1. Sociodemographic and health characteristics stratified according to age. Brazil, 2013 (n = 52,929)

Variables	Adults (n = 37,947)				Older adults (n = 14,982)			
	n	%[a]	95% CI[b]	% missing	n	%[a]	95% CI[b]	% missing
Sex				0.0				0.0
Male	15,368	47.1	(46.2; 48.1)		4.908	40.5	(38.7; 42.2)	
Female	22,579	52.9	(51.9; 53.8)		10.074	59.5	(57.8; 61.3)	
Marital status				1.1				1.5
Living without a partner	18,210	52.0	(51.0; 53.0)		7.557	43.1	(41.4; 44.8)	
Living with a partner	19,304	48.0	(47.0; 49.0)		7.204	56.9	(55.2; 58.6)	
Skin color				1.1				18.6
White	14,867	44.9	(43.8; 45.9)		7.402	61.3	(59.4; 63.2)	
Black	18,983	55.1	(54.1; 56.2)		4.790	38.7	(36.8; 40.6)	
Educational level, years				0.8				2.9
0-8	7,115	30.6	(29.6; 31.6)		7.405	69.3	(67.8; 70.7)	
9-11	15,532	41.1	(40.2; 42.0)		3.761	17.3	(16.3; 18.5)	
≥ 12	14,984	28.3	(27.5; 29.2)		3.381	13.4	(12.4; 14.4)	
Demographic macroregion				0.0				0.0
North	10,896	10.5	(10.2; 10.9)		2.805	7.0	(6.6; 7.5)	
Northeast	12,729	25.7	(25.0; 26.3)		4.884	22.2	(21.1; 23.2)	
Southeast	5,327	44.1	(43.1; 45.2)		2.574	51.8	(50.1; 53.5)	
South	3,457	7.9	(7.5; 8.2)		2.399	9.5	(8.9; 10.1)	
Center-West	5,538	11.8	(11.3; 12.2)		2.320	9.5	(8.9; 10.1)	

95% CI = 95% confidence interval.

[a]Values weighted for the inverse of existence of landline telephones and the number of adults living in the household of the interviewee; [b]95% confidence interval in weighted sample.



[a]Values weighted for the inverse of the existence of landline telephones and the number of adults living in the interviewee's house.

Figure 1. The proportion[a] of concomitant non-communicable chronic diseases (NCDs), according to age groups. Brazil, 2013 (n = 52,929).

Tables 2 and **3** indicate the associations between sociodemographic variables and multimorbidity categories. In **Table 2**, for multimorbidity consisting of two chronic diseases, the odds increased according to the advancement of the age group (40 to 49 years, OR: 7.07 [CI: 5.67; 8.82]; 50 to 59 years, OR: 13.71 [CI: 11.04; 17.03]) and were also higher for individuals living with a partner (OR: 1.27 [CI: 1.08; 1.50]). On the other hand, the odds decreased with higher educational levels (9 to 11 years, OR: 0.73 [0.62; 0.86]; 12 years and over, OR: 0.67 [CI: 0.56; 0.81]), in comparison with adults with no and one disease. For multimorbidity consisting of three diseases, the odds increased according to the advancement of the age group (40 to 49 years, OR: 11.44 [CI: 6.27; 20.86]; 50 to 59 years, OR: 28.57 [CI: 15.90; 51.34]) and were also higher for individuals living with a partner (OR: 1.70 [CI: 1.28; 2.26]). The odds decreased with higher educational levels (9 to 11 years, OR: 0.57 [CI: 0.43; 0.74]; 12 years and over, OR: 0.47 [CI: 0.34; 0.64]), in comparison with adults with no and one disease. The odds for this group were also associated with the demographic macroregion, indicating that the southeastern and southern regions were more exposed than the other demographic macroregions. For the last category, multimorbidity consisting of four diseases, the odds increased only according to the advancement of the age group (40 to 49 years, OR: 13.76 [CI: 3.49; 54.21]; 50 to 59 years, OR: 30.01 [CI: 8.01; 112.5]) and decreased with higher educational level (9 to 11 years, OR: 0.40 [CI: 0.22; 0.74]; 12 years and over, OR: 0.30 [CI: 0.15; 0.60]), in comparison with adults with no and one disease. It can be seen that the odds ratio increased with increasing numbers of NCDs, thus expressing a potential profile.

Among older adults, being female was associated with two, three and four diseases (OR: 1.62 [CI: 1.33; 1.96]; OR: 1.68 [CI: 1.28; 2.21]; and OR: 2.52 [CI: 1.39; 4.57], respectively). For multimorbidity consisting of two diseases, the odds increased among

Table 2. Association* of sociodemographic indicators with multimorbidity in terms of the number of non-communicable chronic diseases (NCDs), among adults (n = 37,947)

Variables	2 NCDs versus 0 and 1		3 NCDs versus 0 and 1		4 NCDs versus 0 and 1	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex		0.641[a]		0.775[a]		0.841[a]
Male	1.00		1.00		1.00	
Female	0.94 (0.83; 1.12)		0.96 (0.74; 1.25)		1.06 (0.60; 1.88)	
Age group, years		< 0.001[b]		< 0.001[b]		< 0.001[b]
18-29	1.00		1.00		1.00	
30-39	4.36 (0.44; 5.52)		5.00 (2.62; 9.44)		1.50 (0.34; 6.59)	
40-49	**7.07 (5.67; 8.82)**		**11.44 (6.27; 20.86)**		**13.76 (3.49; 54.21)**	
50-59	**13.71 (11.04; 17.03)**		**28.57 (15.90; 51.34)**		**30.01 (8.01; 112.5)**	
Marital status		0.004[a]		< 0.001[a]		0.889[a]
Living without a partner	1.00		1.00		1.00	
Living with a partner	**1.27 (1.08; 1.50)**		**1.70 (1.28; 2.26)**		1.04 (0.77; 2.64)	
Skin color		0.230[a]		0.226[a]		0.264[a]
White	1.00		1.00		1.00	
Black	1.10 (0.94; 1.29)		1.18 (0.90; 1.55)		1.42 (0.77; 2.65)	
Educational level, years		< 0.001[b]		< 0.001[b]		< 0.001[b]
0-8	1.00		1.00		1.00	
9-11	**0.73 (0.62; 0.86)**		**0.57 (0.43; 0.74)**		**0.40 (0.22; 0.74)**	
≥ 12	**0.67 (0.56; 0.81)**		**0.47 (0.34; 0.64)**		**0.30 (0.15; 0.60)**	
Demographic macroregion		0.638[a]		0.097[a]		0.638[a]
North	1.00		1.00		1.00	
Northeast	1.07 (0.91; 1.26)		1.22 (0.88; 1.68)		0.97 (0.51; 1.83)	
Southeast	1.02 (0.85; 1.22)		**1.45 (1.00; 2.09)**		1.49 (0.78; 2.87)	
South	1.03 (0.84; 1.25)		**1.52 (1.06; 2.17)**		1.13 (0.54; 2.34)	
Center-West	0.92 (0.74; 1.15)		1.02 (0.68; 1.55)		1.17 (0.53; 2.59)	

OR = odds ratio; 95% CI = 95% confidence interval; P = significance level.

[a]Heterogeneity; [b]Tendency.

*Values weighted for the inverse of the existence of landline telephones and the number of adults living in the interviewee's house.

Analysis adjusted for sex, age, marital status, skin color and demographic macroregion (first level), and education level (second level).

Boldface indicates statistical significance (P < 0.05).

individuals with black skin color (OR: 1.31 [CI: 1.05; 1.62]) and decreased according to the educational level (9 to 11 years, OR: 0.68 [CI: 0.56; 0.83]; 12 years and over, OR: 0.63 [CI: 0.50; 0.79]), in comparison with adults with no and one disease. For multimorbidity consisting of three diseases, the odds increased among individuals living with a partner (OR: 1.45 [CI: 1.06; 1.98]) and decreased according to the educational level (9 to 11 years, OR: 0.58 [CI: 0.45; 0.77]; 12 years and over, OR: 0.49 [CI: 0.35; 0.69]), in comparison with adults with no and one disease. Lastly, an inverse association between multimorbidity consisting of four diseases and living in the southeastern and central-western demographic macroregions was also observed (**Table 3**).

DISCUSSION

In this study, the aim was to identify sociodemographic factors associated with multimorbidity due to non-communicable chronic diseases among adults and older adults in Brazil. Among adults, the main sociodemographic factors related to multimorbidity due to two, three and four chronic diseases were age between 40 to 59 years, the lowest educational level and the fact that they lived in the southern and southeastern regions. Among older adults, being female and having the lowest educational level were the characteristics that presented the most consistent associations with occurrences of multimorbidity, while residing in the southeastern and central-western regions was an inverse feature.

In the present study, older women were at greater risk of NCD multimorbidity. However, among adults, this same result was not seen. In a review of the literature by Marengoni et al.,[14] on the multimorbidity process in relation to aging, it was indicated that women characterized this state of health more clearly. Another study identified higher risk for women regardless of age, with a magnitude lower than in the present study (OR = 1.12).[15] The higher risk presented by women in this age group can be attributed to the postmenopausal period[16] and to the fact that women have greater knowledge of medical diagnoses.[17]

Table 3. Association* of sociodemographic indicators with multimorbidity in terms of the number of non-communicable chronic diseases (NCDs), among older adults (n = 14,982)

Variables	2 NCDs versus 0 and 1		3 NCDs versus 0 and 1		4 NCDs versus 0 and 1	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex		**< 0.001**[a]		**< 0.001**[a]		**0.002**[a]
Male	1.00		1.00		1.00	
Female	**1.62 (1.33; 1.96)**		**1.68 (1.28; 2.21)**		**2.52 (1.39; 4.57)**	
Age group, years		0.420[b]		0.356[b]		0.143[b]
60 to 69	1.00		1.00		1.00	
70 to 79	1.10 (0.89; 1.37)		1.33 (0.98; 1.81)		0.65 (0.39; 1.10)	
≥ 80	0.76 (0.56; 1.04)		1.03 (0.61; 1.75)		0.57 (0.21; 1.58)	
Marital status		0.580[a]		**0.018**[a]		0.278[a]
Living without a partner	1.00		1.00		1.00	
Living with a partner	1.06 (0.85; 1.33)		**1.45 (1.06; 1.98)**		0.74 (0.43; 1.28)	
Skin color		**0.016**[a]		0.380[a]		0.814[a]
White	1.00		1.00		1.00	
Black	**1.31 (1.05; 1.62)**		1.14 (0.86; 1.51)		0.94 (0.59;1.52)	
Educational level, years		**< 0.001**[b]		< **0.001**[b]		0.369[b]
0-8	1.00		1.00		1.00	
9-11	**0.68 (0.56; 0.83)**		**0.58 (0.45; 0.77)**		0.73 (0.38;1.38)	
≥ 12	**0.63 (0.50; 0.79)**		**0.49 (0.35; 0.69)**		0.79 (0.40; 1.57)	
Demographic macroregion		0.581[a]		0.327[a]		0.504[a]
North	1.00		1.00		1.00	
Northeast	0.07 (0.87; 1.31)		1.04 (0.77; 1.40)		0.70 (0.42; 1.17)	
Southeast	0.92 (0.72; 1.17)		1.00 (0.70; 1.43)		**0.52 (0.28; 0.97)**	
South	1.18 (0.93; 1.49)		1.24 (0.89; 1.73)		0.93 (0.54; 1.61)	
Center-West	0.92 (0.74; 1.15)		0.97 (0.71; 1.33)		**0.37 (0.20; 0.69)**	

OR = odds ratio; 95% CI = 95% confidence interval; P = significance level.

[a]Heterogeneity; [b]Tendency.

*Values weighted for the inverse of the existence of landline telephones and the number of adults living in the interviewee's house.

Analysis adjusted for sex, age, marital status, skin color and demographic macroregion (first level), and education level (second level).

Boldface indicates statistical significance (P < 0.05).

Advancement of age among adults presented a tendency to increase the risk of accumulation of NCD multimorbidity. On the other hand, among the older adults, there was no association with this variable. The results from the present study were in line with findings from the United States,[18] Australia[19] and middle-income countries such as China, Ghana, India, Mexico, Russia and South Africa.[20] Especially between the ages of 50 and 60 years, the aging process is associated with significant transitions that give rise to diminished autonomy, mental health, quality of life and physical functioning.[21] According to Willcox, Ash and Catignani,[22] aging can be attributed to genetically engineered mechanisms, neuronal-endocrine failures and modifications resulting from the oxidative stress proteins and deoxyribonucleic acid (DNA) of cellular lipids. These alterations increase chronic inflammatory states, since they are not controlled mainly by behavioral factors, and they therefore exposed personal effects to the appearance of NCDs.[22]

Considering marital status, the adults and the older adults with partners were at greater risk of having multimorbidity consisting of two and three NCDs, respectively. Other studies have also found this association of risk among adults,[4,23] which can be attributed to changes to unhealthy habits, with increasing burden of disease appearing over the course of the routine that characterizes marital transition.[24] Evidence for this association had already been presented,[25] but assessment of multimorbidity consisting of concomitant diseases constitutes a new approach. This may be explained differently among adults, in the light of the transition of the marital situation. Another interpretation that might be suggested is that individuals with a partner are more likely to use healthcare services than are those without a partner.[26]

The adults' skin color did not show any association with multimorbidity, but among the older adults, there was higher risk of multimorbidity with two NCDs among individuals with black skin color. This result can be characterized in social or biological terms. Socially, older adults with black skin color have social, economic and cultural barriers regarding their living and health conditions, which reflect the unequal distribution of risk factors, protective factors and health problems accumulated over the course of their lives.[27] From a biological point of view, people with black skin color

present higher risk of hypertension,[28] which leads to higher exposure to new diseases concomitantly, i.e. multimorbidity.

Adults with more years of schooling presented protection against multimorbidity, especially with regard to dealing with four diseases simultaneously. The same association was also found among older adults, but in relation to occurrences of two and three NCDs. Other studies investigating the association of schooling with multimorbidity have also found protection, especially in adulthood.[4] This result can be attributed to these individuals' knowledge of disease prevention, health promotion measures and care and control measures after a disease has become established. Actions towards providing such care and management would, for example, change modifiable factors associated with NCDs and would entail correct use of medications. A trend towards protection was also found in populations older than 60 years of age in Scotland[1] and the United States,[23] among individuals with higher educational levels. Longer schooling reflects better social conditions, with consequent indication of characteristics favoring access to information and healthcare services. A study by Bosma et al.[29] made this relationship clear by pointing out that higher educational levels among older adults allowed health self-care interventions to be more effective.

Lastly, regarding the demographic macroregions of Brazil, there was a risk of multimorbidity with two NCDs among adults living in the southeastern and southern regions, while there was protection with four NCDs in the southeastern and central-western regions among older adults. Brazil is a country of continental dimensions with diverse settlements, demographics, climates and cultures, which lead to peculiar features with regard to data interpretation. For adults, the southeastern and southern regions may present greater risk because areas with more urban lifestyles present greater inequalities in healthcare and more discrepant socioeconomic indicators, which are considered to be a proxy for multimorbidity.[3] The counterpoint described for the older adult population can be explained by the higher proportion of financial resources that are allocated to primary healthcare in the southeastern and central-western regions of Brazil,[30] which enables better prevention and control measures regarding health outcomes, including NCDs.

We recognize that there were some limitations to this study that need to be considered before interpreting the results. The main limitation was the number of NCDs included as multimorbidities. This hampers comparisons with data from other countries or from using different instruments. Moreover, the measurements were self-reported, which required that the interviewees were aware that the disease had been diagnosed. The fact that Brazil's public healthcare programs give the population broad access to primary healthcare also needs to be considered.[31] Our study did not assess the contributions that may have been made by substantial numbers of other diseases and their severity.

Furthermore, the obesity classification was based on self-reported weight and height information and should be considered cautiously. Lastly, even though the sample was representative nationally, it is necessary to restrict the extrapolation of the results. Only individuals residing in the capitals of the Brazilian states and those who had landline telephones were considered, although the weighting used in Vigitel aimed to minimize this source of bias.

CONCLUSION

The numbers of diseases in the Brazilian population among adults and older adults have sociodemographic determinants with regard to defining multimorbidity. The variables presented differences in the magnitudes of effect in analyses on the age groups of adults and older adults. The disparity among adults was in relation to the advancement through the decades of life; and among older adults, in relation to being female. These findings are significant because they relate to a current primary healthcare topic, aimed mainly at public healthcare in Brazil. The future implications may be contained in preventive and therapeutic multicomponent care programs within primary healthcare in Brazil and other middle-income countries. This possibility allows actions based on construction of informational materials, training of professionals and organization of activities directed to women's population, individuals of older age, those living with a partner and those with lower educational levels.

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Address for correspondence:
Marina Christofoletti
Campus Reitor João David Ferreira Lima, s/nº
Trindade — Florianópolis (SC) — Brasil
CEP 88040-900
Tel. (+55 48) 3721-8519 — Fax. (+55 48) 3721-6240
E-mail: marinachriss@outlook.com.br

Low molecular weight heparin is useful in adult COVID-19 inpatients. Experience during the first Spanish wave: observational study

Jose Ramon Gonzalez-Porras[I], Moncef Belhassen-Garcia[II], Amparo Lopez-Bernus[III], Luis Mario Vaquero-Roncero[IV], Beatriz Rodriguez[V], Cristina Carbonell[VI], Raul Azibeiro[VII], Alberto Hernandez-Sanchez[VIII], Jose Ignacio Martin-Gonzalez[IX], Juan Miguel Manrique[X], Gloria Alonso-Claudio[XI], Felipe Alvarez-Navia[XII], Jose Ignacio Madruga-Martin[XIII], Ronald Paul Macias-Casanova[XIV], Jorge García-Criado[XV], Francisco Lozano[XVI], Jose Carlos Moyano[XVII], Miguel Vicente Sanchez-Hernandez[XVIII], Víctor Sagredo-Meneses[XIX], Rafael Borras[XX], Jose María Bastida[XXI], Guillermo Hernández-Pérez[XXII], Antonio Javier Chamorro[XXIII], Miguel Marcos[XIV], Jose Angel Martin-Oterino[XXV]

Complejo Asistencial Universitario de Salamanca (CAUSA); Instituto de Investigación Biomédica de Salamanca (IBSAL); and Universidad de Salamanca (USAL), Salamanca, Spain

[I]MD, PhD. Physician, Department of Hematology, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0003-3266-7996
[II]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-2230-1256
[III]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-7524-4056
[IV]MD, PhD. Physician, Department of Anesthesiology and Reanimation, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-0079-2111
[V]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-6511-2084
[VI]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-6271-5111
[VII]MD. Physician, Department of Hematology, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-3382-3674
[VIII]MD. Physician, Department of Hematology, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain https://orcid.org/0000-0002-6601-3096
[IX]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-3389-1810
[X]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0003-3294-2724
[XI]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-8987-899X
[XII]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-9317-8873
[XIII]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-0167-191X
[XIV]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0001-8734-7872
[XV]MD. Physician, Department of Emergency, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0003-0595-9539
[XVI]MD, PhD. Physician, Department of Angiology and Vascular Surgery, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-1591-9015
[XVII]MD, PhD. Physician, Department of Clinical Biochemistry, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0003-4886-9365
[XVIII]MD. Physician, Department of Anesthesiology and Reanimation, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-0427-1735
[XIX]MD. Physician, Department of Intensive Care Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-6386-352X
[XX]MD. Physician, Department of Emergency, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0001-5743-9768
[XXI]MD, PhD. Physician, Department of Hematology, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-8007-3909
[XXII]MD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0001-8610-5425
[XXIII]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0002-2345-2873
[XXIV]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/0000-0003-1269-4487
[XXV]MD, PhD. Physician, Department of Internal Medicine, Complejo Asistencial Universitario de Salamanca (CAUSA), Instituto de Investigación Biomédica de Salamanca (IBSAL), Universidad de Salamanca (USAL), Salamanca, Spain. https://orcid.org/00000-0002-5598-5180

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ABSTRACT

BACKGROUND: The intensity of the thromboprophylaxis needed as a potential factor for preventing inpatient mortality due to coronavirus disease-19 (COVID-19) remains unclear.

OBJECTIVE: To explore the association between anticoagulation intensity and COVID-19 survival.

DESIGN AND SETTING: Retrospective observational study in a tertiary-level hospital in Spain.

METHODS: Low-molecular-weight heparin (LMWH) status was ascertained based on prescription at admission. To control for immortal time bias, anticoagulant use was analyzed as a time-dependent variable.

RESULTS: 690 patients were included (median age, 72 years). LMWH was administered to 615 patients, starting from hospital admission (89.1%). 410 (66.7%) received prophylactic-dose LMWH; 120 (19.5%), therapeutic-dose LMWH; and another 85 (13.8%) who presented respiratory failure, high D-dimer levels (> 3 mg/l) and non-worsening of inflammation markers received prophylaxis of intermediate-dose LMWH. The overall inpatient-mortality rate was 38.5%. The anticoagulant nonuser group presented higher mortality risk than each of the following groups: any LMWH users (HR 2.1; 95% CI: 1.40-3.15); the prophylactic-dose heparin group (HR 2.39; 95% CI, 1.57-3.64); and the users of heparin dose according to biomarkers (HR 6.52; 95% CI, 2.95-14.41). 3.4% of the patients experienced major hemorrhage. 2.8% of the patients developed an episode of thromboembolism.

CONCLUSIONS: This observational study showed that LMWH administered at the time of admission was associated with lower mortality among unselected adult COVID-19 inpatients. The magnitude of the benefit may have been greatest for the intermediate-dose subgroup. Randomized controlled trials to assess the benefit of heparin within different therapeutic regimes for COVID-19 patients are required.

INTRODUCTION

The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as coronavirus disease-19 (COVID-19), is a new pandemic that appeared in the city of Wuhan, China, in December 2019.[1,2] Over the past four months, COVID-19 has become a worldwide pandemic, such that 32,150,495 cases and 982,680 deaths globally have been reported. In Spain, 682,267 cases and 45,252 deaths were reported up to September 24, 2020. Although the majority of COVID-19 cases have resolved spontaneously, some have developed various fatal complications, including organ failure, septic shock, pulmonary edema, severe pneumonia and SARS.[3]

Current data support the concept that disseminated intravascular coagulation (DIC) in sepsis is a coagulation disorder induced by infection, and that it also represents an acute systemic inflammatory response that leads to endothelial dysfunction.[4,5] Recent data in the literature show that severe COVID-19 is commonly complicated with coagulopathy and that DIC might exist in the majority of deaths.[6] Moreover, a remarkably high incidence of venous thromboembolism (VTE) has been reported in patients hospitalized with COVID-19.[7]

Heparin may have positive effects on COVID-19 patients.[8] The American College of Chest Physicians (ACCP) recommends use of the Padua prediction score, which is a validated risk assessment model, in order to identify hospitalized medical patients who are at high risk of VTE and who should therefore

receive thromboprophylaxis during their hospital stay.[9] However, the substantially high incidence of VTE and overt DIC among COVID-19 patients could justify use of extensive thromboprophylaxis.

Based on these findings, it seems that prophylactic doses of heparin for patients with severe COVID-19 and coagulopathy could be useful, and this has been recommended by some expert consensuses.[8,10-12] Nonetheless, the high incidence of coagulopathy and thrombotic complications that is seen among COVID-19 patients despite use of antithrombotic prophylaxis could be important for decision-making with regard to the intensity of thromboprophylaxis to be applied. Therefore, the benefits of high doses of antithrombotic drugs in COVID-19 cases need to be clarified.

OBJECTIVE

The present study was designed to explore the intensity of the thromboprophylaxis needed as a potential factor for preventing in-hospital mortality associated to COVID-19.

METHODS

Study design and population

We performed a retrospective observational study in Spain on all patients with a diagnosis of COVID-19 who had been hospitalized at the University Hospital of Salamanca between March 1, 2020, and April 7, 2020. The diagnosis of COVID-19 was performed made in accordance with the interim guidance from the World Health Organization. It was then confirmed through detection of the ribonucleic acid (RNA) of SARS-CoV-2 in the microbiological laboratory of the University Hospital of Salamanca.[13] The only exclusion criterion was age below 18 years. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital of Salamanca (code: CEIm PI2020-04-472) on April 16, 2020.

Laboratory procedures and data collection

The baseline characteristics of the patients were retrospectively collected from the electronic medical record system and from the concomitant therapies. We started a registry of patients hospitalized due to COVID 19 in our hospital that was updated every day. A COVID team (acknowledgement section) was in charge of collection of clinical and biological variables. The final outcome (survivor or non-survivor) was also extracted from the medical records. The samples for coagulation tests were collected on admission. Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and D-dimer were detected using an ACL TOP 500 CTS coagulation analyzer and original reagents (Werfen Spain SAU, L'Hospitalet de Llobregat, Spain). The DIC-ISTH score was calculated on the basis of the general criteria of the International Society on Thrombosis and Haemostasis (ISTH).[14]

Heparin prescription

The patients' low-molecular-weight heparin (LMWH) status was ascertained based on prescription at admission. They were stratified according to the LMWH regimen received, into four groups: non-heparin, prophylactic-dose heparin, therapeutic-dose or heparin dose according to biomarkers.

The prophylactic-dose heparin group was defined as patients who received prophylactic LMWH starting from admission, with prescription in accordance with the Padua VTE risk assessment model.[9]

The prophylactic-dose heparin patients were treated with enoxaparin (40 mg) or bemiparin (3,500 units subcutaneously (SC)) once daily, or if they had a creatinine clearance (CLCr) lower than 30 ml/min upon starting on LMWH, the doses would be enoxaparin (20 mg) or bemiparin (2500 units SC), once daily. Because of warnings about increased thrombotic risk among COVID-19 patients, our local guidelines have endorsed the use of prophylactic-dose heparin as a measure to prevent VTE, for all adult COVID-19 inpatients since March 20, 2020.

Therapeutic-dose heparin, consisting of enoxaparin (1 mg/kg SC bid) or bemiparin (115 IU anti-Xa/kg SC), once daily, was prescribed from the time of admission for patients who were taking oral anticoagulants before admission and who presented very high risk of thrombosis.

From April 30 onwards, we used specified heparin doses for high thrombotic-risk patients (heparin dose according to biomarkers). This cohort comprised patients receiving prophylactic LMWH who presented respiratory failure, high D-dimer levels (> 3 mg/l) and non-worsening of inflammation markers. The per-protocol dimer-D cutoff used was six times greater than the upper limit of normality. This heparin-dose group according to biomarkers presented suspicion of pulmonary embolism, but angiographic computed tomography (CT) did not confirm any presence of pulmonary embolism (PE). This group received enoxaparin (1 mg/kg) or bemiparin (5000 units SC), once daily (intermediate dose of heparin). For any patients with CLCr lower than 30 ml/min, enoxaparin or bemiparin was administered at 0.5 mg/kg or 3500 units SC once daily, respectively.

In the non-heparin group, the patients did not receive any heparin treatment, due to contraindication and/or a low risk of VTE, as shown by the Padua model.

Information on any side effects was also collected from the medical records. Special attention was given to bleeding events: major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial bleeding, or intramuscular bleeding with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dl or more, or leading to transfusion of two or more units of whole blood or red cells.[15] VTE was defined as deep venous thrombosis (DVT)

diagnosed through ultrasonography, or as pulmonary embolism (PE) diagnosed through helical chest computed tomography (CT) scan. For arterial thrombotic events, ischemic stroke, myocardial infarction and systemic arterial embolism, the World Health Organization definitions were used.

Statistical analysis

A descriptive statistical analysis was performed after including all the data in an Excel spreadsheet (Microsoft Corp., Redmond, Washington, United States). The normality of distribution of the continuous variables among survivors and non-survivors was evaluated by means of the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as the mean (with standard deviation, SD); non-normal variables were reported as the median (with interquartile range, IQR, 25th to 75th percentile). Qualitative values were presented as percentages and absolute numbers.

We used nonparametric tests to compare quantitative variables if the distribution was not normal (Mann-Whitney U test) and parametric tests if it was normal (Student's t test). The Fisher exact test or chi-square test was used for comparison of categorical variables, as appropriate. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for COVID-19 death.

Anticoagulant use after admission was analyzed as a time-dependent variable. The follow-up started at the admission and continued until death or right censoring (June 1, 2020), whichever occurred first. The time metric was days since the baseline. The main analysis was performed by adjusting the Cox regression model for variables with significant statistically differences in the univariate analysis for mortality, to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for COVID-19 deaths. The analysis was performed separately for: (i) users of any anticoagulant drug compared with nonusers; (ii) users of prophylactic-dose heparin compared with anticoagulant nonusers; (iii) users of therapeutic-dose heparin compared with anticoagulant nonusers; and (iv) users of heparin dose according to biomarkers compared with anticoagulant nonusers. To control for immortal time bias, anticoagulant use was analyzed as a time-dependent variable.

The significance level was set at $P < 0.05$. The Statistical Package for the Social Sciences 21 software (SPSS; IBM, Chicago, Illinois, United States) and the Stata 15 software (Stata Statistical Software: release 15, 2017; StataCorp LLC, College Station, Texas, United States) were used to perform the statistical analysis.

RESULTS

A total of 690 consecutive COVID-19 patients admitted to the University Hospital of Salamanca were enrolled. At the time of this analysis (June 1, 2020), 266 patients (38.5%) had died, 422 (61.4%) had been discharged and one (0.1%) remained hospitalized. The inpatient mortality rate was 38.5%. The median age of the study population was 72 years (IQR: 64-85). There were 413 male patients (59.8%) and comorbidities were present in nearly half of the patients (48.9%) (**Table 1**).

The treatment for COVID-19 was not homogeneous and changed over time in accordance with the national and international recommendations: 341 patients (49.4%) received corticosteroids, 439 (63.6%) received hydroxychloroquine and 388 (56.2%) received lopinavir/ritonavir. Tocilizumab, to manage cytokine storm syndrome, was administered to 207 (30%).

Heparin was administered to 615 patients from the time of hospital admission (89.1%). The median time on treatment with LMWH was 14 days (IQR ± 8). 75 patients (10.8%) did not receive any heparin.

Baseline characteristics of the patients and features predicting survival (comparison between survivors and non-survivors)

The survivors were significantly younger (median: 67 years) versus non-survivors (81 years) ($P < 0.001$). Patients with Charlson comorbidity index ≥ 1 were statistically more frequently non-survivors than survivors (80.2% versus 51.3%; $P < 0.001$). In addition, non-survivors presented higher D-dimer levels (1.3 mg/l versus 0.7 mg/l; $P < 0.001$) and longer PT (13.5 sec versus 12.7 sec; $P = 0.001$) than survivors. The DIC-ISTH score [2 (0-2) versus 2 (2-3)] was quite similar between the groups. The treatment with LMWH was associated with a lower inpatient mortality rate (**Table 1**).

Baseline characteristics, treatment received, UCI admission and mortality among the patients (comparison between heparin subgroups)

Out of the 615 patients who received heparin, 410 (66.7%) received a prophylactic dose, 120 (19.5%) received a therapeutic dose and 85 other patients (13.8%) undergoing LMWH prophylaxis presented respiratory failure, high D-dimer levels (> 3 mg/l) and non-worsening of inflammation markers, and thus received an intermediate heparin dose (heparin-dose group according to biomarkers). **Table 2** shows the baseline characteristics, treatments received, intensive care unit (ICU) admission and mortality according to heparin group.

There were statistically significant differences among the four heparin groups regarding age, comorbidities, prothrombin time, aPTT time, platelet count, lymphocyte count, lactate dehydrogenase (LDH) levels and disseminated intravascular coagulation-International Society on Thrombosis and Haemostasis (DIC-ISTH) scores on admission. The younger patients with fewer comorbidities were more likely to be in the heparin-dose group according

Table 1. Baseline characteristics and coagulation parameters of COVID-19 patients on admission

	Total (n = 690)	Survivors (n = 424)	Non-survivors (n = 266)	P-value
Age, mean (± standard deviation)	72.48 (13.83)	67.17 (13.39)	81.18 (9.43)	< 0.001
Sex, male/female, n	416/274	253/174	163/100	0.477
Pneumonia, n (%)	422 (61.2)	269 (63.0)	153 (58.2)	0.207
BMI > 30, n (%)	146 (26.1)	100 (28.1)	46 (22.7)	0.147
Charlson comorbidity index ≥ 1, n (%)	428 (62.3)	218 (51.3)	210 (80.2)	< 0.001
On admission				
PT (sec), median (IQR)	12.9 (11.5-14.8)	12.6 (11.4-14.2)	13.5 (11.6-16.8)	<0.001
aPTT (sec), median (IQR)	33.6 (30.8-36.9)	33.6 (31.5-36.6)	33.76(30.5- 37.4)	0.762
Fibrinogen (mg/dl), median (IQR)	637 (504-796)	619 (493-769)	666 (529-808)	0.138
D-dimer (g/l), median (IQR)	0.8 (0.5-1.70)	0.7 (0.4-1.1)	1.3 (0.8-3.17)	< 0.001
Platelets (x10^9/l), median (IQR)	186 (144-244)	187 (146-250)	1813(141-232)	0.314
Lymphocytes (x10^9/l), median (IQR)	0.88 (0.64-1.23)	0.95 (0.70-1.27)	0.74 (0.55-1.13)	0.001
LDH (U/l), median (IQR)	358 (286-458)	338 (276-425)	403 (313-530)	< 0.001
DIC-ISTH score, median (IQR)	2 (0-2)	2 (0-2)	2 (2-3)	< 0.001
Treatments				
Heparin, n (%)	615 (89.1)	400 (93.7)	215 (81.7)	< 0.001
Corticosteroids, n (%)	368 (53.3)	219 (51.3)	149 (56.7)	0.170
Hydroxychloroquine, n (%)	645(93.9)	416 (98.1)	229 (87.1)	< 0.001
Lopinavir/ritonavir, n (%)	581 (84.2)	388 (91.5)	193 (73.0)	< 0.001
Tocilizumab, n (%)	216 (31.3)	158 (37.0)	58 (22.1)	< 0.001

BMI = body mass index; PT = prothrombin time; aPTT = activated partial thromboplastin time; IQR = interquartile range; LDH = lactate dehydrogenase; DIC = disseminated intravascular coagulation; ISTH = International Society on Thrombosis and Haemostasis.
Normal ranges: PT (11.1 – 15.8 seconds); aPTT (27- 40 seconds); fibrinogen (130-400 mg/dl); D-dimer (< 0.5 g/l); platelet count (150 x10^9/l – 400 x10^9/l); lymphocyte count (1.2-3.5x10^9/l); LDH (135-225).

Table 2. Baseline characteristics and coagulation parameters of COVID-19 patients according to heparin group

	Non-heparin (n = 75)	Prophylactic-dose heparin (n = 410)	Therapeutic-dose heparin (n = 120)	Heparin dose according to biomarkers (n = 85)	P-value
Age, mean (± standard deviation)	75.2(15.5)	71.7 (14.1)	76.3 (11.2)	67.7 (11.9)	0.004
Sex, male/female, n	46/29	239/171	71/49	60/25	0.208
BMI, mean (± standard deviation)	29.4 (4.9)	28.9 (5.3)	28.8 (4.8)	30.4 (6.5)	0.911
Pneumonia, n (%)	40 (53.3)	255(62.2)	74 (61.7)	53 (62.4)	0.535
Charlson comorbidity index > 1, n (%)	51 (69.9)	241 (58.8)	87 (73.1)	49 (57.6)	0.014
On admission					
PT (sec), median (IQR)	13.3 (11.4-15.6)	12.4 (11.4-13.8)	16.1 (12.4-23.6)	13.2 (11.8-15.8)	< 0.001
aPTT (sec), median (IQR)	33.5 (30.1-36.6)	33.2 (30.9-35.4)	34.1 (30.3- 38.1)	36.5 (32.9-42.1)	< 0.001
Fibrinogen (mg/dl), median (IQR)	571 (498-721)	637 (493-796)	621 (532-769)	708 (538-832)	0.052
D-dimer (g/l), median (IQR)	1.1 (0.5-3.4)	0.8 (0.5-1.6)	0.75 (0.4-1.3)	0.9 (0.5- 2.2)	0.101
Platelets (x10^9/l), median (IQR)	167 (124-232)	191 (146-253)	179 (144-235)	180 (140-238)	0.034
Lymphocytes (x10^9/l), median (IQR)	0.91 (0.59-1.28)	0.94 (0.66-1.28)	0.75 (0.61-1.04)	0.84 (0.61-1.11)	0.017
LDH (U/l), median (IQR)	353 (277-484)	351 (278-441)	364 (286-476)	392 (307-512)	0.019
DIC score, median (IQR)	2 (2-3)	2 (0-2)	2 (2-3)	2 (0-3)	< 0.001
Treatments			Total 126		
Corticosteroids, n (%)	22 (29.3)	208 (50.7)	84 (70)	54 (63)	<0.001
Hydroxychloroquine, n (%)	57 (76.0)	390 (95.1)	115 (96.6)	83 (100)	< 0.001
Lopinavir/ritonavir, n (%)	50 (66.7)	3467 (84.6)	105 (88.2)	78 (94-0)	< 0.001
Tocilizumab, n (%)	9 (12)	116 (28.3)	36 (20.0)	55 (64.7)	< 0.001
ICU admission, n (%)	5 (6.7)	21 (5.1)	13 (10.8)	41 (48.2)	< 0.001
Death, n (%)	48 (64.0)	134 (32.7)	57 (47.5)	24 (28.2)	< 0.001

BMI = body mass index; PT = prothrombin time; aPTT = activated partial thromboplastin time; IQR = interquartile range; LDH = lactate dehydrogenase; DIC = disseminated intravascular coagulation; ISTH = International Society on Thrombosis and Haemostasis; ICU = intensive care unit.
Normal range: PT (11.1-15.8 seconds); aPTT (27-40 seconds); fibrinogen (130-400 mg/dl); D-dimer (< 0.5 g/l); platelet count (150 x10^9/l-400 x 10^9/l); lymphocyte count (1.2-3.5x10^9/l); LDH (135-225).

to biomarkers. The gender, body mass index (BMI), presence of pneumonia and levels of fibrinogen and D-dimer at diagnosis were similar in all the heparin groups. The percentage of intensive care unit (ICU) admission was higher in the heparin-dose group according to biomarkers. The inpatient mortality was lower in the heparin-dose group according to biomarkers (28.2%) and the prophylactic-dose group (32.7%).

COVID-19 survival in relation to use of heparin

Figure 1 shows the overall survival based on type of heparin use. The anticoagulant nonuser group presented higher mortality risk than any LMWH users (HR 2.1; 95% CI: 1.40-3.15). Three other variables retained their independent prognostic value for predicting higher inpatient mortality: age, DIC-ISTH score and LDH levels. **Table 3** shows the results subdivided according to the use of different heparin doses.

The anticoagulant nonuser group also presented higher mortality risk than the prophylactic-dose heparin group (HR 2.39; 95% CI, 1.57-3.64). According to this model, the other mortality risk factors were age, Charlson comorbidity index and LDH levels.

The anticoagulant nonusers were at significantly higher risk of COVID-19 death than were the therapeutic-dose LMWH users (HR 2.69; 95% CI, 1.61–4.50). Age, DIC-ISTH scores and LDH levels were the other mortality risk factors.

Lastly, the anticoagulant nonuser group presented higher mortality risk than the users of heparin dose according to biomarkers (HR 6.52; 95% CI, 2.95-14.41).

Bleeding and thromboembolic complications

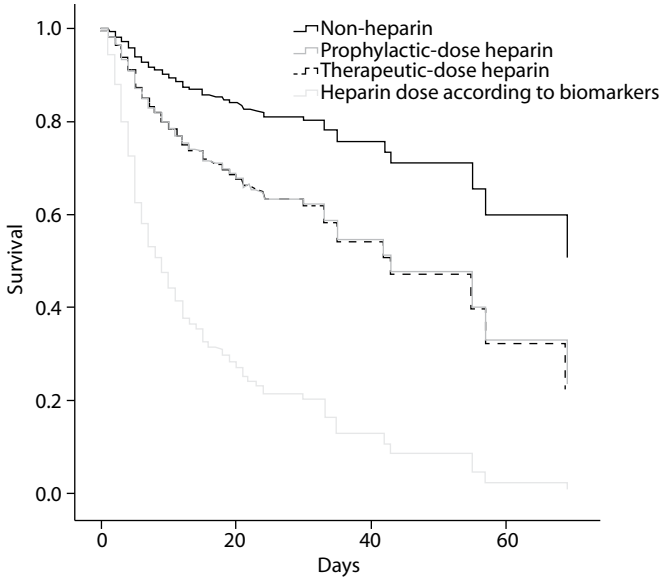
Among the 690 patients, 24 patients (3.4%) experienced major hemorrhage, but only one case was fatal (**Table 4**). Two cases of major bleeding complications occurred in patients without heparin (2.6%), eight cases of major hemorrhage occurred in the low-heparin-dose group (1.9%), six cases of major bleeding complications occurred among the patients with therapeutic-dose heparin (5%) and eight cases of major bleeding occurred in the heparin-dose group according to biomarkers (9.4%) (P = 0.007, between heparin groups). Nineteen patients (2.8%) developed an episode of thromboembolism, which was fatal in three cases (**Table 5**).

DISCUSSION

We report in this retrospective observational study how the administration of LMWH at the time of admission was associated with a reduced mortality rate among unselected adult COVID-19 patients. The magnitude of the benefit may have been greatest for the group of patients who received a heparin dose according to biomarkers. It should be noted that overall, although major bleeding was more frequently reported in the higher dose groups, only one fatal event was reported. In addition, young patients with no comorbidities, low LDH levels and low DIC-ISTH scores at the time of admission presented a significantly lower risk of inpatient mortality.

Overall, infection is a common cause of disseminated intravascular coagulation. Inflammation, infection and other factors can lead to excessive suppression of fibrinolysis and a disrupted anticoagulant system.[16] Previous reports have observed that COVID-19 patients with severe pneumonia may develop significant abnormalities of coagulation features, DIC and ischemic changes in different tissues. In fact, DIC appeared in most of the deaths in those reports.[6] SARS-CoV-2 can hyperactivate the innate immune system in excess, thereby causing cytokine storms and damage to the microvascular system and activating coagulation and fibrinolysis. Interleukin-6 (IL-6) is a key factor in the inflammatory factor storm induced by SARS-CoV-2.[17,18] On the other hand, ischemia and hypoxia reperfusion injury may contribute to the hypercoagulable state. In this regard, early recognition of COVID-19-associated coagulopathy could be very helpful in anticipating and dealing with the outcomes.

There is no strong evidence to support the idea that routine anticoagulation therapy would be effective for preventing sepsis.[19] A meta-analysis on randomized controlled trials comparing LMWH versus placebo in sepsis suggested that LMWH might reduce mortality among septic patients.[20] Another recent meta-analysis suggested that anticoagulation therapy would be beneficial only for patients with sepsis-induced DIC and not for the entire population



P-value < 0.001 between non-heparin group and prophylactic-dose group;
P-value < 0.001 between non-heparin group and therapeutic-dose group;
P-value < 0.001 between non-heparin group and heparin-dose group according to biomarkers.

Figure 1. Overall survival based on type of heparin use.

of patients with sepsis.[21] Moreover, the guidance for diagnosis and treatment of DIC provided by the ISTH states that use of therapeutic doses of heparin should be considered in cases of DIC in which thrombosis is predominant.[22] A multicenter cohort study conducted by Japanese institutions reported that use of high-intensity anticoagulation therapy was associated with better outcomes among patients with sepsis-induced DIC.[23]

Currently, there is little information on the use of LMWH in relation to COVID-19. Anticoagulant therapy that was implemented mainly using LMWH at a prophylactic dose was associated with a better prognosis in a series of COVID-19 patients in China, but the infection level was severe in all patients.[8] However, in our study, we show how the use of a prophylactic dose of LMWH starting from the time of admission to the hospital significantly reduced the inpatient mortality rate among all adult COVID-19 patients. Our findings can possibly be explained by the differences in ethnicity, age (our median age was 72 years, versus 65 years in the Chinese population) and sample size. Our results are in line with expert opinion, which recommends the use of prophylactic LMWH in hospitalized COVID-19 patients.[11] However, in addition, we suggest that the intensity of the thromboprophylaxis used may be a potential factor for preventing in-hospital mortality associated with COVID-19.

Table 3. Cox regressions. All heparin users compared with nonusers, prophylactic-dose heparin users compared with anticoagulant nonusers, therapeutic-dose heparin users compared with anticoagulant nonusers and heparin-dose users according to biomarkers compared with anticoagulant nonusers. Anticoagulant use was analyzed as a time-dependent variable

	Multivariable-adjusted hazard ratios*
All anticoagulant users compared with nonusers	
None	2.10 (1.40-3.15)
Any	Ref
Age	1.89 (1.62-2.20)
DIC-ISTH score	1.23 ()1.07-1.41)
LDH level	1.00 (1.00-1.00)
Prophylactic-dose heparin users compared with anticoagulant nonusers	
None	2.39 (1.57-3.64)
Prophylactic-dose heparin	Ref
Age	2.05 (1.71-2.46)
Charlson comorbidity index	1.79 (1.10-2.93)
LDH levels	1.00 (1.00-1.00)
Therapeutic-dose heparin users compared with anticoagulant nonusers	
None	2.69 (1.61-4.50)
Therapeutic-dose heparin	Ref
Age	1.73 (1.33-2.17)
DIC-ISTH score	1.22 (1.00-1.50)
LDH levels	1.00 (1.001-1.00)
Heparin-dose users according to biomarkers compared with anticoagulant nonusers	
None	6.52 (2.95-14.64)
Heparin dose according to biomarkers	Ref
Age	1.65 (1.22-2-23)
LDH levels	1.00 (1.00-1-00)

*Multivariable-adjusted hazard ratios (with 95% confidence intervals) in relation to deaths. Adjusted variables are age, Charlson comorbidity Index, DIC-ISTH score, LDH, lymphocytes, prothrombin time and treatments.
DIC = disseminated intravascular coagulation; ISTH = International Society on Thrombosis and Haemostasis; LDH =lactate dehydrogenase.

Besides its use as an anticoagulant, heparin has demonstrated excellent anti-inflammatory properties in animal models and clinical trials.[24] Use of LMWH was found to reduce serum IL-6 levels, which are a key factor in patients with severe COVID-19, and to reduce TNF-α levels.[25] Heparin has been seen to exert an inhibitory effect on replication activity and against attachment and entry of enveloped viruses, in relation to several viruses: human herpes simplex virus (HSV), human immunodeficiency virus (HIV), SARS coronavirus and influenza virus (H5N1).[26] Moreover, heparin prevents Zika virus-induced cell death of human neural progenitor cells.[27] Therefore, the potential anti-inflammatory and antiviral properties of LMWH might partly explain its beneficial mechanism.

Thromboprophylaxis using high doses of LMWH may lead to bleeding, which can be fatal. In our series, major bleeding was presented in 3.4% of the patients and the bleeding rate was significantly higher in the high-heparin-dose group (7.3%). The incidence of major bleeding in critically ill patients who received LMWH prophylaxis was reported to range from 1.2% to 5.4% in three trials.

The rate of thrombosis in our series seemed very low (2.8%). The exact prevalence or incidence of venous thromboembolism in COVID-19 patients is unknown. Different reports have indicated VTE rates ranging from 11% to 31%, and the highest incidence of VTE has been found among patients admitted to intensive care units.[28]

Thrombotic complications have only rarely been described in COVID-19 patients. Klok et al. recently reported that the cumulative incidence of thrombotic complications among ICU patients was 31%.[7] This cumulative incidence is remarkably high, and was in spite of the finding that all the patients had received at least standard doses of thromboprophylaxis. Those authors emphasized the recommendation to strictly apply pharmacological thrombosis prophylaxis to all COVID-19 patients admitted to an ICU, and strongly suggested that the level of prophylaxis should be increased towards high prophylactic doses.[7] In another study among hospitalized patients with COVID-19, the overall estimated pooled incidence of VTE was 17.0%.[29]

Table 4. Major hemorrhage events in COVID-19 patients

Site of bleeding	Heparin group	Days after starting use of heparin	Criterion for defining event as major bleeding	Fatal
Intracranial	Dose according to biomarkers	1	Critical organ	No
Intracranial	Non-heparin	19*	Critical organ	Yes
Lung	Dose according to biomarkers	3	Transfusion of 2 units of RBCs	No
Lung	Prophylactic-dose	5	Transfusion of 2 units of RBCs	No
Gastrointestinal	Non-heparin	7*	Transfusion of 8 units of RBCs	No
Gastrointestinal	Prophylactic-dose	5	Transfusion of 4 units of RBCs	No
Gastrointestinal	Prophylactic-dose	7	Transfusion of 2 units of RBCs	No
Gastrointestinal	Prophylactic-dose	5	Transfusion of 2 units of RBCs	No
Gastrointestinal	Prophylactic-dose	9	Transfusion of 2 units of RBCs	No
Gastrointestinal	Prophylactic-dose	12	Transfusion of 2 units of RBCs	No
Gastrointestinal	Dose according to biomarkers	6	Transfusion of 2 units of RBCs	No
Gastrointestinal	Therapeutic-dose	9	Transfusion of 2 units of RBCs	No
Gastrointestinal	Prophylactic-dose	3	Transfusion of 2 units of RBCs	No
Gastrointestinal	Therapeutic-dose	13	Fall in Hb level of 3 g/dl	No
Gastrointestinal	Therapeutic-dose	12	Fall in Hb level of 2 g/dl	No
Tracheostomy	Dose according to biomarkers	7	Transfusion of 2 units of RBCs	No
Tracheostomy	Dose according to biomarkers	9	Transfusion of 2 units of RBCs	No
Tracheostomy	Dose according to biomarkers	6	Transfusion of 2 units of RBCs	No
Genitourinary	Prophylactic-dose	5	Fall in Hb level of 3 g/dl	No
Genitourinary	Therapeutic-dose	14	Fall in Hb level of 2 g/dl	No
Genitourinary	Therapeutic-dose	10	Fall in Hb level of 2 g/dl	No
Chest wall hematoma	Dose according to biomarkers	9	Fall in Hb level of 3 g/dl	No
Hematoma catheter size	Dose according to biomarkers	14	Transfusion of 6 units of RBCs	No
Hematoma catheter size	Therapeutic-dose	18	Fall in Hb level of 3 g/dl	No

*In this situation (non-heparin treatment), days after inpatient admission.

Table 5. Thromboembolic events in COVID-19 patients

Type of event	Heparin group	Cardiovascular risk factors	Days after starting treatment	Fatal
Pulmonary embolism	Therapeutic-dose	88 years, male, hypertension, dyslipidemia, stroke	1	No
Pulmonary embolism	Dose according to biomarkers	74 years, male, hypertension, dyslipidemia	10	No
Pulmonary embolism	Dose according to biomarkers	56 years, male	22	No
Pulmonary embolism	Therapeutic-dose	74, male, hypertension, atrial fibrillation, rheumatoid arthritis	1	No
Pulmonary embolism	Prophylactic-dose	64 years, female, asthma	6	No
Pulmonary embolism	Prophylactic-dose	73 years, female,	45	No
Pulmonary embolism	Dose according to biomarkers	63 years, male, hypertension, obesity	6	No
Pulmonary embolism	Dose according to biomarkers	66 years, male	8	No
Pulmonary embolism	Prophylactic-dose	82 years, female, hypertension, diabetes	9	No
Deep venous thrombosis	Prophylactic-dose	64 years, male, dyslipidemia	12	No
Deep venous thrombosis	Prophylactic-dose	74 years, female	1	No
Deep venous thrombosis	Dose according to biomarkers	47 years, female, catheter	6	No
Portal thrombosis	Dose according to biomarkers	83 years, female, hypertension, diabetes, dyslipidemia, gallbladder cancer in 2018	2	No
Stroke	Prophylactic-dose	62 years, female, dyslipidemia	16	No
Stroke	Therapeutic-dose	84 years, male, atrial fibrillation,	2	Yes
Myocardial infarction	Dose according to biomarkers	85 years, male, hypertension, diabetes, prior myocardial infarction	3	Yes
Myocardial infarction	Dose according to biomarkers	81 years, male, hypertension, diabetes, dyslipidemia, prior myocardial infarction	2	No
Myocardial infarction	Non-heparin	93 years, female, hypertension	2*	Yes
Critical limb ischemia	Prophylactic-dose	64 years, male, hypertension, diabetes, smoking	10	No

*In this situation (non-heparin treatment), days after inpatient admission.

In our cohort, the percentage of ICU patients with VTE was only 11%. In addition, our use of higher doses of LMWH in a high percentage of patients could explain our low incidence of VTE. Our findings stress the need for exploring the optimal dose of LMWH among COVID-19 patients. In this setting, the hypothesis supporting the notion that high doses of anticoagulants will reduce the risk of thrombosis, DIC and mortality, compared with low doses of anticoagulants, in patients with COVID-19 infection, will be explored in several randomized clinical trials.[30] Recent real-world data have shown that early starting of prophylactic anticoagulation, compared with no anticoagulation, among patients admitted to hospital with COVID-19, was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events.[31] In addition, in a recent press release dated January 22, 2021, from the United States National Institutes of Health (NIH), which is coordinating a multiplatform randomized controlled trial (RCT), it was reported that therapeutic-dose anticoagulation had been found to be beneficial for decreasing the need for organ support among patients who did not require ICU-level care when they entered the study, regardless of D-dimer level, with a trend toward less mortality.[32]

Increased D-dimer levels in patients with severe COVID-19 have commonly been reported to be a predictor for a dismal outcome. Several authors have observed that patients with severe COVID-19 presented D-dimer levels that were 2.5 to 5-fold higher than those in patients without this.[6,30-35] Zhou et al. found an association between higher D-dimer levels (9-fold higher) and mortality among patients with severe COVID-19.[34] The risk of severe illness was more frequent in patients with D-dimer levels above 0.5 mg/l.[33] A pooled analysis on four retrospective observational studies found that D-dimer levels were considerably higher in COVID-19 patients with severe disease than in those without this (weighted mean difference: 2.97 mg/l; 95% CI: 2.47-3.46 mg/l), but the heterogeneity across the four studies was relatively high (i.e. $I^2 = 94\%$; $P < 0.001$).[36] Petrilli et al. showed that there was a relationship between D-dimer level and its trajectory and the frequency of adverse clinical events.[37] In our unselected cohort of COVID-19 patients, the median D-dimer level on admission was significantly higher in non-survivors (2.1 g/l) than in survivors (0.9 g/l), in the univariate analysis, but the prognostic impact of this finding was not maintained in the multivariate analysis. According to our model, the DIC-ISTH score, which includes D-dimer data, is a more valuable criterion with independent prognostic value for predicting inpatient mortality risk.

In addition, the mortality risk index also included age, LDH, underlying diseases, DIC-ISTH score and use of LMWH, which would facilitate identification of patients with high mortality risk, among unselected adult COVID-19 cases at the time of hospital admission. In fact, the reported area under the receiver operating characteristic curve for this category is of great value (COVID-19 mortality index 0.869).

The benefit of heparin doses needs to be balanced against the risk of bleeding. We observed an excess of bleeding complications in patients who received the highest heparin dose. Along the same lines, bleeding events were observed in another study in 7.8% of the patients hospitalized with COVID-19 and were sensitive to use of escalated doses of anticoagulants and to the nature of data collection.[29]

The limitations of our study are those that are inherent to an observational retrospective single-center study. Potential selection and immortal time bias do exist in this kind of study. Through assessing the potential role and magnitude of this confounding, the inherent differences between the heparin groups can be understood. We had detailed information on patient characteristics among the heparin groups. The analyses were adjusted for multiple background variables to minimize bias. The outcome was survival at the time of the analysis: at that time, only one patient was still hospitalized. On the other hand, to control for immortal time bias, the anticoagulant dose was analyzed as a time-dependent variable.

Although our study focused on coagulation parameters, other variables could also impact on mortality. The concomitant therapy, including LMWH, was not assessed in relation to a control. The true rate of VTE was also perhaps underestimated due to the impossibility of carrying out imaging studies on some patients with clinically suspected VTE. Nonetheless, our report describes the experience of a single center with a large patient population that was homogeneously managed in accordance with the local guidelines, which were regularly updated with the emerging information. If a multicenter study had been conducted, this might have given rise to introduction of additional confounding factors, due to the heterogeneity of management protocols across the centers.

CONCLUSIONS

Our results suggest that application of LMWH at the time of admission significantly reduced the mortality rate among these unselected adult COVID-19 inpatients. The LMWH dose could have prognostic impact, although overall, major bleeding was more frequently reported in the high-dose group. Further research is needed to tailor heparin prophylaxis and ascertain the correct dose for adults COVID-19 patients.

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Address for correspondence:
Jose María Bastida
Department of Hematology,
University Hospital of Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL)
Paseo de San Vicente, s/nº
Salamanca, 37007
Spain
Tel. +34923291100 (Ext - 55931)
E-mail: jmbastida@saludcastillayleon.es

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Patients' preferences regarding physicians' gender: a clinical center cross-sectional study

Carolina Matté Dagostini[I], Yan De Assunção Bicca[II], Miguel Bertelli Ramos[III], Sabrina Busnello[IV], Murillo Cesar Gionedis[V], Natália Contini[VI], Asdrubal Falavigna[VII]

Centro Clínico (CECLIN), Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil

[I]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0003-4189-7339

[II]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0003-4336-2426

[III]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0002-5932-0186

[IV]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0002-2896-2813

[V]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0002-6482-352X

[VI]Undergraduate Medical Student, Department of Neurosurgery, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0003-0895-9593

[VII]MD, MSc, PhD. Coordinator, Health Sciences Undergraduate Program, Universidade de Caxias do Sul (UCS), Caxias do Sul (RS), Brazil.
https://orcid.org/0000-0002-0016-3198

KEYWORDS:
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ABSTRACT

BACKGROUND: Even with the significant growth of female representation within medicine, inequality and prejudice against this group persist.

OBJECTIVE: To analyze patients' preferences regarding the gender of physicians in general and according to different specialties, and the possible reasons behind their choice.

DESIGN AND SETTING: Cross-sectional study at the Clinical Center of the University of Caxias do Sul, Brazil.

METHODS: Over a three-month period in 2020, 1,016 patients were asked to complete a paper-based 11-item questionnaire.

RESULTS: The majority (81.7%; n = 830) of the patients did not have a preference regarding the gender of physicians in general. The preference rate for same-gender physicians was 14.0% (n = 142/1,016), and this preference was more common among female than among male patients (17.6% versus 7.0%; odds ratio, OR = 2.85; 95% confidence interval, CI = 1.80-4.52; P < 0.001). When asked about their preference for the gender of the specialist who they were waiting to see, the overall preference rate for a same-gender professional was 17.2% (n = 175). Preference for same-gender specialists was higher for specialties essentially based on pelvic or breast examination (i.e. gynecology, urology, proctology and mastology), compared with others (33.4% versus 9.7%; OR = 4.69; 95% CI = 3.33-6.61; P < 0.001).

CONCLUSIONS: The patients' model for choice of their physician does not seem to involve physicians' gender in general or in the majority of medical specialties. The data presented in this study may make it easier to understand patients' preferences and concerns.

INTRODUCTION

Gender disparity is defined as a social phenomenon in which discrimination against others occurs due to their gender (male or female).[1] In the field of healthcare, women represent 70% of the worldwide workforce, and this percentage has increased sharply over recent years.[2] Currently, even with the significant growth of female representation in field of medicine, inequality and prejudice against this group persists.[3,4] It has been shown that female residents are notably more likely to be mistreated, both by patients and hospital staff, which may lead to higher rates of burnout syndrome and suicidal thoughts among this gender, compared with male colleagues.[5]

The idea that patients will choose their healthcare provider based on gender is an issue that has been discussed in the literature, albeit to a limited extent. Some previous studies have shown that patients seem to have a predilection in favor of male physicians for general medical care.[6-9] Among the medical specialties of obstetrics and gynecology, most patients were found to report a female preference when selecting this specialist.[10,11] In contrast, other studies within the emergency department and orthopedic specialties revealed that there was neither any patient preference for the physicians' gender, nor any propensity towards same-gender physicians.[12,13] Some authors have argued that the reasons behind this divergence in the literature may encompass factors such as cultural and regional influences, as well as the specialty studied.[14,15]

While the representativeness of women in medicine has already been widely discussed and studied, few publications have focused on patients' views on the topic.[3] The literature still lacks studies that have assessed patient reception in the light of the increasing numbers of women in the most varied medical specialties. Analysis on patients' preference for male or female physicians within clinical care is an important tool to be considered in studies on patients' perceptions, since this elucidates gender disparities regarding physicians in the field of healthcare.

OBJECTIVE

The aim of this study was to analyze patients' preferences regarding physicians' gender in general and according to different medical specialties, at a single center, along with the possible reasons behind their choice.

METHODS

Study design and location

A cross-sectional study was conducted using a paper-based questionnaire on patients' preference for physicians' gender. It was carried out between October and December 2020, at the Clinical Center of UCS (Centro Clínico, Universidade de Caxias do Sul, CECLIN-UCS), a public secondary-level healthcare center for medical specialties, in Caxias do Sul, Rio Grande do Sul, Brazil. The adult medical specialties present at CECLIN-UCS at the time of the study were: urology, general surgery, nutrology, cardiology, general surgery, cardiac surgery, vascular surgery, thoracic surgery, plastic surgery, bariatric surgery, dermatology, endocrinology, gastroenterology, geriatrics, gynecology, hematology, infectiology, mastology, nephrology, neurology, orthopedics, ophthalmology, otorhinolaryngology, pneumology, proctology and rheumatology. Data collection took place through a paper-based questionnaire that was designed and distributed to patients by the researchers.

Ethics committee

This study was previously approved by the Research Ethics Committee of the University of Caxias do Sul (CEP-UCS), under protocol number 29785920.7.0000.5341, approved on April 13, 2020. Prior to application of the questionnaires, each patient gave written informed consent to use of their information in clinical studies. The principles of the Helsinki Declaration were followed.

Population studied

To be included, patients needed to: (1) be waiting for an appointment at CECLIN-UCS; (2) be ≥ 18 years old; and (3) agree to participate in the study by signing the free and informed consent statement. Incomplete questionnaires were excluded.

Sample size calculation

For the purposes of sample size calculation, we considered a significance level of 5%, absolute error of 5% and population size of 50,000 people, corresponding to the average annual attendance at CECLIN-UCS. The resulting sample size was 382 individuals.

Questionnaire on patients' preference for physicians' gender

This paper-based 11-item questionnaire written in Portuguese (**Attachment 1**) was anonymous. It was divided into three sections: (1) general information; (2) patients' preference for physicians' gender in general; and (3) patients' preference for physicians' gender according to medical specialties.

The general information section asked about the individual's age, biological sex, sexual orientation, marital status, level of education, monthly income expressed as Brazilian minimum wages per month, which was 1045.00 reais in 2020, and medical specialty within which the patient was being seen. The sections on patients' preference for physicians' gender in general and patients' preference for physicians' gender according to medical specialties included two questions each. The former asked about the individual's preference for the gender of physicians in general and the reasons for this preference. The latter also asked about preference and reasons, but specifically in relation to the specialty within which the patient was waiting for the appointment.

Outcomes

The primary outcome consisted of the patients' preference for the physicians' gender in general. The secondary outcomes were: (1) the patients' preference for the physicians' gender according to medical specialties; (2) reasons for gender preference; and (3) comparison of gender preference between male and female patients.

Statistical analysis

We used IBM SPSS Statistics for Windows, version 23.0, released 2015 (Armonk, New York, United States: IBM Corp.). Age presented asymmetrical distribution ($P < 0.001$ in the Kolmogorov-Smirnov test) and was presented both as the median ± quartile deviation and as the mean ± standard deviation and its respective 95% confidence interval (95% CI). Age means were compared using the nonparametric Mann-Whitney test. Age groups were defined in terms of quartiles. Categorical variables were presented as frequencies and percentages. Comparisons of these variables were made using the chi-square test or Fisher's exact test. The significance level was set at 0.05. The crude and adjusted odds ratios (OR and AOR) were obtained by means of binary logistic regression. The model for the preference for same-gender physicians in general considered the following variables relating to the participants: gender (male or female), age group (< 44, 44-55, 56-65 or > 65 years) and educational level (up to complete elementary school or at least incomplete high school).

RESULTS

Demographic data

Among the 1,041 questionnaires received, 1,016 were complete and were therefore included in the analysis. The median and mean ages of the respondents were, respectively, 55.0 ± 10.9 years

and 54.3 ± 15.4 years, ranging from 18 to 93 years (P25 = 44.0; P50 = 55.0; P75 = 65.75). The majority of the patients were women (66.0%; n = 671) and self-reported that they were heterosexual (94.7%; n = 962). The most frequent marital status was "married" (47.9%; n = 487). Regarding schooling, 66.9% (n = 680) had not completed high school education. Most of the respondents (89.1%; n = 905) had an income of up to two Brazilian minimum wages per month. **Table 1** shows the detailed demographic data on the participants.

Patient preference for physician gender in general

The majority (81.7%; n = 830) of the patients did not have a preference regarding the gender of physicians in general (**Table 2**). The rate of preference for same-gender physicians was 14.0% (n = 142/1,016), and this preference was more common among female patients than among male patients (17.6% versus 7.0%; AOR = 2.56; 95% CI = 1.60-4.10; P < 0.001) (**Table 3**). Women were more likely to prefer female physicians than were men (17.6% versus 4.9%; OR = 4.12; 95% CI = 2.43-6.97; P < 0.001). Men, in turn, were slightly more likely to prefer male physicians than were women (7.0% versus 4.0%; OR = 1.78; 95% CI = 1.01-3.14; P = 0.04). **Figure 1** illustrates the reasons behind the preference for male or female physicians according to patient gender. The most common reason for preferring same-gender physicians was "feeling more comfortable with them".

The mean age of the patients who preferred same-gender physicians was lower (49.3 years; 95% CI = 46.4-52.2) than that of those who did not have a preference (55.12 years; 95% CI = 54.1-56.1) (P < 0.001). The age group with the highest preference for same-gender physicians was the youngest group (< 44 years) (**Table 3**). Those who had a level of education up to complete elementary school did not have a statistically significant difference regarding preference for physicians' gender, compared with those who had at least incomplete high school education (14.0% versus 14.0%, AOR = 0.70; 95% CI = 0.46-1.04; P = 0.08) (**Table 3**).

Patients' preference for physicians' gender according to medical specialties

When asked about the gender of the specialist who they were waiting to see, the overall rate of preference for a same-gender professional was 17.2% (n = 175). For specialties that are essentially based on pelvic or breast examination (i.e. gynecology, urology, mastology and proctology), patients were more likely to prefer same-gender specialists, compared with other specialties (33.4% versus 9.7%; OR = 4.69; 95% CI = 3.33-6.61; P < 0.001). Among specialties with more than 20 responses, the highest preferences were observed for gynecology (41.3%; n = 71/172), urology (27.0%; n = 17/63), proctology (22.9%; n = 8/35), mastology (22.6%; n = 12/53) and general surgery (22.5%; n = 9/40) (**Table 4**). **Figure 2** illustrates the reasons behind the preference for a same-gender specialist for specialties essentially based on pelvic or breast examination and for other specialties. The most common reason was "feeling more comfortable with them".

Table 1. Detailed demographic data on the participants

Variable	Frequency (%)
Sex	
Female	671 (66.0)
Male	345 (34.0)
Age	
< 44 years	251 (24.7)
44-55 years	260 (25.6)
56-65 years	251 (24.7)
> 65 years	254 (25.0)
Sexual orientation	
Heterosexual	969 (95.4)
Homosexual	22 (2.2)
Bisexual	22 (2.2)
Asexual	3 (0.3)
Marital status	
Single	215 (21.2)
Married	583 (57.4)
Divorced or widowed	218 (21.4)
Educational level	
No formal education	43 (4.2)
Incomplete elementary school	363 (35.7)
Complete elementary school	159 (15.6)
Incomplete high school	115 (11.3)
Complete high school	208 (20.5)
Incomplete university education	77 (7.6)
Complete university education	51 (5.0)
Monthly income[a]	
< 1 minimum wage	303 (29.8)
1-2 minimum wages	602 (59.3)
> 2 minimum wages	111 (10.9)
Specialty of the appointment	
Gynecology	172 (16.9)
Gastroenterology	142 (14.0)
Cardiology	105 (10.3)
Vascular surgery	93 (9.2)
Endocrinology	76 (7.5)
Urology	63 (6.2)
Mastology	53 (5.2)
General surgery	40 (3.9)
Proctology	35 (3.4)
Pneumology	35 (3.4)
Nephrology	29 (2.9)
Bariatric surgery	27 (2.7)
Ophthalmology	22 (2.2)
Other[b]	124 (12.2)
Total	**1,016 (100.0)**

[a]Income is expressed as Brazilian minimum wages per month; [b]Other refers to specialties with ≤ 20 responses (rheumatology, neurology, otolaryngology, nutrology, dermatology, geriatrics, hematology, cardiac surgery, plastic surgery, orthopedics, thoracic surgery, infectiology, oncology and hepatology).

DISCUSSION

Our findings suggest that most of the patients did not have a preference regarding the gender of physicians in general. It was also demonstrated that preference for same-gender physicians was higher among female patients than among male patients. For specialties essentially based on pelvic or breast examination (i.e. gynecology, urology, proctology and mastology), compared with others, there was a marked preference for specialists of the same gender.

The proportion of women in the medical profession has increased over recent decades, and more markedly so over recent years.[16-18] According to data from the World Health Organization (WHO), women make up about 70% of the worldwide workforce within the field of healthcare.[2] Reports on medical demographics in Brazil in 2020 showed that women accounted for 46.6% of physicians in this country, and that in three Brazilian states (Rio de Janeiro, Pernambuco and Alagoas), their proportion already surpassed 50%.[17] Among younger physicians, female gender predominates, with 58.5% in the age group up to 29 years old, and 55.3% in the group between 30 and 34 years old.[17] Women's representation within medicine started to increase in 1970 and continued to grow until 2009, when they first surpassed men to represent the majority of medical professionals, accounting for 50.4% of all registered physicians.[18] Since then, this proportion has continued to progressively increase, reaching 57.5% in 2019.[17]

The difficulties that women encounter when entering surgical residency are commonly associated with factors such as long training, pre-existing prejudice in the surgical environment, lack of credibility in their abilities and prejudices stemming from patients and family members alike who believe in the tradition of male dominance within surgical specialties.[5,19-23] In evaluating discrimination, abuse, harassment and burnout outcomes in surgical residency programs, Hu et al.[5] found that acts of mistreatment, both from patients and hospital staff, occurred more often against women; 65.1% of female respondents reported gender discrimination and 19.9% recounted sexual harassment. That study also revealed that mistreatment was an impactful factor in the development of burnout syndrome (38.5%) and suicidal thoughts among residents (4.5%), and that women were more likely than male colleagues to report burnout symptoms (42.4% versus 35.9%; odds ratio, 1.33; 95% CI, 1.20 to 1.48).[5]

Nonetheless, a cohort study carried out by Huang et al. revealed that the two genders demonstrated similar diagnostic efficacy.[24] Thus, it appears that the gender-based inequality between physicians does not stem from differences in clinical and diagnostic skills.[25-27] Even though many of these challenges are still encountered by women when choosing a residency program, this scenario seems to be changing for the better. As Dineen et al.[13] remarked in their findings, medicine as a whole has seen a tremendous rise in female representation over the past years, albeit at a slower pace within surgical specialties.

Regarding patients' preference for the gender of their healthcare provider, previous studies have shown that in most cases, there is no tendency towards either males or females.[6,12,28] Kerssens et al., in a study developed in the Netherlands, showed that among 961 patients questioned about their preference for physicians' gender, there was virtually no difference with regard to the majority of healthcare professionals.[29] Likewise, our results showed that most patients did not have any preference regarding the gender of physicians in general (81.7%) (**Table 2**).

Table 2. Patients' preference regarding their physicians' gender, stratified according to the gender of the patient

Patients' gender	Patients' preference – frequency (%)		
	Prefer male physicians	Prefer female physicians	No preference
Male	24 (7.0)	17 (4.9)	304 (88.1)
Female	27 (4.0)	118 (17.6)	526 (78.4)
Overall	51 (5.0)	135 (13.3)	830 (81.7)

Table 3. Preferences for same-gender physicians stratified according to sex, age group and educational level

Variable	Preference for same-gender physician			
	Frequency (%)	OR (95% CI)	AOR (95% CI)	P-value
Sex				
Female	118/671 (17.6)	2.85 (1.80-4.52)	2.56 (1.60-4.10)	< 0.001
Male	24/345 (7.0)	Reference category		
Age group				
< 44 years	58/251 (23.1)	Reference category		
44-55 years	34/260 (13.1)	0.50 (0.31-0.80)	0.47 (0.29-0.76)	0.002
56-65 years	17/251 (6.8)	0.24 (0.14-0.43)	0.24 (0.13-0.44)	< 0.001
> 65 years	33/254 (13.0)	0.50 (0.31-0.79)	0.48 (0.29-0.82)	0.006
Educational level				
Up to complete elementary school	79/565 (14.0)	Reference category		0.08
At least incomplete high school	63/451 (14.0)	1.00 (0.70-1.43)	0.70 (0.46-1.04)	
Total	**142/1,016 (14.0)**	**N/A**	**N/A**	**N/A**

OR = crude odds ratio; AOR = adjusted odds ratio.

Table 4. Preference for same-gender specialists stratified according to specialty and patients' gender

Specialty	Preference for same-gender specialists – n/total (%)		
	All patients	Female patients	Male patients
Gynecology	71/172 (41.3)	71/171 (41.5)	0/1 (0.0)
Urology	17/63 (27.0)	2/11 (18.2)	15/52 (28.8)
Proctology	8/35 (22.9)	7/18 (38.9)	1/17 (5.9)
Mastology	12/53 (22.6)	12/52 (22.2)	0/1 (0.0)
General surgery	9/40 (22.5)	7/25 (28.0)	2/15 (13.3)
Endocrinology	11/76 (14.5)	9/52 (17.3)	2/24 (8.3)
Gastroenterology	15/142 (10.6)	12/80 (15.0)	3/62 (4.8)
Nephrology	3/29 (10.3)	2/15 (13.3)	1/14 (7.1)
Ophthalmology	2/22 (9.1)	2/13 (15.4)	0/9 (0.0)
Vascular surgery	7/93 (7.5)	3/57 (5.3)	4/36 (11.1)
Bariatric surgery	2/27 (7.4)	1/24 (4.2)	1/3 (33.3)
Cardiology	5/105 (4.8)	2/53 (3.8)	3/52 (5.8)
Pneumology	1/35 (2.9)	1/22 (4.5)	0/13 (0.0)
Other[a]	12/124 (9.7)	9/78 (11.5)	3/46 (6.5)
Total	**175/1,016 (17.2)**	**140/671 (20.9)**	**35/345 (10.1)**

[a]Other refers to specialties with ≤ 20 responses (rheumatology, neurology, otolaryngology, nutrology, dermatology, geriatrics, hematology, cardiac surgery, plastic surgery, orthopedics, thoracic surgery, infectiology, oncology and hepatology).

In contrast, Greene et al.[6] carried out a cross-sectional survey among 915 patients in the United States to investigate whether there would be any preference based on the physician's name alone. They found that the group analyzed had a predilection in favor of male names for their medical care provider, although this was not statistically significant (46.5%; P = 0.19). Moreover, Dineen et al.,[13] in another survey in the United States evaluating patients' preferences when selecting orthopedic providers, found that 14.5% of the patients preferred a female surgeon and that, among these respondents, 89.2% of them were women. In our study, the rate of predilection for a same-gender physician in general was 14.0%, and it was 17.2% when considering preference according to the specialty within which the patient was waiting for a consultation, and this was more frequently observed among females. We also observed that the age group with the highest preference for same-gender physicians was the youngest (< 44 years). The mean age among those who had this tendency was 49.3 years, versus 55.12 years among those who did not (**Table 3**). The prevailing reason for preferring same-gender physicians was "feeling more comfortable with them" (**Figure 1**).

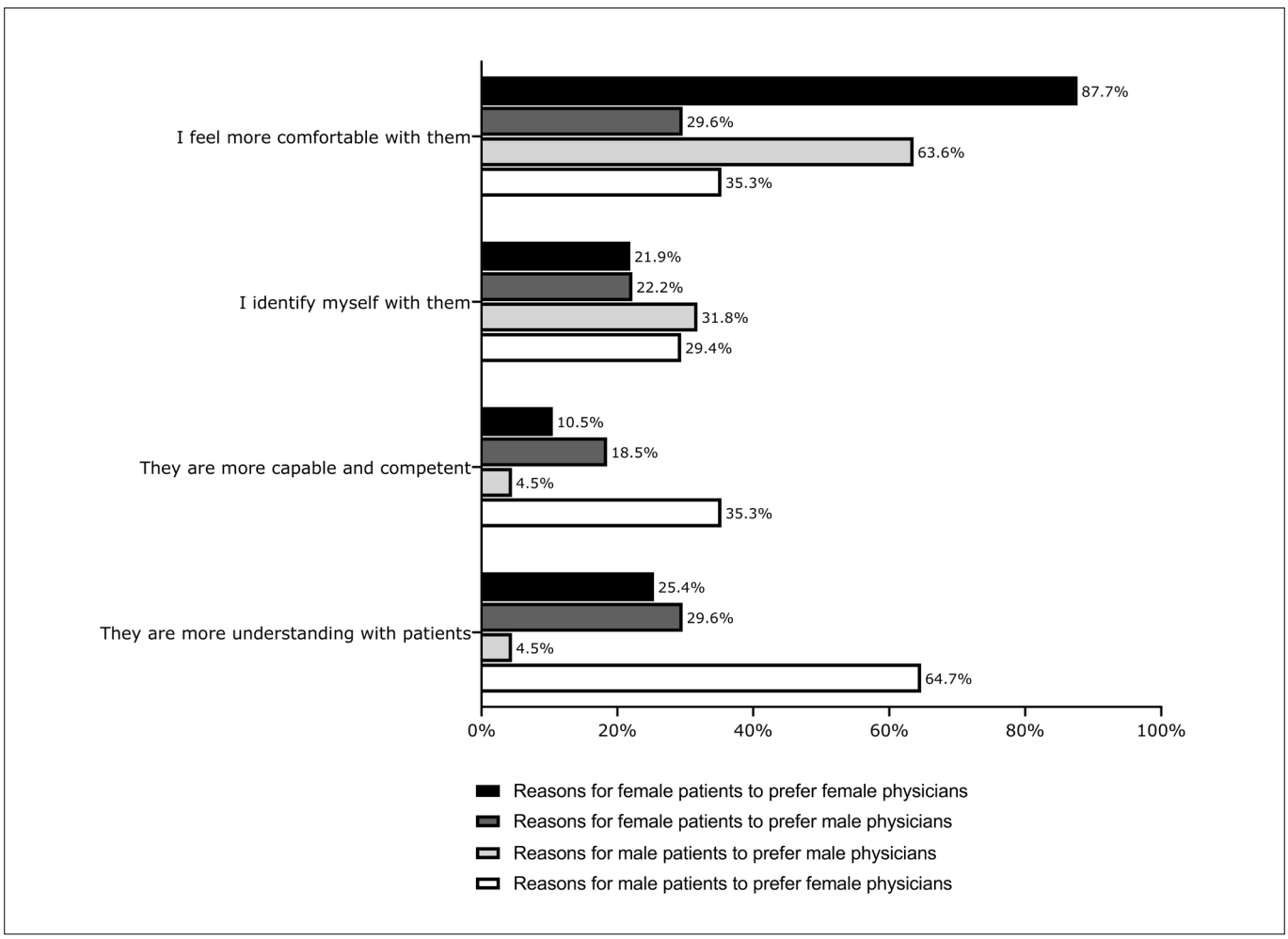

Figure 1. Reasons for preference for male and female physicians in general according to patients' gender.

Despite advances in gender equality within medicine, some medical fields still have higher prevalence of men or women among their specialists.[28,30] In Brazil, women form the majority in dermatology (77.9%), pediatrics (74.4%) and endocrinology (70.6%); while in the United States female-dominated specialties comprise obstetrics and gynecology (83.4%), allergy and immunology (73.5%) and pediatrics (72.1%).[28,31-33] In Brazil, male physicians predominate in urology (97.7%), orthopedic surgery (93.5%) and neurosurgery (91.2%); while in the United States, the male-dominated specialties are orthopedic surgery (84.6%), neurosurgery (82.5%) and interventional radiology (80.8%).[28,31-33]

Previous studies revealed that within specialties based around pelvic or breast examination (such as gynecology and obstetrics, mastology, urology and proctology), preference for same-gender physicians is indeed more frequent.[9-11,27,34-37] In a systematic review of the literature, Janssen et al.[38] evaluated patients' preference in gynecology and obstetrics and reported that 20%-25% mentioned a strong preference for a female specialist. A cross-sectional study in which the aim was to assess gender preference for care providers among urology patients revealed that 42.8% of the patients preferred a male urologist.[37] A descriptive survey evaluating male patients' preference regarding the gender of the physician performing rectal examinations corroborated this, through showing that 51.5% of the patients indicated a preference for a male professional.[9] On the other hand, in a prospective study regarding female preferences for breast surgeon choice, 59% of the patients had no preference for the surgeon's gender.[27]

Our study pointed out that same-gender professionals attending in these fields were 4.69 times more likely to be chosen, compared with the situation in other specialties (33.4% versus 9.7%; OR = 4.69; 95% CI = 3.33-6.61; P < 0.001). Women were more than twice as inclined to choose same-gender physicians as were men (17.6% versus 7%) (**Table 3**). We found that 41.5 % of female patients who came for consultations within gynecology had a same-gender preference, followed by proctology with 38.9% and mastology, 22.2%. In urology, the results showed that 28.8% within the male group had a same-gender preference (**Table 4**).

It is worth noting that these results surprised us. We had expected to find notably higher percentages within these medical fields. The most frequent reason given for same-gender preference, in relation both to specialties that are essentially based on examination of intimate body parts and to other specialties, was "feeling more comfortable with same-gender physicians", although this was much more prevalent for the former group than for the latter (84.9% versus 48.6%) (**Figure 2**). These findings are supported by existing data in the literature. Those studies revealed that female-to-female medical consultations were thought to have a more patient-centered approach, thus promoting increased involvement,

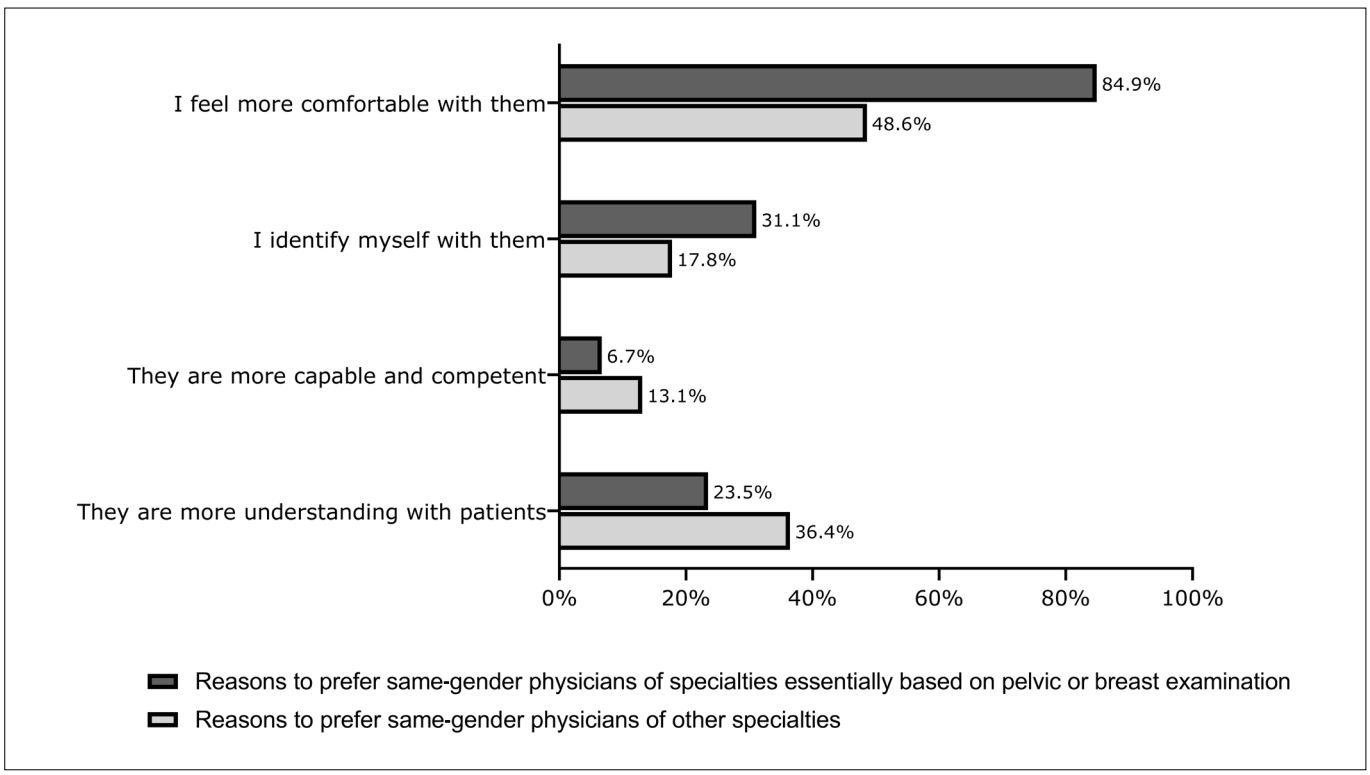

Figure 2. Reasons for preference of same-gender specialists for specialties that are essentially based on pelvic and breast examination, and for other specialties.

while male-to-male interactions were found to be shorter and more focused on the physician's recommendations and instructions.[14,15,39]

We also found that the patients' educational level did not seem to play any important role in gender preference. As detailed in **Table 3**, those who had a lower educational level (up to complete elementary school) did not show a statistically significant difference with regard to preference for physicians' gender, compared with those who had reached a higher level (at least incomplete high school education) (14.0% versus 14.0%). Data regarding whether formal education is an influencing factor in patient predilection for their health professionals' gender are scarce in the literature.

Strengths and limitations

This was an original and innovative study, given that it assessed patients' preference for physicians' gender in a center with a wide variety of medical specialties. In addition, the number of respondents was high (n = 1,016), in comparison with similar studies.[6,8,29] Some patients found it difficult to understand the questions and respective answers if these did not represent the patients' beliefs. In this setting, the researchers tried to clearly explain the meaning of each expression to the respondents when applying the questionnaires. Our study was also prone to selection bias. Patients who supported gender equality may have been more likely to answer the questionnaire than others who did not. Our sample also mainly consisted of patients with a monthly income lower than two minimum wages, and this may have influenced their responses and would not be generalizable to other settings. Furthermore, some specialties may have been underrepresented, with few or no respondents due to lower volume of patients per month (such as orthopedics and cardiac surgery) or because no consultations were available within our center (such as psychiatry and neurosurgery). Lastly, we emphasize that the data presented here were limited to a single center in southern Brazil and should not be fully extrapolated to other regions of this country.

CONCLUSION

In summary, our study showed that, in general, the majority of patients (81.7%) did not have any preference for the gender of their physician. These data demonstrate that the attribute of gender is not uniformly important to all patients. Female patients seemed to prefer a same-gender physician more frequently than did their male counterparts (17.6% vs. 7%). When our patients were asked about gender preference for specialists, the rate of preference for a same-gender professional was 17.2% (n = 175). For medical specialties involving pelvic or breast examination, there was a greater tendency towards preference for same-gender professionals than was noted in relation to other fields (33.4% versus 9.7%).

The current study provides a clearer comprehension of patients' preferences and needs. Healthcare providers may benefit from knowing their patients' educational levels and providing counseling when planning healthcare services. Considering that in Brazil the prevalence of disadvantages and discouragement due to gender is ubiquitous among female physicians and very uncommon among male physicians in certain medical specialties, these data may help to show a change in this scenario to a more equal patient preference.

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Address for correspondence:
Carolina Matté Dagostini
Universidade de Caxias do Sul (UCS)
R. Francisco Getúlio Vargas, 1.130
Caxias do Sul (RS) — Brasil
CEP 95070-560
Tel. (+55 54) 99202-2829
E-mail: carolmdagostini@hotmail.com

Attachment 1. Questionnaire on patients' preference for physicians' gender.

Questionnaire for analysis of patients' preference for physicians' gender, among patients seen at the Clinical Center of the University of Caxias do Sul

1. What is your **AGE?** .....

2. What is your **GENDER**? Check only **ONE** option.
( ) Female
( ) Male

3. What is your **SEXUAL ORIENTATION**? Check only **ONE** option.
( ) Heterosexual
( ) Homosexual
( ) Bisexual
( ) Asexual
( ) Other: .....

4. What is your **MARITAL STATUS**? Check only **ONE** option.
( ) Single
( ) Married
( ) Divorced
( ) Widowed
( ) Common-law marriage
( ) Other: .....

5. What is your **LEVEL OF EDUCATION**? Check only **ONE** option.
( ) No formal education
( ) Incomplete elementary school
( ) Complete elementary school
( ) Incomplete high school
( ) Complete high school
( ) Incomplete university/college graduation
( ) Complete university/college graduation

6. What is your **MONTHLY INCOME** in minimum wages? Check only **ONE** option.
( ) Less than 1 minimum wage per month
( ) From 1 to 2 minimum wages per month
( ) 2 to 3 minimum wages per month
( ) 3 to 4 minimum wages per month
( ) More than 4 minimum wages per month

7. In general, which **PHYSICIAN GENDER** do you prefer? Check only **ONE** option.
( ) Female
( ) Male
( ) I have no preference for gender

8. Considering the answer to the previous question, **WHY** do you prefer to be seen by physicians of this gender? Tick **ALL** the options that fit your answer.
( ) I feel more comfortable when being seen by physicians of this gender
( ) I identify more with physicians of this gender
( ) I believe that physicians of this gender are more capable and competent
( ) I believe that physicians of this gender are more understanding with patients
( ) Other reason: .....
( ) I have no preference for gender

9. What **MEDICAL SPECIALTY** are you consulting with at this clinic?
.....

10. Considering the answer to the previous question, which gender of physician do you prefer to be seen by, in this medical specialty that you are consulting with at this clinic? Check only **ONE** option.
( ) Female
( ) Male
( ) I have no preference for gender

11. Considering the answer to the previous question, **WHY** do you prefer to be seen by physicians of this gender, in this medical specialty that you are consulting with at this clinic? Tick **ALL** the options that fit your answer.
( ) I feel more comfortable when being attended to by physicians of this gender
( ) I identify more with physicians of this gender
( ) I believe that physicians of this gender are more capable and competent
( ) I believe that physicians of this gender are more understanding with patients
( ) Other reason: .....
( ) I have no preference for gender

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Investigation of the effect of ultrasonography-guided bilateral erector spinae plane block on postoperative opioid consumption and pain scores in patients undergoing hepatectomy: a prospective, randomized, controlled study

Gülçin Hacıbeyoğlu[I], Ahmet Topal[II], Tevfik Küçükkartallar[III], Resul Yılmaz[IV], Şule Arıcan[V], Sema Tuncer Uzun[VI]

Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey

[I]MD. Assistant Professor, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
http://orcid.org/0000-0002-9438-3414

[II]MD. Professor, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
https://orcid.org/0000-0001-9832-9741

[III]MD. Professor, Department of General Surgery, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
https://orcid.org/0000-0002-6326-4623

[IV]MD. Assistant Professor, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
https://orcid.org/0000-0002-5527-2893

[V]MD. Assistant Professor, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
https://orcid.org/0000-0002-8634-1150

[VI]MD. Professor, Department of Anesthesiology and Reanimation, Necmettin Erbakan University, Meram Faculty of Medicine, Meram, Konya, Turkey.
https://orcid.org/0000-0002-6205-1706

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Pain.
Analgesia.
Ultrasonography.

AUTHORS' KEY WORDS:
Erector spinae plane block.
Opioid consumption.
Hepatectomy surgery.

ABSTRACT

BACKGROUND: There is still a debate about what constitutes effective and safe postoperative analgesia in hepatectomy surgery. Erector spinae plane (ESP) block may be an important part of multimodal analgesia application in hepatectomy surgery.

OBJECTIVES: To compare the effects of ultrasound-guided bilateral erector spinae plane block combined with intravenous (iv) patient-controlled analgesia (iv PCA), in comparison with iv PCA alone, in hepatectomy surgery.

DESIGN AND SETTINGS: Randomized prospective single-blinded study in a tertiary university hospital.

METHODS: Fifty patients scheduled for elective hepatectomy surgery were included in the study. Patients were randomized into the ESP group or the control group. In the ESP group, bilateral ESP block was performed preoperatively and iv PCA was used. In the control group, only iv PCA was used. Numerical rating scale (NRS) scores at rest and coughing, analgesic requirements and occurrences of nausea and vomiting were recorded.

RESULTS: Intraoperative and postoperative opioid consumption, rescue analgesia requirement and resting and dynamic NRS scores were significantly lower in the ESP group ($P < 0.05$). There was no significant difference between two groups in terms of the presence of dynamic pain after the first postoperative hour. While all patients in the control group had nausea and vomiting, 24% of the patients in the ESP group did not have nausea and vomiting.

CONCLUSION: This study showed that ESP block can be used as a part of multimodal analgesia, with the benefit of reducing opioid consumption and postoperative nausea and vomiting in hepatectomy surgery.

CLINICAL TRIAL REGISTRATION: ACTRN12620000466943.

INTRODUCTION

Hepatectomy is a commonly used treatment option for many benign or malignant liver diseases.[1] Bilateral subcostal incision, surgical retraction and large liver resection, which are all used in hepatectomy surgery, lead to severe postoperative pain in the lower thoracic and abdominal region.

Postoperative analgesia for patients who underwent hepatectomy in protocols for enhanced recovery after surgery (ERAS) is one of the issues which are still discussed and waiting for a solution.[2] The use of intravenous (iv) patient-controlled analgesia (iv PCA) has been demonstrated to be effective in postoperative analgesia, but it should not be ignored that drug metabolism will be influenced in this patient group due to hepatectomy. For this reason, use of multimodal analgesia methods is thought to form a correct approach towards reducing iv opioid consumption.[3] Epidural analgesia provides effective postoperative analgesia following abdominal surgery. However, the changes in coagulation parameters after hepatectomy may pose a risk in patients with epidural catheters.[4] For this reason, safer but easily applicable alternatives are needed for patients who will undergo hepatectomy.

Erector spinae plane (ESP) block is a plane block that was first defined for treating thoracic neuropathic pain and later used for postoperative analgesia in abdominal surgery.[5-7] However, the

number of randomized clinical studies indicating the effectiveness of this block in hepatectomy surgery is limited.[8,9] To the best of our knowledge, there are no clinical studies in the literature researching the effectiveness of ESP block in hepatectomies carried out with bilateral subcostal incision. Therefore, we conducted a prospective randomized clinical study, with the prediction that an ESP block at T8 level, in addition to the iv morphine therapy that we apply in our routine practice in hepatectomies carried out with bilateral subcostal incision, would reduce postoperative opioid consumption and pain scores.

OBJECTIVE

The aim of this study was to compare the effect of ultrasound-guided bilateral erector spinae plane block combined with iv PCA, in comparison with iv PCA alone, in hepatectomy surgery.

METHODS

Study design

This study was designed in an academic university hospital as a prospective randomized controlled single-blinded study, in accordance with the principles defined in the Helsinki Declaration. The study was conducted after obtaining approvals from the university's ethics committee (decision number: 2019/243; approval date: November 13, 2019) and from the Ministry of Health Ethics Committee (66175679-514.04.01-E.214738; approval date: December 14, 2019). It was registered in the Australian New Zealand Clinical Trials Register (Trial ID: ACTRN12620000466943). Written informed consent statements were received from all the patients who agreed to participate in the study.

Patients between the ages of 18 and 65 years, presenting with American Society of Anesthesiologists (ASA) physical status I-III, who had been scheduled to undergo elective hepatectomy surgery in which bilateral subcostal incision would be used as the surgical incision, and for whom a self-retaining retractor would be used, were included in the study. Patients were excluded from the study in the following circumstances: obesity (body mass index > 30 kg/m^2); local skin infection in the area where the needle would be inserted; known allergy to any of the drugs to be used in the study; coagulopathy; chronic opioid consumption; inability to use the PCA device; advanced liver failure; kidney failure; or lack of agreement to participate in the study.

Patient groups and randomization

The patients were randomized and grouped by using the sealed opaque envelope technique. A researcher who was not included in the study performed this procedure. The patients who would not have the block and would only use an iv PCA device for postoperative analgesia comprised the control group. The patients who would undergo preoperative bilateral ESP block and use an iv PCA device postoperatively comprised the ESP group.

Anesthesia application

The same general anesthesia method was applied to all the patients, and the hepatectomy operation was carried out by the same surgical team. Before the operation, all the patients were told about numerical rating scale (NRS) scores for assessing their postoperative pain severity and how to use the iv PCA device. The patients' demographic data and ASA scores were recorded. Routine monitoring and neuromuscular transducer (NMT) monitoring (SJC17200038HA, GE Healthcare, Helsinki, Finland) were performed in the operating room.

Among the patients sedated with 0.03 mg/kg of midazolam (Midolam, Mefar, Istanbul, Turkey), those in the ESP group were subjected to bilateral ESP block with ultrasonography before the induction of anesthesia. In all patients, anesthesia was induced with 40 mg of lidocaine (Jetmonal, Adeka, Samsun, Turkey), 2 mg/kg of propofol (Propofol 1% Fresenius, Fresenius Kabi AB, Uppsala, Sweden), 1 μg/kg of remifentanil (Rentanil, VEM, Tekirdağ, Turkey) and 0.6 mg/kg of rocuronium (Myocron, VEM, Tekirdağ, Turkey). The anesthesia was maintained through inhalation of 0.5-1 MAC desflurane (Suprane, Baxter Healthcare, Puerto Rico, United States) and infusion of remifentanil. The analgesic requirement was monitored using the surgical pleth index (SPI) (SJB17230028HA, GE Healthcare, Helsinki, Finland); the remifentanil infusion dose was set to a SPI below 50; and the total intraoperative remifentanil consumption was recorded.

The patients underwent invasive artery monitoring and right internal jugular vein catheterization via ultrasonography. The surgery was carried out by making a bilateral subcostal incision and using a self-retaining retractor. The duration of the surgery and the surgery performed (right hepatectomy or left hepatectomy) were recorded.

Thirty minutes before the end of the operation, 0.1 mg/kg of iv morphine (Morphine HCl, Idol, Istanbul, Turkey) was administered for postoperative analgesia. The antiemetic ondansetron (Zofran, GlaxoSmithKline, Research Triangle Park, England) was administered to patients at a dose of 0.1 mg/kg, iv. Patients whose muscle relaxation was reversed with sugammadex (Bridion, Patheon Manufacturing Services, North Carolina, United States) were extubated when their Train of Four (TOF) values were ≥ 90%, and they were taken to the post-anesthesia care unit (PACU). Here, an iv PCA device (BodyGuard 575 Pain Manager, Caesarea Medical Electronics GmbH, Lichtenstein, Germany) was attached to patients for postoperative analgesia. PCA was programmed as 1 mg/ml of morphine without a basal infusion dose, as 1 ml per bolus, with a lock-out time of six minutes. Patients were followed

up until their modified Aldrete score reached 9 in the PACU and were then transferred to the intensive care unit of the related clinic.

ESP block application

All the blocks were carried out about 30 minutes before induction of anesthesia. This was done by researchers who would not monitor the postoperative data from the patients (GH, AT). The patients were placed in the prone position, and the skin was prepared with 10% povidone iodine (Poviderm, Necm Chemistry, Istanbul, Turkey). The position of the T7 vertebra at the level of the lower ends of the scapula was determined, and the T8 vertebra one level below this was then detected by palpation.

The T8 spinous process was first seen in the horizontal plane on the midline by using a linear probe covered with a sterile cover at 8 mHz frequency, by means of ultrasonography (Esaote MyLab Six CrystaLine, Genova, Italy). The probe was then turned to the longitudinal plane, and the transverse process was seen approximately 3 cm from the midline to the left lateral and the erector spinae muscle was seen on it.

A 22-gauge 80-mm block needle (Sonoplex, Pajunk Medical, Geisingen, Germany) was advanced craniocaudally in-plane, and the transverse process was touched. The needle was then minimally retracted, and its positioning between the erector spinae muscle and the transverse process was confirmed through hydro-dissection. Following this, 20 ml of 0.375% bupivacaine hydrochloride (Buvicaine, Polifarma, Tekirdağ, Turkey) + 4 mg of dexamethasone (Dekort, Deva, Tekirdağ, Turkey) were injected, and simultaneous local anesthetic dispersion was monitored by means of ultrasonography. The same procedure was performed on the right side.

Loss of hot-cold sensation below and above the bilateral T8 dermatome level, 20 minutes after the block had been performed, was considered to represent successful blocking. The blocked dermatome levels were recorded.

Pain assessment and analgesia protocol

Postoperative pain scores and analgesic requirements were assessed by a research assistant who was blinded to the groups, in the PACU and surgical service. The pain severity was assessed both at rest and during coughing. The NRS during coughing was evaluated as dynamic NRS (DNRS), and if there was a difference of two points or more in relation to the resting NRS, this was defined as the presence of dynamic pain. The resting NRS and DNRS scores at the postoperative 10th minute, 1st hour, 6th hour, 12th hour and 24th hour and morphine consumption at the 1st hour, 6th hour, 12th hour and 24th hour were recorded. Rescue analgesia was applied according to the resting NRS scores. If NRS > 4, this was considered to represent inadequate analgesia, and 0.5 mg/kg of iv meperidine (Petisel, Haver, İstanbul, Turkey) was administered. After 30 minutes, the patient was re-evaluated and, if NRS was still > 4, 0.5 mg/kg of iv meperidine was added. Rescue analgesic requirement and nausea-vomiting over the first postoperative 24 hours were recorded. The severity of nausea was evaluated by the patients on a four-point scale (0: none; 1: mild; 2: moderate; or 3: severe). In the presence of moderate or severe nausea-vomiting, patients were administered additional ondansetron at a dose of 0.1 mg/kg iv.

Primary and secondary outcome criteria

The primary outcome criterion of the study was total morphine consumption over the first postoperative 24 hours. The secondary outcome criteria were the resting and dynamic NRS scores at five different time points (postoperative 10th minute, 1st hour, 6th hour, 12th hour and 24th hour), intraoperative remifentanil consumption and total rescue analgesic requirement over the first postoperative 24 hours. Besides these measurements, changes in the presence of dynamic pain, postoperative nausea-vomiting, dermatome levels in patients who underwent the block, duration of surgery and surgery applied (right hepatectomy or left hepatectomy) were also evaluated.

Sample size calculation

The sample size for this study was calculated using the G*Power software, version 3.1.9.4 for Windows (Universität Düsseldorf, Düsseldorf, Germany), based on a pilot study with 10 patients in each group. Occurrence of a reduction in morphine consumption of at least 30% over the first postoperative 24 hours in the ESP group, compared with the control group, was accepted as clinically significant. According to the pilot study results, morphine consumption over the first postoperative 24 hours was 61.4 mg ± 14.7 mg (mean ± standard deviation, SD) in the control group, while it was 39.2 mg ± 14.7 mg in the ESP group. The sample size required for both groups, with 90% power and an error of 0.01 (two-tailed), was calculated as 21 patients. Considering possible patient dropouts, it was planned to include 25 patients in each group (50 patients in total).

Statistical analysis

The data obtained in this study were evaluated using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (IBM SPSS 23.0 for Windows, Armonk, New York, United States). The frequencies of general demographic characteristics and the descriptive statistical values of all time-dependent measurements were specified. The Shapiro-Wilk test was applied if $n < 30$, and the Kolmogorov-Smirnov test if $n > 30$, during examination of the normality of the scores between the groups. If $P < 0.05$, the values were considered not to have normal distribution between the groups, and if $P > 0.05$, the values were assumed to have a normal distribution between the

groups. After the normality test, the Mann-Whitney U test was applied to investigate differences between the groups. The chi-square test was performed to investigate intergroup dependence in the categorical data. While examining differences and dependence between the groups, 0.05 was used as the significance level. If $P < 0.05$, it was accepted that there was a significant difference between the groups. The Wilcoxon signed rank test was used to examine differences between intragroup time-dependent measurement values. If $P < 0.05$, the measurement values were considered to differ according to time.

RESULTS

A total of 50 patients were included in the study, and no patients were excluded from the study (**Figure 1**). The demographic and surgical data of the two groups were similar to each other (**Table 1**).

Intraoperative remifentanil consumption was significantly lower in the ESP group ($P < 0.01$). Similarly, morphine consumption and rescue analgesic (meperidine) requirement over the first postoperative 24 hours were much lower in the ESP group ($P < 0.01$) (**Table 2**).

Postoperative NRS scores were significantly lower in the ESP group ($P = 0.000$, $P = 0.000$, $P = 0.019$, $P = 0.000$ and $P = 0.000$, respectively) at all time points (10th minute, 1st hour, 6th hour, 12th hour and 24th hour). Likewise, DNRS scores were also significantly lower in the ESP group at all time points ($P = 0.000$, $P = 0.000$, $P = 0.018$, $P = 0.000$ and $P = 0.020$, respectively) (**Figure 2**).

Considering the presence of dynamic pain, this was observed in all the patients in the control group at the 10th minute, while it was only observed in 16% of the patients in the ESP group ($P = 0.000$). While dynamic pain was present in 88% of the control group at the 1st hour, it was present in 24% of the ESP group ($P = 0.000$). There was no significant difference in the presence of dynamic pain at the other times evaluated (**Table 3**).

Evaluation of postoperative nausea-vomiting showed that this was present in all patients in the control group, and it was severe in 40%. On the other hand, 24% of the patients in the ESP group did not have nausea-vomiting (**Figure 3**). It was discovered that an average of 7.36 ± 0.9 dermatome levels (minimum 6, maximum 9) were blocked in patients who had ESP block (**Table 4**).

DISCUSSION

There is still a debate about what constitutes effective and safe postoperative analgesia in hepatectomy surgery. In open-technique hepatectomies, postoperative pain arises from the surgical incision or diaphragmatic irritation, or it is of visceral origin.[10] In ERAS protocols, regional effective methods have been recommended for analgesia, postoperative mobilization and recovery after hepatectomy.[2] Use of iv opioids seems to be the most important part of multimodal analgesia in hepatectomy surgery.[3] However, there is an increasing tendency towards reducing morphine consumption, due to its toxic, immunological and oncogenic effects on the liver, although this is a controversial movement.[11] Nonetheless, additional methods need to be used to reduce the side effects of opioids in postoperative pain management.[12]

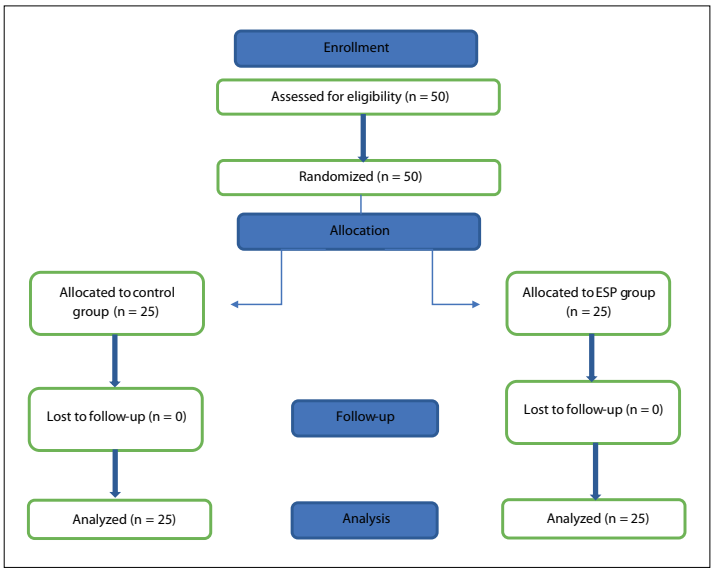

Figure 1. Flowchart of the study.

Table 1. Assessment of demographic and operative data (mean ± standard deviation)

	Control group (n = 25)	ESP group (n = 25)	P-value
Sex (male/female)	19/6	19/6	1.000
Age (year)	47.6 ± 14.6	44.6 ± 17.1	0.484
Weight (kg)	78.7 ± 5.4	76.8 ± 7.0	0.157
Height (cm)	172.5 ± 6.8	172.9 ± 9.5	0.838
BMI (kg/m^2)	26.6 ± 1.9	25.8 ± 2.5	0.240
ASA (I/II/III)	2/18/5	7/12/6	0.394
Duration of surgery (min)	234.4 ± 43	216.2 ± 38.2	0.06
Type of surgery (R/L)	18/7	18/7	1.000

ESP = erector spinae plane; BMI = body mass index; ASA = American Society of Anesthesiologists; type of surgery: R = right hepatectomy, L = left hepatectomy.

Table 2. Assessment of intraoperative and postoperative analgesia requirements

	Control group (n = 25)	ESP group (n = 25)	P-value
Intraoperative remifentanil (mg)	4.6 ± 1.1	3.2 ± 0.9	**0.000**
Postoperative morphine (mg)	96.3 ± 38.7	49.7 ± 16.9	**0.000**
Postoperative meperidine (mg)	109.0 ± 30.37	55.6 ± 39.74	**0.000**

ESP = erector spinae plane.

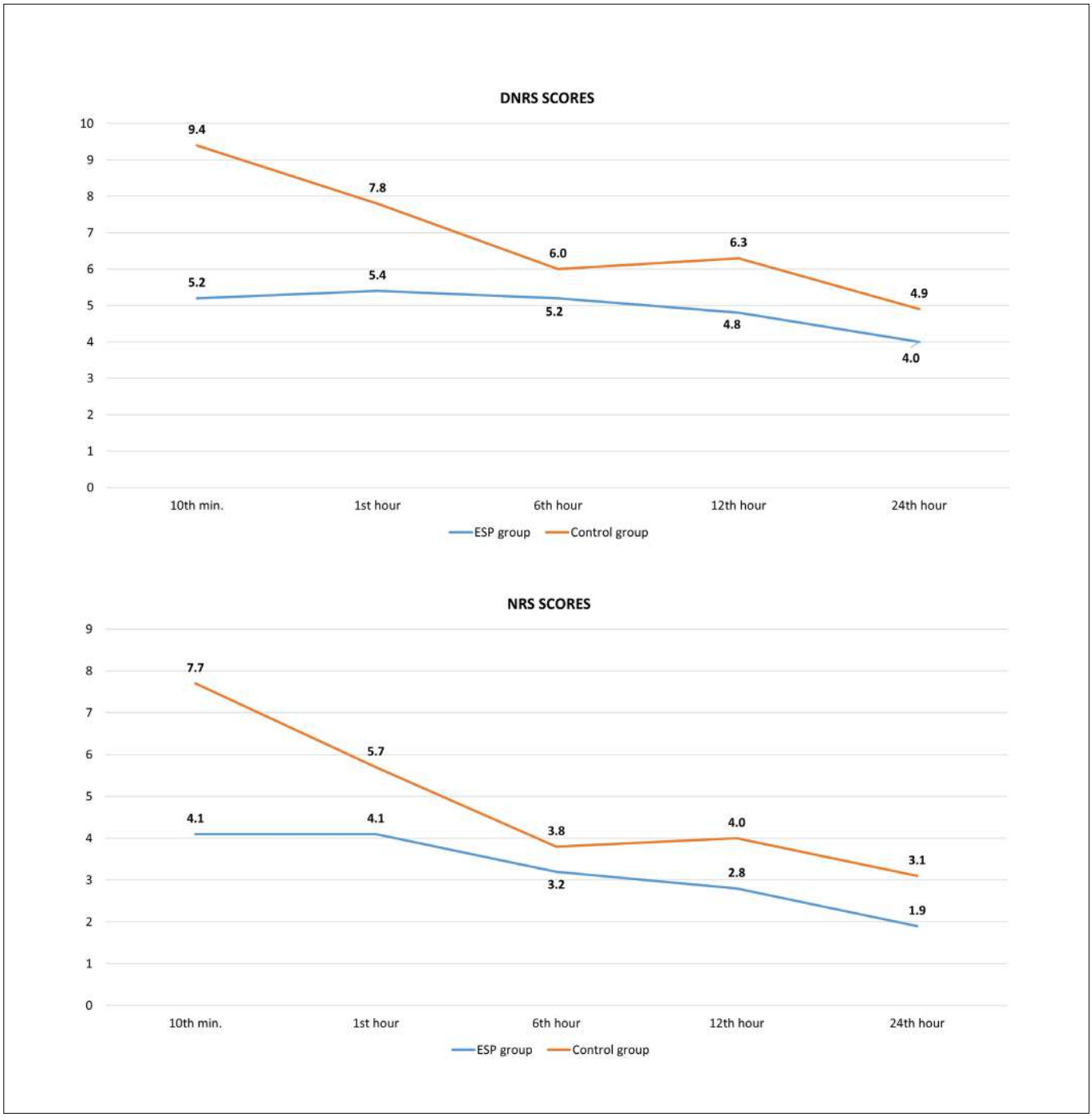

Figure 2. Changes in numerical rating scale (NRS) and dynamic numerical rating scale (DNRS) scores between groups over time.

Although debate continues regarding the visceral effectiveness of the block, we predicted that bilateral ESP block from the lower thoracic region could contribute to postoperative analgesia in hepatectomy surgery, as observed in the cadaver studies.[5,13,14] We applied the block before making the surgical incision since this would reduce the effect of neuromodulation and improve postoperative pain control.[15] Considering that the mean duration of surgery was 216.2 ± 38.2 minutes in the ESP block group, we assume that the main effect of the block was on intraoperative remifentanil consumption. Thus, while the consumption of remifentanil was 3.2 ± 0.9 mg in patients who had ESP block, it was 4.6 ± 1.1 mg in the control group. In the postoperative period, it was found that NRS and DNRS scores and morphine and rescue analgesic consumption were significantly lower in the ESP block group, in all

timeframes. We attribute this result both to the reduction of postoperative hyperalgesia through decreased intraoperative remifentanil consumption and to the analgesic effectiveness of the block.

Different results have been obtained in the literature with regard to ESP block applied in different volumes and concentrations in different types of abdominal surgery. Tulgar et al.[16] evaluated oblique subcostal transversus abdominis plane block and ESP block among laparoscopic cholecystectomy patients, and showed that resting and dynamic NRS scores in both blocks significantly decreased in the first three hours, compared with the control group, which had no block application. After the third hour, no difference in dynamic NRS scores was found. In their study, the ESP block was carried out at T9 level with 20 ml of 0.375% bupivacaine, but dexamethasone was not used.

In a study evaluating 182 patients who underwent ESP block, cases with suspected local anesthetic toxicity were reported.[17] This block, which has a similar effect to paravertebral and intercostal blocks, may have unforeseen systemic toxic effects. This situation requires greater care regarding drug dose and volume adjustment, particularly in bilateral blocks. In our study, we carried out our bilateral block application with 20 ml of 0.375% bupivacaine + 4 mg of dexamethasone. We did not find any signs of systemic toxicity in any of the 25 patients on whom we performed the block. We think that the drug concentration, volume and use of dexamethasone were effective in relation to block efficiency.

Steroid injections may potentially contribute to analgesia by suppressing abnormal pain transmission in damaged nerves,

Table 3. Variation in the presence of dynamic pain between the groups over time

Presence of dynamic pain	Group				P-value
	Control group		ESP group		
	n	%	n	%	
10th minute	25	100.0	4	16.0	**0.000**
1st hour	22	88.0	6	24.0	**0.000**
6th hour	23	92.0	22	88.0	1.000
12th hour	24	96.0	23	92.0	1.000
24th hour	16	64.0	22	88.0	0.098

ESP = erector spinae plane.

Table 4. Dermatome levels blocked among the patients

Patient	Dermatome level	Patient	Dermatome level
Patient 1	T4-T10 **(7)**	Patient 14	T4-T12 **(9)**
Patient 2	T4-T12 **(9)**	Patient 15	T5-T11 **(7)**
Patient 3	T4-T10 **(7)**	Patient 16	T5-T11 **(7)**
Patient 4	T4-T10 **(7)**	Patient 17	T5-T12 **(8)**
Patient 5	T5-T12 **(8)**	Patient 18	T5-T11 **(7)**
Patient 6	T5-T12 **(8)**	Patient 19	T6-T12 **(7)**
Patient 7	T5-T12 **(8)**	Patient 20	T6-T11 **(6)**
Patient 8	T4-T9 **(6)**	Patient 21	T6-T12 **(7)**
Patient 9	T4-T12 **(9)**	Patient 22	T6-T12 **(7)**
Patient 10	T4-T10 **(7)**	Patient 23	T5-T12 **(8)**
Patient 11	T4-T10 **(7)**	Patient 24	T5-T12 **(8)**
Patient 12	T5-T10 **(6)**	Patient 25	T5-T11 **(7)**
Patient 13	T5-T11 **(7)**		

T = thoracic.

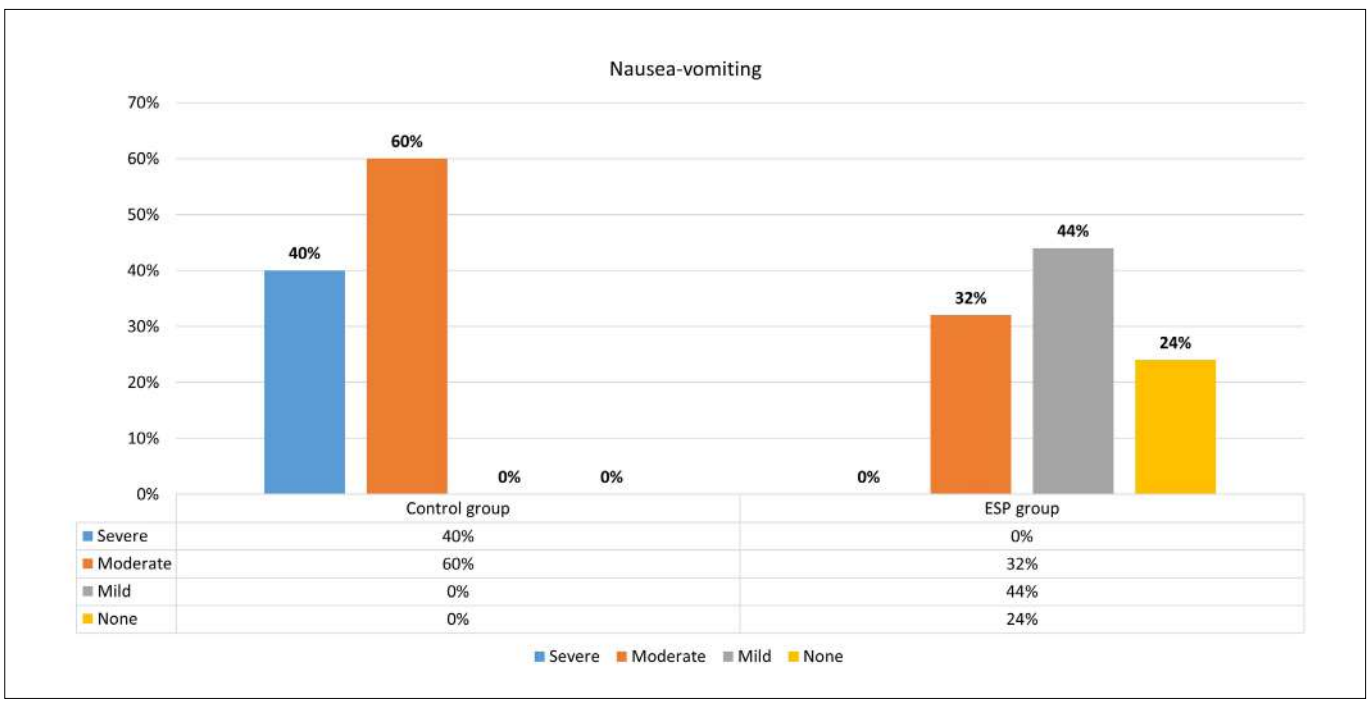

Figure 3. Postoperative presence of nausea-vomiting.

providing the modulation of transmission in normal nerves, and showing an anti-inflammatory effect.[18] There has only been limited use of adjuvant in ESP block in clinical studies in the literature that were conducted to assess postoperative pain.[8,19] In our study, the NRS and DNRS scores, which were high in the first hours in the ESP group, were found to gradually decrease over other timeframes. Although we did not have a control group without dexamethasone for evidence, we think that the emergence of the anti-inflammatory properties of dexamethasone and the rescue analgesics used had an effect on this result. For this reason, we think that different randomized studies should be conducted to support our study, in order to specify the effect of dexamethasone. Furthermore, we investigated the effect of the block in the first postoperative 24 hours. We are of the opinion that it should be investigated whether adjuvant-enhanced ESP block without catheter insertion has an effect on postoperative pain for more than 24 hours.

In the literature, there are two randomized studies investigating the effectiveness of ESP block in hepatectomy surgery.[8,9] In both studies, ESP block was found to reduce the intraoperative remifentanil consumption. Thus, we think that these results provide confirmation of the visceral analgesic property of the block. Kang et al.[9] used an ESP block at T8 bilaterally with 20 ml of 0.5% ropivacaine and compared this with use of 400 mcg of intrathecal morphine, in live liver donors who underwent laparoscopic hepatectomy. The pain scores in patients who underwent ESP block were higher than in those who received intrathecal morphine, but they were within acceptable limits, and postoperative nausea was found to be similar to what we saw in our study. In the study of Kang et al.,[9] multimodal analgesia was administered using a large number of agents, and long-term follow-up such as after 72 hours postoperatively was performed. The pain score in the first 24 hours was 1.3 in the intrathecal morphine group, while it was 2.5 in the ESP group. In our study, the resting NRS score was determined as 1.9 for the ESP group at the 24th hour, whereas the DNRS score was found to be 4.0 for the ESP group. We attribute our higher dynamic pain score to the open technique that was applied for the surgery, the use of retractors and the limited range of analgesics that we used, especially our use of non-steroidal anti-inflammatory drugs (NSAIDs).

Our aim in performing the block at T8 was to relieve the patients' painful breathing, caused by upper abdominal pain that resulted from retraction, and thus to reduce both the dynamic and resting pain scores, which was also successful. However, the difference in the presence of dynamic pain was found to disappear after the first hour. Additionally, although the NRS scores in the ESP group were lower than those in the control group, an average score of 4.1 was detected in the first hours.

Considering the duration of surgery, the postoperative analgesic property of the block may have been reduced, and this may have had a negative effect on resting and dynamic pain scores and on opioid consumption. To prevent this situation, performing the block at more than one level or using a catheter may be preferred options. However, this may be more invasive and open to complications, compared with a single-level injection. For this reason, performing the block with different volumes and concentrations and using different adjuvant agents (such as dexmedetomidine) can be regarded as aims for future studies.

Another reason for this clinical picture may be that the block was not supported with multimodal analgesic drugs. For instance, if the block had been supported through use of NSAIDs or paracetamol, the duration of the positive effect on the presence of dynamic pain could have been extended. We believe that more comprehensive studies should be conducted on this subject.

In the meta-analysis by Kendall et al.,[20] it was reported that one of the most significant effects of ESP block was on postoperative nausea-vomiting, and that this resulted from both the decrease in opioid consumption and the high analgesic efficiency of the block. In our study, postoperative opioid consumption was observed to be significantly lower in the ESP block group. While no nausea-vomiting was encountered in 24% of the patients who underwent the block, 44% had mild and 32% moderate nausea and vomiting. In the control group, on the other hand, nausea and vomiting were observed, and 40% of the cases were severe. We think that we significantly reduced postoperative nausea-vomiting through decreasing morphine consumption over the first 24 hours and through increasing analgesic efficacy with the ESP block.

Our study had some limitations. The methodology was planned in a single-blind manner, which may have affected the objectivity of the results. Another factor with a possible effect on the outcome criteria was that patient homogenization could not be achieved. To fully explain the true analgesic effectiveness of the ESP block, we formed the control group from patients who received systemic analgesics alone. However, lack of a block group without dexamethasone may have prevented us from evaluating the net effect of the adjuvant drug. In addition, dexamethasone, which was used as an adjuvant in the block, had a systemic analgesic effect as well as prolonging the duration of the block. Non-administration of intravenous dexamethasone to the control group may have affected the objective evaluation of analgesic efficacy between the groups. Another limitation was that the data were limited to a short period of time, for such a major surgery. We did not have a chance to determine the duration of the positive effect of the block that we performed. In this study, we administered opioid alone over the first 24 hours, while avoiding NSAIDs and paracetamol because of their hepatotoxic effects, considering that they might have negative effects on the bleeding profile. This can be considered to be another limitation. Much lower NRS and DNRS scores could have been obtained through using analgesics with different effect mechanisms. We preferred to use a concentrated rate of 0.375% in the bilateral block.

Our preoperative application of the block may have caused the signs of local anesthesia toxicity to be masked through general anesthesia. This may have prevented us from objectively assessing the reliability of the bilaterally applied block at this concentration.

CONCLUSION

Ultrasound-guided bilateral erector spinae plane block significantly reduced intraoperative and postoperative opioid use in hepatectomy surgery carried out by means of a bilateral subcostal incision and also relieved postoperative pain experienced during coughing. It also significantly reduced postoperative nausea and vomiting. Erector spinae plane block may be an important part of multimodal analgesia application in hepatectomy surgery, in terms of its easy application and safety, provision of effective analgesia and reduction of opioid side effects. On the other hand, there is a need for multicenter randomized studies aimed at prolonging and strengthening the effect of the block, such as through an appropriate drug dosage and concentration, and through catheter use.

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Address for correspondence:
Gülçin Hacibeyoğlu
Department of Anesthesiology and Reanimation, Faculty of Medicine, Necmettin Erbakan University, Hocacihan Mahallesi, Abdülhamid Han Caddesi, Selçuklu, Konya, Turkey
Tel. +905054455498
E-mail: drgulcin81@gmail.com

Brazilian initial experience with lung transplantation due to irreversible lung fibrosis post-COVID-19 in a national reference center: a cohort study

Flavio Pola dos Reis[I], Lucas Matos Fernandes[II], Luis Gustavo Abdalla[III], Silvia Vidal Campos[IV], Priscila Cilene Leon Bueno de Camargo[V], Samuel Lucas dos Santos[VI], Ivana Teixeira de Aguiar[VII], Juliana Patricia Pires[VIII], Andre Nathan Costa[IX], Rafael Medeiros Carraro[X], Ricardo Henrique de Oliveira Braga Teixeira[XI], Paulo Manuel Pêgo-Fernandes[XII]

Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[I]MD. Attending Surgeon, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-4510-1070

[II]MD, PhD. Attending Surgeon, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0001-9302-1035

[III]MD. Attending Surgeon, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-8785-6068

[IV]MD. Attending Physician, Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0003-3297-5948

[V]MD, PhD. Attending Physician, Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0003-0199-5532

[VI]MD. Lung Transplant Resident, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-9369-8326

[VII]MD. Lung Transplant Fellow, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0003-3362-1826

[VIII]MD. Lung Transplant Fellow. Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-1165-9535

[IX]MD, PhD. Attending Physician, Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-8025-6940

[X]MD. Attending Physician, Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0001-8997-6306

[XI]MD, PhD. Attending Physician, Division of Pulmonology, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. https://orcid.org/0000-0002-3722-4169

[XII]MD, PhD. Full Professor, Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR; Director, Scientific Department, Associação Paulista de Medicina, São Paulo (SP), Brazil. https://orcid.org/0000-0001-7243-5343

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ABSTRACT

BACKGROUND: Lung transplantation (LTx) has been discussed as an option for treating irreversible lung fibrosis post-coronavirus disease 2019 (COVID-19), in selected cases.

OBJECTIVES: To report on the initial experience and management of end-stage lung disease due to COVID-19 at a national center reference in Brazil.

DESIGN AND SETTING: Cohort study conducted at a national reference center for lung transplantation.

METHODS: Medical charts were reviewed regarding patients' demographics and pre-COVID-19 characteristics, post-LTx due to COVID-19.

RESULTS: Between March 2020 and September 2021, there were 33 cases of LTx. During this period, we evaluated 11 cases of severe COVID-19-related acute respiratory distress syndrome (ARDS) that were potentially candidates for LTx. Among these, LTx was only indicated for three patients (9.1%). All of these patients were on venovenous extracorporeal membrane oxygenation (ECMO), and the procedure that they underwent was central venoarterial ECMO. All three patients were still alive after the first 30 postoperative days. However, patient #1 and patient #2 subsequently died due to fungal sepsis on the 47th and 52nd postoperative days, respectively. Patient #3 was discharged on the 30th postoperative day.

CONCLUSIONS: LTx is feasible among these complex patients. Survival over the first 30 days was 100%, and this favors surgical feasibility. Nonetheless, these were critically ill patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an infectious disease with potentially severe manifestations.[1] Most patients with COVID-19 have a mild or asymptomatic disease course; however, about 10% require admission to an intensive care unit (ICU) because of acute respiratory distress syndrome (ARDS).[2] Mortality rates of up to 60% have been reported for this subgroup[3] but, in Brazil, this rate rises to 80%.[4]

Much has been discussed about mechanical ventilation, neuromuscular blockade and prone and extracorporeal membrane oxygenation for ventilatory support[5-7] for these patients. However, some patients evolve with severe lung fibrosis.[8] For this group of patients, lung transplantation (LTx) has been discussed as a treatment option. The first reports of lung transplantation post-COVID-19 were in 2020, first from China[9] and then from Austria.[10] Lung transplantation is potentially lifesaving, but the true effect of the procedure in the acute setting of COVID-19 needs to be very well discussed because these patients are critically ill, with a long hospital stay and associated morbidity.[11]

OBJECTIVE

The objective of this article was to report on the initial experience of LTx for management of end-stage lung disease due to Covid-19 at a national reference center in Brazil.

METHODS

Study design

This cohort study was conducted at the Heart Institute of Hospital das Clínicas (HC), Faculdade de Medicina da Universidade de São Paulo (FMUSP). It is the largest academic, tertiary-level, university-affiliated hospital in Brazil, with 300 adult ICU beds that were dedicated exclusively to caring for COVID-19 patients during the peak of the pandemic.[1] Our institution is also the reference center for ARDS/extracorporeal membrane oxygenation (ECMO) and LTx of the state of São Paulo. This project was approved by our institutional review board under the number CAAE 51617821.2.0000.0068, on October 1, 2021.

Firstly, we entered discussions to determine criteria for evaluating patients with ARDS in association with COVID-19, in a Technical Committee for Thoracic Organ Transplantation for the state of São Paulo, jointly with the three centers that perform lung transplantation in this state. The protocol thus elaborated was then ratified by the Ministry of Health, in a National Technical Committee (**Appendix 1**). We used references published by Cypel and Keshavjee[12] and the guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic (revised February 2021), including our local particularities.

Data collection

Patients' medical charts were reviewed regarding demographic and pre-COVID-19 characteristics, including comorbidities, pre-transplantation profile (including clinical and radiological features, treatment and management, medical course and indications for lung transplantation), perioperative challenges (including transfusion requirements and technical challenges), pathological assessment of the explanted lungs and post-transplantation outcomes. The characteristics of lung donors were also recorded.

Surgical technique

The procedure was performed under general anesthesia through a Clamshell incision. The tracheostomy cannula was removed and a selective tube was placed. Its position was checked by means of fibroscopy. The patient was positioned supinely with the head at the midline. The preparation started at the chin and went down to the abdomen. Venovenous (VV) ECMO was maintained, although with reduced flow of 1.5 liters per minute, without oxygenation. Venoarterial (VA) ECMO with central cannulation was chosen instead of cardiocirculatory assistance.

The lung transplantation procedure was sequential and bilateral. During the reperfusion, the cardiopulmonary assistance was reduced to 1.5 liters per minute and arterial clamping was opened. Following this, the atrial clamping was opened and cardiopulmonary assistance was returned to the previous level. At the end of the procedure, a transesophageal echocardiogram was performed to check that the right and left ventricular function had been preserved. If so, we proceeded with weaning off central ECMO. After the thorax had been closed, the blood gas showed a pO_2/FiO_2 ratio > 250, after weaning off VV ECMO.

ECMO installation

Central VA ECMO with right atrial cannulation for venous drainage and aortic return cannulation was used. The circuit configuration consisted of a centrifugal pump with a polymethylpentene oxygenator (Rotaflow/Quadrox-ID, Getinge Cardiopulmonary AG, Hirrlinger, Germany), connected to 3/8" inner diameter tubing with a bridge between arterial venous limbs. The circuit was primed with Plasma-Lyte. Heparin was titrated to keep the activated clotting time (ACT) around 180-250 seconds, and additional blood products were used when necessary. The arterial flow was calculated in accordance with body surface area, with a target of 70% of the nominal flow. It was corrected when necessary based on the hemodynamic and metabolic demand during the procedure, through monitoring the arterial and venous pressures and the circuit pressure. An ECMO specialist controlled the cardiopulmonary support.

RESULTS

Between March 2020 and September 2021, there were 33 cases of lung transplantations. During this period, we evaluated 11 cases of severe COVID-19-related ARDS that were potentially candidates for LTx. Six cases were evaluated in hospitals within our own complex (HC-FMUSP) and five cases were evaluated by means of telemedicine connections to other national reference centers.

Three of the six cases evaluated in our complex did not proceed further: two patients did not meet the criteria described earlier, i.e. they presented body mass index (BMI) > 35 kg/m^2 and had social issues; and one patient died from sepsis. The other three patients completed the evaluation and were included in the waiting list. By the time when this paper was written, all of these three patients had undergone LTx.

Only one of the cases evaluated by means of telemedicine met all the criteria (Appendix 1). This patient was transferred to our institution on mechanical ventilation. However, after the initial treatment and rehabilitation, she achieved pulmonary improvement and is now in the ward and not dependent on oxygen. We decided to decline to perform lung transplantation at this time, and she will be referred to the clinic after hospital discharge.

During the pandemic, 33 cases of lung transplantation were performed and three of these (9.1%) were due to irreversible pulmonary fibrosis associated with COVID-19. Before COVID-19,

these three patients did not have any comorbidities and had normal lives without addictions. All of these three patients were referred to our hospital for treatment of COVID-19 because we are the reference center for ECMO and LTx. Given the clinical improvement but irreversible lung injury, lung transplantation was proposed. The length of time for which they had been receiving ECMO support at the time of waitlisting for LTx was 83, 52 and 77 days, respectively. All three patients were awake and agreed to undergo LTx. Before the transplantation, their renal, liver and cardiac functions were normal. Their lung allocation scores were 85.751, 85.000 and 82.097 respectively, at the time of waitlisting. Their clinical features are presented in **Table 1**.

Details of the donors are provided in **Table 2**. All of them were brain death donors, through traumatic brain injury. They had normal bronchoscopy and pO_2/FiO_2 ratios of up to 300.

The technical features of the operation are presented in the methods section. The lengths of the surgical procedures (skin to skin) were 465, 515 and 550 minutes, respectively. The total durations of ischemia were 345, 275 and 360 minutes, respectively. There was no need for fresh frozen plasma during the procedures (**Table 3**).

All the patients were still alive after the first 30 postoperative days. However, patient #1 and patient #2 died due to fungal sepsis on the 47th and 52nd postoperative days, respectively. Patient #3 was discharged on the 30th postoperative day. Patient #2 had primary graft

Table 1. Patient characteristics and demographics

Patient	# 1	# 2	# 3
Sex	Male	Female	Male
Age (years)	46	34	31
Height (cm)	174	171	167
Weight (kg)	75	85	75
Body mass index	24.77	29.06	26.8
Blood group	A	A	O
Length of time from COVID-19 diagnosis to ICU admission (days)	8	14	5
Length of time from COVID-19 diagnosis to intubation (days)	9	19	6
COVID-19 specific treatment	Steroids	Steroids	Steroids
Tracheostomy	Yes	Yes	Yes
Type of ventilation	PCV	PCV	PCV
Lung compliance (ml/mbar)	8	6	6
ECLS	VV ECMO (two cannulae)	VV ECMO (two cannulae)	VV ECMO (two cannulae)
Length of ECLS support at the time of waitlisting (days)	83	52	77
Awake for ECLS bridging	Yes	Yes	Yes
Recovered from acute kidney injury	No	No	No
Recovered from sepsis	Yes	Yes	Yes
Creatinine (mg/dl)	1.39	0.35	0.45
Blood urea nitrogen (mg/dl)	94	24	36
Aspartate transaminase (U/l)	19	26	30
Alanine aminotransferase (U/l)	23	38	36
International normalized ratio	1,1	1,2	1.1
C-reactive protein (mg/l)	18	22.9	27.5
Leukocytes (total/mm^3)	9,480	14,000	5,340
Procalcitonin (ng/ml)	-	-	-
Evidence of pulmonary bacterial colonization	*Acinetobacter baumannii* + *Pseudomonas aeruginosa* + *Enterococcus faecalis*	*Acinetobacter baumannii*	*Pseudomonas aeruginosa* R-Carbapenem + *Enterococcus faecalis*
Evidence of fungal colonization	*Candida albicans*	*Candida tropicalis*	
Right ventricular dysfunction	No	No	No
Systolic pulmonary arterial pressure		48	
Time to listing to transplantation (days)	94	76	87
Lung allocation score	85.751	85.000	82.097

ICU = intensive care unit; ECLS = extracorporeal life support; PCV = pressure-controlled ventilation; VV = venovenous; ECMO = extracorporeal membrane oxygenation.

Table 2. Donor features

Patient	# 1	# 2	# 3
Sex	Male	Male	Male
Age (years)	19	34	21
Height (cm)	180	168	170
Weight (kg)	80	72	55
Predicted total lung capacity (liters)	7.14 / 7.30	6.20 / 6.34	5.49 / 5.6
Smoking history (current or past smoker)	Yes	No	Yes
Cause of death	Traumatic brain injury	Traumatic brain injury	Stroke
Chest X-ray	Normal	Normal	Normal
Median intubation time (hours)	72	48	120
PaO_2/FiO_2, at time of offer	316	389	355
$PaCO_2$, at time of offer (mmHg)	48	33	37
Bronchoscopy	Normal	Normal	Normal
Type of donor	Marginal (chest trauma)	Ideal	Marginal (intubation time)
Median Oto score	5	3	2

Table 3. Transplantation features

Patient	# 1	# 2	# 3
Length of time on the waiting list (days)	8	22	50
Clamshell incision	Yes	Yes	Yes
ECMO intraoperative support	Yes	Yes	Yes
Whole lung transplantation	Yes	Yes	Yes
Surgery time (skin to skin) (min)	465	515	550
Total ischemic time (min)	345	275	360
Number of intraoperative pRBC units	5	5	7

ECMO = extracorporeal membrane oxygenation; pRBC = packed red blood cell.

dysfunction at 72 hours (grade 2). No bleeding problems occurred. Patient #1 presented acute cholecystitis and underwent laparoscopic cholecystectomy. All three patients presented acute cellular rejection (grade 2), for which patient #1 and patient #2 received treatments with high doses of steroids. **Table 4** shows the post-LTx features.

DISCUSSION

The world is currently living through the worst pandemic in human history, with more than four million deaths due to COVID-19. There has been widespread discussion of how to prevent and treat COVID-19. In this manner, LTx has become a treatment option for patients with severe ARDS and irreversible pulmonary fibrosis. Nonetheless, the outcomes remain unclear and few data are yet available in the international literature. Patients with severe COVID-19 are critically ill and develop considerable degrees of ICU-related comorbidities at the time that lung transplantation is considered.[11]

When LTx as a treatment for acute illnesses like COVID-19 has been discussed with lung transplantation teams, several ethical questions have been raised.[12] During the pandemic, there has been a reduction in the offer of donors, and procurement teams have had to be more prudent because of the risk of donor-derived infection, given that there are great numbers of COVID-19 asymptomatic patients.[13,14]

Cypel and Keshavjee recommended that transplantation centers should have access to a broad donor pool and would need to have low waiting-list mortality. This will maintain fair and equitable donor organ allocation and provide the chance of life-saving organ transplantation for patients who are more likely to survive.[12] On the other hand, in Brazil, there is no organ allocation score, and the waiting list is generated in accordance with entry time. Therefore, every case of prioritization needs to receive approval from the Technical Committee for Thoracic Organ Transplantation of the state of São Paulo.

Use of telemedicine has grown during the pandemic for several reasons. Our team uses telemedicine to screen cases from other centers, since we are a public/private reference service.[15] Up to the present time, we have discussed the cases of five patients via telemedicine, but only one of them met the criteria. Fortunately, she recovered partially and presented improved lung function. Telemedicine is an important tool in a reference center. Our hospital has started a TELE-ICU service to discuss difficult cases and help physicians anywhere in Brazil to better manage critically ill COVID-19 patients.[16]

Table 4. Features of post-transplantation period

Patient	# 1	# 2	# 3
Induction therapy	Methylprednisolone	Basiliximab + methylprednisolone	Basiliximab + methylprednisolone
Postoperative prolonged ECMO	No	No	No
PGD at 72 hours (grade)	0	2	0
Length of mechanical ventilation (days)	6	11	6
Length of stay in ICU (days)	15	47	7
Bleeding requiring chest reopening	No	No	No
Critical illness neuropathy	Yes	Yes	Yes
Complicated pleural effusion	No	No	Yes
Overall survival	Dead	Dead	Alive
Length of survival (days)	47	52	30
Discharge	No	No	Yes

ECMO = extracorporeal membrane oxygenation; PGD = primary graft dysfunction; ICU = intensive care unit.

The surgical strategy that we use to perform LTx is similar to the one published by the Vienna Group,[10] with a central VA ECMO circuit installed. The VV ECMO was kept running in parallel with a reduced flow of 1.5 liters/minute, while the Vienna Group reduced the flow to 1.0 liters/minute. This tactic allowed greater security throughout the procedures. We emphasize that dissection during native lung pneumonectomy is challenging. Dense pleuropulmonary adhesions were found in case #1 although both cases had pleural drainage. We found highly vascularized and thickened mediastinal and parietal pleura. Furthermore, bulky pulmonary hilar lymphadenopathy was encountered in all cases.[11]

Our results were similar to those of other groups.[9-11,17] After the first cases were published, Cypel and Keshavjee suggested in Lancet Respiratory that recipient selection should be done on the basis of ratifying previous reports, with all ethical considerations.[12] The study that forms the largest publication so far was conducted in accordance with these same considerations.[11]

CONCLUSIONS

This report represents our initial experience with LTx after severe COVID-19, in Brazil. Unfortunately, data remain scarce, as also seen in this study, especially regarding information about long-term outcomes. However, SARS-COV-2 continues to infect hundreds of thousands of people worldwide each day and LTx will always be an option for saving patients with severe COVID-19. Our report showed that LTx is feasible among these complex patients. Survival over the first 30 days was 100%, and this favors surgical feasibility. Nonetheless, these were critically ill patients. We recommend that a multidisciplinary team with institutional engagement should be assembled for such cases. Patients presenting end-stage lung disease alone who are undergoing rehabilitation and are awake can be considered for transplantation. If these patients' conditions deteriorate or improve, they should be withdrawn from the waitlist. For this reason, implementation of a concomitant palliative care approach is fundamental.

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Authors' contributions: Pola dos Reis F: conceptualization (equal), formal analysis (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); Fernandes LM: conceptualization (equal), data curation (equal), methodology (equal), supervision (equal) and writing-original draft (equal); Abdalla LG: formal analysis (equal), investigation (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); Campos SV: conceptualization (equal), investigation (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); Leon Bueno de Camargo PC: formal analysis (equal), investigation (equal), methodology (equal) and writing-original draft (equal); Santos SL: conceptualization (equal), formal analysis (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); Costa AN: formal analysis (equal), investigation (equal), methodology (equal) and visualization (equal); Carraro RM: conceptualization (equal), formal analysis (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); Oliveira Braga Teixeira RH: conceptualization (equal), methodology (equal), writing-original draft (equal) and writing-review and editing (equal); and Pêgo-Fernandes PM: conceptualization (lead), investigation (equal), writing-original draft (equal) and writing-review and editing (lead). All authors approved the final version for publication

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Address for correspondence:
Flavio Pola dos Reis
Divisão de Cirurgia Torácica, Instituto do Coração (InCor), Hospital das Clínicas (HC), Faculdade de Medicina da Universidade de São Paulo (FMUSP)
São Paulo (SP) — Brasil
CEP 05403-000
Tel. (+ 55 11) 2661-5039
E-mail: flavio.pola@hc.fm.usp.br

Appendix 1. Regarding eligibility for evaluation and listing for lung transplantation, the recipient patients must fulfill all the requirements, as follows:

1. Negative SARS-CoV-2 RT-PCR tests – minimum of 2 tests within an interval of 24-48 hours and at least one of the samples needs to be from the inferior respiratory tract (BAL, sputum or tracheal aspirate).
2. Age < 65 years. The transplant center has independence to decide its maximum age limit for lung transplantation, but it must not exceed 65 years. Considering the ISHLT guidelines regarding overall survival, the best outcomes are for recipients < 50 years old (ideal recipients ranging from 18 to 50 years). Out-of-range recipients may be evaluated, but listing will require deliberation by the Technical Chamber of the state of São Paulo.
3. Irreversible pulmonary status, at least 6 weeks after symptoms onset, entailing dependency on invasive mechanical ventilation (24 hours/day) or ECMO > 4 weeks.
4. Body mass index (BMI) ranging from 17 to 27 prior to hospitalization.
5. Hemodynamic stability. Ideally, the recipient should have only one organic dysfunction, and should be able to maintain hemodynamic stability without the need for vasoactive drugs.
6. Absence of active fungal or bacterial infection. Ideally, with the aim of ensuring success for the procedure, the recipient should not present uncontrolled infection complications or use of antimicrobial drugs at the time of listing or prioritization. Multi-drug resistant germ colonization is considered to be a risk factor.
7. Patients need to be awake and agree to lung transplantation; they must understand the need for and the process of evaluation for listing. Caregivers must be assessed by psychologists and nursing teams.
8. Social worker evaluation and approval is required. There needs to have been an absence of history of active smoking prior to the episode of COVID-19.
9. Critically ill neuropathy will be tolerated, provided that there is at least grade 3 motor strength and it is possible to maintain rehabilitation while waiting for the organ.
10. Left ventricle ejection fraction > 50%. Transesophageal echocardiogram without vegetations and no anatomical or functional abnormalities.
11. Left cardiac catheterization without coronary obstructions that cannot be treated percutaneously, for any patient older than 50 years, as long as they have not had recent catheterization or normal coronary CT angiography in the last 2 years. For patients between 40 and 50 years of age, unobstructed coronary angiotomography is required. Pulmonary artery CT angiography is required for all ages.
12. Absence of other chronic or irreversible organ dysfunctions. Absence of other acute disorders, including renal replacement therapy. Justification/reference: the criteria for inclusion on the waiting list need to encompass a creatinine clearance rate greater than 40 ml/min.
13. Signing of the consent form for lung transplantation by a first-degree relative or spouse.
14. The transplantation team has the autonomy to contraindicate the transplantation according to its judgment of the set of clinical information and the evaluation by the multidisciplinary team, regardless of the perception of other teams that provide care for the patient.

INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal accepts manuscripts previously deposited in a trusted preprint server.

São Paulo Medical Journal supports Open Science practices. It invites reviewers to join Open Peer Review practices through acceptance that their identities can be revealed to the authors of articles. However, this is purely an invitation: reviewers may also continue to provide their input anonymously.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal does not charge authors any "open access fees" and submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the

reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.

10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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Bradesco Saúde: **ANS nº 005711**

Central Nacional Unimed: **ANS nº 339679**

Qualicorp Adm. de Benefícios: **ANS nº 417173**

[1]R$237,48 - Plano Clássico Regional São Paulo ADS I-E (EF) (registro na ANS nº 482.833/19-0), da Central Nacional Unimed, faixa etária até 18 anos, com coparticipação e acomodação coletiva, abrangência geográfica de atendimento grupo de municípios (Tabela de Maio/2021 - SP). A disponibilidade e as características da rede médica e/ou do benefício especial podem variar conforme a operadora de saúde escolhida e as condições contratuais do plano adquirido. Planos de saúde coletivos por adesão, conforme as regras da ANS. Informações resumidas. A comercialização dos planos respeita a área de abrangência das respectivas operadoras de saúde. Os preços e as redes estão sujeitos a alterações, por parte das respectivas operadoras de saúde, respeitadas as condições contratuais e legais (Lei nº 9.656/98). Condições contratuais disponíveis para análise. Dezembro/2021.