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Life post-COVID-19: symptoms and chronic complications

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The pandemic caused by the virus SARS-CoV-2 is certainly the biggest challenge to global health today. From the first appearance of the disease that it causes (COVID-19) to the present day, according to Johns Hopkins University, 71,792,772 cases and 1,606,685 deaths have been recorded around the world.[1]

As the duration of the pandemic extends and the number of patients who have recovered increases, many authors have been asking what chronic alterations COVID-19 might cause in this population. Cases of patients with persistent symptoms like dyspnea, fatigue, coughing, chest pain, myalgia and arthralgia have been reported in the literature, even among patients whose acute phase of the disease was mild. Other symptoms that have been reported include depression, cognitive disorders, headache and palpitations.[2]

The frequency with which these symptoms persist has not yet been well established, but some studies have shown that it may be high among patients who have recovered from COVID-19. In a study published in JAMA, 143 patients were followed up for an average of 60 days after discharge from hospital and only 18 (12.6%) of them reported absence of symptoms relating to COVID-19, while 32% had one or two symptoms and 55% had three or more.[3] Repercussions impacting on quality of life occurred in 44.1% of the patients. Halpin et al.[4] followed up a cohort of 100 patients in the United Kingdom after their discharge, including 32 who had been treated in an intensive care unit (ICU). In the ICU group, 72% continued to have some degree of persistent fatigue, around 50 days after their discharge; in the group treated in wards, persistent fatigue was reported in 60.3% of the cases.

The chronic complications that may persist after infection with SARS-CoV-2 mainly affect the respiratory, cardiovascular, renal and neurological systems.

One of the first studies to explore chronic alterations to the respiratory system caused by COVID-19 was published in June 2020. A total of 57 patients were followed up. They underwent a pulmonary function test, a six-minute walking test and chest computed tomography (CT) 30 days after their discharge from hospital. Tomographic alterations were seen in 31 patients (54.3%). Abnormalities in pulmonary function tests were detected in 43 patients (75.4%). In comparison with non-severe cases, the patients presenting severe disease had higher incidence of impairment of diffusing capacity of the lungs for carbon monoxide (DLCO) (75.6% versus 42.5%; P = 0.019). Diminished DLCO, lower respiratory muscle strength and abnormalities on pulmonary imaging were detected in more than half of these COVID-19 patients who were in the initial stage of convalescence.[5]

These data were not completely corroborated by Lerum et al.,[6] who published a prospective study on 103 COVID-19 patients, including 15 cases that were considered severe and were treated in an ICU. Their aim was to report on their patient's quality of life, state of dyspnea, pulmonary function and chest CT findings, three months after their discharge from hospital. They found that a quarter of their patients continued to present opacities on chest CT and diminished diffusion capacity. However, in their sample, this was not reflected in increased dyspnea or impaired pulmonary function. ICU admission was the criterion most associated with the presence of pathological CT findings.

Cardiac alterations have also been targeted in studies. In a cohort study on 100 patients who had recovered from COVID-19, cardiac magnetic resonance imaging (MRI) was performed on

average 71 days after the disease had been diagnosed. Cardiac alterations were found in 78 patients and active myocardial inflammation in 60 patients. This occurred independent of the patient's preexisting conditions, disease severity, general evolution of the acute disease or length of time since the original diagnosis.[7] Nonetheless, the long-term evolution of such cases remains uncertain.

Rajpal et al.[8] also used cardiac MRI but studied a very specific population. They recruited 26 university athletes who had had COVID-19. None of them needed hospitalization. Twelve of them (26.9%) reported having had mild symptoms, while the others had been asymptomatic. None of them were found to present any ST/T wave alterations in electrocardiograms, and all of them had ventricular volumes and functions that were within the normal range, through transthoracic echocardiograms and cardiac MRI. None of the athletes presented elevated serum levels of troponin I. Four of them (15%) had cardiac MRI findings consistent with myocarditis. Thus, the study by Rajpal et al. showed that even among asymptomatic individuals who are physically fit, cardiac alterations may occur. However, the importance of these findings remains unknown.

The neurological alteration that has been most reported after COVID-19 is persistence of olfactory dysfunction. Otte et al.[9] analyzed the sense of smell of 50 consecutive patients, at least three weeks after they had recovered from an acute condition. Among these patients, 94% reported that they had suddenly lost their sense of smell during the course of the disease. At the time of undergoing an olfactory test after their recovery, 38% of the patients still presented a deficiency, while 61.7% of them had completely recovered their sense of smell.

Other neurological alterations that have also been described still need to be studied further to better characterize them. These include alterations of cognition and memory and deregulation of sleep. Some psychiatric alterations have also been reported, such as mood changes involving depression or anxiety.[2]

Other consequences, albeit hypothetical, may also impact the post-COVID-19 population. A study published in the journal *Future Oncology* theorized a potential carcinogenic effect from infection with SARS-CoV-2, especially in the pulmonary tissue, which would possibly translate in the future into increased risk of cancer among these patients.[10]

What can be expected from these chronic alterations, and even how to treat them, remains to be determined. A group of researchers in Recife, Brazil, published an interesting article in which they discussed the potential use of nuclear medicine as a means of mapping the chronic alterations to the lungs, kidneys, heart and endothelium that are caused by SARS-CoV-2.[11]

The pandemic is not over yet. The real damage that it will leave behind will certainly be much greater than what was initially thought. But right now, we need to get ready to treat these patients who have survived COVID-19 and often come back needing treatment for chronic complaints.

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Analysis of scientific production on the new coronavirus (COVID-19): a bibliometric analysis

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AUTHORS' KEYWORDS:
Researchers.
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ABSTRACT

BACKGROUND: The pandemic of the new coronavirus has culminated in a scientific race to seek knowledge about this virus and its treatments, vaccines and preventive strategies, in order to reduce its impact on healthcare and economics worldwide. Hence, it is important to recognize the efforts of researchers who are at the forefront of investigations relating to the new coronavirus.

OBJECTIVE: The present study was carried out with the aim of analyzing the world scientific production relating to COVID-19.

DESIGN AND SETTING: Exploratory and descriptive bibliometric study conducted in the city of Teresina (PI), Brazil.

METHOD: ISI Web of Knowledge/Web of Science (WOS) was chosen as the database. Data-gathering was carried out in May 2020. The data analysis was performed using the HistCite™ software, version 9.8.24, and the VOSviewer bibliometric analysis software, version 1.6.8.

RESULTS: 2,625 published papers that included descriptors within the scope of this investigation were identified. These articles were published in 859 different journals that are indexed in WOS, by 9,791 authors who were linked to 3,365 research institutions, located in 105 countries.

CONCLUSION: Ascertaining scientific production through a bibliometric analysis is important in order to guide researchers on what has already been produced and what is being researched, so as to be able to address gaps in knowledge through future research.

INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) reported the first outbreak of pneumonia in Wuhan City, Hubei Province, China. It was discovered shortly afterwards that this pneumonia was due to a new coronavirus, with genetic characteristics, mode of infection and hosts distinct from the other coronaviruses that were already known. It was given the scientific name of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the infection (disease) that it causes was named COVID-19 (coronavirus disease 2019).[1,2] At the end of January 2020, this epidemic outbreak turned into a pandemic and thus into a public health emergency of international interest.[3]

According to information from the Pan American Health Organization, the pandemic had affected more than 180 countries as of June 30, 2020, with confirmation of 10,185,374 cases of COVID-19 worldwide and 503,862 deaths from it.

Since the beginning of the pandemic, governments and scientists have been working on solutions to prevent rapid spread of the virus and contagion. Healthcare organizations have coordinated a series of protocols and guidelines aimed at improving rapid circulation of information about the pathology and possible treatment protocols and thereby mitigating the impact of the disease. However, despite the research carried out, the transmission mechanisms and clinical spectrum of the disease are still not fully understood, and there is still a lack of treatments and vaccines to control COVID-19.[2,4,5]

In view of this problem, it is essential that scientific production of studies on COVID-19 should be analyzed and expanded. Bibliometric studies have the aim of investigating the collaborative and scientific production network on a research topic, which in this case is on the new coronavirus. This knowledge facilitates recognition of researchers who produce and publish the most on the topic.

OBJECTIVE

The questions that guided this study were the following: Which information sources are of value regarding COVID-19, through the metrics of authorship and citation? What analysis has been done on the indicators of the dynamics and evolution of scientific and technological information about COVID-19? Thus, in the light of these questions, the objective of this study was to analyze the worldwide scientific production relating to COVID-19.

METHODS

Research design

This was an exploratory and descriptive bibliometric study with a quantitative approach that was conducted through defining a database for consultation and the criteria to be used in data-gathering and data representation and analysis.[6]

Data-gathering period

Data-gathering was carried out in May 2020. Search periods available in the database for complete years (1945-2020) were used, in order to allow replication or updating of this study without the need to conduct it again from its inception. Because COVID-19 is a recent topic, the search found that the first result was published in 2019, the year in which the first case of COVID-19 was registered. For this reason, the time period evaluated was from December 2019 to May 11, 2020.

Selection criteria

No refinement filters relating to fields of knowledge, countries or languages of the studies were used. All records of published studies in which the scope of the study included descriptors relating to the research topic were covered.

Data-gathering

The steps followed three procedures: defining the database to be consulted; determining the criteria to be used for data-gathering; and defining the representation and analysis of the data gathered.

ISI Web of Knowledge/Web of Science (WOS) was chosen as the database because of its "academic recognition of being considered one of the most comprehensive bases in several areas of scientific knowledge" and because this database has an important position as a pioneer in bringing together journals from more than 100 fields of knowledge.[7]

The descriptors were defined from the Medical Subject Headings (MeSH) catalogue, from which the following search terms were selected: "(COVID-19) OR ("2019 novel coronavirus disease") OR ("COVID19") OR ("COVID-19 pandemic") OR ("SARS-CoV-2 infection") OR ("COVID-19 virus disease") OR ("2019 novel coronavirus infection") OR ("2019-nCoV infection") OR ("coronavirus disease 2019") OR ("coronavirus disease-19") OR ("2019-nCoV disease") OR ("COVID-19 virus infection")". The quotation marks indicate the exact representation of terms with more than one word. Data-gathering was carried out by searching for these terms, which represented article titles, abstracts, authors' keywords and created keywords.

In this manner, 2,625 articles were identified, and these were used as a set of articles for the bibliometric analyses proposed. It should be noted that all articles found were selected for this investigation, since the focus of the study was to ascertain all the production that had occurred up to the end of the data-gathering period.

Data processing and analysis

The data gathered were then analyzed by exporting these data to the HistCite™ software, version 9.8.24. HistCite is a software package used for bibliometric analysis and information visualization. It was developed by Eugene Garfield, founder of the Institute for Scientific Information and inventor of important information retrieval tools such as Current Contents and the Science Citation Index. This package was used to organize the information and facilitate the analysis. The following items were analyzed: journals with the highest number of records and the number of articles distributed according to the country of origin of the authors.

In addition to these data generated through the software, aspects of the ten articles most cited across the entire WOS were elucidated in order to identify their main contributions to the topic of COVID-19. In addition, an analysis on indicators of the dynamics and evolution of scientific and technological information on this topic was carried out.

The VOSviewer software, version 1.6.8, was used to analyze co-competition networks between keywords. VOSviewer (Visualization of Similarities Viewer) is part of a free software suite for bibliometric analysis and visualization. It was developed by Van Eck and Waltman and is available at: www.vosviewer.com. In analyzing these co-competition networks, it was possible to map out possible research topics relating to COVID-19. The sizes of the nodes that were produced in the networks indicated the frequency of occurrence of keywords, and the relationships between nodes became stronger as the proximity between them became greater.

Ethical aspects

Since this was a bibliometric study, it was not necessary to submit the research project to an ethics committee for research on humans. According to Resolution 466 of 2012, of the National Health Council of Brazil, there is no need for approval from a research ethics committee for studies that use secondary data. However, the present researchers are committed to maintaining

the ethical principles recommended for research of this nature, through respecting ideas and citations and referencing authors and their publications.

RESULTS

In this investigation, 2600 published articles that included descriptors within the scope of this topic were identified. The articles were published in 859 different journals indexed in the WOS, by 9,791 authors who were linked to 3,365 research institutions, located in 105 countries. To produce these articles, 25,053 references were used, with an average of 10 references per article.

China was the country with the largest number of published articles, presenting 645 records. The United States, United Kingdom and Italy were next, with 595, 270 and 269 records, respectively. Brazil was in 15th position, with 48 published papers registered up to the time of the search in this database. The list of the first 15 countries with the largest numbers of articles published in WOS can be seen in **Table 1**.

The journals with the highest numbers of published articles were The Lancet, which had 1,602 citations, and the Journal of Medical Virology, which had 199 citations, from 84 and 69 published papers, respectively. To identify journals with high citation impact, an index was defined by dividing the number of citations by the number of published studies.

The list of the ten journals with the most relevant scientific productions on the subject of COVID-19 is shown in **Table 2**.

Table 1. List of countries with the most production on the topic of COVID-19 in the Web of Science (WOS) database

Ranking	Countries	Number of scientific articles published
1st	China	645
2nd	United States	595
3rd	United Kingdom	270
4th	Italy	262
5th	India	136
6th	Germany	112
7th	Iran	107
8th	Australia	96
9th	Switzerland	86
10th	France	77
11th	Singapore	56
12th	South Korea	55
13th	Turkey	49
14th	Spain	49
15th	Brazil	48

Source: based on data from the Web of Science.

The ten most cited authors relating to the topic of COVID-19 are shown in **Table 3** according to author, title, journal and number of citations, which ranged from 74 to 623.[8-17]

Figure 1 shows the keyword co-occurrence networks for the 2,625 documents in the sample. To facilitate visualization, construction of the network was restricted to keywords with ten or more occurrences, which resulted in 49 nodes that were organized into six different colors, namely: blue, red, green, lilac, yellow and turquoise (clusters). These were the words that most frequently determined the central theme of a body of documents.

DISCUSSION

The COVID-19 pandemic had led to publication of a large number of scientific studies on this subject, conducted around the world. The global dimensions of the direct and indirect effects

Table 2. List of journals with the most production on the topic of COVID-19 in the Web of Science (WOS) database

Ranking	Journal	Country	Number of citations	Number of published scientific articles	Citation index
1st	The Lancet	United Kingdom	1,602	84	19.1
2nd	Journal of Medical Virology	United States	199	69	2.9
3rd	British Medical Journal (BMJ)	United Kingdom	170	215	0.8
4th	Canadian Journal of Anesthesia – Journal Canadien d'Anesthésie	Canada	69	21	3.3
5th	Eurosurveillance	France	44	28	1.5
6th	Cureus	United States	18	54	0.3
7th	Head and Neck – Journal for the Sciences and Specialties of the Head and Neck	United States	10	38	0.2
8th	Indian Journal of Community Health	India	0	24	0.0
9th	Archives of Bond and Joint Surgery (ABJS)	France	0	23	0.0
10th	Archives of Academic Emergency Medicine	Iran	6	21	0.3

Source: based on data from the Web of Science.

Table 3. List of the most cited scientific articles relating to the topic of COVID-19 in the Web of Science (WOS) database

Ranking	Author	Title	Journal	Number of Citations
1st	Huang et al.[8]	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	The Lancet	623
2nd	Chen et al.[9]	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	The Lancet	352
3rd	Lu et al.[10]	Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding	The Lancet	211
4th	Holshue et al.[11]	First Case of 2019 Novel Coronavirus in the United States	New England Journal of Medicine	156
5th	Wu et al.[12]	A new coronavirus associated with human respiratory disease in China	JAMA	139
6th	Rothe et al.[13]	Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany	New England Journal of Medicine	116
7th	Zhou et al.[14]	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	The Lancet	101
8th	Zou et al.[15]	SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients	New England Journal of Medicine	79
9th	Chen et al.[16]	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	The Lancet	76
10th	Liang et al.[17]	Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China	Lancet Oncology	74

Source: based on data from the Web of Science.

of the coronavirus have required quick responses, which have placed scientific production and dissemination at the center of attention. Thus, the bibliometric analysis carried out through this study have enabled characterization of these researchers during the pandemic.[8-17]

China has contributed the largest number of scientific published papers during the COVID-19 pandemic, according to the analysis carried out here (**Table 1**). This can be explained by the fact that China is home to more than 3.61 million licensed doctors, and that this country was the cradle of the current pandemic.[17] The United States is second in the ranking. This can be explained by the fact that it accounts for the largest number of scientific journals on the search platforms used, in addition to being a country in which researchers around the world are interested in publishing their results.

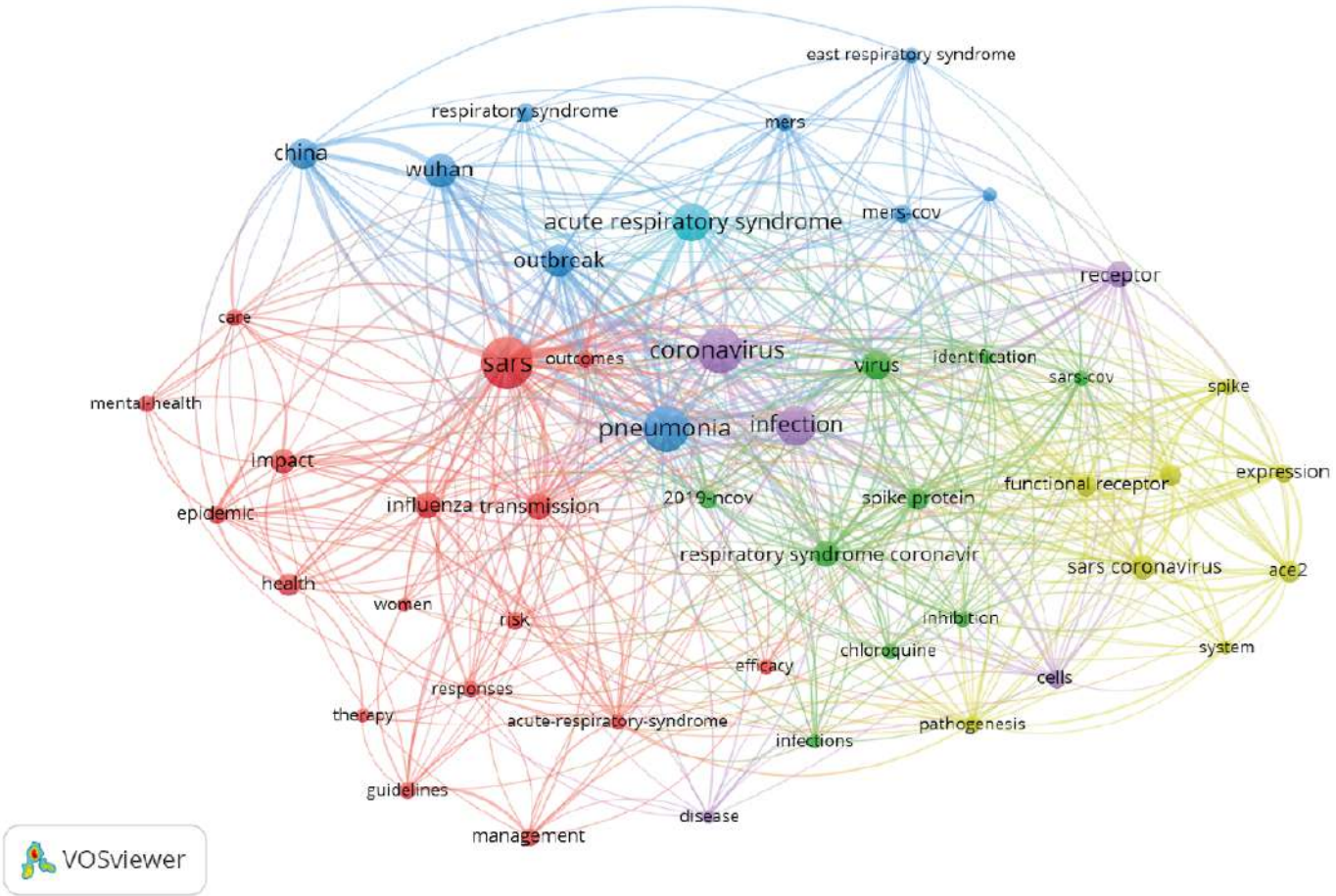
In addition, a large number of authors have taken the opportunity presented by the pandemic and the importance of this topic to increase their numbers of published studies through submitting studies in the form of letters to the editor and short communications. They have filled an urgent need to build up evidence for clinical practice and for organization of healthcare services and systems and intersectoral coping actions.

It can be supposed that the countries that had the next largest numbers of major productions, including the United Kingdom, Italy, India and Germany, were in this position because the first phase of the pandemic reached them shortly after China announced the epidemic outbreaks in that country. These countries also have research laboratories with more robust funding for searching for treatments against the virus. In the case of Brazil, the effects of the disease began to appear later and, thus, this country's scientific production is still rising.[18-22]

Regarding the journals with the highest numbers of citations in WOS, The Lancet, Journal of Medical Virology and British Medical Journal (BMJ) occupied the first, second and third positions, respectively. This was because they are journals of global scope, with high impact factors and rapid publication, and with open calls for submission of manuscripts on this topic.[18-22]

With 623 citations in WOS, the published paper with the greatest impact was by Huang et al.,[8] which was published in The Lancet. This article aimed to describe the epidemiology and the clinical, laboratory and radiological characteristics of patients with COVID-19 infection and to compare characteristics between intensive care and non-intensive care patients. This study was carried out shortly after the discovery of the virus and, thus, the authors showed that gaps existed with regard to knowledge of the origin, epidemiology, duration of human transmission and clinical spectrum of the disease.

Another factor observed was co-occurrence of relationships between pairs of keywords that were determined from the numbers



Source: based on data from the Web of Science.

Figure 1. Co-occurrence networks of keywords relating to the topic of COVID-19 in the Web of Science (WOS) database.

of articles in the database that occurred together, whether in the title, in the abstract or in the list of keywords.[23-24]

In analyzing these networks, it was possible to map out possible research topics on COVID-19. The size of the node indicated the frequency of occurrence of a keyword, and the closer together they were, the stronger their relationship was.

Cluster 1 (red) relates to research addressing the epidemiological picture of the virus since its identification in December 2019. The second cluster (green) shows that, so far, no proven effective treatment for COVID-19 has been found and, hence, researchers have been working on the search for the best therapy for coping with the new coronavirus. The words cited in this cluster suggest that this type of approach was used in the studies analyzed.

Among the nine nodes grouped in cluster 3 (blue), there is a research trail addressing the origin of the disease in Wuhan, in Hubei province, China, where the third coronavirus outbreak in human history occurred. This group also addresses the Middle East respiratory syndrome coronavirus (MERS-CoV), which has a zoonotic origin and is associated with severe and potentially fatal respiratory failure. It is noteworthy that MERS-CoV was the agent responsible for the outbreak in the Middle East that originated in Saudi Arabia, in 2012, with 2,494 cases recorded in 27 countries and 858 deaths (34% lethality).

The fourth cluster (yellow) relates to the behavior of the molecular structures of COVID-19. The nucleic acid of the new coronavirus is a positive-stranded ribonucleic acid (RNA), and its structural proteins include the following: spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid phosphoprotein. It has been shown that the new coronavirus enters epithelial cells through the spike protein and interacts with the host's angiotensin-converting enzyme 2 (ACE2) receptor protein on the surface, thus causing human infection.

The fifth cluster (lilac) reveals the researchers' interest in describing the performance of viral cells in the host organism. These cause serious infection due to the inability to exchange

carbon dioxide and oxygen between lung cells, thereby causing breathing difficulties.

The sixth cluster (turquoise) shows that the most severe cases of COVID-19 evolve into respiratory distress syndrome, which is the main cause of hospitalization and requires immediate care in an intensive care unit.

The findings from this investigation show that bibliometric studies have the important function of characterizing the research carried out on the topic in Brazil and around the world. Through this research design, the origins, institutions, researchers and number of citations of scientific production are noted. In addition, the segments within the topic of COVID-19 that have been most studied can be discerned.

However, the present bibliometric study has limitations. Only a single database was used, i.e. Web of Science™. Although this is a referential platform for scientific citations that was designed to support scientific and academic research with wide coverage in the fields of science and social sciences, it may be necessary to deepen the search using other scientific databases, through further studies. The high number of studies indexed in this database every day made it impossible to analyze them daily, and this can also be cited as a limitation. This led the present researchers to choose to delimit a period within which to obtain data, in order to be able to proceed with their investigation and discussion. Thus, some information may have been lost in this process and the reality may not match the data gathered in the present study.

CONCLUSION

The sources of value regarding COVID-19, which were recognized by means of authorship and citation metrics, comprised 10 studies, among 623 papers published in 859 different journals indexed in the Web of Science, written by 9,791 authors who have links with 3,365 research institutions, located in 105 countries.

The analysis on the indicators of the dynamics and evolution of scientific and technological information on COVID-19 showed that there are gaps in the knowledge of this subject. These gaps are wide and diversified. No join-ups between studies, authors and institutions around the world were demonstrated. There is a need to build knowledge networks within this field that enable more studies that are capable of contributing to the improvement of scientific evidence relating to coping with this pathogen through therapeutics and vaccines.

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Incidence, characteristics and long-term outcomes of patients with diabetic ketoacidosis: a prospective prognosis cohort study in an emergency department

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KEY WORDS (MeSH terms):
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Diabetes complications.
Emergency service, hospital.
Mortality.

AUTHORS' KEY WORDS:
Complications of diabetes mellitus.
Emergency department.
Mortalities.

ABSTRACT

BACKGROUND: Diabetic ketoacidosis is the most frequent hyperglycemic complication in the evolution of diabetes mellitus. Common precipitating factors include newly diagnosed diabetes mellitus, noncompliance with therapy and infections. However, few studies have been conducted in Brazil and none were prospective in design.

OBJECTIVE: To describe the incidence, clinical and laboratory characteristics and precipitating factors of diabetic ketoacidosis among emergency department patients in a tertiary-level teaching hospital in Brazil. We also aimed to identify immediate and long-term mortality within two years.

DESIGN AND SETTING: Prospective prognosis cohort study conduct at a tertiary-level teaching hospital in São Paulo, Brazil.

METHODS: All patients > 12 years old presenting diabetic ketoacidosis who were admitted to the emergency department from June 2015 to May 2016 were invited to participate.

RESULTS: The incidence of diabetic ketoacidosis per 1,000 admissions was 8.7. Treatment noncompliance and infection were the most common causes of diabetic ketoacidosis. The immediate mortality rate was 5.8%, while the six-month, one-year and two-year mortality rates were 9.6%, 13.5% and 19.2%, respectively. Death occurring within two years was associated with age, type 2 diabetes, hypoalbuminemia, infection at presentation and higher sequential organ failure assessment (SOFA) score at admission.

CONCLUSIONS: Diabetic ketoacidosis among patients presenting to the emergency department was relatively frequent in our hospital. Treatment noncompliance and infection were major precipitating factors and presence of diabetic ketoacidosis was associated with immediate and long-term risk of death.

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most frequent hyperglycemic complication in the evolution of diabetes mellitus (DM).[1] It represents a state of metabolic stress and is characterized by a pathological imbalance of insulin deficiency and counterregulatory hormones (glucagon, catecholamines, cortisol and growth hormone), thus forming a triad of marked hyperglycemia, ketosis and metabolic acidosis.[2,3]

Despite the situation of hyperglycemia, the lack of insulin in the setting of elevated counter-regulatory hormones means that glucose is not properly used as energy and ketone production exceeds peripheral utilization. Ultimately, this leads to development of DKA, given that the increase in ketoacid production is so great that metabolic acidosis occurs. Patients with DKA are usually admitted to the emergency department presenting with hyperglycemia associated with polyuria, polydipsia and significant dehydration.[4,5]

Successful therapy requires correction of hypovolemia, hyperglycemia, metabolic acidosis and electrolyte imbalances. Frequent monitoring is also necessary, in order to restore the patient to a normal metabolic state.[2,3] Crucially, the underlying cause of the ketoacidosis needs to be identified and treated, because DKA-related mortality is usually a consequence of the underlying illness.[6] The common precipitating factors of DKA include newly-diagnosed DM, patient noncompliance with therapy and infections.[7–10]

In most studies, the mortality rate attributed to DKA has ranged from 1 to 10%.[2-4] Despite the substantial literature base now available regarding DKA, few studies have yet evaluated adult DKA admissions in Brazil.[11,12] There is thus a lack of proper information on the clinical characteristics, treatment and long-term outcomes of DKA.

OBJECTIVE

Therefore, we proposed and conducted a prospective prognosis cohort study to describe the incidence, clinical and laboratory findings, precipitating factors and inpatient and long-term mortality rates over a two-year period, among DKA patients admitted to the emergency department of a teaching hospital in Brazil.

METHODS

Ethics

This study was approved by the Health Research Ethics Board (protocol number: 48219215.1.0000.5505; date: July 24, 2015) at the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP. All patients enrolled in this study provided written informed consent.

Design, setting and population

This was a prospective prognosis cohort study. All patients older than 12 years of age with a primary diagnosis of DKA who were admitted to the emergency department of the UNIFESP Teaching Hospital, in São Paulo, Brazil, between June 1, 2015, and May 31, 2016, were invited to participate. Potential cases were tracked by our study group in daily visits to the emergency department. The following patients were excluded from the study: patients presenting a hyperosmolar hyperglycemic state; women with previously known pregnancy; and patients with end-stage chronic kidney disease (CKD). Patients with end-stage CKD were excluded because the serum ketonemia test was not available at the hospital during the study period, and so the primary cause of the metabolic acidosis (i.e. whether it was renal or ketoacidosis) could not be defined. All decisions regarding patient admission and intensity of treatment were made at the discretion of the emergency department physicians, without any interference from the study group.

Outcomes

The primary outcome of interest was the incidence of DKA among emergency department admissions. This was defined as a proportion (number of cases per number of admissions during the study period) and as the number of cases per 1,000 emergency department admissions. The secondary outcomes that were determined were the clinical characteristics and laboratory findings at admission; precipitating factors; short-term mortality rate (emergency department and hospital); long-term mortality rates (six-month, one-year and two-year); sequential organ failure assessment (SOFA) score at admission; and Acute Physiology and Chronic Health Evaluation (APACHE-II) score at admission, and its relationship with mortality rates.

Operational definitions

The criteria used were adapted from those of the American Diabetes Association (ADA), which defines DKA as serum glucose of more than 13.9 mmol/l, moderate ketonuria or ketonemia, arterial pH less than 7.30 and serum bicarbonate less than 15 mmol/l.[2-3] DKA severity was evaluated through an adaptation of the ADA grading criteria for severity.[2-3] Treatment noncompliance was defined from documentation in the medical records showing non-adherence to the prescribed therapy, as a contributory factor for DKA.

Data sources

Data were captured from the patients' medical records and details that were missing from the records were obtained from the patients themselves by our team, using a report form designed specifically for this study. The data collected included patients' demographics, course of hospitalization and outcome measurements. The variables included age, sex, duration of DM, type of DM, prehospital medications, chronic kidney disease, comorbidities, precipitation factors, illness severity measurement (APACHE II), organ failure measurement (SOFA score), laboratory findings on admission, length of hospital stay and DKA outcome (discharge or death). The precipitating factors for DKA were defined by the emergency physician.

A follow-up of up to two years was made through tracking administrative data in the hospital, to find any occurrences of outpatient visits, readmission or telephone contact.

Statistical analysis

All the analyses were performed using the SPSS statistical software, version 24.0 (IBM Corp., Armonk, NY, USA). For the descriptive analysis, clinical variables and univariate comparisons between variables were reported as means with standard deviations (SDs) for normally distributed or nearly-normally distributed variables, and as medians plus interquartile ranges (IQRs) for non-normally distributed continuous variables, using the Kolmogorov-Smirnov test for normality; and as frequencies and percentages for categorical variables. In order to compare immediate mortality, total mortality and other categorical parameters with continuous variables, the t test and Mann-Whitney test were used. To compare categorical parameters, the Fisher exact and chi-square tests were used. In comparing mortality with the type of diabetes and associated comorbidities, we used the likelihood ratio. Correlation inferences were made through Pearson and Spearman correlation analyses. $P < 0.05$ was considered statistically significant for all comparisons.

Patient and public involvement

We did not directly include patient and public involvement (PPI) in this study, but the database used in this study was developed with PPI and was updated by a committee that included patient representatives.

RESULTS

During the study period, a total of 55 consecutive patients were admitted to the emergency department with a primary diagnosis of DKA. However, two patients were excluded from further analysis because they had end-stage chronic kidney disease and another patient was also excluded due to known pregnancy status (**Figure 1**).

The total number of admissions to the emergency department during that period was 5,943 patients. Thus, DKA accounted for 0.87% of all admissions (95% confidence interval, CI: 0.68-1.17), i.e. an estimated incidence density of 8.7 per 1,000 admissions.

During the study period, three patients failed proceed with the care provided, despite the medical team's advice, but they were still accounted for in the follow-up. During the two-year follow-up, only one patient was lost (**Figure 1**).

The initial clinical characteristics and laboratory findings of the DKA patients are presented in **Table 1**. Newly diagnosed DM was found in eight patients (15.4%), and 34 (65.4%) were type-1 diabetics. Considering the ADA criteria for DKA severity, 37 patients (71%) met the criteria for severe DKA, 11 (21%) had moderate

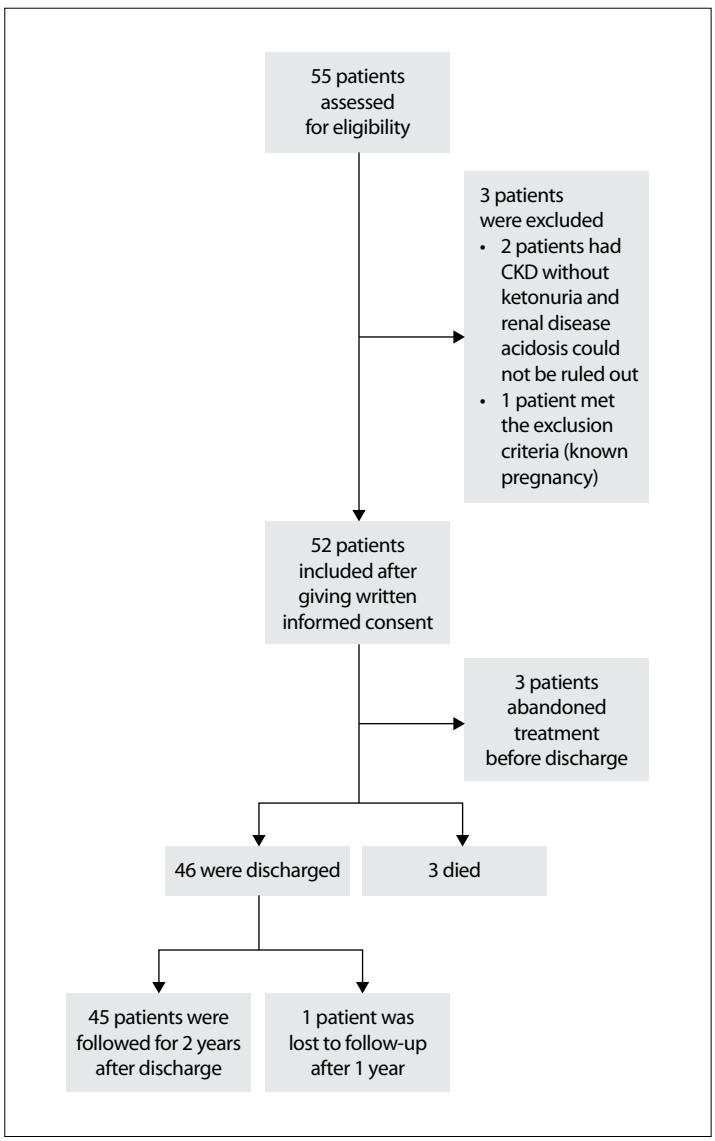

Figure 1. Subjects, eligibility, exclusion and follow-up.

Table 1. Demographic, clinical and laboratory characteristics of DKA patients at admission

Variable	All patients (n = 52)
Age in years, median (IQR)	28 (20-44)
Male, n (%)	23 (44)
Duration of diabetes mellitus in years, median (IQR)	10 (2.25-16.75)
Type of diabetes mellitus, n (%)	
Type 1 diabetes mellitus	34 (65.4)
Type 2 diabetes mellitus	10 (19.2)
New diabetes mellitus diagnosis	8 (15.4)
Medication use before DKA, n (%)	
Insulin use	37 (71.2)
OHA use	7 (13.5)
No treatment	8 (15.3)
Drug abuse, n (%)	4 (7.69)
Psychiatric disease, n (%)	6 (11.53)
Malignant neoplasia, n (%)	2 (3.8)
Serum glucose, mg/dl, median (IQR)	466 (393-639)
Arterial pH, mean ± SD	7.18 ± 0.15
Serum bicarbonate, millimole, mean ± SD	7.5 ± 4.8
Excess base, millimole, mean ± SD	-18 ± 6,2
Arterial lactate, millimole, mean ± SD	2.16 ± 1.12
Serum anion gap, millimole, mean ± SD	26.68 ± 8.65
Serum albumin, g/dl, median (IQR)	4.00 (3.92-4.30)
Calculated serum osmolality, mOsm/kg, median (IQR)	290 (283-304)
Serum sodium, millimole, mean ± SD	131.31 ± 5.87
Serum potassium, millimole, mean ± SD	4.95 ± 1.06
Serum chloride, millimole, mean ± SD	94.88 ± 9.5
Admission creatinine, mg/dl, median (IQR)	1,20 (0.98-1.62)
Admission urea, mg/dl, mean ± SD	50.42 ± 30.13
eGFR, ml/min/1.73 m², mean ± SD	67.90 ± 33.7
History of known CKD, n (%)	5 (9.6)
Total bilirubin, mg/dl, mean ± SD	0.55 ± 0.31
Length of hospital stay in days, median (IQR)	5 (4.00-8.25)
APACHE II, points, mean ± SD	11.8 ± 6.1
SOFA, points, median (IQR)	1.5 (0-3.25)
DKA classification, n (%)	
Mild	4 (7.7)
Moderate	11 (21.2)
Severe	37 (71.1)

DKA = diabetic ketoacidosis; IQR = interquartile range; SD = standard deviation; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = sequential organ failure assessment; OHA = oral hypoglycemic agents.

DKA and 4 (8%) had mild DKA. However, only 24 (46.1%) were transferred to an intensive care unit and most patients were treated in the emergency department and then discharged after resolution, or were transferred to a ward.

The most frequent precipitating factors for DKA in our study were poor compliance with treatment and infection (**Figure 2**). Urinary tract infection was most common (61%), followed by pneumonia and skin or soft tissue infection. Other conditions that precipitated DKA included acute pancreatitis (3.8%), pregnancy (3.8%) and drug abuse (1.9%) (**Figure 3**).

The immediate mortality rate was 5.8%, and no patient was readmitted to our emergency department within a 30-day period. The six-month, one-year and two-year overall mortality rates were respectively 9.6%, 13.5% and 19.2%. The SOFA and APACHE scores did not show any correlation with immediate mortality (**Table 2**), although higher SOFA scores at admission were associated with long-term mortality risk. In addition to higher SOFA score, older age, type-2 DM, lower serum albumin level and presentation of

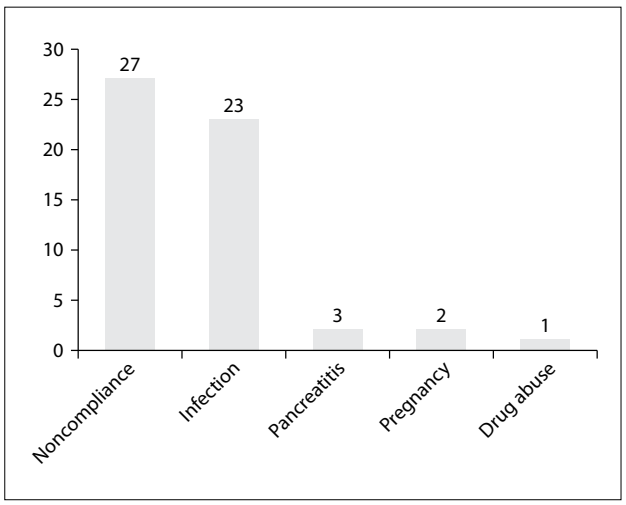

Figure 2. Precipitant factors in diabetic ketoacidosis. More than one cause may apply for each patient.

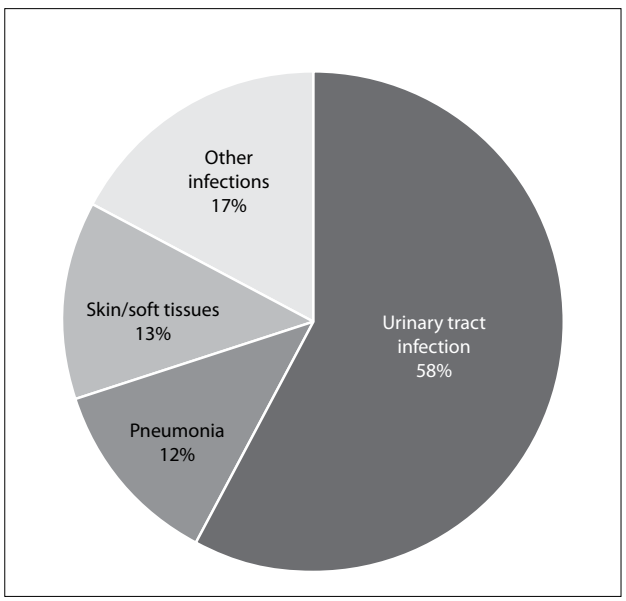

Figure 3. Causes of infection in patients with diabetic ketoacidosis.

Table 2. Clinical characteristics and outcomes of DKA patients according to in-hospital mortality after DKA admission

	All patients (n = 52)	In-hospital mortality		P-value
		Alive (n = 49)	Dead (n = 3)	
Age, years, median (IQR)	28 (20-4 4)	28 (20-41)	63 (42-68)	0.12[a]
Sex				0.08[b]
Male, n (%)	23 44.2)	20	3	
DM diagnosis, n				0.14[b]
New DM diagnosis	8	8	0	
DM1	35	34	1	
DM2	9	7	2	
APACHE II, points, mean ± SD	11.8 ± 6.1	12.02 ± 6.44	17 ± 11.53	0.21[a]
SOFA score, points, median (IQR)	1.5 (0-3.25)	1 (0-3)	4 (1-4)	0.23[a]
No. of comorbidities, n (%)				0.25[b]
None	21	20	1	
1	13	14	0	
2 or more	16	14	2	
Infection				0.08[b]
No	29	29	0	
Yes	22	20	3	
DKA severity, n (%)				1.00[b]
Mild/moderate	15	14	1	
Severe	36	35	2	
pH, mean ± SD	7.18 ± 0.15	7.17 ± 0.15	7.33 ± 0.07	0.07[a]
Excess base, mmol/l, mean ± SD	-18 ± 6.2	-19.1 ± 6.13	-12.1 ± 3.35	0.28[a]
Serum potassium, millimole, mean ± SD	4.95 ± 1.06	5.01 ± 1.04	3.93 ± 0.86	0.15[a]
Serum anion gap, millimole, mean ± SD	26.68 ± 8.65	26.92 ± 8.71	22.83 ± 7.95	0.47[a]
Serum glucose, mg/dl, median (IQR)	466 (393-639)	459 (391-648)	558 (423-640)	0.70[a]
Serum albumin, g/dl, median (IQR)	4.00 (3.92-4.30)	4.00 (4.00-4.35)	3.50 (2.30-4.00)	0.06[a]
Osmolality, mOsm/kg, median (IQR)	290 (283-304)	290 (284-304)	300 (283-304)	0.52[a]

Continue...

Table 2. Continuation

	All patients (n = 52)	In-hospital mortality		P-value
		Alive (n = 49)	Dead (n = 3)	
Lactate, mmol/l, mean ± SD	2.16 ± 1.12	2.18 ± 1.14	1.88 ± 0.83	0.66[a]
Lactate, n (%)				
< 2 mmol/l	28	26	2	1.00[b]
≥ 2 mmol/l	24	23	1	
Lactate, n (%)				
< 4 mmol/l	48	46	3	1.00[b]
≥ 4 mmol/l	3	3	0	
Duration of DM, years, mean ± SD	10.54 ± 9.66	10.23 ± 9.82	15.67 ± 5.13	0.13[a]
Length of stay, days, median (IQR)	5 (4.00-8.25)	5 (4.00-8.00)	21 (4.00-8.00)	0.12[a]

[a]Mann-Whitney U or paired t test; [b]Fisher exact test or likelihood ratio test; DKA = diabetic ketoacidosis; IQR = interquartile range; DM = diabetes mellitus; SD = standard deviation; SOFA = sequential organ failure assessment.

infection as a precipitating factor gave rise to significant higher risk of mortality over the long term (**Table 3**). No other characteristics showed significant correlations with either immediate or long-term mortality.

DISCUSSION

We conducted a single-center prospective prognosis cohort study on all patients older than 12 years of age who were admitted to the emergency department with DKA, with the aim of describing the incidence, precipitating factors, laboratory characteristics and inpatient and long-term mortality. Few studies have evaluated the characteristics and long-term outcomes of adult DKA patients, and the two major studies performed in Brazil were limited by their study design (retrospective medical record review) or focused solely on a pediatric population.[11,12]

Other studies focused only on intensive care unit (ICU) patients.[13] However, one previous large study on DKA admissions found wide variability in ICU use for DKA patients (range: 2.1-87.7%), and found that hospitals with greater numbers of DKA admissions were less likely to admit these patients to the ICU.[14] Likewise, in our study, although 37 (71%) of the patients had severe DKA, less than half were transferred to an intensive care unit, and most patients were treated in the emergency department. This confirms the importance of studying DKA patients within the emergency department setting and not only in the ICU.

We found that DKA represented less than 1% of total admissions at our hospital. Nonetheless, that still represented about one case a week over the one-year period. About two thirds of the patients were type-1 diabetics, but almost 20% of the patients with DKA had type-2 diabetes. Therefore, emergency department ED physicians need to consider DKA as a DM complication among type-2 diabetes patients presenting with hyperglycemia.

Table 3. Clinical characteristics and outcomes of DKA patients according to end-of-follow-up (two-year) mortality after DKA admission

	All patients	End-of-follow-up (two-year) mortality		P-value
	(n = 51)	Alive (n = 41)	Dead (n = 10)	
Age, years, median (IQR)	28 (20-44)	23 (20-38)	49 (28-67)	**≤ 0.001**[a]
Sex				
Male, n (%)	23 (44.2)	17 (73.9)	6 (26.1)	0.31[b]
DM diagnosis, n				
New DM diagnosis	8	8	0	**≤ 0.001**[b]
DM1	34	29	5	
DM2	10	5	5	
APACHE II, points, mean ± SD	12.31 ± 6.76	11.93 ± 6.05	12.0 ± 7.11	0.97[a]
SOFA score, points, median (IQR)	1.5 (0-3.25)	1 (0-2)	4 (2.5-6.5)	**≤ 0.001**[a]
No. of comorbidities, n (%)				
None	22	21	1	**0.001**[b]
1	13	12	1	
2 or more	16	8	8	
Infection				
No	29	27 (93.1%)	2 (6.9%)	**≤ 0.01**[b]
Yes	22	14 (63.6%)	8 (36.4%)	
DKA severity, n (%)				
Mild/ moderate	15	10 (66.7)	5 (33.3)	0.13[b]
Severe	36	31 (86.1)	5 (13.9)	
pH, mean ± SD	7.18 ± 0.15	7.16 ± 0.13	7.24 ± 0.22	0.32[a]
Excess base, millimole, mean ± SD	-18 ± 6.2	-19.5 ± 5.8	-21.2 ± 7.4	0.13[a]
Serum anion gap, millimole, mean ± SD	26.68 ± 8.65	27.44 ± 8.40	23.29 ± 9.50	0.76[a]
Serum potassium, millimole, mean ± SD	4.95 ± 1.06	4.98 ± 0.99	4.90 ± 1.39	0.22[a]
Osmolality, mOsm/kg, median (IQR)	290 (283-304)	290 (286-302)	296 (282-325)	0.56[a]
Serum glucose, mg/dl, median (IQR)	466 (393-639)	459 (383-648)	548 (395-687)	0.53[a]
Serum albumin, g/dl, median (IQR)	4 (3.9-4.3)	4 (4-4.6)	3.35 (3.0-3.62)	**< 0.001**[a]
Lactate, mmol/l, mean ± SD	2.16 ± 1.12	2.13 ± 1.09	2.36 ± 1.39	0.63[a]
Lactate, n (%)				
< 2 mmol/l	27	22 (82)	5 (19)	1.00[b]
≥ 2 mmol/l	24	19 (80)	5 (20)	
Lactate, n (%)				
< 4 mmol/l	48	39 (81.3)	9 (18.8)	0.48[b]
≥ 4 mmol/l	3	2 (66.7)	1 (33.3)	
Duration of DM, years, mean ± SD	10.69 ± 9.7	10.17 ± 9.88	12.81 ± 9.08	0.26[a]
Length of stay, days, median (IQR)	5 (4.00-8.25)	5 (4.00-7.00)	12 (4.75-18.00)	**0.01**[a]

[a]Mann-Whitney U or paired t test; [b]Fisher exact test or likelihood ratio test; DKA = diabetic ketoacidosis; IQR = interquartile range; DM = diabetes mellitus; APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = sequential organ failure assessment; SD = standard deviation.

We identified infection and noncompliance with DM treatment as the predominant precipitants for DKA, as previously shown by other studies.[8-10] Noncompliance has repeatedly been identified as an important and potentially avoidable precipitant across all age groups.[10,15-17] Psychosocial factors seem to contribute to noncompliance, including lower socioeconomic status and self-reported treatment error (i.e. incorrect management of insulin during illness).[10]

Moreover, some patients with both infection and treatment noncompliance have been counted within the rates for both of these precipitants. Many studies have not found a clear cause for some DKA patients, probably because of their retrospective design. In our study, we found the precipitating cause for every DKA case, possibly because our review of hospital records involved a careful search for medical impressions of treatment non-adherence and we objectively asked patients about treatment compliance preceding DKA. This may have revealed the true high rate of treatment non-adherence in DKA cases, as done previously by Weinert.[11]

Overall, the immediate inpatient mortality among adults in the United Kingdom and United States is less than 1%. However, it may reach rates higher than 5% among the elderly and among patients with severe comorbid conditions.[2] On the other hand, DKA mortality remains high in developing countries, such as Kenya (30%) and Libya (11.7%).[18,19] The immediate inpatient mortality associated with DKA in the present study was 5.8%, and it can be argued that our mortality rate has yet not reached the low levels of developed countries. It can also be argued that resource constraints, lower access to intensive care, public health issues and socioeconomic factors may contribute to higher mortality rates in developing countries.[20,21] In addition, the mortality rate among our patients rose progressively and, after the two-year follow-up period, approximately one in every five patients with DKA admitted to the emergency department during the data-gathering period of our study had died. Although APACHE II had previously been shown to be an important predictor of DKA-associated mortality,[22] that was not demonstrated by our data. Indeed, we did not find any correlation between inpatient mortality and the variables analyzed. Nonetheless, older and type-2 diabetes patients were at higher risk of long-term mortality, as also were those who presented with infection. This can be partially explained by the fact that sepsis survivor patients remain at substantially increased risk of death after recovery.[21]

Interestingly, although the ADA severity classification did not show any association with mortality, higher SOFA score at admission was associated with long-term mortality. The SOFA score ultimately represents dysfunction of target systems and organs, and we can argue that assessment of SOFA scores for DKA patients in the emergency department not only is important but also is essential, since these scores seem to predict mortality more accurately.

Hypoalbuminemia was also associated with total long-term mortality among our DKA patients. Low albumin levels had already been correlated with mortality risk among hospitalized patients, and our data confirm the findings of previous studies that found associations between low serum albumin and worse long-term outcomes.[23]

Regardless of the explanation, our study, like previous studies, seems to suggest that DKA patients still have a higher mortality rate long after discharge.[13] This seems to be especially so among older type-2 diabetic patients, those with more than one comorbidity and infection at presentation, those with higher SOFA score and those with lower serum albumin at admission. Overall, we would like to propose that DKA should be understood as a mortality marker in DM patients and that such patients should be followed more closely by a diabetes specialist, in order to attempt to improve treatment compliance and maybe prevent some of these deaths over the long term, even though this has not yet been shown through research.[13]

Furthermore, some DKA episodes among DM patients might be preventable, given that noncompliance with treatment is a major precipitating factor. The fact that noncompliance remains one of the most common precipitant factors for DKA patients admitted to the emergency department would imply that an important gap exists between research, treatment options and healthcare delivery. These patients could benefit from patient-centered strategies that focus on DM education and address patients' barriers to treatment and access to diabetes care.[2,24]

LIMITATIONS

Firstly, this was a non-controlled study with a relatively small sample size that had few mortality events. This was mainly because we used a convenience sample, thereby limiting the statistical power. However, the design of this study was prospective and therefore it was singular, among studies performed at emergency departments in Brazil and elsewhere, especially considering its long-term (two-year) follow-up.

Secondly, this was a single-center study and the DKA patients were admitted to a public tertiary-level teaching hospital in a large urban area in Brazil. Accordingly, our results may have limited generalizability to other areas that have differing healthcare systems.

The classification of diabetes as type 1 or type 2 was determined through previous evaluation by the patient's physician and this was not verified in this study. Cross-checking of the DM classification could not be performed because laboratory tests of greater sophistication, such as c-peptide and type-1 diabetes autoantibodies, were not available in the emergency department. It therefore remains possible that some of the DM patients could actually have presented rarer types of diabetes, such as LADA or MODY.

CONCLUSIONS

We conducted the first Brazilian prospective study on DKA patients in the emergency department setting, with long-term follow-up. DKA in adult patients presenting to this department was found to be relatively frequent in our hospital and was associated with both short-term and long-term risk of death. Noncompliance and infection were major precipitating factors for DKA among these patients, and survivors remained at risk of long-term mortality. Thus, we propose that DKA serves as a mortality marker for DM patients, especially for those who are older type-2 diabetics, with infection, and who present with high SOFA score and hypoalbuminemia at hospital admission. Interventions aimed at overcoming therapy compliance barriers and providing nutritional support might prevent avoidable cases and improve the long-term outcomes.

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Direct healthcare costs and their relationships with age at start of drug use and current pattern of use: a cross-sectional study

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Drug dependence costs.
Direct costs.

ABSTRACT

BACKGROUND: It is well known that early start of drug use can lead users to psychosocial problems in adulthood, but its relationship with users' direct healthcare costs has not been well established

OBJECTIVES: To estimate the direct healthcare costs of drug dependency treated at a community mental health service, and to ascertain whether early start of drug use and current drug use pattern may exert influences on these costs.

DESIGN AND SETTING: Retrospective cross-sectional study conducted at a community mental health service in a municipality in the state of São Paulo, Brazil.

METHODS: The relationships between direct healthcare costs from the perspective of the public healthcare system, age at start of drug use and drug use pattern were investigated in a sample of 105 individuals. A gamma-distribution generalized linear model was used to identify the cost drivers of direct costs.

RESULTS: The mean monthly direct healthcare costs per capita for early-start drug users in 2020 were 1,181.31 Brazilian reais (BRL) (274.72 United State dollars (USD) according to purchasing power parity (PPP)) and 1,355.78 BRL (315.29 USD PPP) for late-start users. Early start of drug use predicted greater severity of cannabis use and use of multiple drugs. The highest direct costs were due to drug dependence combined with alcohol abuse, and due to late start of drug use.

CONCLUSIONS: Preventive measures should be prioritized in public policies, in terms of strengthening protective factors before an early start of drug use.

INTRODUCTION

The prevalence and incidence of drug use in Brazil have increased over recent years, and the age at the start of use has become much lower than in the past.[1,2] The Second Brazilian National Survey on Alcohol and Drugs (Levantamento Nacional de Álcool e Drogas, LENAD) showed that among adolescents aged 14 to 17 years, 4.3% were frequent users of cannabis in the past year, 2.3% were frequent users of cocaine, 0.8% frequently used crack and 60% had used alcohol before their 15th birthday.[2] Additionally, Brazil is ranked as the second largest cocaine market in the world, and national consumption accounts for 20% of the world's cocaine market.[3,4]

Early drug use during adolescence is deleterious for the brain maturation process[5,6] and has both short and long-term health consequences,[5-9] including cognitive impairment,[10] substance use disorder,[9] reduced educational and occupational attainment[7,8] and engagement in illicit activities.[11,12] In this regard, preventive programs have been widely implemented for reducing drug use among adolescents and, consequently, for avoiding economic and social costs.[13-15]

The great economic impact of substance-related disorders on individuals and society was demonstrated through a study on the burden of diseases in Brazil.[16] This showed that, among the diseases that contributed most to disability-adjusted life years (DALYs) in this country, disorders relating to use of alcohol and other drugs jumped from third place in 1990 to first in 2016 among men, and from tenth to seventh among women, over the same period. Furthermore, substance-related disorders have been indicated to be one of the costliest health conditions for a healthcare system,[17-19] especially regarding hospitalization.[20]

In Brazil, there is a lack of data on the costs according to different drug users' profiles, especially considering their relationship to age at the start of use. The long-term economic impact

of early drug use on the healthcare system needs to be examined. Through this, public healthcare managers can be supported in their decision-making process with regard to allocating the available public healthcare resources more effectively, for prevention and treatment strategies. In this study, we hypothesize that an early start to drug use might be a predictor of higher direct costs for the public healthcare system.

OBJECTIVES

The aims of this study were to estimate the direct costs due to treatments for individuals dependent on alcohol and other drugs, at a public community mental health service; and to ascertain the potential influences of age at the start of drug use and current drug use pattern on direct healthcare costs. In addition, the potential economic consequences for the public healthcare system were discussed.

METHODS

Study design

This was a retrospective cross-sectional study on the relationships between direct healthcare costs and age at the start of drug use and drug use pattern, among individuals undergoing treatment for substance-related disorders at a community mental healthcare service. The cost analysis was conducted from the public healthcare perspective. This study was approved by the Research Ethics Committee of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP), under number 0296, in 2015.

Setting and participants

The study sample consisted of 105 subjects with a pattern of moderate-to-severe alcohol/drug use who were undergoing treatment at a public community mental health service, the Psychosocial Care Center for Users of Alcohol and Other Drugs (Centro de Atenção Psicossocial para usuários de álcool e outras drogas – CAPS-ad) in the city of Rio Claro, state of São Paulo, Brazil. CAPS-ad is a community-based mental health service that promotes public comprehensive care for people aged 18 years or over with substance-related disorders. It is the reference for substance-related treatment within the public healthcare network in Brazil. This CAPS-ad serves the population of the city of Rio Claro and another four small neighboring municipalities, covering a demographic area with 216,000 inhabitants. The service has a multiprofessional healthcare staff of two psychiatrists, one general practitioner, one nurse, two nursing technicians, two psychologists, two occupational therapists and one social worker.[21]

The inclusion criteria were that the subjects need to be aged 18 years or older, be undergoing treatment at CAPS-ad, be able to understand the interviewer's questions and meet the criteria for a pattern of moderate or severe drug use with regard to at least one drug, i.e. 11 points or more for alcohol use and 4 points or more for cannabis, alcohol and cocaine/crack use, in accordance with the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).

Early and late-onset drug use

Subjects who began using alcohol, cannabis, cocaine or crack at age 15 years or younger were classified into the "early onset" drug use group. Subjects who started using these drugs at age 16 years or later were classified into the "late onset" drug use group. There is no cutoff age that defines early and late onset of drug use in the literature. It was suggested in some previous studies that this cutoff point could be defined according to the epidemiological data on drug use of the region studied.[9,22] In some developed countries, "early onset" drug use has been considered to be use that occurs up to the age of 17 years and "late onset" as use that occurs at the age of 18 years or later.[9] However, a Brazilian national survey from 2012 showed that the onset of drug use occurred at a much earlier age in this country.[1,2]

Data collection

Data on direct health costs were collected using a "bottom-up" approach based on patient-level microdata, through application of the Brazilian version of the Client Socio-Demographic and Service Receipt Inventory (CSSRI),[23,24,25] between March 1, 2015, and August 30, 2017. Information on the number of days in treatment and age at onset of drug use were assessed through a semi-structured questionnaire developed by the research team of this study.

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST 2.0), which has been validated for use in Brazil,[26] was applied to evaluate the current alcohol, cannabis and cocaine/crack use pattern. ASSIST consists of eight questions or items that have the aim of investigating the intensity, frequency and problems associated with the use of each substance. The respondents' answers were classified according to the following categories of use: occasional use (0-3 points), substance abuse (4-26 points for cannabis and cocaine/crack; 11-26 points for alcohol) and possible dependence (27 points or higher).[27]

Direct healthcare costs

Data on direct costs were collected for the 30 days preceding participation in this study, in relation to the following components:

- *CAPS-ad healthcare staff care* comprised home visits; visits to psychiatrists and general practitioners; and individual and group sessions with occupational therapists, psychologists, social workers and nurses and nurse assistants.

- *Medications* included psychotropic and non-psychotropic medicines.
- *Hospital care* incorporated care received in psychiatric and general hospitals.
- *Outpatient care* included CAPS-III, which has the same CAPS-ad service structure but an around-the-clock service, 24 hours a day and 7 days a week, with crisis support beds for all cases of mental disorders in its coverage area. This also included non-psychiatric medical specialty outpatient services and dental assistance outpatient service.
- *Primary care* included primary care provided by nurses and doctors.
- *Transport* included bus tickets to CAPS-ad, emergency mobile medical care (Serviço de Atendimento Móvel de Urgência, SAMU) and inter-municipal transportation for treatment at CAPS-ad.

Unit costs were available for the year 2015. These were then adjusted for inflation up to the year 2018, in accordance with the general market price index (IGP-M), a Brazilian inflation rate index measured by the Getúlio Vargas Foundation (Fundação Getúlio Vargas, FGV).[28] Costs in Brazilian reais (BRL) were also converted to United States dollars (USD) using purchasing power parity (PPP) exchange rates.[29]

The unit cost values were calculated by means of a top-down approach, in accordance with municipal accounting data provided by the local public healthcare manager.[30] For situations in which these data were not available, the current scientific literature was consulted.[31,32]

Unit costs for medications were estimated from information provided by the municipal government regarding the prices paid for these medicines in the year 2015. For some medicines used by the subjects, the purchase prices were not available from the municipal government. In such situations, the medication prices database,[33] a Brazilian database on prices paid by the public healthcare sector for purchases of medicines, was consulted.

Data analysis

Initially, descriptive analysis was conducted. This was followed by an analysis on associations between variables and early and late onset of drug use. Associations between nominal variables were verified using the chi-square test or, in cases of small samples, Fisher's exact test. Student's t test was used to compare mean costs and the nonparametric Mann-Whitney test was used to compare numerical variables of non-normal distribution.

Inferential analysis was then conducted, in which "direct cost" was defined as the dependent variable in a gamma-distribution generalized linear model (GD-GLM) with a log binding function and marginal gamma distribution.[34] This model was chosen because of the nature of the dependent variable which was numerical, with non-negative values and asymmetry. The reasonableness of choosing this distribution was verified using Anscombe residuals.[34]

The GD-GLM had two sequential stages of analysis: univariate and multivariate. For the univariate analysis, variables that demonstrated significant associations (a significance level of 5% or $P \leq 0.05$) with the age of onset of drug use and those that we intended to investigate as possible direct cost predictors were selected. Predictive variables that showed associations with the dependent variable at a significance level of 20% in the univariate analysis, except for the current age and time of treatment (control variables), were selected for the multivariate models.

The choice of a significance level of 20% came from the relationship between sample size and the number of predictor variables analyzed in the univariate regression model. In other words, it was considered that variables showing significance of up to 20% in the univariate model could be significant at 5% in the final multivariate model. Thus, no significant predictive variable would be disregarded for the final multivariate regression model. For the predictive variables present in numerical and categorical forms that were both significant in the univariate model, the form in which the association with the dependent variable was more significant was selected. Subsequently, the variables that did not present significance at the 5% level were excluded one by one, in order of significance, using the backward method. The analyses were performed using the STATA 12 (StataCorp, Texas, 2011)[35] statistical package.

RESULTS

Totals of 59 early-onset substance users (56.2%) and 46 late-onset substance users (43.8%) composed the study sample (n = 105). The mean ages at onset of alcohol, cannabis, cocaine and crack use were, respectively, 15.2 years (standard deviation, SD = 5.7), 15.6 years (SD = 5.6), 20.2 years (SD = 8.6) and 23.9 years (SD = 12).

Table 1 shows the sociodemographic profile of the sample according to early or late onset of drug use. The mean age of the entire sample was 42.7 years (SD = 11.0), and there was a significant difference (P = 0.01) between the ages of the early-onset group (40.5 years; SD = 11.0) and the late-onset group (45.6 years; SD = 9.4). On average, early-exposed users were five years younger than the late-exposed users. The mean length of time spent undergoing the current treatment at CAPS-ad was 46.4 days overall (SD = 87.8). For the early-onset group, this number was 42.2 days (SD = 83.7) and for the late-onset group it was 51.7 days (SD = 93.6) (P = 0.58).

Table 2 presents data on past and current drug use patterns, as measured through ASSIST, according to early or late onset of

drug use. There were significant differences between the early and late onset groups regarding the *second drug of experimentation* and *current cannabis use pattern*. More than half (54.3%) of the subjects with late-onset drug use did not try a second drug or further drugs, compared with 28.8% of the early-onset group (P = 0.02). This latter group had a higher number of subjects who met the criteria for abuse and possible dependence on cannabis, compared with the group of late-onset users (P = 0.04).

Table 3 describes the subjects' consumption of healthcare network resources. On average, the late-onset group more often used *group sessions with nurse* (P = 0.04) *and psychologist* (P = 0.03), *nurse routine individual care sessions* (P = 0.00) and *visits to a general practitioner* (P = 0.04). These results are reflected in the direct healthcare costs per capita, shown in **Table 4**. The late-onset group showed higher mean monthly costs for *visits to general practitioner* (P = 0.04), *group sessions with nurse* (P = 0.04), *group sessions with psychologist* (P = 0.01), *nurse routine individual care sessions* (P = 0.00) and *bus ticket to CAPS-ad* (P = 0.04), in comparison with the early-onset group.

The mean monthly per capita direct cost adjusted for inflation in 2020 was BRL 1,181.31 (USD 274.72 PPP) for the early-onset drug use group and BRL 1,355.78 (USD 315.29 PPP) for

Table 1. Sociodemographic profile of the sample according to early or late onset of drug use

	Total n (%)	Early onset (n = 59) n (%)	Late onset (n = 46) n (%)	P
Gender (male)	86 (81.9)	49 (83.1)	37 (80.4)	0.73
Marital status				
Single	52 (49.5)	35 (59.3)	17 (37.0)	0.07
Married	32 (30.5)	13 (22.0)	19 (41.3)	
Divorced	18 (17.1)	9 (15.3)	9 (19.6)	
Widower	3 (2.9)	2 (3.4)	1 (2.2)	
Religion				
Catholic	38 (36.2)	21 (35.6)	17 (37.0)	0.50
Protestant	47 (44.8)	24 (40.7)	23 (50.0)	
Atheist	12 (11.4)	9 (15.3)	3 (6.5)	
Other	8 (7.6)	5 (8.5)	3 (6.5)	
Educational level				
Illiterate	3 (2.9)	1 (1.7)	2 (4.3)	0.15
Incomplete elementary school	42 (40.0)	23 (39.0)	19 (41.3)	
Completed elementary school	26 (24.8)	15 (25.4)	11 (23.9)	
Incomplete high school	10 (9.5)	9 (15.3)	1 (2.2)	
Completed high school	23 (21.9)	11 (18.6)	12 (26.1)	
Postgraduate	1 (1.0)	0 (0.0)	1 (2.2)	
Occupation				
Formally employed	26 (24.8)	16 (27.1)	10 (21.7)	0.65
Sick leave	3 (2.9)	1 (1.7)	2 (4.3)	
Retired	7 (6.7)	3 (5.1)	4 (8.7)	
Informal job	11 (10.5)	7 (11.9)	4 (8.7)	
Unemployed	58 (55.2)	32 (54.2)	26 (56.5)	
Not the first treatment attempt at CAPS-ad	55 (52.4)	32 (54.2)	23 (50.0)	0.66

Chi-square test or Fisher's test, P ≤ 0.05. CAPS-ad = Psychosocial Care Center for Users of Alcohol and Other Drugs.

Table 2. Lifetime and current drug use pattern (ASSIST) according to early or late onset of drug use

	Total (n = 105) n (%)	Early onset (n = 59) n (%)	Late onset (n = 46) n (%)	P
Lifetime drug use				
First drug of experimentation				
Alcohol	63 (62.4)	38 (64.4)	25 (59.5)	0.24
Cannabis	14 (13.9)	9 (15.3)	5 (11.9)	
Cocaine/crack	11 (10.9)	8 (13.6)	3 (7.1)	
Alcohol and cannabis	5 (5.0)	1 (1.7)	4 (9.5)	
Multiple drugs	8 (7.9)	3 (5.1)	5 (11.9)	
Second drug of experimentation				
Alcohol	10 (9.9)	6 (10.2)	4 (9.5)	0.00
Cannabis	20 (19.8)	11 (18.6)	9 (21.4)	
Cocaine/crack	16 (15.8)	13 (22.0)[A]	3 (7.1)[B]	
Multiple drugs	13 (12.9)	12 (20.3)[A]	1 (2.4)[B]	
None	42 (41.6)	17 (28.8)[A]	25 (59.5)[B]	
Age at first use: mean (SD)				
Alcohol[1]	15.2 (5.7)	13.2 (2.5)	18.1 (7.5)	< 0.00[b]
Cannabis[2]	15.6 (5.6)	14.5 (4.4)	17.6 (7.2)	< 0.00[c]
Cocaine[3]	20.2 (8.6)	17.6 (5.0)	25.0 (11.6)	0.00[c]
Crack[4]	23.9 (12.0)	23.3 (11.0)	25.0 (14.3)	0.66[b]
Current drug use pattern				
ASSIST – alcohol				0.90
Occasional use	24 (22.9)	11 (23.9)	13 (22.0)	
Abusive use	32 (30.5)	13 (28.3)	19 (32.2)	
Possible dependence	49 (46.7)	22 (47.8)	27 (45.8)	
ASSIST – cannabis				
Occasional use	80 (76.2)	40 (87.0)	40 (67.8)	0.04[a]
Abusive use	23 (21.9)	6 (13.0)	17 (28.8)	
Possible dependence	2 (1.9)	0 (0.0)	2 (3.4)	
ASSIST – cocaine/crack				
Occasional use	59 (56.2)	28 (60.9)	31 (52.5)	0.39
Abusive use	25 (23.8)	8 (17.4)	17 (28.8)	
Possible dependence	21 (20.0)	10 (21.7)	11 (18.6)	

Chi-square test or Fisher's test([a]), and Student's t([b]) or Mann-Whitney([c]), P ≤ 0.05; (A) and (B) show different percentages between early and late-onset groups; [1]Only for subjects who had used alcohol; [2]Only for subjects who had used cannabis; [3]Only for subjects who had used inhaled cocaine; [4]Only for subjects who had used crack; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test; SD = standard deviation.

the late-onset drug use group. The mean CAPS-ad treatment cost (including healthcare staff assistance, home visits and use of both psychotropic and non-psychotropic medications) was BRL 266.27 in 2015 (BRL 380.66, i.e. USD 88.52 PPP, in 2020) and accounted for 30.8% of per capita total direct cost.

Table 5 presents the GD-GLM univariate analysis results. Predictive variables for which the associations with direct healthcare costs were significant at the 20% level at this stage were selected for multivariate analysis.

Table 6 presents the results relating to the multivariate GD-GLM. In the final model, the predictive variables *age of onset of first drug use* (P = 0.034), *ASSIST alcohol-abusive use* (P < 0.001) and *ASSIST alcohol-possible dependence* (P = 0.049) remained significant. These results showed that for each year later at which the

Table 3. Consumption of healthcare network resources over the last 30 days, in 2015

	Total (n = 105)			Early onset (n = 59)			Late onset (n = 46)			P
	n	Mean (SD)	Minimum-Maximum	n	Mean (SD)	Minimum-Maximum	n	Mean (SD)	Minimum-Maximum	
CAPS-ad										
Home visits	4	1.0 (0.0)	1-1	1	1.0 (0.0)	1-1	3	1.0 (0.0)	1-1	-
Visits to psychiatrist	85	1.2 (0.5)	1-4	44	1.3 (0.6)	1-4	41	1.1 (0.4)	1-3	0.19
Visits to general practitioner	28	1.1 (0.4)	1-3	13	1.0 (0.0)	1-1	15	1.3 (0.6)	1-3	0.04
Group session with nurse	62	3.9 (5.3)	1-40	35	3.8 (6.7)	1-40	27	4.1 (3.0)	1-12	0.04
Nurse routine individual care session	99	12.6 (8.4)	1-42	57	10.3 (7.7)	1-30	42	15.8 (8.3)	2-42	0.00
Group session with psychologist	86	5.7 (4.7)	1-30	47	4.6 (3.1)	1-12	39	7.1 (5.8)	1-30	0.03
Individual session with psychologist	46	3.7 (4.0)	1-20	26	4.0 (5.1)	1-20	20	3.3 (1.6)	1-8	0.26
Group session with social worker	75	4.2 (4.6)	1-24	44	4.0 (4.5)	1-24	31	4.4 (4.7)	1-24	0.36
Individual session with social worker	47	3.1 (3.10)	1-16	26	2.4 (2.3)	1-12	21	3.9 (3.8)	1-16	0.14
Group session with occupational therapist	93	5.48 (4.6)	1-24	50	5.2 (5.0)	1-24	43	5.7 (4.2)	1-18	0.30
Individual session with occupational therapist	24	2.5 (1.7)	1-8	12	2.5 (1.9)	1-8	12	2.5 (1.6)	1-6	0.95
Hospital care										
Psychiatric hospital (days)	5	10.8 (6.5)	4-20	2	17.5 (3.5)	15-20	3	6.3 (2.0)	4-8	0.08
General hospital (visits to ER)	30	1.7 (1.4)	1-6	15	1.4 (0.9)	1-4	15	2.0 (1.8)	1-6	0.89
Outpatient care										
CAPS-III	5	1.0 (0.0)	1-1	2	1.0 (0.0)	1-1	3	1.0 (0.0)	1-1	1.00
Non-psychiatric medical specialties outpatient service	7	1.5 (0.7)	1-3	4	1.5 (0.5)	1-2	3	1.6 (1.1)	1-3	1.00
Dental assistance outpatient service	6	2.1 (1.1)	1-4	2	1.0 (0.0)	1-1	4	2.7 (0.9)	2-4	0.57
Primary care										
Nurse primary care	12	1.2 (0.8)	1-4	7	1.4 (1.1)	1-4	5	1.0 (0.0)	1-1	0.39
Doctor primary care	17	1.9 (1.1)	1-5	7	2.1 (1.4)	1-5	10	1.8 (0.9)	1-3	0.75
Transportation										
Bus ticket to CAPS-ad	55	2.0 (0.9)	1-9	32	1.9 (0.2)	1-2	23	2.3 (1.4)	2-9	0.91
Emergency mobile medical care (per call)	12	1.2 (0.8)	1-4	8	1.0 (0.0)	1-1	4	1.7 (1.5)	1-4	0.15
Intermunicipal transportation for treatment at CAPS-ad (per trip)	10	11.9 (12.7)	2-40	7	10.5 (13.4)	2-40	3	15.0 (13.0)	7-30	0.35

Mann-Whitney test or Student's t test, P ≤ 0.05; SD = standard deviation; CAPS-ad = Psychosocial Care Center for Users of Alcohol and Other Drugs.

Table 4. Direct healthcare costs per capita over the last 30 days, in 2015

	Unit costs description	Cost per unit – BRL	Total (n = 105)		Early onset (n = 59)		Late onset (n = 46)		P
			Mean (SD) – BRL	Minimum-Maximum – BRL	Mean (SD) – BRL	Minimum-Maximum – BRL	Mean (SD) – BRL	Minimum-Maximum – BRL	
TOTAL DIRECT COSTS			**863.8 (1,396.48)**	**33.20-8,338.30**	**778.74 (1,439.14)**	**33.20-8,338.30**	**972.91 (1,347.57)**	**40.35-6,303.13**	**0.48**
CAPS-ad									
Home Visits	One 60-minute home visit by a nurse assistant and a higher-education healthcare professional	35.91	40.45 (5.24)	35.91-44.98	35.91 (0.00)	35.91-35.91	41.96 (5.24)	35.91-44.98	-
Visits to psychiatrist	One individual visit of 30 min	28.16	34.79 (16.05)	28.16-112.64	37.12 (18.99)	28.16-112.64	32.28 (11.88)	28.16-84.48	0.16
Visits to general practitioner	One individual visit of 30 min	28.16	33.19 (13.39)	28.16-84.48	28.16 (0.00)	28.16-28.16	37.55 (17.38)	28.16-84.48	0.04
Group session with nurse	One 90-min group session, with an average of 10 patients	2.97*	11.78 (16.03)	2.97-118.80	11.29 (19.99)	2.97-118.8	12.43 (8.95)	2.97-35.64	0.04
Nurse routine individual care session	One individual session of 15 min to evaluate the patient's general state of health	3.35	42.5 (28.25)	3.35-140.70	34.62 (25.86)	3.35-100.5	53.20 (28.11)	6.70-140.70	0.00
Group session with psychologist	One 90-min group session, with an average of 10 patients	2.80*	16.15 (13.24)	2.80-84.00	12.87 (8.94)	2.80-33.6	20.10 (16.31)	2.80-84.00	0.01
Individual session with psychologist	One individual session of 60 min	18.73	69.22 (75.53)	18.73-374.6	74.92 (97.25)	18.73-374.6	61.81 (31.05)	18.73-149.84	0.26
Group session with social worker	One 90-min group session, with an average of 10 patients	3.96*	16.63 (18.32)	3.96-95.04	15.93 (18.13)	3.96-95.04	17.63 (18.85)	3.96-95.04	0.69
Individual session with social worker	One individual session of 60 min	26.44	82.13 (83.83)	26.44-423.04	64.07 (62.2)	26.44-317.28	104.5 (101.88)	26.44-423.04	0.14
Group session with occupational therapist	One 90-min group session, with an average of 10 patients	3.74*	20.51 (17.43)	3.74-89.76	19.67 (18.9)	3.74-89.76	21.48 (15.72)	3.74-67.32	0.62
Individual session with occupational therapist	One individual session of 60 min	24.98	63.49 (44.18)	24.98-199.84	64.53 (49.34)	24.98-199.84	62.45 (40.56)	24.98-149.88	0.95
MEDICATIONS	Medication price database and municipal data	**	15.51 (15.44)	1.68-83.25	14.21 (12.7)	1.68-52.35	17.13 (18.33)	1.68-83.25	0.48
Psychotropic		**	10.97 (13.04)	0.84-79.44	9.72 (10.65)	0.84-52.35	12.49 (15.47)	0.84-79.44	0.99
Non-psychotropic		**	8.09 (13.28)	0.48-80.76	9.18 (11.40)	1.68-40.68	7.04 (15.01)	0.48-80.76	0.06
Hospital care									
Psychiatric hospital	One bed per day of hospitalization[31]	369.08	3,995.81 (2,424.25)	1,476.32-7,414.31	6,480.60 (1,320.47)	5,546.88-7,414.31	2,339.29 (769.34)	1,476.32-2,953.39	0.08
General hospital	One visit to emergency room (average cost of emergency care at a general medium-sized general hospital emergency room)[30]	436.23	1,036.10 (916.87)	436.26-4,345.74	898.23 (663.79)	436.26-2,810.4	1,173.97 (1.122.)	436.26-4,345.74	0.42

Continue...

Table 4. Continuation.

	Unit costs description	Cost per unit – BRL	Total (n = 105)		Early onset (n = 59)		Late onset (n = 46)		P
			Mean (SD) – BRL	Minimum-Maximum – BRL	Mean (SD) – BRL	Minimum-Maximum – BRL	Mean (SD) – BRL	Minimum-Maximum – BRL	
TOTAL DIRECT COSTS			**863.8 (1,396.48)**	**33.20-8,338.30**	**778.74 (1,439.14)**	**33.20-8,338.30**	**972.91 (1,347.57)**	**40.35-6,303.13**	**0.48**
Outpatient care									
CAPS-III	12-hour night bed (psychiatrist and nursing staff cost, and non-medical direct costs) – municipal data	388.46	86.69 (168.69)	11.25-388.46	199.86 (266.73)	11.25-388.46	11.25 (0.00)	11.25-11.25	0.22
Non-psychiatric medical specialties outpatient service	One appointment (service total average cost in 2015 divided by total number of appointments) – municipal data	115.44	181.41 (90.83)	115.44-346.32	173.16 (66.65)	115.44-230.88	192.40 (133.30)	115.44-346.32	1.00
Dental assistance outpatient service	One appointment (service total average cost in 2015 divided by total number of appointments) – municipal data	95.31	206.51 (111.42)	95.31-381.24	95.31 (0.00)	95.31-95.31	262.10 (91.25)	190.62-381.24	0.05
Primary care									
Nurse primary care	One individual session of 60 min with nurse	18.71	39.13 (20.36)	18.71-74.84	42.94 (20.86)	18.71-74.84	33.8 (20.66)	18.71-56.43	0.43
Doctor primary care	One individual visit of 30 min	70.07	136.02 (80.16)	70.07-350.35	150.15 (102.57)	70.07-350.35	126.13 (64.39)	70.07-210.21	0.75
Transportation									
Ticket for transportation to CAPS-ad	One voucher	3.30	113.76 (100.46)	9.90-594.00	94.67 (84.70)	9.90-396.00	135.05 (113.45)	13.20-594.00	0.04
Emergency mobile medical care	One emergency call	195.28	244.10 (169.12)	195.28-781.12	195.28 (0.00)	195.28-195.28	341.74 (292.92)	195.28-781.12	0.15
Intermunicipal transportation for treatment at CAPS-ad	One round-trip (average cost considering driver, fuel and toll costs divided by the average number of patients transported)	14.90	86.39 (90.73)	14.90-286.40	76.77 (95.8)	14.90-286.40	108.85 (91.83)	52.15-214.80	0.35

Mann-Whitney test or Student's t test, P ≤ 0.05; *Cost of one group session per patient; **Unit cost varied according to each medication; SD = standard deviation; BRL = Brazilian real; CAPS-ad = Psychosocial Care Center for Users of Alcohol and Other Drugs; CAPS-III = has the same CAPS-ad service structure but an around-the-clock service, 24 hours a day and 7- days a week, with crisis support beds for all cases of mental disorders in the coverage area.

first drug experimentation occurred there was a 1.1% increase in total direct cost.

In addition, treatment for drug dependents who were also alcohol abusers was 4.4 times more expensive than for dependents who did not use alcohol, and treatment for alcohol-dependent users was twice as expensive as for those who did not use alcohol. Drug dependents who were also alcohol abusers had a higher monthly average direct cost (BRL 2,247.53, i.e. USD 522.68 PPP, *per capita* in 2020) than that of drug dependents who only made occasional use of alcohol (BRL 471.06, i.e. USD 109.54 PPP, *per capita* in 2020) (P = 0.002), as can be seen in **Table 7**.

DISCUSSION

The direct costs were higher for the subjects who met the criteria for both drug-related dependence and alcohol abuse, and were also higher among those in the late-onset group. One potential

Table 5. Results from univariate gamma regression models for direct costs

	Average ratio (95% CI)	P
Gender (female) (ref. = male)	0.939 (0.419-2.108)	0.88
Educational level (ref. = illiterate/incomplete elementary school)		
Completed elementary school/ Incomplete high school	1.031 (0.525-2.026)	0.93
Completed high school or more	0.672 (0.313-1.441)	0.30
School dropout	1.263 (0.643-2.482)	0.49
Days in current treatment at CAPS-ad	0.998 (0.993-1.003)	0.42
Age (years)	1.007 (0.974-1.041)	0.69
Age at onset of drug use		
First drug	1.015 (0.998-1.033)	0.08
Second drug	1.014 (1.000-1.028)	0.04
Alcohol	0.969 (0.927-1.014)	0.17
Cannabis	1.000 (0.967-1.033)	0.99
Cocaine	1.006 (0.982-1.032)	0.62
Crack	1.009 (0.986-1.032)	0.45
Duration of drug use (years)		
Alcohol	0.994 (0.973-1.017)	0.62
Cannabis	0.991 (0.968-1.014)	0.44
Cocaine	0.997 (0.969-1.026)	0.83
Crack	1.012 (0.974-1.050)	0.54
ASSIST (highest score among all drugs)	0.996 (0.957-1.037)	0.84
ASSIST (total numerical score)		
Alcohol	1.017 (0.987-1.048)	0.26
Cannabis	0.992 (0.952-1.033)	0.69
Cocaine/crack	1.000 (0.977-1.024)	0.99
ASSIST – alcohol (ref. = occasional use)		
Abusive use	4.771 (2.445-9.313)	< 0.00
Possible dependence	2.355 (1.271-4.365)	0.00
ASSIST – cannabis (ref. = occasional use)		
Abusive use	0.866 (0.409-1.834)	0.70
Possible dependence	0.329 (0.034-3.180)	0.33
ASSIST – cocaine/crack (ref. = occasional use)		
Abusive use	1.596 (0.768-3.316)	0.21
Possible dependence	0.892 (0.409-1.942)	0.77

P ≤ 0.05; CI = confidence interval; ref. = reference; CAPS-ad = Psychosocial Care Center for Users of Alcohol and Other Drugs; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test.

explanation for the higher costs among late-onset drug users may be that, as demonstrated by previous studies,[9] these users' profiles show that they had better adherence to the proposed treatments. This may imply better treatment outcomes and higher direct costs to the public healthcare system, in comparison with those of early-onset drug users.

However, the sample selection bias, small sample size, retrospective study design and low representativeness of all alcohol and drug users' profiles may also have influenced this result. Considering the low adherence to treatment among early-onset drug users, we hypothesize that if they developed a severe drug use pattern earlier than the late-onset group, the early-onset drug users

Table 6. Results from initial and final multivariate gamma regression models for direct costs

	Initial model		Adjusted final model	
	average ratio (95% CI)	P	average ratio (95% CI)	P
Days in current treatment at CAPS-ad	1.000 (0.996-1.004)	0.899	1.000 (0.996-1.004)	0.90
Age (years)	1.006 (0.978-1.036)	0.673	1.005 (0.979-1.031)	0.72
Age at onset of drug use				
First drug	1.011 (0.981-1.043)	0.472	1.015 (1.001-1.029)	0.03
Second drug	1.003 (0.978-1.029)	0.821	-	-
Alcohol	0.996 (0.953-1.042)	0.876	-	-
ASSIST – alcohol (ref. = occasional use)				
Abusive use	4.288 (2.102-8.749)	< 0.001	4.381 (2.210-8.688)	< 0.00
Possible dependence	1.996 (0.976-4.082)	0.058	2.023 (1.002-4.084)	0.04

CI = confidence interval; CAPS-ad = Psychosocial Care Center for Users of Alcohol and Other Drugs; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test; ref. = reference.

Table 7. Per capita direct costs according to ASSIST results for alcohol, cannabis and cocaine/crack, in 2015 – Brazilian reais (BRL)

Direct costs	N	Mean	Standard deviation	Minimum	Maximum	1st quartile	Median	3rd quartile	P
	105	863.80	1,396.48	33.20	8,338.30	171.91	452.57	780.52	
Alcohol									
Occasional use	24	310.53[B]	228.63	33.20	807.49	77.06	288.12	498.02	
Abusive use	32	1,481.62[A]	2,072.98	37.79	8,338.30	326.82	638.88	1,440.60	0.00
Possible dependence	49	731.32	999.79	47.18	5,268.34	168.28	455.64	802.73	
Cannabis									
Occasional use	80	901.71	1,418.34	33.20	8,338.30	183.24	460.73	774.44	
Abusive use	23	781.26	1,396.99	40.17	6,824.33	103.60	354.12	807.49	0.57
Possible dependence	2	296.51	210.15	147.91	445.10	-	-	-	
Cocaine/crack									
Occasional use	59	771.09	1.063.24	47.18	5,268.34	173.35	438.77	800.40	
Abusive use	25	1,230.72	2,015.31	33.20	8,338.30	162.32	536.89	1,228.38	0.38
Possible dependence	21	687.48	1.327.56	37.79	6,303.13	135.48	312.95	621.05	

Kruskal-Wallis test, P ≤ 0.05; (-) not presented due to the small number of cases; (A) and (B) presented different means according to Dunn-Bonferroni multiple comparisons.

would be unlikely to be found in the community mental health center. Therefore, the direct costs of early-onset drug users may have been underestimated because they may have been accessing types of treatment that were more complex and more costly (i.e. hospitalizations), and because the present study did not consider costs relating to mortality.

This hypothesis can be discussed in the light of results from previous studies. A Brazilian study demonstrated that crack and cocaine users aged 25 years or over fitted a drug user profile that was quite prevalent and recurrent in general hospital emergency rooms in São Paulo.[36] A 30-year prospective study conducted in New Zealand found that substance dependence, failure to obtain educational qualifications and criminal convictions in adulthood were predicted by early exposure to drugs (up to age 15 years).[37] Andreuccetti et al.[38] found that 37% of the victims of violent, sudden or unexpected deaths in the city of São Paulo were younger than 30 years of age; 55.3% had ingested alcohol (the most prevalent drug) or had used other drugs (cocaine, cannabis or sedatives and anxiolytics, in decreasing prevalence) before they died; and 15.9% had some form of criminal history. Among this last group, the rate of use of drugs other than alcohol and the rate of use of multiple drugs were higher than they were among victims who had no criminal history.

Although the early onset of drug use did not predict higher direct costs in the way in which we had originally hypothesized this, it did predict greater severity of cannabis and multiple drug use in adulthood. These data corroborate a 2017 Brazilian study conducted by Castaldelli-Maia et al.[39] that showed that there is an ongoing change in the role that cannabis plays in the culture of drug experimentation among Brazilian adolescents. Moreover, these data indicate that, as is also occurring in other countries like Spain,[40] the age at which cannabis experimentation starts is becoming similar to the ages at which alcohol and tobacco use start. This same study also showed that cannabis use acted as a predictor of alcohol use and had significant relationships with subsequent use of cocaine, prescription opioids and tranquillizers.

Therefore, these data can inform policymakers and society about the risks of early-onset cannabis use, considering the important role that early-onset use of this drug could be playing in predicting subsequent abuse of and dependence upon multiple drugs. These data also reinforce the notion that preventive measures should be prioritized in substance-related national policies in terms of strengthening protective factors before early-onset drug use might occur, and in the interests of preventing further severe and multiple drug use.

In 2013, three public preventive programs targeting drug use were implemented in Brazil.[41] However, no official data exist in relation to the implementation costs of these programs; moreover, the effectiveness of only one of these programs, the #TamoJunto program, has been evaluated. Sanchez et al.[42] investigated this program through a randomized clinical trial (RCT).

The #TamoJunto program, a Brazilian adaptation of a European program called Unplugged,[43] was implemented at high schools, focusing on adolescents aged 10 to 14 years. Unlike the European program, in which exposure to Unplugged was associated with significantly lower prevalence of daily use of cigarettes, episodes of drunkenness and use of cannabis over the past thirty days,[44] the Brazilian version promoted a protective effect regarding first inhalant use, had no effects on the prevalence of past-month drug use and showed increased relative risk of first alcohol use, i.e. a potential iatrogenic effect. In addition, the RCT demonstrated that the program had no effect on students' beliefs about drug use but found that those who originally had more negative beliefs about drug use had lower drug consumption during the follow-up than those who had positive beliefs.[45] These results indicate that there is a need for further studies that consider Brazilian cultural factors, in order to implement preventive public policies regarding drug use among youths in this country. Thus, the results led the federal government to reconsider continuation of the #TamoJunto program expansion as a public drug prevention policy.[41]

Despite Brazil's initial attempts to implement drug use prevention programs, national alcohol and drug policies have mainly been directed towards adults with substance-related disorders, and with a focus on resource allocation to hospitalization and tertiary-level treatment.[46,47] This is due particularly to the current austerity policy and the resource allocation constraints that Brazil has been facing as a result of the economic crisis over recent years. In 2018, for instance, the Brazilian federal government invested BRL 90 million, comprising BRL 40 million from the Ministry of Justice, BRL 10 million from the Ministry of Social Development and BRL 40 million from the Ministry of Health, in private clinics that focus on inpatient treatment for drug dependence. However, such treatments have not been proven to be effective or cost-effective for treating people with substance-related disorders.[48] This scenario underscores the importance of economic evidence for planning drug and alcohol policies.

In terms of the economic impact on the public healthcare system, the mean monthly direct costs per capita in our sample were almost 4.4 times greater than the mean per capita public healthcare expenditures in Brazil in 2015, while the costs for those who were both drug dependent and alcohol abusers were 7.5 times greater than national per capita healthcare expenditure in that year, according to data from the Organization for Economic Cooperation and Development.[49] According to another national survey developed by the Brazilian Federal Council of Medicine,[50] the mean annual per capita healthcare expenditure in São Paulo in 2017 was BRL 656.91, representing only 3.2% of the mean monthly per capita cost

of a drug dependent who is also an alcohol abuser (BRL 1,728.43 or USD 519.00 in 2017).

The current drug use situation in Brazil has alerted healthcare workers and government officials to the need to estimate its economic impact on the Brazilian public healthcare system in order to develop specific public policies, especially focused on prevention, targeting the highest risk groups. Public policies oriented toward preventing early-onset drug use among adolescents may reduce the economic impact that substance-related disorders have on the public healthcare system. These may also help adolescents avoid both developing dependence upon multiple drugs and having their consequences in adulthood.

There are several limitations to this study. Two related limitations comprised the small sample size and low representativeness of all the alcohol and drug users' profiles. This indicates that caution is needed in making generalizations. Another limitation was the retrospective study design, which did not permit analysis of possible cost variations according to each user's profile from his or her age at the onset of drug use to the age at the time of participation in this study. Lastly, there was some uncertainty regarding inaccuracies of cost estimations, given the large territorial extent of Brazil and regional differences in values aggregated to the components of the costs considered.

CONCLUSIONS

Our results are useful for alerting policymakers towards addressing national preventive policies against drug use, for the young population. Preventive measures should be prioritized within national alcohol and drug policies, in order to strengthen protective factors before early onset of drug use, especially regarding alcohol and cannabis, and to avert further severe and multiple drug use. Therefore, our findings suggest that there is a need to conduct further prospective studies on adolescents' drug use, their pathways through the healthcare system, the costs of their drug use and the social outcomes among these individuals.

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Descriptive epidemiological study on patients with movement disorders, with emphasis on Parkinson's disease

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ABSTRACT

BACKGROUND: Knowing the epidemiological profile is relevant for improving healthcare practices. Movement disorders are neurological disorders characterized by the presence of involuntary movements. They have a negative impact on patients' quality of life.

OBJECTIVES: To outline the frequencies of the different diagnoses seen among patients, along with their demographic characteristics, at a hospital in São Paulo (SP), Brazil, and to highlight the clinical aspects of those with Parkinson's disease.

DESIGN AND SETTING: Retrospective descriptive epidemiological analysis at a specialized outpatient clinic in a state public hospital in São Paulo.

METHODS: Patients treated at this clinic over a four-year period were analyzed. Diagnoses, demographic variables and associations with clinical aspects of Parkinson's disease were evaluated.

RESULTS: Out of the 680 medical records analyzed, 58.4% related to females. Most patients were over 60 years of age, white, married and teachers. The most frequent diagnosis was Parkinson's disease, followed by essential tremor and dystonia. Parkinson's disease presented in the mixed clinical form; the most common initial symptom was tremor. The akinetic-rigid clinical form occurred in younger individuals and mostly presented with postural instability and freezing of gait in the early years of disease.

CONCLUSIONS: Parkinson's disease, essential tremor and dystonia were the most frequent diagnoses. Characteristics like sex, frequency of other pathological conditions and the clinical and demographic aspects of Parkinson's disease were consistent with the data in the relevant literature.

INTRODUCTION

Epidemiological studies are widely reported in the literature,[1-4] and are extremely valuable for improving healthcare practices. Epidemiological information is an instrument for healthcare planning that informs guidelines and improvements.[5-7] Consequently, analysis on certain factors such as risk, morbidity and mortality, prevalence of certain diseases and assistance provided to patients is required.[5] Such information facilitates identification of a population profile and allows comparison of characteristics with data in other studies that have been consolidated in the literature.[6-8]

Some studies on neurological diseases have revealed that one of the most recurrent diagnoses consists of movement disorders.[9] These are neurological disorders resulting from lesions in the basal nuclei, which result in involuntary movements.[10] These disorders are broadly classified into two major groups: hyperkinetic and hypokinetic syndromes. Hyperkinetic syndromes are characterized by hyperactive involuntary and uncontrollable movements, such as ballism, athetosis, dystonia, tremor, tics, myoclonus and others.[11-13] Antagonistically, hypokinetic syndromes, for which the prototype is Parkinson's disease, are characterized by slowness and decreased voluntary movements (bradykinesia/akinesia), in addition to muscle stiffness, resting tremor and postural instability.[11-13] This group also includes other parkinsonian syndromes, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration and vascular and drug-induced secondary parkinsonism.[14]

Parkinson's disease is considered to be the second most common degenerative disorder after Alzheimer's disease.[15] Although its etiology is not yet well defined, it is characterized by degeneration of dopaminergic neurons in the nigrostriatal system of the basal nuclei.[16] The prevalence of Parkinson's disease in the general population has been estimated to be 0.3%,[17] such that it affects approximately 1% of individuals over 60 years of age[15-17] and 4% to 5% of those over 85 years of age.[15]

Progressive supranuclear palsy is considered to be the second most common form within the range of parkinsonian syndromes. Its incidence is approximately 5.3 cases per 100,000 people between 50 and 99 years old, and its prevalence ranges from 4.9 to 6.5/100,000.[18] Another example of parkinsonian syndrome is MSA, with an estimated incidence of 0.6 cases per 100,000 people, and a prevalence of 1.86-4/100,000, although there are few published studies on this.[15,19] Additionally, several other movement disorder-related diagnoses exist, thus highlighting the importance of evaluating their behavior.

These data are necessary for evaluating neurological institutions and services, and are important for identifying risk factors and geographical differences that might influence the development of treatment strategies. Knowledge of the characteristics and prevalence of diagnoses in this environment is required, in order to make comparisons with studies published previously.

OBJECTIVE

The objective of this study was to outline the frequencies of the different diagnoses seen among patients, along with their demographic characteristics, at the movement disorders outpatient clinic of a state public hospital, in São Paulo (SP), Brazil, and to highlight the clinical aspects of those with Parkinson's disease.

METHODS

This study consisted of a retrospective descriptive epidemiological review of data obtained from the medical records of patients seen at the neurology outpatient clinic specializing in movement disorders in a state public hospital, in São Paulo, Brazil. The medical records were searched based on a survey of patients with scheduled appointments who were seen at the movement disorders outpatient clinic. The analysis period comprised four years, starting from December 2009, when an electronic appointment scheduling system was implemented. The data were collected after the study protocol had been approved by an Internal Review Board (Ethics Committee) on May 13, 2014 (number 668.444/ CAAE: 305294 14.6.0000.5463) and had been authorized by the person in charge of the Medical Archive and Statistics Service (SAME).

Analysis on the medical records was previously authorized and scheduled as a maximum number of 20 medical records per day. The records were analyzed individually in the medical file sector of the state public hospital, by one of the doctors responsible for this research. The study exclusively included patients who had been diagnosed with movement disorders.

The patients' diagnoses were recorded from the medical records. The clinical evolution of the anamnesis and neurological examination were analyzed based on the diagnostic criteria. This information was described by neurology specialists in the movement disorder department. The entire procedure was supervised by chief neurologists.

The following demographic data were collected: age, sex, skin color, profession and marital status. In addition, correlations of the following relationships were assessed: "clinical diagnosis versus age"; and "clinical diagnosis versus sex".

Considering that the most frequent etiology would be Parkinson's disease, the following clinical characteristics were evaluated: initial symptoms, clinical form of the disease, freezing of gait and postural instability within the first five years of the disease. In addition, the following clinical correlations were considered: "clinical form versus age"; and "clinical form versus freezing of gait and postural instability".

The retrospective nature of this study was characterized as a limitation, considering that there was therefore a possibility of missing information. It is important to highlight that when information was not explicitly reported, these data were classified as not described (ND). Patients who did not have a defined etiological diagnosis due to lack of follow-up at the clinic or insufficient information were classified as "unspecified".

The data were expressed as absolute and relative frequencies for adequate statistical treatments. The chi-square and Fisher's exact tests were applied, depending on the distribution of values in the groups. The Stata statistical software, version 13.1, (StataCorp, 2013: Stata Statistical Software, Release 13; College Station, TX, United States) was used in all analyses and the confidence level was set at 95%, i.e. a P-value < 0.05 was considered significant. It is important to note that, when the total number of cases evaluated that were described as "ND" was less than 10%, these were not considered in the study because they were not statistically significant.

RESULTS

Out of the 790 medical records analyzed, 680 were selected because they involved a diagnosis of movement disorders. Of these, 277 records included a diagnosis of Parkinson's disease. Thus, in order to demonstrate the analysis more clearly, the results are presented in two stages: (1) Parkinson's disease analysis; and (2) diagnoses of other movement disorders.

Parkinson's disease

We observed higher occurrence of the mixed clinical form of Parkinson's disease, which was present in 77.6% of all of these patients. The tremulous (TREM) and akinetic-rigid (AR) forms accounted for 18.4% of the case, and the other 4% of the medical records of Parkinson's disease did not specify the form. The most common initial symptom reported by the patient was tremor. It is important to emphasize that the diagnoses of postural instability and freezing of gait were not present in the first five years of follow-up, as described in **Table 1**.

The Parkinson's disease analysis showed that 66.7% of the patients above 61 years of age were diagnosed with the mixed form, and 71.4% of the patients below 61 years were diagnosed with the AR form. In 46.1 of the patients with the TREM form, the onset was when they were above 71 years old.

Table 2 shows that there was an association between early diagnosis and the AR form. We found that the older the patient was at diagnosis, the greater the probability of occurrence of the mixed and TREM forms was.

No individual with the TREM form in our sample presented postural instability and freezing of gait within the first five years of the disease. This characteristic was also observed in most patients with the mixed form. Furthermore, there was higher relative frequency of instability and freezing of gait among individuals with the AR form, thus indicating less favorable conditions for those patients.

The results from this analysis were compared with studies in the literature. This demonstrated that similar methodologies had been used to study Parkinson's disease in different parts of the world. The frequencies of occurrence described in previously published reports[5,6,11,14] suggested that Parkinson's disease was the most common cause of movement disorders in the entire population studied, which was consistent with the results from our analysis. However, an increasing number of secondary and atypical diagnoses of parkinsonism exist and need to be considered. Consequently, an analysis of other movement disorder diagnoses is presented in the following section, in detail.

Analysis on other movement disorder diagnoses

The results from the analysis on the data collected during the study period showed that the most frequent diagnoses were Parkinson's disease (40.7%), essential tremor (15.4%) and dystonia (13.1%). The remaining diagnoses accounted for 33.6% of the cases. The frequencies of syndromic and etiological diagnoses of movement disorders are described in **Table 3**. The pattern shown in **Table 3** was also observed in several similar studies conducted in other regions,[5,6,10-13] including the study by Bhidayasiri et al.[7] and a study at the Columbia University Medical Center in conjunction with the Baylor College of Medicine, in which approximately 43,000 patients were analyzed.[14]

In our study, a diagnosis of parkinsonism was described in 336 records, of which 81.7% were attributed to Parkinson's disease. The other diagnoses included 9.1% with no defined etiology, which was classified as unspecified parkinsonism. Out of that total, 5.6% were diagnosed with drug-induced (n = 11) and vascular (n = 8) secondary parkinsonism. Atypical parkinsonism had an incidence of 3.5%, consisting of Lewy body disease (LBD) (n = 4), multiple system atrophy (n = 4) and progressive supranuclear palsy (n = 4).

The second most frequent pathological condition documented in the present study was 97 cases of essential tremor, which is one of the most common diagnoses in neurology outpatient clinics, often surpassing the number of Parkinson's disease cases. Its worldwide prevalence is widely variable, with descriptions ranging from one to more than 200 cases per 1,000 individuals.[15] Other etiologies for tremor were found in 31.2% of the cases. These cases included the following types: unspecified (n = 26), drug-induced (n = 4), others represented by a specific writing task (n = 3), Holmes (n = 2), orthostatic (n = 1) and psychogenic (n = 8).

Dystonia, which had the highest incidence, is a frequent condition reported in most studies,[5,8] and was diagnosed in 89 cases in our study, all corresponding to primary dystonia. **Table 4** shows the

Table 1. Distribution of patients with Parkinson's disease treated in the movement disorders outpatient clinic of a state public hospital, São Paulo (SP), 2017

Total	n	%
	277	100
Clinical form of the disease		
Akinetic-rigid	36	13
Tremulous	15	5.4
Mixed	215	77.6
Not described	11	4
Initial symptom of the disease		
Tremor	167	60.3
Rigidity	56	20.2
Postural instability	9	3.3
Bradykinesia	7	2.5
Not described	38	13.7
Postural instability (first 5 years of the disease)		
No	148	53.4
Yes	88	31.8
Not described	41	14.8
Freezing of gait (first 5 years of the disease)		
No	164	59.2
Yes	30	10.8
Not described	83	30

Source: research data.

Table 2. Analysis of the association between the clinical form of Parkinson's disease and age at diagnosis, postural instability and freezing of gait among patients diagnosed with Parkinson's disease who were treated at the movement disorders outpatient clinic of a state public hospital, São Paulo (SP), 2017

	Form of Parkinson's disease			P-value
	AR	TREM	Mixed	
	n (%)	n (%)	n (%)	
Age at diagnosis				
< 61 years	25 (71.4)	2 (15.4)	70 (33.3)	< 0.001
61-70 years	4 (11.4)	5 (38.5)	76 (36.2)	
71 years or older	6 (17.2)	6 (46.1)	64 (30.5)	
Postural instability				
No	16 (48.5)	12 (100)	118 (62.8)	0.007
Yes	17 (51.5)	0 (0)	70 (37.2)	
Freezing of gait				
No	16 (69.6)	11 (100)	135 (86.0)	0.043
Yes	7 (30.4)	0 (0)	22 (14.0)	

Source: research data. AR = akinetic-rigid; TREM = tremulous.

classification of primary dystonia according to anatomical location. Out of the total number of cases analyzed, 78 were focal, four were generalized and six were segmental dystonia. The focal dystonia cases accounted for 37.2% and corresponded to the cervical type, followed by 23.1% with writer's cramps, 17.9% each for upper-limb and blepharospasm cases and 3.8% for oromandibular cases.

The presence of dystonia has also been reported in the literature, at rates ranging from 2-50 cases per million (early onset dystonia) to 30-7,320 cases per million (late onset dystonia). This reflects the need for new epidemiological studies such as the present one.[12,13] According to the published reports, the occurrence rate has not changed over the years. Siemers and Reddy[11] reported dystonia in 17% of their movement disorder cases, which was a higher prevalence than that of their tremor cases (12%).

In the present study, chorea was present in 2.4% of the cases, Huntington's disease accounted for 1% of the cases and other forms such as vascular, Huntington-like type 2 and unspecified chorea totaled 1.4%. Ataxia had an occurrence of 1.1%, and the diagnoses of restless leg syndrome, tardive dyskinesia and tics represented 4.1% in our sample.

The demographic data, described in **Table 4**, showed that 58.4% of the patients were female and 41.6% were male. There was greatest frequency (31.3%) of the 71 to 80-year age group, followed by 61 to 70 years (25.7%) and above 80 years (21.5%). We found that 84.8% of the patient sample self-identified as white, and 64.4% were married. The most frequent professional activity was as a teacher (16.2%), followed by housewife/husband (11.8%) and general service assistant (2.2%). However, 35.9% of the medical records did not have any information on professional activity.

Both sexes exhibited high frequency of parkinsonism, followed by tremor. However, proportionally higher frequencies of restless leg syndrome (76.9%), dystonia (73%) and myoclonus (65.6%) were present in female patients, while tic (60%) and tardive dyskinesia (60 %) were more common in males. Parkinsonism had similar distribution between the male and female groups, as described in **Table 5**, which shows absolute and relative values.

Table 3. Frequencies of diagnoses among patients treated in the movement disorders outpatient clinic of a state public hospital, São Paulo (SP), 2017

Total	N	Relative %	Total %
	680	100	100
Parkinsonism (n = 336)			
Parkinson's disease	277	81.7	40.7
Atypical parkinsonism	12	3.5	1.8
Secondary parkinsonism	19	5.6	2.8
Not specified	28	9.1	4.1
Tremor (n = 141)			
Essential	97	68.8	14.3
Drug-induced	4	2.8	0.6
Not specified	26	18.4	3.8
Others	14	10.0	2.1
Dystonia (n = 89)			
Primary	89	100	13.1
Myoclonus (n = 61)			
Hemifacial spasm	61	100	9.0
Ataxia (n = 8)			
Spinocerebellar ataxia type 2	1	12.5	0.1
Spinocerebellar ataxia type 3	1	12.5	0.1
Spinocerebellar ataxia type 6	2	25	0.3
Not specified	4	50	0.6
Chorea (n = 17)			
Huntington's disease	7	41.2	1.0
Huntington-like 2	1	5.9	0.1
Vascular	5	29.4	0.7
Not specified	4	23.3	0.6
Tardive dyskinesia (n = 5)			
Tardive dyskinesia	5	100	0.7
Restless leg syndrome (n = 13)			
Restless leg syndrome	13	100	1.9
Tics (n = 10)			
Tourette's disease	2	20	0.3
Others	8	80	1.2

Source: research data.

Table 4. Demographic characteristics of patients treated at the movement disorders outpatient clinic of a state public hospital, São Paulo (SP), 2017

Total	680 (n)	100 (%)
Sex		
Female	397	58.4
Male	283	41.6
Age		
< 30 years	2	0.3
31 to 50 years	51	7.5
51 to 60 years	93	13.7
61 to 70 years	175	25.7
71 to 80 years	213	31.3
81 years or more	146	21.5
Race		
White	576	84.8
Mulatto	23	3.4
Black	45	6.6
Not described	36	5.3
Marital status		
Married	418	64.4
Divorced	42	6.2
Single	108	15.9
Widower	81	11.9
Not described	31	4.6
Profession		
Teacher	110	16.2
Housewife/husband	80	11.8
Service assistant	15	2.2
Others	231	33.9
Not described	244	35.9

Source: research data.

The distribution of the diagnoses according to age group revealed a statistical difference between the groups listed. Parkinsonism was more frequent in the age groups above 60 years, while dystonia showed higher frequency in individuals aged 60 years or less. The other syndromes had uniform distribution, or were highly influenced by low sample sizes in the groups, e.g. the distribution of ataxia. These analyses are described in **Table 5**.

DISCUSSION

Neuroepidemiology aims to determine the presence of neurological diseases in the population and acts as an instrument for healthcare planning and improvement. This has undergone increasing changes due to increases in life expectancy.

The retrospective use of medical records for data collection (included missing or incomplete data) was a limitation of this study. This can be explained in terms of difficulty in interpreting the documented information and variability in the quality of documentation among professionals. However, the most important information for the purpose of this study was indeed documented, i.e. the final diagnosis and clinical details.

This study demonstrated that high frequency of Parkinson's disease was present. A previous study conducted in Brazil indicated that the incidence of this pathological condition was 68.9% among a total of 338 patients,[20] a result that was similar to ours. Other studies have indicated high incidence of this diagnosis, in several countries, such as Thailand,[7] Spain,[10,18] United States,[11] Mexico,[16] India,[8] Denmark[21] and Brazil.[20,22,23]

In contrast, other research showed lower prevalences in Africa,[24] China[25] and some countries in Latin America, such as Argentina[26] and Bolivia,[27] compared with developed countries, especially in Europe. The demographic factors in this study showed that there was slight predominance among females, with an F:M ratio of approximately 1.03. On the contrary, other published reports have shown higher prevalence among males.[22,26]

Parkinson's disease may be classified into three clinical forms: tremulous, akinetic-rigid and mixed. As indicated in this study, the mixed form is considered to be most frequent. This conclusion is corroborated by results found in other published studies.[14,28,29] In our study, the clinical forms were correlated with age, and we showed that most patients presenting the tremulous form (84.6%) were over 60 years of age, thus confirming the results of Pagano et al.[30] Approximately 71.4% of the patients with the akinetic-rigid form were diagnosed under the age of 60 years. Previous reports have demonstrated biological differences between the clinical forms of Parkinson's disease.[14,31]

Resting tremor was reported in this study, in 60.3% of the patients at the onset of the disease. It is considered to be the most frequent initial symptom in the mixed and tremulous forms.[29] Delval et al.[32] showed that 27% of the patients analyzed in their study presented with a history of freezing of gait at the first evaluation, with a considerable increase observed eight years after the initial diagnosis.[33] Other published reports confirmed the results from this study, thus suggesting that freezing of gait occurs with higher frequency in the akinetic-rigid form of the disease.[32]

As previously stated, the most frequent diagnosis in our study was Parkinson's disease. However, increasing numbers of cases of secondary and atypical parkinsonism cases are common. This result was found in a previously published study,[7] which showed that vascular parkinsonism was the second most frequent cause (4.9%), and that multiple system atrophy (MSA) and Lewy body disease (LBD) were the most common atypical parkinsonian syndromes (drug-induced parkinsonism was not found). However, studies in other countries have shown different patterns, depending on the region studied. Rodríguez-Violante et al.[16] evaluated 647 patients in Mexico, among whom 46 were diagnosed with parkinsonism (atypical and secondary), representing 7.1% of a sample in which the most frequent diagnoses were vascular parkinsonism, progressive supranuclear palsy (PSP) and Lewy body disease.

Colosimo et al.[17] conducted a longitudinal retrospective analysis on data from the PRIAMO study in Italy, in which 1,307

Table 5. Distribution of movement disorder patients according to sex and age, São Paulo (SP), 2017

Diagnosis	PK	Tremor	RLS	Ataxia	Myoclonus	Chorea	TD	Dystonia	Tics
Sex									
Female	175 (52.1)	86 (61.0)	10 (76.9)	5 (62.5)	40 (65.6)	10 (58.8)	2 (40.0)	65 (73.0)	4 (40.0)
Male	161 (47.9)	55 (39.0)	3 (23.1)	3 (37.5)	21 (34.4)	7 (41.2)	3 (60.0)	24 (27.0)	6 (60.0)
Age (years)									
< 51	10 (3.0)	9 (6.8)	0 (0)	4 (50.0)	7 (11.5)	3 (17.6)	1 (20.0)	15 (16.9)	4 (40.0)
51-60	22 (6.5)	17 (12.9)	1 (7.7)	2 (25.0)	13 (21.3)	3 (17.6)	1 (20.0)	32 (36.0)	2 (20)
61-70	80 (23.8)	40 (30.3)	2 (15.4)	0 (0)	18 (29.5)	5 (29.4)	1 (20.0)	26 (29.2)	3 (30.0)
71-80	122 (36.3)	40 (30.3)	7 (53.8)	2 (25.0)	19 (31.1)	3 (17.6)	0 (0)	10 (11.2)	1 (10.0)
> 80	102 (30.4)	26 (19.7)	3 (23.1)	0 (0)	4 (6.6)	3 (17.6)	2 (40.0)	6 (6.7)	0 (0)

Source: research data. PK = parkinsonism; RLS: restless legs syndrome; TD = tardive dyskinesia.

patients were diagnosed as presenting atypical and secondary parkinsonism. Among these, 6.4% had vascular parkinsonism, 2.6% MSA, 2.3% PSP, 1.1% LBD and 0.8% corticobasal degeneration (a diagnosis not present in the present study). Nevertheless, in a similar study conducted in Spain to evaluate the older population, it was reported that the most frequent etiologies were drug-induced and vascular parkinsonism.[18]

Those etiologies were also present in other recent studies. Savica et al.[19] reported that out of 906 cases of parkinsonism in the United States, 11.9% corresponded to the drug-induced form, a result that differed from the present study. However, a review of previously published surveys conducted in Brazil showed predominance of secondary drug-induced and vascular parkinsonism.[20,22] Notably, some of the studies mentioned above have presented considerable numbers of parkinsonism cases of undetermined etiology, thus emphasizing the need for standardization of clinical evaluations and for possible use of supplementary examinations for better etiological definition.

Hemifacial spasm is characterized by segmental facial myoclonus, which was the fourth most common diagnosis found in the present study. A previously published report by Batla et al.[34] showed that the incidence of this condition was 7% in India. Other surveys conducted in the cities of Barcelona and Madrid indicated that the incidence of hemifacial spasm was 1.8% and 5%, respectively.[5,10] Although hemifacial spasm is a common complaint in neurology outpatient clinics, its frequency does not differ significantly from that of other extrapyramidal diseases.[5] This pattern was also observed in a study by Fahn et al.[14] in the United States, which showed the same frequency of this pathological condition as found in the present study.

Our results for ataxia and chorea were similar to those in other published reports.[6,7,10,11] However, one study in Ethiopia reported that the prevalence of ataxia was more than twice that of chorea, even surpassing the rate of diagnosing dystonia.[6] These results suggest that there was a lack of uniformity in the data for making this diagnosis.

Huntington's disease has been described as the primary cause of genetic chorea, which is the most prevalent type of chorea. A study conducted in the city of São Paulo, Brazil, on 119 medical records from patients diagnosed with chorea showed that 79% of the samples corresponded to Sydenham's chorea, Huntington's disease and vascular chorea.[35] Another study conducted in Brazil on the genetic causes of chorea showed that the incidence of Huntington's disease was 89.4%, of which 3.8% were Huntington-like type II cases, which is the second most common cause of chorea.[36] Vascular chorea was the second most common cause of non-genetic chorea in the present study, thus confirming the results of Piccolo et al.,[37] who reported that vascular chorea accounted for 41% of their cases in Italy.

The etiological classification of ataxias showed subtle predominance of spinocerebellar ataxia type 6 (SCA6), which has low prevalence in Brazil. This distribution differed from what has been reported in other countries, i.e. 30% prevalence in Australia, 28% in Japan and 15% in the United States.[38] In our study, SCA2 and SCA3 both had incidences of 12.5%. Despite the low frequency in our study, these etiologies are recognized as the most frequent types.[39] Similar results were also found in other studies.[38-40]

The diagnoses of tics and tardive dyskinesia were infrequent in our study, and also infrequent in other movement disorder outpatient clinics.[5, 6,11] Fahn et al.[14] reported that tics and Tourette's syndrome together accounted for the diagnoses of 6.4% out of a total of 2,753 patients in the United States. Similar results were also found in another study conducted in Brazil.[41]

Lastly, the demographic characteristics reported in the present study corroborated what was observed in most studies in the literature. Females predominated among the diagnoses of ataxia,[39] chorea,[35,37] myoclonus, parkinsonism,[23] dystonia[12] and tremor,[5,15] while males predominated in the other cases. Movement disorders predominated among adult and older patients. The younger diagnostic groups were represented by ataxia, tics and dystonia.[5,6,8]

CONCLUSIONS

Knowledge of the characteristics of movement disorder patients helps to model and promote better diagnostic and treatment strategies for this population. This study showed higher frequencies of diagnoses of Parkinson's disease, essential tremor and dystonia, and the patients were predominantly white, female, aged between 71 and 80 years, teachers and married. The mixed clinical form of Parkinson's disease with an initial symptom of resting tremor was found in higher numbers of patients. The akinetic-rigid (AR) clinical form of Parkinson's disease tended to occur in younger individuals, with symptoms of postural instability and freezing of gait that developed earlier. On the other hand, the mixed and tremulous forms of Parkinson's disease had greater likelihood of late onset. The present study showed that there is a need for more complete medical records, to enable better healthcare practices and epidemiological follow-up for patients. This would result in better diagnoses and strategies for analyzing the profile of patients with movement disorders.

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Neck pain and associated factors in a sample of high school students in the city of Bauru, São Paulo, Brazil: cross-sectional study

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ABSTRACT

BACKGROUND: Neck pain is a major public health problem.

OBJECTIVE: The aim of the present study was to determine the prevalence of neck pain among high school students and to analyze associations with sociodemographic variables, use of electronic devices, habitual physical activity practices and mental health problems.

DESIGN AND SETTING: Cross-sectional epidemiological study on a sample of high school students in the city of Bauru, São Paulo, Brazil.

METHOD: Participants were selected through cluster sampling in two stages and data were collected via face-to-face interviews. Data collection comprised the following steps: 1. sociodemographic characteristics; 2. use of electronic devices; 3. habitual physical activity levels; 3. mental health; and 4. neck pain.

RESULTS: A total of 1,628 participants were interviewed. The prevalence of neck pain was 49.1% (95% confidence interval, CI 46.7 to 51.5), with 40.4% (95% CI 37.0 to 43.7) in men and 57.5% (95% CI 54.2 to 60.9) in women. The variables associated with in neck pain were: female (prevalence ratio, PR = 2.04), use of cell phone in standing posture (PR = 1.47), use of tablet in sitting posture (PR = 1.72), length of computer use greater than 3 hours/day (PR = 1.54), length of cell phone use greater than 3 hours/day (PR = 1.54), length of tablet use greater than 3 hours/ day (PR = 1.34) and mental health problems (PR = 1.56).

CONCLUSION: There is high prevalence of neck pain among students and striking associations with female sex, use of electronic devices and mental health problems.

INTRODUCTION

Nowadays, in various activities of daily life and at school and at work, individuals of all ages often use electronic equipment (televisions, computers, video games, mobile phones and tablets).[1,2] In a review study, it was shown that 79% of the population between 18 and 44 years old used their cell phones almost all the time.[2,3] It has been shown in the literature that systematic use of this equipment has a consequent negative impact on people's health, such as sleep pattern changes, tiredness, anxiety, depression, overweight, decreased levels of physical activity, headaches, stress and pain in the shoulders, hands, low back and neck.[3,4]

Neck pain is considered by the World Health Organization (WHO) to be the fourth largest health problem with regard to generation of disability in the general population. It is the eighth largest cause of disability among young people between 15 and 19 years old.[5-7]

The one-year prevalence of neck pain ranges from 4.8% to 79.5%. These rates may be related to sociodemographic factors,[2,8-11] conditions associated with school (type and weight of the school bag and how it is transported; and the school furniture design),[8,12] use of electronic devices (such as televisions, computers, tablets and cell phones)[8,10,11,13,14] and mental health problems.[2,5,10,15]

Studies on neck pain and factors associated with this are important because the effects of neck pain may negatively interfere with leisure, sports and school activities.[16-19] In addition, adolescent neck pain has been correlated with chronic pain in adulthood and often follows a pattern of recurrent exacerbations and remissions. Adolescent neck pain is thus an important predictor of these problems in later life.[5,17]

It is important to note that, regarding electronic equipment, especially the use of tablets and cell phones, there is no Brazilian data on this relationship. Therefore, new knowledge on this relationship will contribute to other epidemiological investigations, meta-analyses and systematic reviews.

OBJECTIVE

The objective of this study was to determine the prevalence of neck pain among high school students and to analyze the associations with sociodemographic variables, use of electronic devices, habitual physical activity practices and mental health problems.

METHODS

Ethics

This investigation was approved by the local ethics committee (protocol number 1,972,579; date: March 20, 2017).

Study design

Through a cross-sectional study, data on 1,628 students from high schools in Bauru, São Paulo, Brazil, were analyzed.

Participants

This study was based on data collected for the project "*Back pain and associated factors among high school students: a longitudinal study*", financed by the Research Support Foundation of the State of São Paulo (Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP), under procedural number 2016/182837. The subjects comprised adolescents aged 14 to 18 years of both sexes who were attending the first and second years of high school in the mornings in the urban area of Bauru, SP, Brazil.

The sample (n = 1366) was obtained by means of conglomerate sampling in two stages. The primary sampling units were the schools and the secondary sampling units were the classes within the first two years of high school education in the schools that had previously been selected. Thus, the sample of school children was formed by all the students in the classes that formed the secondary sampling units that were selected within the sample of schools that formed the primary sampling units.[20] The criteria adopted for exclusion of some students from the schools that had been randomly selected for the study were the following: below the age of 14 years; above the age of 18 years; non-submission of informed consent form signed by parents or guardians; and refusal to participate.[20]

Taking into account both the inclusion and the exclusion criteria, the questionnaire of this study was answered by 1628 students between March and June 2017.

Instruments

Age, gender, skin color, income and marital status were evaluated through self-reported questions: age was divided into three age groups; marital status was categorized as single, married or widowed/separated; skin color was categorized as white, black or brown; and income was grouped into five bands (up to one minimum monthly wage; two to five minimum wages; six to ten minimum wages; 11 to 20 minimum wages; more than 20 minimum wages).[20,21]

The questions that participants were asked regarding their use of electronic devices (television, computer, tablet or cell phone) were the following:

1. Do you watch television? (a. yes. b. no);
2. How many times a week do you watch television? (a. once or twice. b. three or four times. c. five times. d. more than five times);
3. How many hours a day do you watch television? (a. less than one hour. b. two hours. c. three hours. d. four hours. e. five hours. f. more than five hours a day);
4. Do you use a computer? (a. yes. b. no);
5. What type of computer do you use? (a. desktop. b. laptop.);
6. What is the height of your computer screen? (a. eyes above the midpoint of the screen. b. eyes approximately at the midpoint of the screen. c. eyes below the midpoint of the screen);
7. How many times a week do you use your computer? (a. once or twice. b. three or four times. c. five times. d. more than five times);
8. How many hours a day do you use your computer? (a. less than one hour. b. two hours. c. three hours. d. four hours. e. five hours. f. more than five hours a day);
9. What is your eye-to-screen distance while using your computer? (a. < 20 cm. b. 20 cm to 25 cm. c. 25 cm to 30 cm. d. > 30 cm);
10. Do you use a cell phone? (a. yes. b. no);
11. In which posture do you use your cell phone? (a. standing. b. sitting. c. lying down. d. semi-lying down);
12. What is your average daily time spent using your cell phone? (a. less than one hour. b. two to three hours. c. three to four hours. d. more than four hours);
13. What is your eye-to-screen distance while using your cell phone? (a. < 10 cm. b. 10 cm to 15 cm. c. 15 cm to 20 cm. d. > 20 cm);
14. Do you use a tablet? (a. yes. b. no.);
15. In which posture do you use your tablet? (a. standing. b. sitting. c. lying down. d. semi-lying down);
16. What is your average daily time spent using your tablet? (a. less than one hour. b. two to three hours. c. three to four hours. d. more than four hours);
17. What is your eye-to-screen distance while using your tablet? (a. <10 cm. b. 10 cm to 15 cm. c. 15 cm to 20 cm. d. > 20 cm).[2,11]

The Baecke Questionnaire of Habitual Physical Activity, in its version validated for use in Brazil, was used to verify the level of habitual physical activity practice.[22] To classify the students, they were subdivided into quartiles according to the individual total score provided by the instrument, which resulted in the following physical activity groups: sedentary (1st quartile); moderately active (2nd and 3rd quartiles); and active (4th quartile).[22,23]

Mental health was evaluated using the Strengths and Difficulties Questionnaire (SDQ), in the version validated for use in Brazil by Fleitlich.[24] The questionnaire contains 25 items that are grouped into five scales (hyperactivity, emotional symptoms, behavioral

problems, relationship problems and pro-social behavior) containing five items each. Among these 25 items, 10 relate to skills, 14 relate to difficulties and one is considered neutral. Each of the items can be answered as "false", "more or less true" or "true". The score for each of the scales is obtained by summing the scores for the five items, thus generating a score that ranges from 0 to 10. The scores for hyperactivity, emotional symptoms, behavioral problems and peer relationship problems are added together to generate a total score for difficulties, ranging from 0 to 40.

According to the author of the scale, total scores greater than or equal to 20 are considered "abnormal" (clinical), i.e. they indicate that there are great difficulties in relation to what is being evaluated, thus requiring specialized intervention. Scores between 16 and 19 indicate limitations, i.e. that the child or adolescent already has some difficulty that, if not properly cared for, may deteriorate and impair their development. Scores less than or equal to 15 are regarded as normal. These cutoff points have been published in the literature and are available on the internet at www.sdqinfo.com.[24,25]

Presence of neck pain was assessed by means of the Nordic questionnaire, as validated and adapted for use within Brazilian culture,[26] through the following question: "In the last twelve months, did you feel any pain or discomfort in your cervical spine?" Neck pain was defined as pain, suffering or discomfort in the area between the occipital bone and the third thoracic vertebra, and between the medial margins of the scapulae.[27,28] To make it possible for respondents to better specify the neck region where the pain was, an image of the spinal regions was shown in different colors.[26]

Data collection procedure

After gaining approval from the State Department of Education and obtaining consent from the adolescents' parents or guardians, baseline data were collected by undergraduate and postgraduate students between March and June 2017.[21] On this data collection day, the researcher explained the objectives of the study to the students and informed them that their participation would be voluntary in nature and that they had the right to leave the study at any time and the right to confidentiality of their data. Subsequently, the researcher gave guidance regarding filling out the questionnaire and remained available to deal with any doubts that the students might have had. At the time of answering the questionnaire, there was no communication between the students.[20]

For students who were absent at the time of the initial data collection, three extra visits were made to all of the schools, to collect data. Students who continued to be absent after these visits were considered lost. Students who refused to answer were considered to be refusals.[20]

Data analysis

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

Prevalences, confidence intervals, bivariate analyses and Poisson regression analyses between neck pain and all the independent variables were calculated, including determination of the significance levels and the estimated relative risk of the 95% confidence intervals.

Poisson regression analysis with robust variance was performed in accordance with the theoretical-conceptual hierarchical model. A reference category was established for all variables, which was taken to be the category with the lowest risk. The variables were organized in four levels according to the temporal and causal relationships of neck pain. The adjustment of the first level was performed using all the variables that belonged to this level. The second level was adjusted using variables from the previous level that presented P-values < 0.10, and using those that belonged to the second level. The third level was adjusted using variables from the first and second levels with P-values < 0.10, and using those that belonged to the third level. The fourth level was controlled for the three previous levels (**Figure 1**). For variables that would remain in the regression model, a regressive selection process was used, such that all the variables with P-values < 0.05 were left in the final model.[29,30]

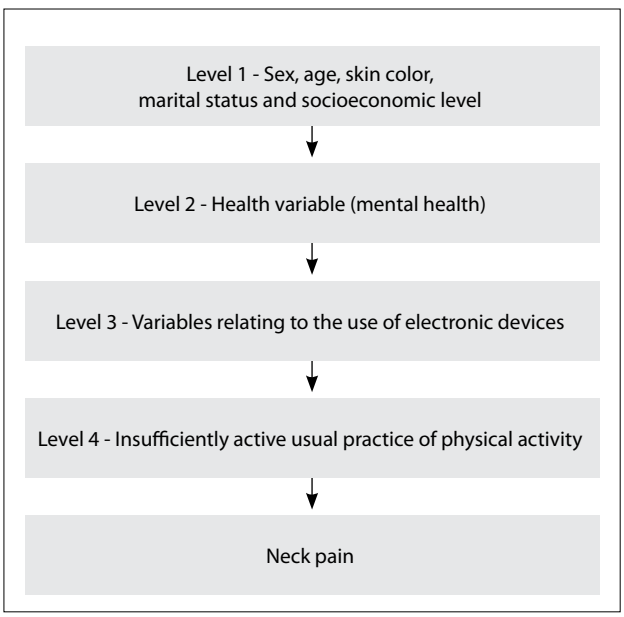

Figure 1. Proposed analysis model for studying neck pain prevalence.

RESULTS

A total of 1628 students were analyzed, after deduction of 2.05% of refusals from the final percentage. Regarding the sociodemographic characteristics of the sample, 51.5% of the males and 53.7% of the females were in the first year of high school; 87% of the males and 82.5% of the females were in the age group of 15 to 18 years; 47.4% of the males and 51.9% of the females were white; and 85.9% of the males and 97.2% of the females were single. Regarding the level of physical activity, most of the males (46.5%) and females (50.7%) were classified as sufficiently active, while 16.4% of the males and 35.7% of the females were insufficiently active. Regarding the mental health variable, 68.7% of the males and 42.3% of the females were considered normal, while 11.3% of the males and 30.0% of the females were classified as "clinically abnormal".

Table 1 shows the data on the use of electronic devices by these adolescents.

Table 1. Distribution of absolute and relative frequencies of use of electronic devices among high school adolescents according to sex

Factors	Sex			
	Male (n = 798)		Female (n = 830)	
	n	%	n	%
Do you watch television?				
No	123	15.4	67	8.1
Yes	675	84.6	763	91.9
How many times do you watch television per week				
Up to 2 times	168	24.7	205	21.1
3 times or more	507	67.2	558	63.5
Number of hours of television/day				
Up to 2 hours	383	48.0	376	45.3
3 hours or more	292	36.6	387	46.6
Do you use a computer?				
No	105	13.2	215	25.9
Yes	693	86.8	615	74.1
What type(s) of computer?				
Desktop	344	43.1	224	27.0
Laptop	263	33.0	339	40.8
Desktop and laptop	86	10.8	52	6.3
Height of the computer screen				
Eye level above the screen midpoint	153	19.2	114	13.7
Eye level at the screen midpoint	473	59.3	435	52.4
Eye level below the screen midpoint	67	8.4	66	8.0
How many times do you use a computer/week?				
Up to 2 times	184	23.1	295	35.5
3 times or more	509	63.8	320	38.6
How many hours of computer use/day?				
Up to 2 hours	250	31.3	341	41.1
3 hours or more	443	55.5	274	33.0
Do you use a cell phone?				
No	33	4.1	9	1.1
Yes	765	95.9	821	98.9
What is your posture when using your cell phone?				
Standing	276	34.6	282	34.0
Sitting	403	50.5	441	53.1
Lying down	436	54.6	491	59.2
Semi-lying down	215	26.9	344	41.4
Daily length of cell phone use				
Up to 2 hours	220	27.6	125	15.1
3 hours or more	545	68.3	696	83.9
Do you use a tablet?				
No	656	82.2	649	78.2
Yes	142	17.8	181	21.8
What is your posture when using your tablet?				
Standing	25	3.0	47	5.6
Sitting	83	10.4	102	12.3
Lying down	68	8.5	82	9.9
Semi-lying down	26	3.3	56	6.7
Daily length of tablet use				
Up to 2 hours	94	11.8	149	18.0
3 hours or more	48	6.0	32	3.9

The overall prevalence of neck pain was 49.1% (95% CI 46.7 to 51.5), while it was 40.4% among the males (95% CI 37.0 to 43.7) and 59.6% among the females (95% CI 54.2 to 60.9).

The bivariate analysis **(Table 2)** showed that neck pain was associated with female sex and mental health problems.

Neck pain was significantly associated with use of a cell phone in a standing posture and when semi-lying down, with daily use of a cell phone totaling more than three hours and with use of a tablet and its use in a sitting posture **(Table 3).**

In the analysis on multiple factors, after adjustment through logistic regression according to the hierarchical model, cervical pain remained associated with: female gender, length of use of a computer greater than three hours per day, use of a cell phone in a standing posture, use of a cell phone totaling more than three hours per day, use of a tablet totaling more than three hours per day, use of a tablet in a standing posture, use of a tablet in a sitting posture and mental health problems (**Table 4**).

DISCUSSION

It was found in this study that 41.9% of the students reported having neck pain. This finding was similar to what had been

Table 2. Bivariate analysis on neck pain in relation to sociodemographic characteristics, physical activity level and mental health problems among adolescents

Factors	Neck pain		
	n	%	PR (95% CI)*
Gender			
Male	322	40.2	1.00
Female	478	59.8	1.43 (1.29-1.58)
Age range			
14 years	133	16.6	1.00
15 to 18 years	667	83.4	0.91 (0.80-1.03)
Marital status#			
Married	28	3.5	1.00
Single	772	96.5	0.98 (0.75-1.28)
Race			
White	407	50.9	1.00
Black	57	7.1	0.79 (0.64-0.98)
Brown/mixed	287	35.9	0.99 (0.89-1.10)
East Asian	29	3.6	0.98 (0.75-1.28)
Indigenous	20	2.5	1.05 (0.77-1.34)
Level of physical activity			
Very active	185	23.1	1.00
Sufficiently active	387	48.4	1.07 (0.94-1.22)
Insufficiently active	217	27.1	1.13 (0.98-1.29)
Mental health problems			
Normal	362	45.3	1.00
Borderline	214	26.8	1.46 (1.30-1.64)
Clinical	213	26.6	1.56 (1.39-1.75)

*Adjusted according to age and/or sex; #The legal age for marriage in Brazil is 16 years (Law No. 13,811/19 of the Brazilian Civil Code).
PR = prevalence ratio; CI = confidence interval.

Table 3. Bivariate analysis on neck pain in relation to use of electronic devices among adolescents

Factors	Neck pain		
	n	%	PR (95% CI)*
Do you watch television?			
No	99	12.4	1.00
Yes	701	87.6	0.94 (0.81-1.08)
How many times do you watch television per week?			
Up to 2 times	177	22.1	1.00
3 times or more	524	65.5	1.04 (0.92-1.17)
Number of hours of television/day			
Up to 2 hours	361	45.1	1.00
3 hours or more	340	42.5	1.05 (0.95-1.17)
Do you use a computer or videogame?			
No	143	17.9	1.00
Yes	657	82.1	1.12 (0.98-1.28)
What type(s) of computer?			
Desktop	297	37.1	1.00
Laptop	323	40.4	1.00 (0.89-1.11)
Desktop and laptop	37	4.6	1.02 (0.81-1.30)
Height of the computer screen			
Eye level above the screen midpoint	164	20.5	1,00
Eye level at the screen midpoint	427	53.4	1,00 (0,88 – 1,14)
Eye level below the screen midpoint	66	8.3	0,99 (0,81 – 1,21)
How many times do you use a computer/week?			
Up to 2 times	247	30.9	1.00
3 times or more	410	51.3	0.96 (0.86-1.08)
How many hours of computer use/day?			
Up to 2 hours	287	35.9	1.00
3 hours or more	370	46.3	1.07 (0.96-1.19)
Do you use a cell phone?			
No	17	2.1	1.00
Yes	783	97.9	1.22 (0.84-1.77)
What is your posture when using your cell phone?			
Standing			
No			1.00
Yes	316	39.5	1.23 (1.11-1.36)
Sitting			
No			1.00
Yes	435	54.4	1.10 (0.99-1.22)
Lying down			
No			1.00
Yes	459	57.4	1.01 (0.91-1.11)
Semi-lying down			
No			1.00
Yes	303	37.9	1.16 (1.05-1.28)
Daily length of cell phone use			
Up to 2 hours	145	18.1	1.00
3 hours or more	638	79.8	1.22 (1.07-1.40)
Do you use a tablet?			
No	613	76.6	1.00
Yes	187	23.4	1.23 (1.10-1.38)
What is your posture when using your tablet?			
Standing			
No			1.00
Yes	48	6.0	1.20 (0.99-1.47)
Sitting			
No			1.00
Yes	119	14.9	1.31 (1.07-1.60)
Lying down			
No			1.00
Yes	90	11.3	1.07 (0.89-1.29)
Semi-lying down			
No			1.00
Yes	52	6.5	1.13 (0.93-1.38)
Daily length of tablet use			
Up to 2 hours	142	17.8	1.00
3 hours or more	45	5.6	0.96 (0.77-1.20)

*Adjusted according to age and sex.
PR = prevalence ratio; CI = confidence interval.

reported in Shanghai, China (40.8%),[2] Taiwan (46.4%)[11] and Thailand (44.7%),[12] while it was lower than in Las Vegas, United States (67.9%)[8] and Korea (81.6%)[10] and higher than in Saudi Arabia (23.7%)[13] and Australia (27.5%).[15] Sociocultural, demographic, economic and professional differences may have influenced the prevalence rates in these various locations.[20]

The outcome remained associated with female gender, length of use of a computer greater than three hours per day, use of a cell phone in a standing posture, use of a cell phone totaling more than three hours per day, use of a tablet totaling more than three hours per day, use of a tablet in a standing posture, use of a tablet in a sitting posture and mental health problems.

Neck pain was associated with female gender, thus corroborating the findings from other studies on adolescents.[2,12,14] This gender-based difference may be related to a lower pain threshold among women, hereditary factors and higher mental stress among women, besides the fact that they present less strength and smaller body size than men.[2,8,10,31]

Table 4. Multivariate logistic regression, for associations of variables with neck pain among adolescents

Factors	Neck pain	
	P-value	Adjusted PR (95% CI)
Sex*		
Male	0.001	1.00
Female		2.04 (1.66-2.07)
Use of a tablet in a standing up posture**		
No	0.01	1.00
Yes		1.54 (1.25-1.90)
Use of a cell phone in a standing up posture**		
No	0.001	1.00
Yes		1.47 (1.21-2.50)
Use of a tablet in a sitting posture**		
No	0.01	1.00
Yes		1.72 (1.09-2.77)
Daily length of cell phone use**		
Up to 2 hours	0.001	
3 hours or more		1.26 (1.08-1.98)
Daily length of computer use**		
Up to 2 hours	0.03	1.00
3 hours or more		1.14 (1.01-1.30)
Daily length of tablet use**		
Up to 2 hours	0.002	1.00
3 hours or more		1.34 (1.11-1.61)
Mental health problems***		
Normal		1.00
Borderline	0.001	1.01 (0.57-1.80)
Clinical		2.32 (1.28-4.19)

*Adjusted for demographic and socioeconomic variables; **adjusted for the variables of the first and second stages and for the variables relating to use of electronic equipment; ***adjusted for the first-stage variables and mental problems.
CI = confidence interval; PR = prevalence ratio.

Use of computers, cell phones and tablets for more than three hours a day was associated with the outcome of neck pain, and this lined up well with the findings from other investigations.[2,11,13,32] As mentioned above, the mechanism for pain development may be related to an association of inappropriate postures, static work and repetitive movements in manual activities. In addition, gender, type of activity, levels of physical and mental health and family relationships can contribute to higher numbers of hours of use of electronic equipment.[32,33]

Neck pain was associated with use of cell phones and tablets in a standing posture. Using electronic equipment in a standing position causes individuals to perform greater cervical flexion when looking at the screen. This increases the muscle activity of the cervical extensors, which is a significant risk factor for cervical pain.[34]

The sitting posture when using a cell phone was a factor associated with neck pain, and this corroborated data from other studies.[4] It was previously shown that for the head to be stabilized and maintained in an upright position, there is a need for greater activity of the cervical and thoracic extensor muscles.[8] This prolonged isometric contraction of the cervical extensors promotes increased muscle tension and stress, thus causing pain. In addition, postures with greater cervical flexion, such as using a cell phone resting on one's lap or on a table, further increase the cervical extensor tension.[8,9]

Neck pain was associated with a clinical category relating to mental health problems, similar to what was observed in other investigations.[15,35,36] High levels of mental problems are related to increased muscle tension, which possibly affects the nutrition of intervertebral discs, nerve roots and other vertebral tissues. This also leads to adoption of incorrect postures and gives rise to a set of adverse events such as ineffective survival strategies, anxiety, depression, diet, sleep and sedentariness, i.e. a set of factors that contribute to muscle and joint pain.[35-37]

Limitations

This study presents some limitations, given that it was based on interviews and, thus, response and memory bias may have occurred. Because of the cross-sectional nature of this study, it was not possible to know the random direction of the pain and mental problem variables. A longitudinal investigation would be required in order to resolve this issue: this was address by our research group through following up these students. Another limitation was that our students came from public schools, which limits the possibility for generalization of these data to students at private schools.

The strengths of this study were that this was one of the first Brazilian investigations to examine the role of factors relating to use of electronic and mental health equipment in the appearance of

cervical pain in young people; is use of a validated questionnaire to evaluate the results; and the large number of students interviewed.

CONCLUSIONS

Collectively, it was concluded that neck pain had high prevalence and striking associations with the following: female gender; length of use of a computer greater than three hours per day; use of a cell phone in a standing posture; use of a cell phone for more than three hours per day; use of a tablet for more than three hours per day; use of a tablet in a standing posture; use of a tablet in a sitting posture; and mental health problems.

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Diabetes and hypertension are associated with lowered cognitive performance among middle-aged Brazilian adults: cross-sectional analyses nested in the longitudinal Pró-Saúde study

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ABSTRACT

BACKGROUND: Cardiovascular risk factors are frequently associated with lowered cognitive performance among elderly people, but rarely among middle-aged adults.

OBJECTIVES: To investigate associations between cardiovascular risk factors (age, physical inactivity, smoking, alcohol use, hypertension and diabetes) and lower cognitive performance among middle-aged (45-64 years) Brazilian adults.

DESIGN AND SETTING: Cross-sectional study nested within the Pró-Saúde cohort. From 2,876 baseline study participants (1999), we randomly selected 488 participants and gave them validated and standardized cognitive tests (2012).

METHODS: We used multiple linear and logistic regression analyses to detect associations of cardiovascular risk factors with crude scores in cognitive tests on memory (word test) and executive function (verbal fluency tests), and with overall cognitive performance scores, respectively.

RESULTS: All cognitive test scores presented statistically significant inverse associations with age and direct associations with education. There was no association between lower cognitive performance and smoking or alcohol use. In both 1999 and 2012, after adjusting for sex, age and schooling, being physically active was inversely associated with lower performance regarding late memory. For individuals with diabetes in 1999, there was an association with lower performance regarding executive function, while there was a borderline association for those reporting it only in 2012. Having a diagnosis of hypertension since 1999 was associated with lower performance regarding both memory and executive functions, while reporting hypertension in 2012 was associated with lower performance regarding executive function.

CONCLUSIONS: Aging, low schooling and cardiovascular risk factors may represent life course disadvantages associated with cognitive decline even among middle-aged Brazilian adults.

INTRODUCTION

Cognitive dysfunction is a major disabling condition among elderly people, which becomes a heavy burden on families and society. From 1990 to 2016 worldwide, the number of individuals with dementia increased from 20.2 million (95% uncertainty interval, UI: 17.4-23.5) to 43.8 million (95% UI: 37.8-51.0), and this 117% increase can mainly be attributed to population growth and aging. Estimates have shown that Brazil had the second highest age-standardized prevalence of dementia (1,037 cases per 100,000 population; 95% UI: 882-1,220) in 2016.[1]

Cardiovascular risk factors are predictors for cognitive decline and dementia among the elderly.[2] Recently, hypertension and diabetes mellitus were shown to be directly associated with cognitive decline not only among elderly people but also in the middle-aged population in developed countries.[3-5] In Brazil, a cross-sectional analysis on around 15,000 Brazilian civil servants aged 35 to 74 years showed that there was a significant association between presence of diabetes and decreased performance both in memory and in executive functions.[6]

Over the last 30 years, although mortality due to cardiovascular diseases has been declining in Brazil, the prevalence of diabetes and hypertension has been rising, along with obesity.[7]

Life expectancy in Brazil has shown a steady increase from 68.4 years in 1990 to 75.2 years in 2016.[8] These changes are likely to have a profound societal impact in this country, which has

marked social inequalities and social and healthcare services that are insufficient to address the problems associated with an aging population.[9] It is likely that poor social conditions may be responsible for the premature onset and higher burden of dementia in Brazil.[9]

Brazil has high incidence of diabetes, hypertension and dementia. We hypothesized that cardiovascular risk factors, including hypertension and diabetes, might be associated with lowered cognitive performance, not only in the elderly but also among middle-aged adults in Brazil.

OBJECTIVE

We investigated the hypothesis that cardiovascular risk factors might be associated with lowered cognitive performance among middle-aged adults in Brazil. Our subjects were Brazilian civil servants participating in the Pró-Saúde study, a cohort study in Rio de Janeiro, Brazil, that had the goal of evaluating several dimensions of health-related determinants.[10]

METHODS

We conducted this cross-sectional study nested within the Pró-Saúde cohort.[10] From 2,876 participants involved in the baseline studies in 1999, a subsample was randomly selected from all strata: both sexes, two age groups (less than 50 years versus 50 years or over) and two educational levels (less than high school versus high school or more). There was no difference in clinical and sociodemographic characteristics between the participants in this study sample and those of the baseline population (data not shown).

In 2012, cognitive tests were given to 488 participants aged 35-64 years. We analyzed their cognitive performance according to sociodemographic characteristics (sex, age and schooling) and cardiovascular risk factors (smoking, physical inactivity, alcohol use and presence of diabetes and hypertension), which were investigated both in 1999 and in 2012. Since exposures can change over time, the presence of each risk factor was described as present only in 1999 or only in 2012, or present both in 1999 and in 2012. All participants with diabetes in 1999 confirmed that they still had the disease in 2012, and this analysis was therefore presented as cases described just in 2012 or in both 1999 and 2012. The other risk factors presented changes over the period. Thus, these were described as reported just in 1999 or just in 2012, or both in 1999 and in 2012.

We excluded 40 participants (8.8%) who reported having previously had a stroke or who reported use of drugs that can interfere with cognition: antipsychotics, anticonvulsants, antiparkinsonian drugs and anticholinesterase drugs. Cases of previous stroke were excluded based on self-reported morbidity within a medical diagnosis. All participants were told to bring their prescriptions and the packages of any drugs that they had been using during the preceding two weeks.[10]

A standardized questionnaire was applied to investigate whether the participants had smoked at least one hundred cigarettes during their lifetime and how many alcoholic beverages they had consumed over the preceding two weeks. Leisure-time physical activity was assessed via a dichotomous response (yes, no) regarding whether this had been practiced over the previous two weeks.[10] Hypertension was defined based on reported use of antihypertensive drugs and on systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.[11] Diabetes was defined through reported use of antidiabetic drugs and through fasting glucose level ≥ 126 mg/dl or glycated hemoglobin (HbA1C) level ≥ 6.5%.[12]

Age was classified into a reference category (35-44 years old) and two groups of middle-aged adults (45-54 and 55-64 years old).

We used the international standard classification to stratify education levels: incomplete elementary education (< 8 years); completed elementary education and incomplete secondary education (8-10 years); completed secondary education and incomplete tertiary education (11-14 years); or completed tertiary education (> 14 years).[13]

Validated and standardized cognitive tests to assess cognitive performance were administered in the same order, in a quiet room, by a trained interviewer.[14] These field researchers applied the cognitive tests after undergoing training consisting of eight hours of theory classes and another eight-hour training period with volunteers, followed by certification.

A word memory test was used to assess the participants' immediate memory (learning) by asking them to repeat ten unrelated words presented to them three times. Each word was presented for two seconds, in different orders. Memory recall was assessed by asking the participants to say the same ten words after they had completed other tests. Executive function was assessed by means of verbal fluency tests: 1) a semantic test in which the participants were asked to say as many names of animals as possible; and 2) a phonemic test, in which the participants were asked to say words starting with the letter F (phonemic test), for one minute. This battery of cognitive tests has been found to present moderate reliability for memory and good reliability for executive function.[15,16]

The participants were stratified into two age groups (< 40 and 40+) and four levels of education (< 8, 8-10, 11-14 and > 14 years of schooling), with the aim of enabling adjustments to the scores for associations with age and education. The mean and standard deviation (SD) of the scores from each cognitive test were calculated for each stratum. A composite z-score was calculated by adding the z-scores of the cognitive tests. A composite cognitive test z-score that was one or more SD below the average was considered to represent low cognitive performance.[17]

The statistical analyses were conducted using the STATA software, version 14.0 (Statacorp, College Station, Texas 77845, United States).[18] Multiple linear regression analysis was used to determine associations between sociodemographic variables and the crude scores of tests. Multiple logistic regression was used to examine associations between cardiovascular risk factors and lowered cognitive performance. Both the multivariate logistic model and the linear regression model were adjusted for sex, age and education.[19]

The Research Ethics Committee of the Institute of Social Medicine, Rio de Janeiro State University, approved the study protocol in October 2011, under the number 0041.0.259.000-11. All participants signed a written informed consent statement.

RESULTS

Among the participants, women were slightly predominant (51.8%). Most of the participants (56.9%) had had more than 14 years of schooling, and none of them had had less than 8 years of schooling. During the 13 years of follow-up, 18.6% and 2.1% of the participants developed hypertension and diabetes, respectively.

In univariate analysis, women performed better than men regarding learning (immediate memory). Older age, lower schooling level and presence of hypertension were significantly associated with worse performance in all cognitive tests, while diabetes was associated with worse performance in the phonemic verbal fluency test (**Table 1**).

Further analysis using linear regression showed that there were no or minimal differences in cognitive performance between the

Table 1. Descriptive analysis on cognitive performance according to participants' characteristics. Pró-Saúde study, Brazil, 2012

Variables	n	%	Learning	Recall	Semantic test	Phonemic test
			Median (interquartile interval)			
Sex						
Male	235	48.2	21 (18-24)	7 (6-8)	21 (16-25)	13 (11-16)
Female	253	51.8	22 (19-24)	7 (6-9)	19 (16-23)	13 (10.8-16)
			P = 0.004*	P = 0.049	P = 0.014	P = 0.661
Age group (years)						
35-44	100	20.5	23 (21-26)	8 (7-9)	21 (17-25)	14(11.8-16)
45-54	243	49.8	22 (19-24)	7 (6-8)	21 (16-25)	14 (11-17)
55-64	145	29.7	20 (17-23)	7 (5-8)	18 (14-21)	12 (9-15)
			P < 0.001	P < 0.001	P < 0.001	P < 0.001
Schooling (years)						
8-10	36	7.4	17.5 (16-20)	5 (4-6)	15 (13-20)	10.5 (8-15)
11-14	173	35.7	21 (18-23)	7 (6-8)	19 (15-22)	12 (9-15)
14+	276	56.9	23 (20-25)	8 (6-9)	21 (17-25)	14.0 (12-17)
			P < 0.001	P < 0.001	P < 0.001	P < 0.001
Smoking						
Never	280	62.4	22 (19-24.2)	7.5 (6-9)	20 (16-25)	13 (11-17)
1999	120	26.7	21 (18-23)	7 (6-8)	19.5 (16-23)	13 (10-16)
2012	1	0.2	24 (24-24)	9 (9-9)	25 (25-25)	21 (21-21)
1999 and 2012	48	10.7	20 (17-23)	6 (5-7.2)	18.5 (14.7-22)	12 (9.7-16)
			P = 0.002	P < 0.001	P = 0.048	P = 0.144
Alcohol use						
Never	130	27.7	22 (18-24)	7 (6-8)	19 (16-24)	14 (10.2-17)
1999	55	11.7	22 (19-24)	8 (6-8.8)	21.5 (17-24.8)	13 (10-17)
2012	59	12.5	22 (19-23)	7 (6-9)	19 (16-2.5)	13 (10-15)
1999 and 2012	226	48.1	22 (19-24)	7 (6-8)	20 (16-24)	13 (11-16)
			P = 0.793	P = 0.267	P = 0.312	P = 0.772
Physical activity						
Never	184	39.8	21 (18-24)	7 (5-8)	19 (15-22)	13 (9-15.5)
1999	84	18.3	22 (19-25)	7 (6-8)	21 (16-25)	13 (11-17)
2012	94	20.3	22.5 (19-25)	8 (7-9)	21 (17-24)	14 (11.2-17)
1999 and 2012	100	21.6	22 (19-23)	7 (6-8)	20 (17-25)	13 (11-17)
			P = 0.009	P = 0.002	P = 0.006	P = 0.033
Hypertension						
Never	244	56.1	22 (20-25)	8 (6-9)	20 (16-25)	14 (11-17)
1999	19	4.4	19 (16-23.5)	6 (4-8)	18 (15.5-19)	12 (10.5-13)
2012	81	18.6	21 (19-24)	7 (6-8)	21 (17-24)	13 (11-16)
1999 and 2012	91	20.9	21 (18-23)	7 (5-8)	18 (14-22)	12 (8-16)
			P = 0.002	P < 0.001	P < 0.001	P = 0.001
Diabetes						
Never	423	90.0	22 (19-24)	7 (6-8)	20 (16-24)	13 (11-17)
1999 and 2012	37	7.9	21 (17-23)	7 (5-8)	19 (14-22)	11 (9-14)
2012	10	2.1	19.5 (19-22)	7.5 (6-9)	17 (15.2-19.8)	10 (7-13.8)
			P = 0.112	P = 0.085	P = 0.183	P = 0.002

*P-value from Kruskal-Wallis rank sum test.

two sexes. The scores from all tests showed small decreases with increasing age and clear increases with higher levels of education. For example, the scores in the learning test decreased by 1.70 words (95% confidence interval, CI: -2.15 to -1.25) for every 10 years of aging; and by 4.82 words (95% CI: -6.01 to -3.63) in a comparison between 14+ years and 8-10 years of schooling. The analyses on the coefficient of determination (R^2) demonstrated that a higher level of education had a positive impact on cognitive test scores, such that they were raised by 8% to 14%. On the other hand, aging by 10 years had an inverse influence on cognitive test scores, such that they were lowered by 3% to 10% (**Table 2**).

The multiple logistic regression analysis showed that there was no statistically significant association between lowered cognitive performance and smoking or current alcohol use. After adjustments for sex, age and schooling, being physically active was found to be inversely associated with lowered cognitive performance in the recall memory test both in 1999 and in 2012 (odds ratio, OR = 0.29; 95% CI: 0.12-0.71). Both in 1999 and in 2012, reported diabetes was associated with worse performance in the phonemic verbal fluency test (OR = 5.81; 95% CI: 1.49-22.74), whereas among those with a first diagnosis in 2012, there was a borderline association with lower performance in the same test (OR = 1.88; 95% CI: 0.77-4.55). Both in 1999 and in 2012, reported hypertension was associated with lowered cognitive performance in the late memory test (recall, OR = 2.10; 95% CI: 1.07-4.13) and executive function test (phonemic test, OR = 3.16; 95% CI: 1.49-6.69). Among individuals with a diagnosis of hypertension in 2012, there was a significant association with lowered executive function (phonemic test, OR = 2.24; 95% CI: 1.01-4.98) (**Table 3**).

DISCUSSION

Our findings highlighted associations between lowered cognitive performance and age, schooling, physical activity, diabetes and hypertension among middle-aged Brazilian adults.

Cognitive decline is the result of long-term pathological processes that probably start around 45 years of age. Mild cognitive impairment or dementia becomes more prevalent among elderly people.[20] However, recent cohort studies have also shown cognitive dysfunctions among middle-aged adults.[3,21] Because the populations of Brazil and other low and middle-income countries (LMIC) are becoming older, the epidemic of dementia is expected to expand into these regions, where it remains understudied.[22]

The observed beneficial effect of physical activity on cognition was expected, given that several previous studies have documented its beneficial influence on brain function.[21] The small number of current smokers (10%) in this study may explain the absence of any association between smoking and cognitive performance.

Table 2. Associations (linear regression coefficients) between cognitive test scores and sociodemographic characteristics. Pró-Saúde study, Brazil, 2012

Cognitive tests	Coefficient (95% confidence interval)	R^2 [a]	Coefficient (95% confidence interval)	R^2
Learning				
Female[b]	0.94 (0.28 to 1.59)	0.01	1.05 (0.46 to 1.64)	0.20
Aging (10 years)	-1.70 (-2.15 to -1.25)	0.10	-1.17 (-1.62 to -0.71)	
11-14 years of schooling[c]	-1.95 (-2.6 to -1.29)	0.14	-1.6 (-2.25 to -0.95)	
8-10 years of schooling[c]	-4.82 (-6.01 to -3.63)		-3.8 (-5.03 to -2.58)	
Recall				
Female	0.28 (-0.06 to 0.61)	0.003	0.33 (0.02 to 0.64)	0.16
Aging (10 years)	-0.84 (-1.07 to -0.61)	0.09	-0.59 (-0.83 to -0.35)	
11-14 years of schooling	-0.8 (-1.14 to -0.46)	0.12	-0.62 (-0.96 to -0.98)	
8-10 years of schooling	-2.35 (-2.97 to -1.73)		-1.83 (-2.47 to -1.19)	
Semantic test (animals)				
Female	-1.32 (-2.33 to -0.31)	0.01	-1.16 (-2.10 to -0.22)	0.15
Aging (10 years)	-2.53 (-3.23 to -1.83)	0.09	-1.83 (-2.55 to -1.10)	
11-14 years of schooling	-3.05 (-4.08 to -2.01)	0.10	-2.46 (-3.49 to -1.43)	
8-10 years of schooling	-5.38 (-7.26 to -3.49)		-3.74 (-5.68 to -1.79)	
Phonemic test (letter F)				
Female	0.02 (-0.80 to 0.83)	-0.002	0.15 (-0.64 to 0.93)	0.08
Aging (10 years)	-1.16 (-1.74 to -0.58)	0.03	-0.64 (-1.24 to -0.03)	
11-14 years of schooling	-2.33 (-3.17 to -1.49)	0.08	-2.13 (-2.99 to -1.28)	
8-10 years of schooling	-3.6 (-5.13 to -2.07)		-3.04 (-4.66 to -1.42)	

[a]Adjusted R^2; [b]Male as a reference; [c]14+ years of school as a reference.
CI = confidence interval.

Our study corroborates the association that was found between presence of diabetes and lower cognitive performance among the participants of the Brazilian Longitudinal Study of Adult Health (Estudo Longitudinal de Saúde do Adulto, ELSA-Brasil), which also included civil servants at educational institutions and used the same battery of cognitive tests.[6] Moreover, in ELSA-Brasil, measurement invariance was analyzed via multiple-group confirmatory factor analysis: the findings suggested that differences in cognitive performance based on those tests indicated true differences.[23]

Lower cognitive performance is a plausible marker for chronic vascular diseases, given that diabetes and hypertension cause vascular damage and cognitive impairment. This association corroborates the vascular hypothesis of Alzheimer's disease, first proposed in 1993. This suggested that cardiovascular risk factors are likely to play a critical role in cognitive decline during aging.[2] Two recent reviews on the effects of diabetes and hypertension on cognitive performance have reinforced these associations.[24,25] Cardiovascular and carotid artery diseases can cause chronic brain hypoperfusion many years before any symptoms of cognitive impairment are seen.[2] Cognitive dysfunction in diabetes is associated with multiple disorders, such as chronic hyperglycemia, microvascular disease, altered sensorium, cortical atrophy and abnormalities in white matter tracts, along with abnormalities of brain metabolites.[20]

Other studies have also shown that education has greater influence on cognition than does age.[17,26] Although some cognitive tests that are less dependent on education have been proposed in Brazil, the Pró-Saúde study used international standardized tests that had been validated for use in Brazil, in order to be able to compare our results with those from other cohort studies around the world. Further studies are important for enabling better investigation of associations between the risks of cardiovascular diseases and cognitive performance among less educated people.

The strengths of this study include (a) its choice of an adult or middle-aged population from a middle-income country; and (b) its methodological rigor in data collection. However, the study limitations include its small sample and its cross-sectional design, which prevented us from making solid causal inferences between cognitive performance and the associated variables. Importantly, our analyses did not consider the length of time since the medical diagnosis of diabetes and hypertension had been made. Nor did it consider disease severity or successful disease control. Moreover, this study did not include cognitive tests on attention and mental speed. Given that diabetes is associated with mental and motor slowing, less severe cognitive decline may also be associated with these cognitive functions.[21]

CONCLUSIONS

Aging, low schooling level and cardiovascular risk factors may represent disadvantages over the course of life that operate through biological and social mechanisms and result in lowered cognitive performance and cognitive decline.[27] Since currently there are no effective disease-modifying cures or treatments for

Table 3. Association between lowered cognitive performance and cardiovascular risk factors. Pró-Saúde study, Brazil, 2012

Variables	Learning	Recall	Semantic test	Phonemic test
	Odds ratio (95% confidence interval)*			
Physical activity				
Never	1.0	1.0	1.0	1.0
1999	0.14 (0.04-0.42)	0.46 (0.22-0.95)	0.57 (0.27-1.22)	0.27 (0.11-0.71)
2012	0.86 (0.41-1.83)	0.29 (0.12-0.71)	0.61 (0.28-1.35)	0.48 (0.21-1.12)
1999 and 2012	0.82 (0.40-1.68)	0.71 (0.36-1.40)	0.80 (0.39-1.65)	0.71 (0.33-1.53)
Hypertension				
Never	1.0	1.0	1.0	1.0
1999	2.2 (0.71-6.83)	3.03 (1.00-9.22)	0.89 (0.26-3.09)	2.19 (0.6-7.91)
2012	0.99 (0.45-2.19)	1.37 (0.65-2.86)	0.56 (0.24-1.33)	2.24 (1.01-4.98)
1999 and 2012	0.92 (0.44-1.95)	2.10 (1.07-4.13)	1.21 (0.62-2.37)	3.16 (1.49-6.69)
Diabetes				
Never	1.0	1.0	1.0	1.0
1999 and 2012	0.40 (0.05-3.36)	0.78 (0.15-3.97)	0.34 (0.04-2.81)	5.81 (1.49-22.74)
2012	2.01 (0.88-4.58)	1.83 (0.83-4.07)	1.58 (0.67-3.71)	1.88 (0.77-4.55)

*After adjustment for sex, age and schooling.

the majority of the diseases that lead to dementia, prevention is crucial for decreasing the burden of dementia on patients and society.[1] Prevention should start early and be continued throughout the individual's life scan, as already recommended for other chronic diseases.

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The impact of the COVID-19 pandemic on emergency general surgery: a retrospective study

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ABSTRACT

BACKGROUND: The COVID-19 pandemic has affected healthcare systems worldwide. The effect of the pandemic on emergency general surgery patients remains unknown.

OBJECTIVE: To reveal the effects of the COVID-19 pandemic on mortality and morbidity among emergency general surgery cases.

DESIGN AND SETTING: Data on patients who were admitted to the emergency department of a tertiary hospital in Samsun, Turkey, and had consultations at the general surgery clinic were analyzed retrospectively.

METHODS: Our study included comparative analysis on two groups of patients who received emergency general surgery consultations in our hospital: during the COVID-19 pandemic period (Group 2); and on the same dates one year previously (Group 1).

RESULTS: There were 195 patients in Group 1 and 132 in Group 2 ($P < 0.001$). While 113 (58%) of the patients in Group 1 were women, only 58 (44%) were women in Group 2 ($P = 0.013$). Considering all types of diagnosis, there was no significant difference between the two groups ($P = 0.261$). The rates of abscess and delayed abdominal emergency diseases were higher in Group 2: one case (0.5%) versus ten cases (8%); $P < 0.001$. The morbidity rate was higher in Group 2 than in Group 1: three cases (1.5%) versus nine cases (7%); $P = 0.016$.

CONCLUSIONS: The COVID-19 pandemic has decreased the number of unnecessary nonemergency admissions to the emergency department, but has not delayed patients' urgent consultations. The pandemic has led surgeons to deal with more complicated cases and greater numbers of complications.

INTRODUCTION

The disease caused by the new coronavirus started in Wuhan, China, and has spread all over the world. It was named Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020.[1]

The COVID-19 pandemic has endangered health worldwide and has also threatened healthcare professionals. Elective interventions have been postponed around the world because of the COVID-19 pandemic, in order to make empty beds in the hospitals and intensive care units available for people suffering from the COVID-19 disease. However, it is not possible to delay emergency patients and emergency interventions.

Emergency cases are probably the most dangerous situation for healthcare workers, since it is unclear whether patients admitted to the emergency department carry COVID-19. People do not want to leave their homes and go to hospitals, for fear of the COVID-19 pandemic. This raises a number of questions: Are people coming late for admission to the emergency department because of the COVID-19 pandemic, even if they are sick? Does this lead surgeons to encounter more complicated and more difficult cases? Have the mortality and morbidity rates relating to emergency surgery performed during the COVID-19 pandemic period increased?

OBJECTIVE

Our aim in this study was to investigate the effects of the COVID-19 pandemic on emergency general surgery cases, through the characteristics of our clinical data.

METHODS

All the procedures performed in this study that involved human participants were conducted in accordance with the ethical standards of our institution's research ethics committee and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was conducted with approval from our hospital's ethics committee (approval number: 2020/366; approval date: June 15. 2020).

Our study included retrospective analysis on patients who received emergency general surgery consultation in our hospital during the COVID-19 pandemic period and on the same dates one year previously. The patients were divided into two groups. Group 1 included patients who were seen one year before the pandemic episode, between March 15, 2019, and May 15, 2019. Group 2 included patients who were seen between March 15, 2020 and May 15, 2020, i.e. during the COVID-19 pandemic period.

The patients' demographics, general findings (age and gender, etc.) and emergency diagnoses, and the results from those who underwent surgery (type of surgery, length of stay and complications, etc.) were recorded separately for Group 1 and Group 2. Differences between the groups were investigated.

The data were analyzed using the SPSS tools, version 18 (SPSS Inc., Chicago, IL, United States). We used descriptive statistics, chi-square tests and Mann-Whitney U tests to analyze the data. Statistical significance was accepted at $P < 0.05$.

RESULTS

There were 195 patients in Group 1 and 132 patients in Group 2 ($P < 0.001$; **Table 1**). While 82 patients (42%) in Group 1 were male and 113 (58%) were female, these proportions changed to 74 men (56%) and 58 women (44%) in Group 2. There was a significant difference between the groups in this regard ($P = 0.013$; **Table 1**). There was no difference in median age between the groups (53 years versus 50 years, respectively; $P = 0.177$).

There were no significant difference between the groups in terms of the following clinical characteristics: chronic diseases (diabetes mellitus, hypertension, coronary artery disease, etc., $P = 0.104$), time elapsed from the beginning of complaints to admission to the emergency department ($P = 0.933$), proportion of trauma patients ($P = 0.608$), rate of hospitalization with refusal of treatment ($P = 0.283$) and length of hospital stay ($P = 0.430$) (**Table 1**). In Group 2, four patients (3%) with a COVID-19 diagnosis or suspicion of this had consultations regarding emergency surgery.

The diagnoses of patients who had consultations regarding general surgery and the results from patients who underwent surgery are also shown in **Table 1**. In both groups, non-specific abdominal pain was diagnosed most frequently: 33 cases (17%) in Group 1 versus 31 cases (23.5%) in Group 2. When all types of diagnosis were considered, there was no significant difference between the two groups ($P = 0.261$).

While the rate of emergency general surgery (EGS) was 40 cases (30%) in Group 2, it was 41 cases (21%) in Group 1 ($P = 0.079$; **Table 1**). Although there was no statistical difference in this regard, the patients in Group 2 had a higher rate of surgery. The most common type of surgery in both groups was appendectomy: 18 cases (9%) versus 19 cases (14%), respectively. There was no difference in the variety of operations between the groups ($P = 0.441$; **Table 1**). The rates of abscesses and delayed abdominal emergency diseases were significantly higher in Group 2: one case (0.5%) versus ten cases (8%), respectively; $P < 0.001$. The mortality rates were similar between the groups, but the morbidity rate was significantly higher in Group 2 than in Group 1: three cases (1.5%) versus nine cases (7%); $P= 0.016$ (**Table 1**).

DISCUSSION

The COVID-19 pandemic has brought an ongoing situation that has spread around the world and is affecting people negatively. It has been reported globally that the pandemic has stressed healthcare systems and threatens the ability to provide patients with full and adequate care.[2]

We conducted this study in the light of changes to patients' tendencies for admission to the emergency department. Many articles have been published emphasizing the effects of the COVID-19 pandemic on many surgical procedures that would be performed either under elective or under emergency conditions and the precautions that should be taken.[2-8] However, during the COVID-19 pandemic period, when most elective surgeries were not being performed, no study has yet been conducted on how emergency applications are affected and how the pandemic has affected the morbidity and mortality of emergency surgeries. In this study, we wanted to discuss this.

When we evaluated the results from our own clinic, we found that the rate of consultation for general surgery for patients who had been admitted to the emergency department decreased significantly, as was predicted (132 patients versus 195 patients; $P < 0.001$; **Table 1**). Patients may have been afraid of acquiring COVID-19 and, hence, the number of admissions to the emergency department decreased. Moreover, the number of emergency consultations for general surgery likewise decreased.

The finding in **Table 1** to which attention is drawn is that the gender of the patients in Group 2 was significantly male. Women accounted for 58% (113) in Group 1, but only 44% (58) in Group 2 ($P = 0.013$). This result brings two things to mind: either women were afraid of the pandemic and did not come to the emergency room; or, in the pre-pandemic period, women kept the emergency services unnecessarily busy.

As seen in **Table 1**, there was no difference regarding the duration of complaints and the time of emergency admission ($P = 0.933$).

This makes us think that when people had real intractable pain, they sought admission to the emergency department irrespective of the pandemic. Considering the fact that more men were admitted to the emergency department during the pandemic period, this strengthens the idea that women had sought admission to the emergency department in the pre-pandemic period even though they did not have any emergency disease.

Although it was thought that people would not accept hospitalization during the COVID-19 pandemic period because they were afraid of this disease, there was no difference between the

Table 1. Demographics, general findings, diagnoses and results from patients who underwent surgery

	Group 1 (2019) [n (%)]	Group 2 (2020) [n (%)]	P
Total number of patients	**195**	**132**	**< 0.001**
Sex			
Male	82 (42)	74 (56)	**0.013**
Female	**113 (58)**	**58 (44)**	
Median age (with interquartile range), in years	53 (39)	50 (40)	0.177
Additional diseases*			
Yes	105 (53.8)	59 (44.7)	0.104
No	90 (46.2)	73 (55.3)	
Time between the onset of complaints and admission to the emergency room**			
Time period < 24 hours	91 (46.9)	61 (46.2)	0.933
Time period ≥ 24 hours and < 48 hours	36 (18.6)	23 (17.4)	
Time period ≥ 48 hours	67 (34.5)	48 (36.4)	
Traumatized			
Yes	16 (8.2)	13 (9.8)	0.608
No	179 (91.8)	119 (90.2)	
COVID-19-positive or suspected case	-	4 (3)	**0.014**
Refusal to accept hospitalization or treatment	20 (10.3)	9 (6.8)	0.283
Length of stay in the hospital, [median (with interquartile range)], in days	4.50 (7)	6.00 (8)	0.430
Patient diagnoses			
Nonspecific abdominal pain	33 (17)	31 (23.5)	
Acute appendicitis	21 (11)	21 (16)	
Acute hepatobiliary infections***	27 (14)	14 (11)	
Acute mesenteric ischemia	5 (2.5)	3 (2)	0.261
GIS perforations	7 (3.5)	3 (2)	
Intestinal obstructions	25 (13)	8 (6)	
GIS bleeding	6 (3)	2 (1.5)	
Other diagnoses	71 (36)	50 (38)	
Emergency general surgery	**41 (21)**	**40 (30)**	0.079
Types of surgery			
Appendectomy	18 (9)	19 (14)	
Colon or small bowel resection	4 (2)	10 (8)	
Hartman procedure	1 (0.5)	1 (0.8)	
Bridectomy	1 (0.5)	1 (0.8)	
Stoma creation	2 (1)	1 (0.8)	0.441
Primary repair for GIS perforation	3 (1.5)	1 (0.8)	
Total gastrectomy	1 (0.5)	1 (0.8)	
Herniography	6 (3)	2 (1.5)	
Diagnostic laparotomy	1 (0.5)	2 (1.5)	
Others	4 (2)	2 (1.5)	
Abscessed or delayed cases	**1 (0.5)**	**10 (8)**	**< 0.001**
Mortality	6 (3.1)	4 (3.0)	0.625
Morbidity	**3 (1.5)**	**9 (7)**	**0.016**

*Diabetes mellitus, hypertension, coronary artery disease, chronic kidney failure etc.; **The time between the onset of the patient's complaints and his presentation to the emergency room; ***Acute cholecystitis, acute pancreatitis, acute cholangitis etc.; GIS = gastrointestinal system.

two groups in our results (P = 0.283; **Table 1**). Again, only four patients (3%) in Group 2 were COVID-19-positive or were suspected cases. This very low rate suggested that the healthcare workers dealing with the emergency patients did not need to be overly anxious about COVID-19.

Lima et al. suggested that, among patients admitted to the emergency department with acute abdomen, if they undergo abdominal computed tomography (CT), chest CT should be added even if there is no respiratory complaint.[9] We therefore requested chest CT for all our patients who would undergo emergency surgery. However, the low number of COVID-19-positive or suspected cases among our patients showed that it was wrong for us to perform chest CT on all patients. Consequently, in our opinion, it is unnecessary to have chest CT for all patients.

The diagnoses among the patients who had consultations for general surgery were similar in Group 1 and Group 2 (P = 0.261; **Table 1**). Nonspecific abdominal pain was diagnosed most frequently in both groups: Group 1, 33 cases (17%); Group 2, 31 cases (23.5%) (**Table 1**). There was no significant difference between the rates of patients undergoing emergency surgery, but the operation rate among the patients in Group 2 was higher than among those in Group 1: Group 1, 41 cases (21%); Group 2, 40 cases (30%); P = 0.079 (**Table 1**).

Fewer patients were admitted to the emergency department during the COVİD-19 pandemic, but a higher proportion then underwent surgery. This result supports the idea that some of the patients admitted to the emergency department before the pandemic were not really emergencies.

During the pandemic, many things have changed regarding the approach to emergency general surgery patients. Suggestions such as applying laparotomy instead of laparoscopy and treating acute appendicitis with antibiotic therapy instead of surgery if no perforation is presented were added to the algorithms.[10,11] Our appendectomy rates did not decrease during the pandemic period (Group 2), as seen in **Table 1**, because the new directive to treat acute appendicitis with antibiotics was implemented only after the period studied here. Because we will change our algorithm from now on, our appendectomy rate will decrease.

The rates of intra-abdominal abscesses and delayed emergency surgical cases were found to be significantly higher in Group 2: one case (0.5%) versus ten cases (8%), respectively; P < 0.001. Considering that there was no difference between the two groups in terms of the time between the onset of patients' complaints and their admission to the hospital, delays in making diagnoses may have been due to the time-consuming evaluations that physicians and surgeons undertook in the initial period of the pandemic. Di Saverio et al. suggested that all emergency general surgery patients should be tested for COVID-19, but that the testing process should not delay emergency surgery.[12]

Through having thoracic tomography performed on all our patients who would undergo emergency surgery, we may have lost time for these patients and may have consequently encountered cases that were more complicated. We performed various examinations, especially thoracic computed tomography scans, to ascertain whether any of our patients undergoing emergency surgery had COVID-19. This was a self-protection reflex to guard against this disease, but the time loss in making the diagnosis may have led to greater complications among these cases. Given that many surrounding hospitals have been serving as pandemic hospitals, patients in these hospitals have not been undergoing operations. Cases requiring urgent surgical intervention are directed to tertiary-level hospitals like ours. This may therefore have caused delays in operations for these patients.

While the mortality rate seen among cases of emergency laparotomy is 14-20% in the literature,[13] our mortality rates were lower and our two groups had similar rates: Group 1, six cases (3.1%); Group 2, four cases (3%) (**Table 1**). However, our morbidity rates were significantly higher during the pandemic period. This may have related to delayed diagnoses or delayed operations: three cases (1.5%) versus seven cases (7%) (P = 0.016).

During the COVID-19 pandemic, one of our patients died due to this disease. Also during the pandemic period, one surgeon and one nurse working in our clinic were diagnosed with COVID-19 and were treated in our hospital. COVID-19 poses a great risk to healthcare professionals, given that it is a disease that has not yet been fully identified and for which no cure is yet available. This inevitably worries all healthcare professionals, including surgeons. In particular, it may cause delays in making diagnoses and treating emergency surgical patients among whom it is not certain whether they might have COVID-19.

Our study has some shortcomings. We were unable to add the durations of the operations into our study data because these were not recorded. If they had been recorded, some differences between the groups might have been seen. Again, it should be kept in mind that we may have encountered more complicated cases because our hospital is a tertiary-level hospital.

The strength of our study is that it was the first to investigate the effects of the COVID-19 pandemic on emergency general surgery.

CONCLUSION

The COVID-19 pandemic has had the result of decreasing the number of unnecessary nonemergency admissions to our emergency department, but it has not delayed urgent consultations for emergency cases. In our opinion, the processes of making diagnoses and undertaking emergency surgery on patients have been negatively affected by the COVID-19 pandemic period. The pandemic has led surgeons to deal with more complicated cases and greater numbers of complications.

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Long-term results from modified sphincteroplasty in patients with traumatic sphincter injury: a retrospective study

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Surgery [subheading].

AUTHORS' KEY WORDS:
Anal sphincter.
Anal incontinence.
Sphincteroplasty.

ABSTRACT

BACKGROUND: The results from sphincteroplasty may worsen over time. Reseparation of the rectum and vagina/scrotum in conjunction with sphincteroplasty achieves good results. Improving the surgical effect of sphincteroplasty through perineal body reconstruction is crucial.

OBJECTIVE: To evaluate the long-term results from anterior sphincteroplasty and perineal body reconstruction (modified sphincteroplasty) among patients with traumatic sphincter injury.

DESIGN AND SETTING: Retrospective study among patients who underwent modified sphincteroplasty in a university hospital between January 2006 and December 2018. Fifty patients were evaluated in detail.

METHODS: The following variables were evaluated: gender, age, additional disease status, time interval between trauma and surgery, surgical technique, duration of hospitalization, follow-up period after surgery, manometric values, electromyography results, magnetic resonance imaging scans, Wexner scores, satisfaction levels with surgery and surgical outcomes.

RESULTS: The patients' mean age was 44.6 ± 15.1 years. The median follow-up period was 62 months (range, 12-118). The mean Wexner scores preoperatively, postoperatively in first month (M1S) and at the time of this report (AAS) were 15.5 ± 3.2, 1.9 ± 3.15 and 3.9 ± 5.3, respectively. Although improvements in the patients' mean Wexner scores became impaired over time, the postoperative Wexner scores were still significantly better than the preoperative Wexner scores (P = 0.001).

CONCLUSION: Good or excellent results were obtained surgically among patients with traumatic sphincter injury. Performing perineal body reconstruction in addition to sphincteroplasty can provide better long-term continence. Surgical outcomes were found to be better, especially among patients younger than 50 years of age and among patients who underwent surgery within the first five years after trauma.

INTRODUCTION

Continence is one of the main factors that determine the quality of life.[1] Pelvic muscle groups, sphincter function, nervous system, rectal compliance, fecal contents and cognitive functions act towards maintaining continence.[2] Fecal or anal incontinence (AI) may be defined as involuntary leakage of rectal contents or inability to delay defecation until an appropriate time.[1] Incontinence causes social and psychological problems as well as medical and economic effects, adversely affects the quality of life and is generally kept secret by the patients.[3-6]

Although sphincter structure is preserved in non-traumatic situations such as diabetes mellitus and neurological disease, structural loss or weakness in the sphincters usually occurs through traumatic conditions such as anorectal surgeries, obstetric injuries and traumas[2,4,7-11]

Many surgical and non-surgical methods with different success rates may be preferred in treatments for AI. According to the severity of the complaints and the development mechanisms of the disease, AI can be managed conservatively through diet, antidiarrheal medicine and biofeedback.[4] Surgical treatment is usually performed, when the anal sphincter has an anatomical defect or when conservative treatment is not successful.[12,13] The success rates of various surgical techniques range from 25% to 90%.[14,15] There is no consensus on which method is most effective for treating traumatic sphincter injury.[8]

Sphincteroplasty is the commonly preferred surgical treatment among the surgical options.[14,15] It has the considerable advantage that it does not require any purchase of additional equipment or any cost.[1,4,16,17] However, the results obtained from sphincteroplasty may become impaired over time. The patient's age, cause of the injury, timing of surgery, timing of postoperative assessment and variation in surgical techniques are among the factors that may affect the success of

sphincteroplasty.[4,5,9,12,18] Reseparation of the rectum and the vagina/scrotum in conjunction with sphincteroplasty achieves good results, and performing perineal body reconstruction in addition to sphincteroplasty can provide better long-term continence.[19]

OBJECTIVE

In this study, we aimed to evaluate the long-term results from anterior sphincteroplasty and perineal body reconstruction (modified sphincteroplasty) among patients with traumatic sphincter injuries.

METHODS

This study was approved by our university's local ethics committee (number: 2018/203). Seventy-four surgical patients with AI who were seen between January 2006 and December 2018 were evaluated retrospectively. Patients older than 65 years of age with poor health status (n = 4), patients with past surgical history due to AI (n = 2), patients with multiple sphincter injuries (n = 3), patients with inflammatory bowel disease (n = 3), patients with neurological disease (n = 7), patients with diabetes mellitus (n = 2) and patients with lack of data (n = 7) were excluded from the study. A total of 50 patients who underwent modified sphincteroplasty were evaluated in detail.

The sphincter defect was evaluated preoperatively by means of pelvic magnetic resonance imaging (MRI), in all patients. Early reconstruction was defined as 'surgery performed within 14 days after the trauma'. A preoperative evaluation using anal manometry and anal electromyography (EMG) was performed in the cases of patients without early reconstruction. Patients with AI following vaginal delivery had grade 3 injuries (involving partial or complete disruption of the anal sphincter complex, i.e. including the external anal sphincter and the internal anal sphincter) and grade 4 injuries (involving disruption of the anal mucosa in addition to the sphincter complex).[20]

The patients' AI scores were evaluated using the Cleveland Clinic Florida Incontinence Scoring Scale (Wexner score) preoperatively, postoperatively in the first month (M1S) and at the time of this report (AAS). The assessment comprised five items: frequency of AI (for solid, liquid and gas components), wearing of pads and lifestyle alteration due to AI.[21] The total score (range: 0-20) was calculated by summing the '0-4' points for each parameter (0 points for complete continence and 20 points for complete incontinence, according to the Wexner score).

In addition, the patients' satisfaction was evaluated using the Cleveland Clinical Quality of Life Score, on a scale of 1-10 points (1 point, 'lowest' satisfaction score of patient; 10 points, 'highest' satisfaction score relating to surgery).

The outcome was classified as excellent (full continence), good (incontinence in relation to flatus or sporadic loss of liquid stool was encountered postoperatively, after less than one month); moderate (incontinence was regularly experienced in relation to liquid/solid stools, but incontinence episodes were reduced by 50% or more postoperatively); or poor (persistent AI with less than 50% reduction of incontinence episodes postoperatively).[15] All the data were obtained using medical record and interviews.

Intervention techniques

Bowel preparation and urinary drainage with a catheter were not routinely performed. Antibiotic prophylaxis was administered, consisting of 1 g of cefazolin and 500 mg of metronidazole. The operations were performed in the lithotomy position by the same surgical team (TC, MOT). The final aim of the surgery was to perform reconstruction of the pelvic floor for continence (**Figure 1**).

Anterior sphincteroplasty was performed under direct vision. A curvilinear incision was made in the perianal area and the dissection was completed with preservation of the rectal wall. Both sides of the puborectalis muscles were dissected until the mesorectum tissue appeared. We attempted to preserve the pudendal nerves by avoiding excessive dissection laterally. Subsequently, bulbospongiosus muscles were introduced and the tissue layers (puborectalis muscles, external sphincter muscles, internal anal sphincter muscles and mucosa) were sutured at the midline, from deep to superficial, using 2-0 delayed absorbable polyglactin suture material (Vicryl, Ethicon Inc, NJ, United States) (**Figure 2**).

The external anal sphincters were mainly reconstructed using an overlapping technique (**Figure 3**). In most cases, overlapping sphincter reconstruction was performed by attempting to preserve muscle mass without removing the fibrotic area at the median line. Lastly, the bulbospongiosus muscles were reconstructed, and the posterior part of the bulbospongiosus muscles, median edge of the transverse perineal muscles, anterior part of the puborectalis muscles and anterior part of the external anal sphincter muscles were combined in the anterior

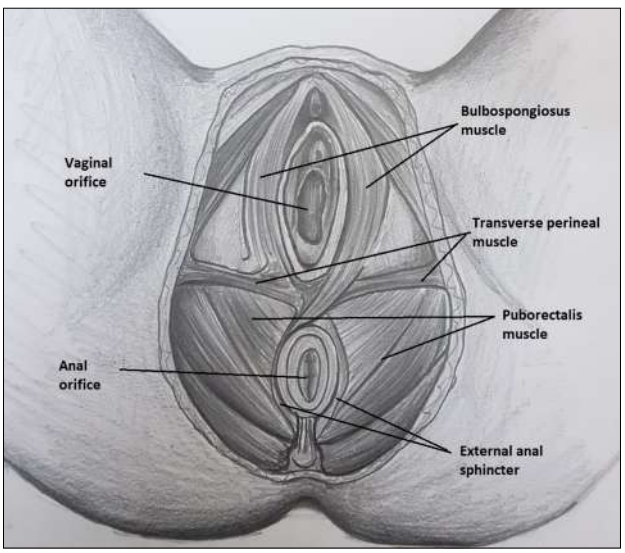


Figure 1. The final aim of reconstruction to obtain continence.

part to reconstruct the perineal body (**Figure 4**). We aimed to create a circular muscle mass around the anal canal. Surgical drains were not used routinely (**Figure 5**). According to the status of the perineal injury, a temporary stoma was provided for fecal diversion.

The patients were discharged from the hospital after bowel movements had become reestablished. They were evaluated post-operatively after the first week, first month, third month, sixth month, first year and at the time of making the current report.

Statistical analysis

The patients were evaluated regarding gender, age, additional disease status, time interval between trauma and surgery, surgical technique, duration of hospitalization, follow-up period after surgery, manometric values, EMG results, MRI scans, Wexner scores, satisfaction levels with surgery and surgical outcomes. Variables were presented as percentages (%), means ± standard deviations (SD) and medians (minimum-maximum). Categorical variables were evaluated using the chi-square test. Continuous variables were assessed using one-way ANOVA. Groups were

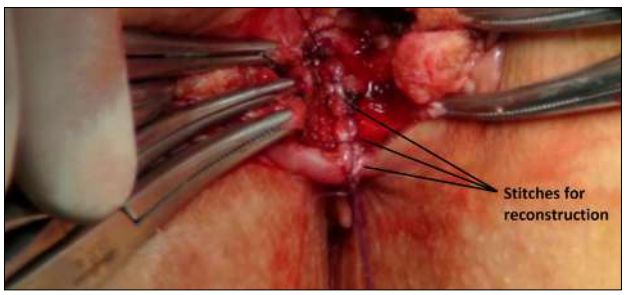


Figure 2. Reconstruction of sphincter muscles in patient with traumatic sphincter injury.

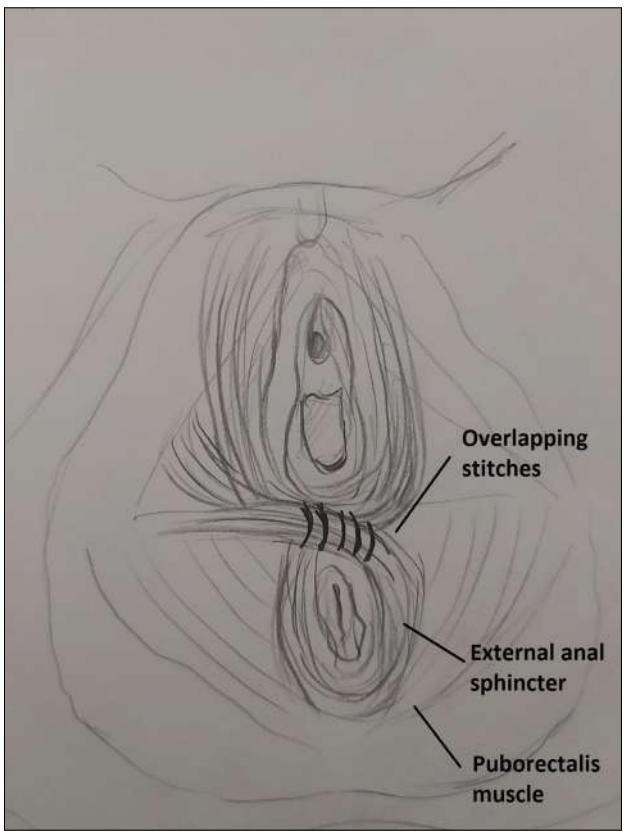
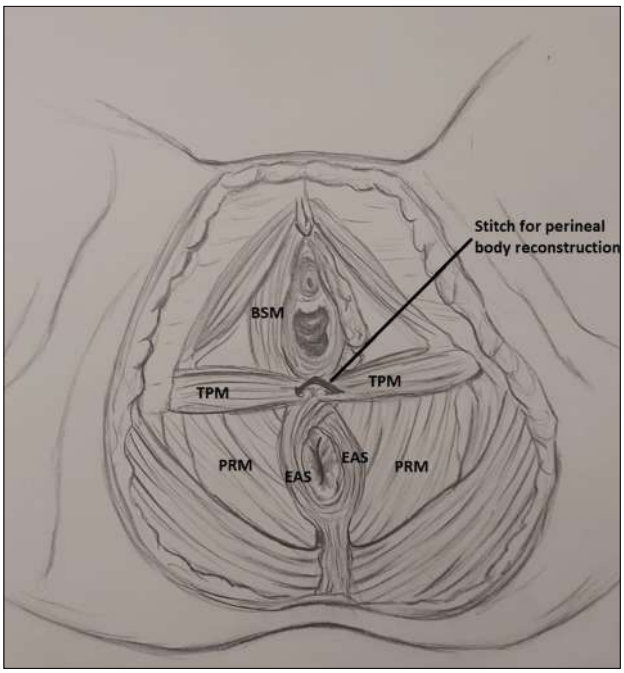


Figure 3. Illustration of overlapping sphincteroplasty.



BSM = bulbospongiosus muscle; TPM = transverse perineal muscle; PRM = puborectalis muscle; EAS = external anal sphincter muscle.

Figure 4. Reconstruction of perineal body with stitch.

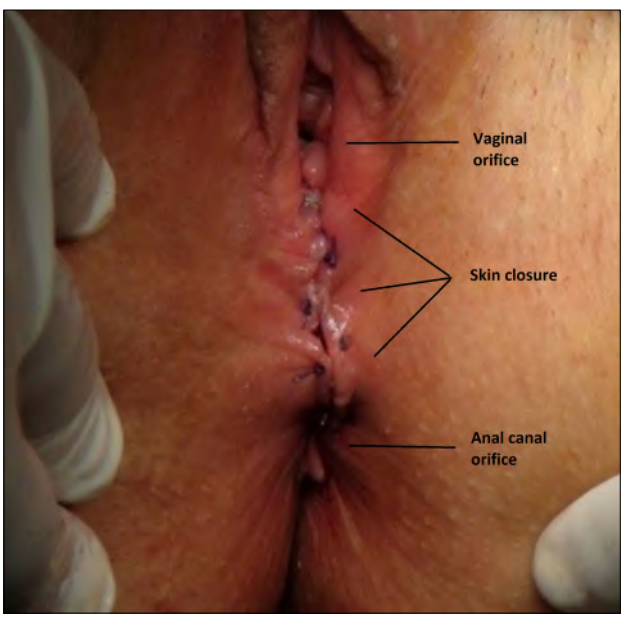


Figure 5. Final view: reseparation of rectum and vagina.

compared using the chi-square test or Mann-Whitney U test. Wexner scores were compared between different time points by means of ANOVA. The statistical analysis was performed using the SPSS 15.0 software (SPSS, Chicago, IL, United States) and $P < 0.05$ was considered statistically significant.

RESULTS

Out of the total of 50 patients evaluated in our study (**Table 1**), most of them were women (72%). The major cause of traumatic sphincter injury was vaginal delivery (54%) in this study.

All the patients underwent modified sphincteroplasty; overlapping sphincteroplasty was performed in the majority of the cases (82%). Eight patients with perineal injuries following traffic accidents and other blunt trauma underwent simultaneous modified sphincteroplasty and fecal diversion with loop colostomy. The mean duration of closure of the stoma was 9.5 ± 2.8 months. The mean duration of hospitalization was 4.0 ± 4.6 days, and no mortality was detected. Eleven patients developed postoperative wound infection and four patients had wound dehiscence. No patient underwent additional surgery for postoperative wound complications. The median follow-up period was 62 months (range: 12-118).

Manometric measurements were obtained from 54% of the patients (n = 27), both preoperatively and postoperatively. The preoperative measured mean resting pressure became elevated in the postoperative period (respectively, 52.11 ± 17.55 cmH_2O and 57.37 ± 16.26 cmH_2O; P = 0.2585). The preoperative measured mean squeeze pressure also became elevated in the postoperative period (respectively, 93.63 ± 33.56 cmH_2O and 113 ± 35.03 cmH_2O; P = 0.037).

The mean preoperative Wexner score was higher than the mean M1S Wexner score and mean AAS Wexner score. Although the improvement in mean Wexner score decreased over time, it was still better than the preoperative values (preoperative versus M1S, $P < 0.001$; preoperative versus AAS, $P < 0.001$; M1S versus AAS, P = 0.024).

Among the 50 patients evaluated here, 32 (64%) were younger than 50 years of age. There was a statistically significant difference in mean AAS Wexner score between the age groups (younger or older than 50 years), and improvements in mean AAS Wexner score were obtained among the patients younger than 50 years of age (P = 0.024).

Out of 36 patients who were operated within the first five years after their sphincter injury, 16 patients underwent early reconstruction. Although there was no statistically significant difference in AAS Wexner score for patients who underwent early reconstruction, statistically significant better results were obtained among the patients who underwent surgery within first five years after the trauma (P = 0.031).

Continence of gases, fluids and solids was achieved at M1S, respectively in 72% (n = 36), 86% (n = 43) and 92% (n = 46) of the patients after the modified sphincteroplasty. However, the continence rates for gases, fluids among these patients at AAS were, respectively, 64% (n = 32), 74% (n = 37) and 84% (n = 42). The postoperative improvement in continence status remained stable in 36 patients during the follow-up period, while the continence status of the other 14 patients deteriorated to varying degrees over time. Good or excellent continence was obtained in 84% of patients at AAS.

There was no statistically significant difference in AAS Wexner score or in patients' satisfaction with surgery, between the overlapping and end-to-end modified sphincteroplasty groups ($P > 0.05$ for both). The mean score regarding satisfaction with surgery was 8.1 ± 2.5. Although satisfaction with surgery was perfect (10 points) in 42% of the patients (n = 21), the level of satisfaction with surgery was below 5 points in 10% of the patients (n = 5). Lower AAS Wexner scores correlated with greater satisfaction with surgery.

DISCUSSION

All the patients in this study presented traumatic anal sphincter injury. Modified sphincteroplasty was performed in all cases, and the levels of satisfaction with surgery remained high over the long term. Incontinence scores were lower among patients younger than 50 years of age and among patients who underwent surgery within the first five years after the trauma.

Incontinence is a symptom of varying severity that can range from mild leakage of gas to complete loss of fecal control. It has been reported that its prevalence generally ranges from 1% to 21%,

Table 1. Results from the patients and surgery

	n (%)	Mean ± standard deviation (SD)
Sex		
Women	36 (72)	
Men	14 (28)	
Etiology		
Vaginal delivery	27 (54)	
Anorectal surgery	12 (24)	
Nonsurgical trauma (any other trauma or abuse)	11 (22)	
Surgery		
Overlapping sphincteroplasty	41 (82)	
End-to-end sphincteroplasty	9 (18)	
Surgery		
Early reconstruction (within 14 days)	16 (32)	
Elective surgery	34 (68)	
Mean age		44.6 ± 15.1 years
Interval between injury and surgery		5.6 ± 8.2 years
Mean Wexner score		
Preoperative		15.5 ± 3.2
First postoperative month		1.92 ± 3.15
At the time of this report		3.9 ± 5.3

although it is seen more frequently among individuals over the age of 65 years.[2] Different incidence rates may be associated with variations in the definition of "incontinence". 'Anorectal incontinence', 'AI' and 'fecal incontinence' may be used to describe incontinence.[2,4,7-9] While uncontrolled leakage of gases and stools is defined as AI,[4] fecal incontinence usually describes leakage of stools.[8] Diarrhea, neurological diseases, surgical or obstetrical trauma and advanced age are among the causes of AI.[7] Primary incontinence may be seen as a result of congenital diseases, and secondary incontinence may be seen in acquired cases.[2]

The most common etiological reason for referrals to colorectal surgeons is traumatic sphincter injury, among the many different cases. It is crucial to obtain detailed anamnesis of each case. However, it needs to be borne in mind that some patients may tend to respond incorrectly during questioning to obtain the detailed past medical history.

During the physical examination, the perineal region and anoderm is evaluated for any tears or leakage. Detailed evaluation is crucial for differentiating leakage from AI in diseases such as rectal prolapsus.[12,15-17] It is important to recognize the type, frequency and extent of AI. Scoring systems have been developed for evaluation of AI. One of the most widely used scales is the Wexner scoring system.[21] All of the patients in the present study presented acquired traumatic sphincter injuries, and the Wexner scoring systems were used for assessment of AI at different times among these patients.

Diagnostic endoanal ultrasonography (USG), anorectal manometry, pudendal nerve evaluation, EMG, defecography and colonoscopy may be performed.[2] Predictions from preoperative manometric measurements may yield conflicting outcomes.[9,18,22] In manometric measurements made in the present study, there was no significant postoperative result regarding the mean resting pressure, which was more related to internal anal sphincters. Statistically significant results were obtained with regard to mean squeeze pressures postoperatively, which were associated with external sphincter functions and voluntary contraction.

MRI identifies the structure of the external anal sphincters and puborectalis muscles, and also the pelvic floor structure.[13] We mainly used MRI for our evaluations; USG is valuable but technically difficult, especially among patients with severe trauma in the early period.

Biofeedback, dietary recommendations, regulation of medications, arrangement of fibers and use of medical drugs can reduce the symptoms of AI.[2,17] Sphincteroplasty is one of the most preferred treatments, especially among patients with anatomical sphincter defects after trauma.[3-5,17,23] Especially among patients with traumatic sphincter injury, anterior sphincteroplasty may reduce their complaints, and the overlapping technique should be the first surgical option among different forms of sphincteroplasty.[2,12,15-17]

Artificial sphincter applications, sacral nerve stimulation, graciloplasty, anal encircling methods, tibial nerve stimulation, Secca® procedure (Curon Medical, Inc., Fremont, CA, United States), gluteoplasty and antegrade enema applications are other surgical treatment options in addition to sphincteroplasty.[4,5,17] However, it should be noted that most of these methods are expensive due to their use of additional implants during the procedure.[4] The short-term success rates of different types of treatment have been reported to range from 31% to 83%.[4,16,17]

Over long-term follow-up, decreasing success rates have previously been reported.[1,17] Sphincteroplasty has been reported to yield short-term improvement (68-74%) in AI, but the success rate may decline to 0-50% over time.[1,4,12,16,24] Damage to the distal branches of the pudendal nerve during surgery, variation in surgical technique, suture breakage and muscle denervation with age are some of the possible causes of this deterioration over the long term.[16,25]

Despite this deterioration of continence, patients may feel satisfied with their surgical outcomes and quality of life.[17] Lehto et al. reported improvement in both fecal incontinence and quality of life among patients in all age groups after sphincteroplasty.[22] However younger patients (< 50 years old) had better surgical outcomes than older ones.[9,15,22] In the present study, the postoperative mean AAS Wexner score of younger patients (18-50 years old) was also significantly better than those of patients older than 50 years ($P = 0.024$).

Some studies have pointed out that biofeedback treatment or reoperation might be useful for preserving the good results.[16,25,26] Modified sphincteroplasty was performed on all patients in this study. Significant improvement in continence was observed in most of the patients during the long follow-up period (median of 62 months; range, 12-118 months). Similar or worse outcomes after sphincteroplasty were reported in some other studies with long follow-up periods (60 months or longer).[4,12,17,24] It was considered that the possible reasons for a successful outcome in the present study may have related to the surgical technique and the patient group selected, such as those with traumatic sphincter injury.

In the present study, overlapping sphincteroplasty was performed in the majority of cases (82%). Perineal body reconstruction was performed in all cases and lateral dissection was limited during the surgery. According to our experience, strengthening of all the available functional muscles, restoration of normal anatomy and reseparation of the rectum and vagina/scrotum in conjunction with use of modified sphincteroplasty increased the success rate. It has been emphasized that, especially in cases of high-grade obstetric injuries, reconstruction should be performed by an expert and specialist team during the early period.[20] In the present study, modified sphincteroplasty was performed always by same expert

surgical team. Although better results were not obtained among patients who underwent early reconstruction (P = 0.308), patients who underwent modified sphincteroplasty within five years after the trauma had better results than did those whose surgery was performed later.

There are some limitations to our study. Firstly, this was a retrospective study, and endoanal USG and manometry data were not obtained in all cases. Secondly, the results were not compared among the etiological subgroups in detail because of the small sample size. On the other hand, the study population was homogenous and long-term follow-up was obtained.

CONCLUSION

Good or excellent results were obtained through use of modified sphincteroplasty, especially in treating traumatic sphincter injury. The surgical outcomes were found to be better among patients younger than 50 years of age and among patients who underwent surgery within the first five years after their trauma. It is crucial to recognize patients with AI and to direct them to centers with reconstruction experience, without delay. Lastly, perineal body reconstruction may provide long-term preservation of improvement when combined with anterior sphincteroplasty, among patients with traumatic AI.

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Experience of 2003 SARS has a negative psychological impact on healthcare workers in the COVID-19 pandemic: a cross-sectional study

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Severe acute respiratory syndrome.
Occupational stress.
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Pandemics.

AUTHORS' KEY WORDS:
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Highly infectious disease.
Total stress scores.
Subscale.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has instilled fear and stress among healthcare workers.

OBJECTIVES: The aim of this study was to assess work stress and associated factors among healthcare workers during the COVID-19 outbreak and to evaluate whether prior experience of treating severe acute respiratory syndrome (SARS) had a positive or negative influence on healthcare workers' stress levels during the COVID-19 pandemic.

DESIGN AND SETTING: Cross-sectional survey in a tertiary hospital in Kaohsiung City, in southern Taiwan.

METHODS: The survey was conducted using an online self-administered questionnaire to measure the stress levels among healthcare workers from March 20 to April 20, 2020. The stress scales were divided into four subscales: worry of social isolation; discomfort caused by the protective equipment; difficulties and anxiety regarding infection control; and workload of caring for patients.

RESULTS: The total stress scores were significantly higher among healthcare workers who were aged 41 or above, female, married, parents and nurses. Those with experience of treating SARS reported having significantly higher stress scores on the subscale measuring the discomfort caused by protective equipment and the workload of caring for patients. During the COVID-19 outbreak, frontline healthcare workers with experience of treating SARS indicated having higher stress levels regarding the workload of caring for patients than did non-frontline healthcare workers with no experience of treating SARS.

CONCLUSIONS: Work experience from dealing with the 2003 SARS virus may have had a negative psychological impact on healthcare workers amidst the COVID-19 outbreak.

INTRODUCTION

Infectious disease outbreaks are always important issues that need to be to learned from, tackled and prevented. The coronavirus disease 2019 (COVID-19), a novel virus causing pneumonia that was first reported in Wuhan, China, is spreading locally and internationally. According to a report from the World Health Organization (WHO),[1] over three million people around the world were confirmed to have COVID-19 between December 2019 and April 30, 2020, and approximately 217,000 of them died, which resulted in a mortality rate of approximately 7%.

Symptoms of COVID-19 appear within about 2 to 14 days after infection with the virus, and the disease progresses rapidly from an asymptomatic state or mild symptoms to severe symptoms. COVID-19 is highly transmissible between humans, is associated with high morbidity rates, and may potentially lead to fatality. This instills fear not only among the public but also among healthcare workers. Moreover, healthcare workers involved in diagnosis, treatment and care of patients with COVID-19 are at greater risk of contracting the disease. Therefore, they may have a higher possibility of developing psychological distress and other mental health symptoms.

COVID-19 is similar to the severe acute respiratory syndrome (SARS) that first infected humans in the Guangdong province of China in November 2002 and quickly spread throughout several parts of the world from 2002 to 2003. The SARS outbreak affected 26 countries and resulted in more than 8,000 cases in 2003.[2]

Taiwan was unable to remain free from SARS and the first case of this disease appeared on March 10, 2003. It then spread to multiple regions of Taiwan. Between March and June 2003, there were 346 cases of SARS in Taiwan.[3] This outbreak in 2003 not only caused extraordinary public health concerns but also led to tremendous psychological distress, particularly among healthcare workers.

These workers suffered from acute stress disorders;[4] feared contagion and infection of their families, friends and colleagues with the SARS virus; and felt stigmatized and rejected in their neighborhoods because of their hospital work.[4] Furthermore, these healthcare workers reported feeling reluctance to work or had considered resigning.[4,5] In addition, healthcare workers who cared for SARS patients but did not become infected continued to experience substantial psychological distress, even one to two years after the outbreak.[6]

OBJECTIVE

We hypothesized that healthcare workers who had had care experience relating to SARS in 2003 might be more stressed during the COVID-19 outbreak in Taiwan. The goal of this study was to better understand what factors contributed to the levels of stress experienced by healthcare workers, what aspects of their work might put pressure on them, and whether their prior SARS epidemic experience had enabled or inhibited their work with regard to dealing with the pandemic. With the above information, hospital administrators may better understand how to take action to provide psychological support measures or interventions to reduce the burden on healthcare workers in future infectious pandemics.

METHODS

Study design and study population

A cross-sectional survey was conducted in a tertiary-level hospital in Kaohsiung City, in southern Taiwan, from March 20 to April 20, 2020, amidst the COVID-19 pandemic in Taiwan. The survey was conducted using a web-based questionnaire and excluded new recruits, outsourced workers, research assistants and other non-regular hospital employees. Details of the survey website were provided to the survey participants through their mailboxes and the researchers compiled the responses for analysis. For this study, participants were recruited from the three main categories of hospital staff who presented the possibility of close contact with the suspected COVID-19 patients or with specimens that had been obtained for testing, namely doctors, nurses and medical technicians. The medical technicians mentioned here were those who assisted in making medical diagnoses by performing tests that had been requested by physicians and hospitals, such as medical and radiological technologists.

The questionnaire contained the following two sections. First, there were items asking about the participants' demographic characteristics, including age, gender, marital status, being a parent, occupation, educational level, years of work experience, experience of caring for patients with SARS and experience of caring for suspected or confirmed patients with COVID-19. Second, the "Psychometric Evaluation of Healthcare Workers' Stress Related to Caring for Patients with a Highly Infectious Disease" scale developed by Chuang and Lou for 2003 SARS was used.[7] The stress scales were divided into four subscales, which measured the worry of social isolation (10 items), discomfort caused by the protective equipment (8 items), difficulties and anxiety regarding infection control (7 items) and the workload of caring for patients (7 items). Each of these 32 items was rated on a four-point Likert scale (0: not at all, 1: about the same as usual, 2: slightly more severe than usual, 3: more severe than usual) to assess the degree of stress caused by various factors. The total score could range from 0 to 96. A higher total score would indicate a greater degree of stress, such that a total score from 47 to 96 would denote severe stress, while a score from 0 to 46 would indicate mild to moderate stress. A score of 0 would indicate absence of stress.

Statistical analysis

The software package JMP 13.0 for Windows (SAS Institute Inc, Cary, North Carolina, United States) was used for statistical analysis. Continuous variables relating to demographic characteristics and perceived work stress were presented as the mean ± standard deviation (SD); categorical variables were presented as counts and percentages. Correlations between variables were analyzed using Pearson's product-moment correlation coefficient and were compared using the chi-square and Levene tests. Logistic regression on different variables was also used to evaluate the effect of the variables on the total stress scale.

Ethics

This study was reviewed and approved (IRB Number: KMUHIRB-E(I)-2020008; approval date: April 7, 2020) by the institutional review board of the participating hospital. Data were collected anonymously, and background data were deidentified. Information about the respondents that was obtained in this study was handle in accordance with the principles of confidentiality and privacy.

RESULTS

Characteristics of participants

Out of the 492 healthcare workers who completed this questionnaire, 51 were male (10.4%) and 441 were female (89.6%). The demographic characteristics of these healthcare workers are displayed in **Table 1**.

Their mean age was 38 years (ranging from 23 to 65 years) and their average length of work experience was 12.4 years. Approximately half of the respondents were married (50.6%) and were parents (43.7%). Most of the respondents were nurses (82.8%), followed by medical technicians (9.8%) and doctors (8.1%). A total of 427 respondents (86.8%) had graduated from college or university at not more than bachelor level, while the remaining respondents (13.2%) had also reached higher degree levels (master's or doctoral degree). Ninety-three respondents (18.9%) had prior work experience at the time of the SARS outbreak and 57 (11.6%) were frontline healthcare workers who were directly involved in the diagnosis, treatment and care of patients with COVID-19.

Table 1. Demographic characteristics of the healthcare workers (n = 492)

Characteristic	Healthcare workers
Median age (IQR), years	38 (23-65)
Gender, n (%)	
Male	51 (10.4)
Female	441 (89.6)
Work experience, mean (SD), years	12.4 (9)
Marital status, n (%)	
Unmarried	243 (49.4)
Married	249 (50.6)
Number of children, n (%)	
≥ 1	215 (43.7)
none	277 (56.3)
Occupation, n (%)	
Doctor	40 (8.1)
Nurse	404 (82.1)
Medical technician	48 (9.8)
Educational level, n (%)	
College/university	427 (86.8)
Institute (MSc and PhD)	65 (13.2)
Experience with SARS, n (%)	
No	435 (88.4)
Yes	57 (11.6)
Caring for patients with suspected or confirmed COVID-19, n (%)	
No	399 (81.1)
Yes	93 (18.9)

IQR = interquartile range; SD = standard deviation; SARS = severe acute respiratory syndrome.

The stress levels of healthcare workers amidst the COVID-19 pandemic

The total stress score was collated and analyzed in relation to different variables (see **Table 2**). The respondents aged 41 years or above (score of 50.9 ± 16.4) reported having significantly higher stress scores than those below 40 years of age (46.4 ± 16.0), when facing the COVID-19 pandemic (P = 0.0026). In addition, female healthcare workers reported significantly higher stress levels than males (49.0 ± 16.5 versus 43.5 ± 13.7; P = 0.0109). Respondents who were married (50.1 ± 16.9) reported higher levels of stress than those who were unmarried (46.7 ± 15.5) (P = 0.0186) and respondents who were parents (50.1 ± 17.3) reported significantly higher stress scores than those who had no child (P = 0.0409). Furthermore, nurses reported the highest total stress score (49.5 ± 16.2; P = 0.0063), followed by medical technicians (44.6 ± 14.8) and doctors (42.3 ± 17.7). The following factors: educational level, prior work experience with SARS and whether having cared for patients with suspected or confirmed COVID-19 infection, had no significant influence on the total stress score. Total stress scores from 47 to 96 indicate severe stress and scores from 0 to 46 indicate mild to moderate stress.

Further analysis via logistic regression on different variables (**Table 3**) showed that the odds of being in the group with severe stress increased significantly when respondents were older (adjusted odds ratio, OR: 1.028; P = 0.028) or nurses (compared with medical technicians, adjusted OR: 2.075; P = 0.037). Although not statistically

Table 2. Total stress scores among the healthcare workers facing the COVID-19 pandemic

Variable	Number (%)	Total stress scale (mean ± SD)	T	P-value
Age (23 to 65 years)				
≤ 40	263 (53.5)	46.4 ± 16.0	−3.03	0.0026*
> 41	229 (46.5)	50.9 ± 16.4		
Gender				
Male	51 (10.4)	43.5 ± 13.7	2.62	0.0109*
Female	441 (89.6)	49.0 ± 16.5		
Marital status				
Unmarried	243 (49.4)	46.7 ± 15.5	2.36	0.0186*
Married	249 (50.6)	50.1 ± 16.9		
Number of children				
≥ 1	215 (43.7)	50.1 ± 17.3	2.05	0.0409*
None	277 (56.3)	47.1 ± 15.4		
Occupation				
Doctor	40 (8.1)	42.3 ± 17.7	F:5.12	0.0063*
Nurse	404 (82.1)	49.5 ± 16.2		(2 > 1)
Medical technician	48 (9.8)	44.6 ± 14.8		
Educational level				
College/university	427 (86.8)	48.8 ± 15.8	1.15	0.2539
Institute (MSc and PhD)	65 (13.2)	45.9 ± 19.3		
Experience of SARS				
No	435 (88.4)	47.8 ± 15.7	1.95	0.0560
Yes	57 (11.6)	53.2 ± 20.0		
Caring for patients with suspected or confirmed COVID-19 infection				
No	399 (81.1)	51.4 ± 17.3	1.94	0.0529
Yes	93 (18.9)	47.8 ± 16.0		

*P < 0.05; SD = standard deviation; SARS = severe acute respiratory syndrome.

significant, respondents who were married (adjusted OR: 1.736; P = 0.138) or doctors (compared with medical technicians, adjusted OR: 1.222; P = 0.669) showed a positive relationship with being in the group with severe stress. On the contrary, those who were male (adjusted OR: 0.659; P = 0.296) or parents (adjusted OR: 0.720; P = 0.385) showed a negative relationship with being in the group with severe stress.

Influence of SARS work experience on healthcare workers

The healthcare workers were divided into two groups according to whether they had experience of treating SARS. The total stress score and the scores from the four subscales were analyzed in each group (see **Table 4**). During the COVID-19 pandemic, although not statistically significant, the healthcare workers with SARS work experience had higher total stress levels (score of 53.2 ± 20.0) than those with no SARS work experience (47.8 ± 15.7). Further analysis on the four subscales revealed that the healthcare workers with experience of treating SARS reported having significantly higher stress scores on two of the four subscales, i.e. discomfort caused by the protective equipment and workload of caring for patients (16.5 ± 5.4 versus 14.8 ± 4.9; 13.2 ± 4.9 versus 11.1 ± 4.5, respectively), amidst the COVID-19 outbreak. On the other hand, there was no significant difference in subscale scores relating to the worry of social isolation and the difficulties and anxiety regarding infection control, among the healthcare workers during the COVID-19 outbreak, between those with and without experience of treating SARS. For 57 respondents with SARS work experience, 38 respondents (66.7%) were in the group with severe stress and the remaining 19 respondents (33.3%) were in the group with mild to moderate stress. Further analysis via multivariable logistic regression (**Table 3**) showed that, compared with the healthcare workers with no SARS work experience, those with SARS work experience (adjusted OR: 1.516; P = 0.186) had a positive relationship with being in the group with severe stress.

Stress scores of healthcare workers according to two factors

The respondents were categorized into four groups according to two factors, namely, SARS work experience and caring for suspected or confirmed COVID-19 cases (refer to **Table 5**). The frontline healthcare workers with SARS experience had the highest total stress score (56.4 ± 20.2), followed by non-frontline healthcare workers with SARS work experience (51.6 ± 19.9), frontline healthcare workers with no SARS work experience (50.1 ± 16.4), and non-frontline healthcare workers with no SARS work experience (47.3 ± 15.5). Two of the four subscales (the worry of social isolation and the workload of caring for patients) showed increasing trends regarding the total stress score among the healthcare workers. Furthermore, the frontline healthcare workers with SARS work experience (14.4 ± 4.5) demonstrated significantly higher stress levels than the non-frontline healthcare workers with no SARS work experience (10.9 ± 4.5), in relation to the subscale of the workload of caring for patients.

Table 3. Factors affecting the odds of being in the group with severe stress

Variables	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age	1.033 (1.013-1.053)	0.001*	1.028 (1.003-1.054)	0.028*
Gender (male: female)	0.497 (0.269-0.896)	0.022*	0.659 (0.296-1.432)	0.296
Marital status (married: unmarried)	1.686 (1.181-2.413)	0.004*	1.736 (0.844-3.663)	0.138
Number of children (≥ 1: none)	1.533 (1.071-2.199)	0.020*	0.720 (0.337-1.494)	0.385
Occupation				
Doctor	1.232 (0.522-2.917)	0.633	1.222 (0.488-3.083)	0.669
Nurse	2.074 (1.130-3.906)	0.020*	2.075 (1.052-4.181)	0.037*
Medical technician	Reference		Reference	
Experience of SARS				
SARS (+)[c]	1.936 (1.095-3.530)	0.026*	1.516 (0.827-2.858)	0.186
SARS (-)[d]	Reference		Reference	

OR = odds ratio; CI = confidence interval; SARS = severe acute respiratory syndrome; SARS (-): no experience of SARS; SARS (+): experience of SARS; . *P < 0.05.

Table 4. Psychometric evaluation on the healthcare workers with or without experience of severe acute respiratory syndrome (SARS) amidst the COVID-19 pandemic

Subscale	All	SARS experience		T/x²	P-value
	n = 492	Yes, n = 57	No, n = 435		
Worry of social isolation	13.0 ± 6.3	14.7 ± 7.8	12.8 ± 6.0	1.77	0.0817
Discomfort caused by the protective equipment	15.0 ± 5.0	16.5 ± 5.4	14.8 ± 4.9	2.36	0.0185*
Difficulties and anxiety regarding infection control	9.0 ± 3.8	8.7 ± 4.9	9.0 ± 3.7	0.43	0.6705
Workload of caring for patients	11.4 ± 4.6	13.2 ± 4.9	11.1 ± 4.5	3.25	0.0012*
Total stress scale	48.4 ± 16.3	53.2 ± 20.0	47.8 ± 15.7	1.95	0.0560
Mild to moderate stress[a], number (%)	233 (47.4)	19 (33.3)	214 (49.2)	5.09	0.0241*
Severe stress[b], number (%)	259 (52.6)	38 (66.7)	221 (50.8)		

[a]Mild to moderate stress: total score 0-46; [b]Severe stress: total score 47-96; *P < 0.05.

DISCUSSION

The cross-sectional survey used in this study was completed by 492 respondents and the mean total stress score was 48.4 ± 16.3 points. Most participants were female, were nurses, had been educated to college or university level and had no prior experience of treating SARS.

In this survey, the total stress score was significantly higher among healthcare workers aged 41 or above who were female, married, parents and nurses. The total stress score did not show any significant differences with regard to education level, having SARS work experience or having cared for suspected or confirmed cases of COVID-19. Furthermore, respondents who were older or were nurses had higher odds of being in the group with severe stress during the COVID-19 outbreak.

Nurses not only had higher total stress scores than physicians or medical technicians, but also had significantly higher odds of being in the group with severe stress in facing the COVID-19 pandemic. This was consistent with previous findings that demonstrated that SARS had caused a significant level of distress among emergency department staff, with the highest levels of distress among nurses, followed by doctors and healthcare assistants.[8] The higher stress among nurses was attributable to the following reasons: nursing is a highly stressful occupation; nurses are exposed to patients with suspected or confirmed COVID-19 for long periods; and the inconvenience caused by stringent infection control measures is a source of stress.

Being a parent also gave rise to a higher total stress score in this study. This may be attributed to the fear among these healthcare workers that if they contracted COVID-19, they could spread the disease to their children, be separated from and not able to see their children, or would face inconvenience in taking care of their children. Furthermore, a recent study conducted in tertiary-level hospitals found that nurses, women, frontline workers and workers at the epicenter of COVID-19 reported experiencing greater severity of symptoms of depression, anxiety, insomnia and distress.[9]

One intriguing finding from the present study was that healthcare workers with SARS work experience presented significantly higher stress scores on the subscales relating to discomfort caused by the protective equipment and the workload of caring for patients. However, no significant differences in the total stress score were found.

Prior experience of treating SARS had either positive, negative or neutral psychological impacts on the healthcare workers when they were faced with another pandemic; in this case, COVID-19. A survey completed by healthcare workers who practiced respiratory medicine during the SARS outbreak in Hong Kong showed that these workers remained highly stressed one year after the outbreak. The perceived stress levels were higher and were associated with higher levels of depression and anxiety, and higher posttraumatic stress scores.[10] A study on healthcare workers in Taiwan who had taken care of suspected SARS patients, both at the first stage and a year later, indicated that the stress was initially in response to the life-threatening nature of the SARS epidemic. The stress experienced thereafter was from their jobs, families and stressful events within daily life, rather than from a continuation of previous symptoms caused by vulnerability to or complications from stress created by the SARS attack.[11] In another study, SARS work experience resulted in increased mental preparedness and implementation of stringent infection control measures that led to lower impact of events on stress scores among physicians and nurses, as well as lower prevalence rates for posttraumatic stress disorder in response to the COVID-19 pandemic.[12]

A complete set of personal protective equipment (PEE) is imperative and paramount for curbing the spread of COVID-19 when dealing with suspected or confirmed cases. However, healthcare workers who wear a complete set of personal protective equipment have experienced states of tension and fatigue, thereby increasing the difficulty of their work and becoming more prone to burnout.[13] In the present study, the healthcare workers with SARS work experience had higher stress scores due to the discomfort experienced through using personal protective equipment. The three most troublesome effects were the following: skin damage to their hands from frequent hand washing and use of disinfectants; the inconvenience of going to the bathroom wearing PPE; and restriction of the intake of water and food because of wearing a complete set of PPE.

Because hand hygiene compliance is essential amidst the COVID-19 pandemic, prevention of skin dermatitis caused by constant hand washing and sanitizing among healthcare workers has been found to be important for increasing hand hygiene compliance.[14] For lipophilic enveloped viruses, such as SARS-CoV-2,

Table 5. Psychometric evaluation on the healthcare workers, in four subgroups according to their experience of severe acute respiratory syndrome (SARS) and whether they were caring for suspected or confirmed COVID-19 cases

Subscale	SARS (–)		SARS (+)		F	P value	Tukey's HSD
	1. COVID (–) n = 38	2. COVID (+) n = 19	3. COVID (–) n = 361	4. COVID (+) n = 74			
Worry of social isolation	12.6 ± 6.1	13.8 ± 5.7	14.0 ± 7.7	16.2 ± 8.0	2.73	0.0434	No difference
Discomfort caused by the protective equipment	14.8 ± 5.0	15.0 ± 5.0	16.3 ± 5.8	16.8 ± 4.6	1.92	0.1250	
Difficulties and anxiety regarding infection control	9.0 ± 3.5	9.2 ± 4.3	8.6 ± 4.7	8.9 ± 5.3	0.21	0.8915	
Workload of caring for patients	10.9 ± 4.5	11.2 ± 4.6	12.7 ± 5.0	14.4 ± 4.5	5.71	0.0080	4 > 1*
Total stress scale	47.3 ± 15.5	48.1 ± 16.3	51.6 ± 19.9	56.4 ± 20.2	2.79	0.0402	No difference

SARS (-) = no experience of SARS; SARS (+) = experience of SARS; COVID (-) = non-frontline, not caring for patients with suspected or confirmed COVID-19 infection; COVID (+) = frontline, caring for patients with suspected or confirmed COVID-19 infection; Tukey's HSD = Tukey's Honestly Significant Difference test; *P < 0.05.

it has been emphasized that alcohol-based sanitizers should have a good quantity of antimicrobial properties and should have good skin tolerability, compared with handwashing with soap and water. This would reduce the potential for skin dermatitis.[15]

In this study, we categorized participants as those who had prior experience of treating SARS and those without prior SARS work experience. These two groups were further divided into four subgroups depending on whether they were or were not caring for suspected or confirmed cases of COVID-19. There was an upward trend in the total stress scores among healthcare workers who had SARS work experience and were caring for suspected or confirmed cases of COVID-19. The highest stress scores were seen among frontline healthcare workers with SARS work experience. Two subscales, the worry of social isolation and the workload of caring for patients, revealed similar increasing trends in stress scores. Furthermore, compared with non-frontline healthcare workers with no SARS work experience, our analysis indicated that there were significantly higher stress scores among frontline healthcare workers with SARS work experience, in relation to the subscale of the workload of caring for patients. Consistent with previous findings, frontline healthcare workers were found in our study to have experienced the highest psychological burden during the COVID-19 pandemic.[9] Moreover, our study implied that prior experience of treating SARS might be a factor contributing negatively to the stress levels experienced by frontline healthcare workers during the COVID-19 outbreak.

The importance and benefits of psychiatric measures or interventions for high-risk healthcare workers amidst pandemics, towards reducing their stress levels, have been emphasized in several studies. It was demonstrated that psychiatric services were significantly effective in helping healthcare workers manage their stress during the SARS outbreak.[16] During the COVID-19 pandemic, a psychological intervention plan was proposed, which included measures within three main areas: first, construction of a medical team for psychological interventions, with provision of online courses to guide medical staff in dealing with common psychological problems; second, launching of a psychological assistance hotline team offering guidance and supervision for solving psychological problems; and third, implementation of these psychological interventions.[17] The psychological intervention measures should be based on the needs of healthcare workers and should be tailored to different cultural backgrounds, religious beliefs and personal preferences.

The present study has several limitations. First, it was limited in scope because it only investigated a limited number of healthcare workers in one tertiary-level hospital in southern Taiwan. Thus, the results cannot be generalized to all Taiwanese healthcare workers. Likewise, this study did not include nonmedical personnel in the hospital (e.g. allied healthcare professionals, pharmacists, administrators, clerical staff and maintenance workers) who may also have suffered from psychological distress amidst the COVID-19 outbreak. Second, because of the cross-sectional design of this study, it was only able to assess healthcare workers' work stress at the time of the survey. It thus lacked longitudinal observation of the participants. Third, apart from the factors identified in this study, there may be additional factors contributing to work stress among healthcare workers. Fourth, the non-inclusion of a scale for evaluating depression was also a limitation of this study.

CONCLUSIONS

In summary, healthcare workers who are older than 40, female, married, parents or nurses are prone to have higher total stress scores amidst the COVID-19 pandemic. The odds of being in the group with severe stress were significantly higher when the respondents were older or nurses. Furthermore, healthcare workers with SARS work experience reported having higher total stress scores and had higher odds of being in the group with severe stress, although this was not statistically significant compared with healthcare workers without SARS work experience. Specifically, healthcare workers with experience of treating SARS showed greater distress on the subscales relating to the discomfort caused by the protective equipment and the workload of caring for patients in the COVID-19 pandemic. In addition, frontline healthcare workers with SARS work experience also had higher stress scores on the subscale of the workload of caring for patients.

Due to limitations of workforce, finance and time, data for this study were collected only from one medical center in southern Taiwan. It is recommended that future studies should include larger sample sizes and should make comparisons between groups with the same numbers of study subjects in other tertiary-level hospitals in Taiwan. Moreover, a longitudinal study design should be adopted in order to follow up the long-term effect of COVID-19 on healthcare workers.

It was clear from this study that experience of treating the 2003 SARS outbreak had a partly negative psychological impact on these healthcare workers facing the COVID-19 outbreak. Thus, hospital administrators should provide psychological measures or interventions in order to reduce the burden on healthcare workers amidst the COVID-19 pandemic.

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Poor sanitation and transmission of COVID-19 in Brazil

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ABSTRACT

Coronavirus is a family of viruses that cause respiratory infections. From cases first recorded in China at the end of 2019, a new type of virus in this family, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered. The disease caused by this virus, COVID-19, was brought into Brazil by people in social classes with greater purchasing power, but groups with larger demographic dimensions have tended to become more affected over time. Poor sanitation can generate risky situations and behavior among people who live in spaces with characteristics that limit their quality of life. Installation of piped water in homes and basic education for the population are fundamental measures for disease control, including in relation to COVID-19. In this updating article, the COVID-19 pandemic was analyzed in the context of iniquities in Brazil (comparing these with the situation in other countries). A bibliographic search of texts relating to basic sanitation, socioeconomic development and transmission of COVID-19 in Brazil and worldwide was conducted.

INTRODUCTION

The dissemination of COVID-19 is a challenging public health problem within today's globalized world. Globalization has expanded the world's crossroads to make them more complex, which has given rise to the need to take a new look at new problems.[1]

COVID-19 was brought into Brazil from outside the country, by people in social classes with greater purchasing power. Given that it is a disease spread through social contact, it can be suggested that groups with larger demographic dimensions would tend to become more affected over time. Within this context, it is necessary to reflect on the work and housing conditions of salaried workers, in relation to those in precarious self-employment. Among the latter, their circulation imposed by the search for subsistence is a factor that increases the risk and also leading to risky behaviors with regard to the pandemic.[2]

Social inequalities generate more precarious situations, which can lead to illness and death. Inequalities are a differential feature among the various social structures present in Brazil. The COVID-19 pandemic has shown that historically neglected population groups are among those most affected, especially with regard to higher risk of death.[3] Its consequences have further stressed the need to invest in wastewater treatment infrastructure and sanitation in developing countries.[4]

OBJECTIVE

The aim of this study was to analyze the COVID-19 pandemic in the context of unjust and avoidable inequalities (called iniquities) in Brazil.

A bibliographic search of texts relating to basic sanitation, socioeconomic development and transmission of COVID-19 itself was carried out. The focus was on discussion of the pandemic and on making connections with Brazil's structural problems and comparisons with other countries, especially those of low to medium developmental level (i.e. similar to Brazil).

COVID-19

The coronavirus family of viruses causes respiratory infections. A new type of virus from this family was discovered on December 31, 2019, subsequent to the first recorded cases in China, and was named SARS-CoV-2. The disease caused by the new virus, COVID-19, gives rise to clinical conditions that range from asymptomatic infection to severe respiratory conditions. Its symptoms can vary from a simple cold to severe pneumonia, and the most common of these symptoms are a

runny nose, coughing, sore throat, fever and difficulty in breathing. It is transmitted from a sick person to another individual through close contact: via handshaking, droplets of saliva, coughing, sneezing, sputum or contaminated objects/surfaces.[5]

The recommendations for prevention of COVID-19 comprise frequent handwashing with soap (or sanitization with 70% gel alcohol); keeping a minimum distance of two meters from anyone who is coughing or sneezing; not sharing personal items (drinking glasses, cutlery and plates); keeping environments clean and ventilated; avoidance of unnecessary movement of people on the streets; and use of masks, which can be homemade. If a person feels sick, with flu symptoms, he or she should avoid physical contact with other people and should stay at home for at least 14 days.[5]

BASIC SANITATION IN BRAZIL

Several studies have highlighted the importance of water supply and sewage treatment.[4,6-11] When these are absent, this can impact the health of the population, especially through the spread of worm diseases and increased incidence of diseases such as malaria and schistosomiasis.[12] Although basic sanitation has been recognized as an essential human right, universal access to it is far from being reached.[11]

In Brazil, recognition of the need for water and sewage services involves the three spheres of government (federal, state and municipal), trade unions, political parties, companies (national and foreign) and financial corporations, with a plurality of social agents and interests. Thus, water and sewage services can be understood as a basic human right. However, in Brazil, this issue ends up reaching a higher level of contention, given that both public and private administrative bodies seek to exploit the cultural, economic, symbolic and social capital surrounding this basic human right, as an instrument for bargaining and domination.[13]

Despite advances towards reducing inequalities that have been achieved in Brazil over recent decades,[14] this country still faces great difficulties in terms of water supply and sewage collection and treatment. In one study,[15] it was shown that, in 2017, some Brazilian state capitals presented a very low level of provision of piped water supply, such that less than 40.0% of the population received these services (Macapá and Porto Velho, respectively, with water service indicators of 39.1% and 33.1%). Regarding sewage, Belém, Macapá and Porto Velho were among the 20 worst cities in the 2017 sanitation ranking with, respectively, total sewage service indicators of 12.6%, 8.9% and 3.4%. Thus, even in regions with abundant water resources, such as the Amazon region, there are difficulties in accessing drinking water because of lack of infrastructure (collection, treatment and supply). The same is seen with regard to sewage, which can be portrayed as a problem of natural resource management, given that lack of sewage treatment leads to pollution of water courses in the Amazon region.[16]

In relation to the COVID-19 pandemic, poor sanitation can generate risky situations and behaviors among people who live in spaces with characteristics that limit their quality of life.[2] It can also be a risk factor for diseases such as dengue, given that water storage in large buckets (because of the absence of piped water) and inadequate waste management have been considered to be factors responsible for maintaining this disease.[17] Within this context, several studies have been highlighting the possibility of transmission of COVID-19 through feces and urine,[4,18-20] which can lead to worse scenarios in the long run.[4]

Adverse bio-socio-ecological factors and difficulties in accessing healthcare services are still a reality in Brazil[21] and other Latin American countries.[22,23] These problems have led to establishment of certain diseases as everyday experiences for people.[21] Therefore, installation of piped water in homes and basic education for the population,[24] including health education activities for communities,[25] are fundamental measures for disease control, including in relation to COVID-19.

COVID-19 AND INIQUITIES IN BRAZIL

The evident inequalities in Brazil, in which the existential minimum is compromised,[26] have meant that the COVID-19 pandemic has constituted a major challenge for this country.[27] Brazil still has a long way to go towards universalization and equity of provision of basic sanitation services, even in metropolitan regions.[28]

In addition to the lack of basic sanitation, drug use, deaths due to accidents and urban violence, and respiratory problems associated with pollution, continue to form part of the public health agenda in Brazil. This is true in all its urban regions, but these issues especially affect the populations of vulnerable communities in peripheral areas. Consequently, the growing social vulnerability and expansion of social segregation have had an impact on the distribution of diseases in different regions and at different geographical scales. These factors have favored reemergence of old endemic diseases and emergence of new diseases.[29]

For COVID-19, like other diseases,[30] a healthier socio-spatial environment is required in order to overcome it. Lack of environmental improvements, thereby perpetuating disease, is one of the consequences of socially reproduced iniquities in Brazil[29] and in other less developed countries.[31] The inequalities in this country mean that diseases tend to affect the poor population and the people most exposed to social contagion, more severely. This population includes people living in peripheral areas, people in prisons, homeless people who have been gathered into shelters, people dependent on public transportation, workers who deal with other people (these represent a large proportion of the Brazilian working population)[32] and vulnerable populations who live in slums (favelas).[33-35]

Within this context, a single city may present socio-spatial inequalities (as observed in Rio de Janeiro),[36] which can be seen in the population's

socioeconomic and cultural behaviors. This has also been observed in Kuwait, where the relationship between poor housing conditions (including in densely populated areas) and increased transmission of COVID-19 among communities of migrant workers was highlighted.[37]

Given the scenario of iniquities in Brazil, implementation of social isolation measures has become complex. Although these measures have been brought in within all administrative spheres,[38] they are presented differently throughout the country. A study that analyzed factors associated with the population's behavior during the current social isolation (quarantine) showed that among people with higher education and income, 45.8% declared that social interaction was the most affected aspect of their lives. On the other hand, among people with lower income and education, 35% declared that financial problems were having the greatest impact. Thus, it can be seen that possession of income provides the possibility to transcend needs towards a life of choices (and with the ability to exercise freedom of choice). However, when income is unsatisfactory, this makes it mandatory to go to the streets to search for job opportunities.[39] This reality has also been observed in sub-Saharan African countries, where individuals in households without basic necessities were more likely to violate control measures through going out from the home to meet their needs. Hence, it is clear that vulnerabilities and the risk of transmission of COVID-19 transcend national and international scales.[32]

Studies on health inequalities in favelas started to be conducted long ago.[40] These studies have demonstrated that health inequalities have been a reality in these areas, and many others, for a long time. Peripheral settlements (macro-scale) and favelas (micro-scale) in Brazil are an expression of socio-spatial segregation. They represent situations of poverty based on precarious social conditions and infrastructure (and even differences in income from work), in enclaves in metropolitan territories.[41]

Socio-spatial inequalities can be observed within a single city, shown by socioeconomic and cultural differences in the population.[42] These lead to differences regarding COVID-19 transmission. In Rio de Janeiro, it was observed that initially the neighborhoods in the South Zone were the most affected by the disease. The districts of the North Zone (in general, of lower-income populations) showed higher mortality rates due to COVID-19, which may have reflected a lack of access to healthcare services.[36] This socio-spatial differentiation was also observed in Bangladesh, where greater risks of transmission of COVID-19 were observed in the central and southeastern regions of the country. Furthermore, it was also highlighted in that study that measures to reduce disease transmission (such as social distancing) are extremely important, especially in countries with inadequate healthcare services.[43]

The social conditions under which individuals are born, raised, live, work and grow old are responsible for the differences in health situation that are observed between countries and even within them. It is important to emphasize that these differences are unjust and preventable and that this is why they are called health iniquities.[44]

FINAL REMARKS

The new coronavirus pandemic has posed a challenge to humanity. However, its effects have tended to be more acute in populations that present greater iniquities and will tend to become worse until a definitive solution to the pandemic is reached. Hand hygiene, a preventive measure for COVID-19,[14] is still a privilege in Brazil, since in several regions of the country, many homes do not have access to water and basic sanitation.[45] Because universal access to water and basic sanitation has not yet been implemented,[11] this basic human right remains far from being achieved.[13] Absence of universal access directly impacts the population's health[12] and constitutes an avoidable iniquity.[42]

Several other problems continue to form part of the public health agenda in Brazil and in other countries,[37,46] affecting mainly vulnerable populations in peripheral areas. Understanding the social conditions under which individuals live is central for implementing public policies based on solidarity, social rights and democracy, so as to ensure healthier socio-spatial environments and enable reduction of the effects of the pandemic. For this, it is necessary to analyze the information regarding the pandemic in terms of race/color, income and other social determinants, thus making it possible to have differentiated actions for the places, areas and regions of greatest vulnerability.

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Knee extension strength and handgrip strength are important predictors of Timed Up and Go test performance among community-dwelling elderly women: a cross-sectional study

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ABSTRACT

BACKGROUND: Handgrip and knee extension strengths have each been used to characterize disability. However, it has been reported that the association between handgrip and knee extension strengths is weak.

OBJECTIVE: To evaluate the influence of knee extensor and handgrip muscle strength on Timed Up and Go (TUG) test results among elderly women with worse (≥ 10 seconds) and better (< 10 seconds) performance, after controlling for confounders.

DATA AND SETTING: Cross-sectional study on a sample selected according to convenience, carried out in a federal public institution of higher education.

METHODS: Assessment of handgrip was carried out using the Jamar dynamometer (Lafayette Instrument Company, Inc., Lafayette, United States). Knee extensor muscle performance was measured using an isokinetic dynamometer (Biodex System 3 Pro; Biodex Medical Systems, Inc., United States), The confounding factors were education, age, comorbidities, body mass index and Geriatric Depression Scale and Human Activity Profile scores. Functional performance was assessed through the TUG test. A backward linear regression model was used.

RESULTS: 127 elderly women performed the TUG test in more than 10 seconds and 93 in less than 10 seconds. However, regardless of test performance, handgrip strength and knee extension strength comprised the reduced final model.

CONCLUSIONS: Knee extension strength and handgrip strength might be particularly useful indicators for measuring disability.

INTRODUCTION

Knee extension and handgrip strengths have each been used to predict functional performance.[1] Caballer et al. observed significant correlations (-0.57) between rectus femoral cross-sectional area and Timed Up and Go (TUG) test performance in a sample of 122 adults aged 65 and older.[2] Di Monaco et al. evaluated 123 elderly women and found a significant correlation (-0.41) between handgrip strength and time taken to complete the TUG test.[3]

However, it has been reported that the association between handgrip strength and knee extension strength is weak. Felicio et al. investigated the correlation between handgrip strength and the isokinetic muscle performance of knee extensors and flexors among elderly women living in the community (n = 221). Most of the muscle variables analyzed with their isokinetic dynamometer did not show any significant correlation with handgrip strength.[4] In a study on 764 elderly individuals, Chan et al. found a weak association between knee extension strength and handgrip muscle strength when the results were adjusted for sex and age ($R^2 = 0.17$).[5]

OBJECTIVE

To evaluate the influence of knee extensor strength and handgrip muscle strength in the TUG test among elderly women with worse (≥ 10 seconds) and better (<10 seconds) performance, after controlling for confounders.

METHODS

Participants and setting

This was a cross-sectional study approved by a local ethics committee on May 31, 2010 (ETIC 0038.0.203.000-10). Sample selection was carried out according to convenience. The study included women living in the community aged 65 years and over. The exclusion criteria were cognitive dysfunction,[6] acute inflammatory conditions, musculoskeletal discomfort and visual or hearing losses.

Testing procedures

Muscle performance of knee extensors

The muscle performance of the knee extensors was measured using the Biodex System 3 Pro isokinetic dynamometer (Biodex Medical System, Shirley, United States). The data analysis was carried out using only the results obtained from the dominant lower limb, and concentric-concentric mode was selected for the assessment.[7] The angular velocity selected was 60°/switch, with five repetitions, and the isokinetic variable used was work/body mass because this is most representative of muscle function.[8]

Handgrip strength

Handgrip strength was measured by means of a maximal isometric test, using the PC5030JI Jamar device (Sammons Preston, Bolingbrook, United States), performed on the dominant upper limb. The participants were positioned in accordance with the recommendations of the American Society of Hand Therapy. An average of three trials was calculated to obtain a final score.[9]

Confounding factors

The confounding factors included in the analysis were education, age, number of comorbidities, body mass index (BMI), Geriatric Depression Scale (GDS-15) score[10] and Human Activity Profile (HAP) score.[11]

Timed Up and Go test

The Timed Up and Go (TUG) test involves getting up from a chair, walking three meters around a marker placed on the floor, coming back to the same position and sitting down on the chair again.[12]

Data analysis

Comparisons between the groups were made using the t test. A backward linear regression model was used to investigate the influence of knee extensor strength and handgrip muscle strength on the TUG test results among elderly women with worse (≥ 10 seconds) and better (< 10 seconds) performance. The dependent variable was the TUG test result. The independent variables were age, education, BMI, HAP, GDS, mini-mental state examination (MMSE), number of comorbidities, knee extensor strength and handgrip muscle strength. Regarding the model assumptions, multicollinearity was considered to have an inflation factor of variance of > 10. The analysis on homoscedasticity was performed using graphical observations of predicted and observed values. The independence of residuals was determined using the Durbin-Watson test. For all analyses, we used a significance level of 0.05. The statistical analyses were carried out using the Statistical Package for the Social Sciences (PASW Data Collection, version 20.0; SPSS, Chicago, United States).

RESULTS

A total of 220 elderly women met the inclusion criteria for the present study. The descriptive sample characteristics are shown in **Table 1**.

Table 2 presents the results from the reduced backward linear regression model.

Table 1. Descriptive sample characteristics (n = 220)

Variables	TUG > 10 s (n = 127) Mean ± standard deviation	TUG < 10 s (n = 93) Mean ± standard deviation	P-value
Age, years	71.2 ± 4.8	70.6 ± 5.0	0.43
Education, years	5.8 ± 4.2	6.2 ± 3.9	0.40
Body mass index, kg/m^2	29.8 ± 5.8	28.3 ± 4.5	0.02*
Human activity profile, 0-94	69.0 ± 11.9	75.0 ± 9.7	< 0.001*
Geriatric Depression Scale, 0-15	3.7 ± 2.9	3.2 ± 2.5	0.23
Mini-mental state examination, 0-30	25.6 ± 3.0	26.3 ± 2.9	0.10
Comorbidities, n	2.7 ± 1.5	2.4 ± 1.5	0.16
Work/body weight of knee extensors, %	115.1 ± 29.4	127.8 ± 34.1	< 0.001*
Handgrip strength, kgf	20.4 ± 4.7	22.0 ± 4.2	0.01*
Timed Up and Go test, seconds	11.7 ± 1.6	8.7 ± 1.0	0.00*

*Statistically significant.

Table 2. Results from linear regression model (n = 220)

Dependent variable = TUG ≥ 10 s (n = 127)		
Model	**Adjusted R^2**	**P-value**
1	**0.20**	**< 0.001***
Model 1: education (standardized β = -0.17); human activity profile (standardized β = -0.29); work/body weight of knee extensors (standardized β = -0.07); handgrip strength (standardized β = -0.23)		
Dependent variable = TUG < 10 s (n = 93)		
Model	**Adjusted R^2**	**P-value**
2	**0.06**	**0.03***
Model 2: age (standardized β = -0.26); work/body weight of knee extensors (standardized β = -0.12); handgrip strength (standardized β = -0.09)		

*Statistically significant.

DISCUSSION

A single measurement to provide an overall estimate of functionality reduces the time and cost of evaluation. The present study presents preliminary evidence of the importance of knee extension strength and handgrip strength in relation to functional performance, even after adjustment.

Handgrip strength is a measurement that has been widely studied in the literature and can be used as a screening tool for impairments among elderly people. However, this measurement does not eliminate the need for specific assessment. In this regard, Bohannon[13] compared the capacities of handgrip strength and knee extension strength to correlate with gait speed among elderly people. Knee extension forces showed a correlation with gait speed, whereas grip strength forces did not. Knee extension force measurements satisfactorily identified patients with gait speeds < 0.40 m/s. These results demonstrated the importance of lower limb strength over handgrip strength, in relation to functional performance.

Clinicians need to be cautious in generalizing from handgrip strength as a predictor of functional status. Muscles evaluated using a manual dynamometer are not recruited in tasks that involve supporting bodyweight; static contractions are rarely required for daily activities and the muscle strength of the upper and lower limbs is subject to differential decline.[14] Furthermore, other factors may have an influence on handgrip strength. These include grip size,[15] dominance,[16] genetic factors and anthropometric variables.[17,18]

Martien et al.[19] investigated whether knee extension strength is a better predictor of functional performance than handgrip strength. Their study sample consisted of 770 elderly people. Strength was measured using handgrip and knee extension tests. Functional performance was assessed by means of the six-minute walking distance test and a modified physical performance test. They found that only knee extension strength was clearly more predictive than handgrip strength. Recently, Wiśniowska-Szurlej et al. showed that there was a negative correlation between TUG test results and lower-limb strength.[20] This was supported by the findings of Zarzeczny et al.,[21] who showed that the results from the 30-second chair stand test were negatively correlated with those from the TUG test. Whenever possible, handgrip strength and knee extension strength should be used together to assess muscle strength and identify individuals who are vulnerable to poor health outcomes.

CONCLUSIONS

Knee extension strength and handgrip strength might be particularly useful indicators for screening for functional performance among elderly people. Whenever possible, the assessment strategies should be used in a complementary manner.

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Critical analysis on the use of cholecalciferol as a COVID-19 intervention: a narrative review

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KEY WORDS (MeSH terms):
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Coronavirus.

AUTHORS' KEY WORDS:
SARS-CoV-2.
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Prevention.
Treatment.

ABSTRACT

BACKGROUND: The World Health Organization has declared that a pandemic situation exists in relation to the disease caused by the new coronavirus, COVID-19. So far, the absence of a vaccine against the new coronavirus has led people worldwide to seek various therapeutic alternatives, including use of cholecalciferol.

DESIGN AND SETTING: Narrative review developed by a research group at a public university in Recife (PE), Brazil.

METHODS: We searched the literature on the use of cholecalciferol for prevention or treatment of COVID-19, using the MEDLINE and LILACS databases, with the keywords "vitamin D", "cholecalciferol", "SARS-CoV-2", "COVID-19" and "coronavirus", from January 1, 2020, to June 10, 2020. Narrative reviews, cohort studies and ecological studies were selected.

RESULTS: We retrieved 32 references, of which 8 were considered eligible for intensive review and critical analysis. These comprised five narrative reviews, two observational studies and one protocol proposal. Most of the studies selected reported positive effects from use of vitamin D for prevention or treatment of COVID-19. However, there was little quantitative data to assess the real impact of using this vitamin as an intervention against this disease.

CONCLUSIONS: Current studies on vitamin D used for purposes other than bone health promotion cannot be taken as support to justify its use in a disease as recent as COVID-19. Studies of greater robustness, with higher levels of clinical evidence, need to be conducted. Rational use of this vitamin needs to be ensured, thereby minimizing the impacts on the patient and the public healthcare system.

INTRODUCTION

In December 2019, a disease caused by a new coronavirus, COVID-19, caused an epidemic in China and then spread rapidly around the world.[1] The clinical spectrum of the disease caused by the new coronavirus is broad, covering asymptomatic infection, mild infection of the upper respiratory tract and severe pneumonia with respiratory failure. COVID-19 has led many patients to require hospitalization and semi-intensive or intensive care.[2,3] Most complications and deaths have been reported among elderly patients with evidence of underlying diseases, such as cardiovascular, lung or kidney diseases, or cancer.[1]

So far, the absence of a vaccine for the new coronavirus has led people around the world to seek a variety of therapeutic alternatives. Consequently, sales of several drugs that have not been proven to be effective for treating COVID-19 have increased. In Brazil, one of the drugs that have contributed to this statistic was cholecalciferol, also known as vitamin D3. According to data released by the Brazilian Federal Pharmacy Council, the sale of vitamin D grew by about 35% in the first months of 2020, compared with 2019.[4] One of the reasons for this increase is that some reports correlating use of cholecalciferol with an improvement in the immune response and reduced risk of respiratory tract infections have been published.[5-9] However, it needs to be emphasized that these associations have so far only been reported in observational studies and have not been confirmed through controlled clinical studies.[10]

The role of vitamin D in promoting bone health is now well established. Nonetheless, the amounts of supplemental vitamin D to be use remain a subject of constant debate in the 21st century.[11] However, use of cholecalciferol to treat a disease as recent as COVID-19, which is not supported by randomized clinical studies, inevitably falls into the category of irrational use. Irrational use of medicines is a matter of general concern for healthcare professionals, institutions and authorities.

This relates not to the intrinsic risk of the product but, rather, reflects flaws or errors within the process of using it that put users' safety at risk. Incidents with medications can result in physical, social or psychological damage to the patient, as well as contributing to longer hospital stay, which results in cost. These considerations also gain much greater weight in the context of the current pandemic.[12,13]

Some studies have investigated the use of cholecalciferol as a therapeutic alternative for prevention or treatment of COVID-19, but no reviews focusing on critical analysis of this use have yet been conducted.

OBJECTIVE

The objective of the current narrative review was to evaluate the proposition of using cholecalciferol for prevention or treatment of COVID-19 and the resulting implications.

METHODS

We conducted a review of the literature considering the period from January 1, 2020, to June 10, 2020. We used the MEDLINE database (via PubMed) and LILACS (via Virtual Health Library) to identify relevant articles from the starting point of a structured question, created in accordance with the acronym PICO (Population, Intervention, Comparator and Outcomes). The population was defined as "patients with a confirmed or probable diagnosis of COVID-19 infection" and the intervention considered was "vitamin D".

Because the analysis sought to find evidence about the use of a drug that would contribute to the clinical condition of the disease caused by the new coronavirus, terms that specified comparators, outcomes and types of study were not used. Different combinations of keywords and MeSH terms were used as search strategies to ensure a broad search strategy: "vitamin D", "cholecalciferol", "SARS-CoV-2", "COVID-19" and "coronavirus".

Firstly, the titles and abstracts of the references identified through the search strategy were screened, so that potentially eligible studies were preselected. Studies that were human trials, in English or Portuguese, in which immunological parameters in response to the viral infection caused by the new coronavirus were observed, were considered eligible. Animal studies, studies in languages other than Portuguese or English, letters, comments, reports, technical notes and editorial notes were excluded.

The articles thus selected were read in full, independently, by two authors. In cases of disagreement, a third reviewer was consulted. The following data were extracted: author, year of publication, country, study design, age of subjects (years on average), type of coronavirus, sample size, proportion of men (%), funding sources, intervention, comparator, outcomes (clinical, laboratory). In the second stage, the methodological quality and the risk of bias in the text were fully assessed using the Joanna Briggs and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) tools.[14,15]

RESULTS

From the search in the databases, 32 references were identified. After screening the titles and abstracts, eight studies were considered eligible for critical analysis. The search in LILACS using the keywords led to four results concerning the specific topic of interest, but these were excluded in accordance with the eligibility criteria, as described in **Table 1**.

The article selection process is detailed in **Figure 1**. In this process, out of the 32 records identified, only 23 remained after

Table 1. Search of the literature in medical databases, with search strategies used for each database and number of articles extracted

Database	Research strategies	Articles found
MEDLINE (via PubMed)	(Cholecalciferol) AND (coronavirus) OR (COVID-19) OR (SARS-COV2).	8
	(Vitamin D) AND (coronavirus) OR (COVID-19) OR (SARS-COV2).	20
LILACS (via Virtual Health Library)	(Cholecalciferol) AND (coronavirus) OR (COVID-19) OR (SARS-COV2).	0
	(Vitamin D) AND (coronavirus) OR (COVID-19) OR (SARS-COV2).	4

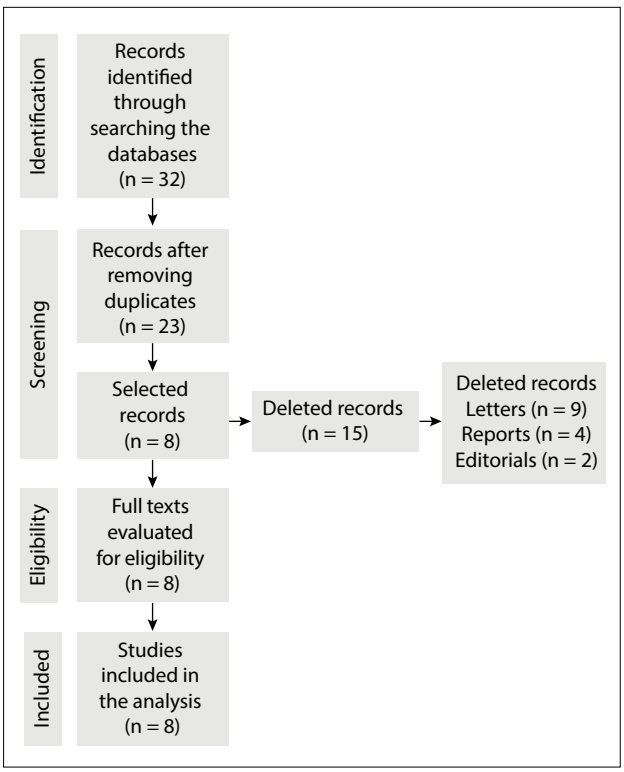

Figure 1. Flow diagram of the study selection process.

removing duplicates and, of these, only eight were selected as eligible, while the other 15 references were excluded through the criteria determined in the methodology, since they were letters, reports or editorials.

Most of the studies included in this review were narrative reviews (n = 5), and there was also one protocol proposal. For these, it was not possible to apply any tool to make an evidence-based critical evaluation. The remaining two studies were observational: one of retrospective nature and the other, an ecological cohort. Only these two studies were evaluated in relation to methodological quality and risk of bias. Despite a lack of robust quantitative data on vitamin D as an intervention against COVID-19, these two studies recommended its use.

DISCUSSION

Main findings

The urgent need to combat the current pandemic of the new coronavirus has led to publication of several new papers suggesting alternative means of therapeutic support, such as use of vitamin D. However, none of these studies have presented high methodological quality. The current review included eight studies, among which there were five narrative reviews, one observational study, one ecological study and one retrospective cohort study. The small number of primary studies on vitamin D for treating COVID-19 made the review difficult since narrative reviews have a high potential for bias.

Analysis on the protocol of the observational study

The study published by Caccialanza et al. suggested that vitamin D3 could be included in a protocol for early nutritional supplementation among patients with COVID-19, outside of the intensive care unit, with the aim of preventing or limiting malnutrition.[16] This clinical protocol was based on evidence from other studies on the use of vitamin D, added to different dietary supplements, for care relating to various viral infections. However, all the studies used in this article to justify the use of this vitamin in relation to non-skeletal clinical conditions, emphasized that the antiviral mechanism of vitamin D had not been fully established, and might not accurately represent its systemic influence. Therefore, it was concluded in those studies that there was a need to conduct well-designed clinical trials.[5-9]

Critical analysis on the narrative reviews

Although the role of vitamin D used for purposes other than bone health promotion is not well established, the five narrative reviews listed in our search were based on the supposed role of this vitamin in providing immunity and/or treating viral respiratory infections, with the aim of suggesting that it might be possible to use it as an intervention tool against COVID-19.[17-21]

According to Iddir et al., vitamin D has the particular capacity to interfere with viral cell infection through interaction with angiotensin-converting enzyme 2 (ACE2) cell input receptors (which are responsible for allowing the virus to enter the host cell).[21] However, some studies have suggested that vitamin D can downregulate the ACE2 receptor, thus decreasing the risk of COVID-19 infection. On the other hand, other studies have suggested that vitamin D positively regulates ACE2, which would increase the level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, thereby indicating contradictory results with limited evidence.[22]

Additionally, the narrative review published by Zabetakis et al.[20] also showed that the data on vitamin D and immune function is ambiguous. A meta-analysis on 25 randomized clinical trials, including 11,000 patients cited by these authors, analyzed the general protective effect of vitamin D supplementation against acute respiratory diseases. However, those trials were inconclusive. Moreover, other studies on vitamin D have not shown that this has any benefit beyond bone health promotion.[21,23] Nonetheless, several authors have speculated that occurrences of low levels of vitamin D may play a role in enabling high incidence of COVID-19, especially because these outbreaks have occurred in winter, as exemplified in a study published by Grant et al.[17,20]

Grant et al. analyzed the role of vitamin D in reducing the risk of respiratory tract infections, through an epidemiological study on influenza and COVID-19 and how vitamin D supplementation can be a useful measure for reducing the risk. According to this narrative review, the evidence that vitamin D has a role in reducing the risk of COVID-19 includes the following facts: the outbreak was during the northern hemisphere winter, when the concentrations of 25(OH)D are at their lowest; the number of cases in the southern hemisphere near the end of its summer was low; vitamin D deficiency contributes to acute respiratory distress syndrome; and lethality rates increase with age and with chronic disease comorbidity, which are both associated with lower concentrations of 25(OH)D.[17]

Not surprisingly, it has been found that serum levels of 25(OH) D are lower in patients with moderate to severe forms of COVID-19, since the comorbidities commonly presented by these individuals (chronic diseases, inflammatory diseases, obesity and diabetes) are primarily associated with vitamin D deficiency. However, this association does not determine causality and, so far, no randomized clinical study has shown any benefit from use of vitamin D in relation to prevention or treatment of COVID-19, as has been highlighted by the Brazilian Society of Endocrinology and Metabology (SBEM).[10]

The review carried out by Grant et al.[17] used data from many articles to address the possible extra-bone effects from use of vitamin D. However, most of these studies were observational and presented high risk of bias. Five clinical studies correlating use

of vitamin D with colds and flu are mentioned in the review by Grant et al., but only two of these reported any beneficial effects.[24-28] Those authors further stated that, to reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 should consider taking 10,000 international units (IU)/day of vitamin D3 for a few weeks to rapidly increase their concentrations of 25(OH)D, followed by 5,000 IU/day.[17]

Nevertheless, another narrative review, published by Hribar et al.,[19] also suggested that daily supplementation of 2,000-5,000 IU/day of vitamin D3, specifically for elderly people with Parkinson's disease, could offer additional protection against COVID-19.[19] Grant et al. also argued that, for the treatment of people infected with COVID-19, higher doses of vitamin D 3 might be useful.[17]

Likewise, a narrative review published by Calder et al.[18] showed, among other conclusions, that supplementation above the recommended dose, but within the safety limits for specific nutrients such as vitamins C and D was necessary in order to increase the resistance to respiratory infections, such as those caused by COVID-19.[18]

Although the authors of the narrative reviews emphasized that further studies were needed because of the current situation relating to the outbreak of COVID-19, it needs to be emphasized that, although the possible extraskeletal action of vitamin D is a topic of scientific interest, no indications for prescription of vitamin D supplementation aimed at effects beyond bone health promotion have yet been approved.[10] Consequently, additional research, with better methodological quality and evidence, is needed before any determination can be made regarding the prophylactic or therapeutic value of vitamin D against COVID-19.[29]

Critical analysis on the original studies

Two original studies, a cross-sectional/ecological study published by Ilie et al.[30] and a retrospective cohort study published by D'Avolio et al.,[31] suggested that a relationship exists between serum vitamin D levels and COVID-19 infection.

The cross-sectional/ecological study published by Ilie et al.[30] showed that there were significant associations between vitamin D levels, the number of cases of COVID-19 and the mortality caused by this infection. These authors suggested that, in several European countries, serum vitamin D levels were strongly associated with the numbers of cases of the disease caused by the new coronavirus and that supplementation with this vitamin could protect against infection by SARS-CoV-2.[30] However, they did not clarify the period of the year over which the serum vitamin D levels were verified in the countries evaluated. This is important because these serum levels are derived from exposure to sunlight, which is influenced by several factors such as latitude, season and local weather conditions.[32] Furthermore, the number of cases per country is affected by the number of tests performed and also by the different measures taken to prevent spreading of the infection. Therefore, the results from this study need to be interpreted cautiously. The authors themselves emphasized that the hypothesis towards which their study pointed would need to be taken forward and investigated using study designs of greater robustness.

The retrospective cohort study published by D'Avolio et al.[31] proposed that concentrations of 25-hydroxyvitamin D would be lower in patients with SARS-CoV-2 who were positive for C-reactive protein (CRP).[31] The study was conducted in Switzerland, among 1,484 patients of both sexes and of ages ranging from 18 to 70 years. However, although its design presented greater strength of evidence than the studies cited above (observational study and narrative reviews), no inclusion/exclusion criteria were established among the study groups. Thus, the only variables assessed were sex and age. Consequently, the profile of the patients seen remained unclear with regard to disease severity, and the description of the study subjects did not allow verification of whether the populations were comparable. Considering that most complications and deaths due to COVID-19 have been reported among elderly patients with evidence of underlying diseases, such as cardiovascular, pulmonary or kidney disease, or cancer, the limiting criteria established in this study increased the risk of bias.[1] Additionally, it needs to be considered that vitamin D levels may also vary according to hormonal, genetic and nutritional factors.[33] Thus, the analysis did not allow identification of whether vitamin D deficiency was an underlying illness rather than the cause. Confounding factors would therefore possibly arise, especially due to the lack of information about the population at the baseline, which could influence the direction of the results. Although the authors considered some of these factors, they did not describe the strategies used to deal with confounding factors.

Therefore, it becomes evident that further research needs to be conducted, especially given that the amount of supplemental vitamin D to be administered continues to be a matter for debate in the 21st century, even in relation to well-established diseases such as those linked to mineral metabolism. The discussion becomes even more complex with regard to a disease as recent as that caused by the new coronavirus.[11,34]

Thus, the urgent need to combat the current pandemic must not override the need to make rational use of medicines. In the case of cholecalciferol, several studies have suggested that vitamin D intoxication may occur when doses greater than 10,000 IU are administered daily, for periods lasting from several months to some years.[35] Therefore, building up a toxic dose of vitamin D through supplementation is a real possibility. This can lead to consequences such as hypercalcemia and hypercalciuria, with consequent risks of renal failure, seizures and death.[10,36,37]

In Brazil, medications are responsible for more than 52% of intoxications in this country, and 15% to 20% of hospital budgets are spent on treatment of complications resulting from them.[38,39] Considering that public healthcare systems worldwide are becoming

depleted through the current pandemic, it is essential that events caused by irrational use of medicines should be avoided and that extrapolation of their use to form treatments for COVID-19 should be discussed better and be based on well-supported clinical studies.

Strengths and limitations

The articles included in this review generated heterogeneous data because of the diversity in the design of the studies (five narrative reviews, two observational studies and one treatment protocol).

The main limitation of this review was the lack of tools for methodological assessment of narrative reviews. Nonetheless, these reviews were maintained in the present study in view of the scarcity of data on the use of vitamin D for treatment of COVID-19. The studies lacked high levels of scientific evidence to support their conclusions.

As far as we know, this was the first study to critically review and evaluate the use of vitamin D as an intervention tool for treatment of COVID-19. Thus, this study is of great value for safe decision-making regarding rational use of this medicine in the context of the current pandemic.

CONCLUSIONS

In the studies included through the systematic search of this review, no robust and conclusive evidence regarding the effectiveness of the use of vitamin D for prevention or treatment of COVID-19 was identified. The studies analyzed presented limitations regarding their designs and methodologies, which implied high risk of bias.

Thus, the current studies on use of vitamin D for purposes other than bone health promotion cannot be taken as support for justifying its use in a disease as recent as COVID-19. Hence, further studies with greater robustness of clinical evidence need to be conducted. Through this, rational use of this vitamin will be ensured and the impacts on patients and the public healthcare system will be minimized.

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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 in the PROSPERO database. 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]

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 "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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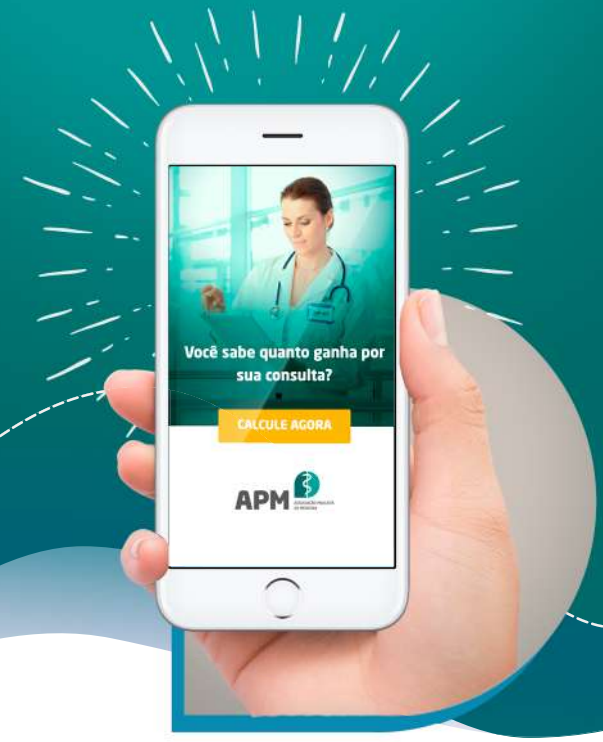

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