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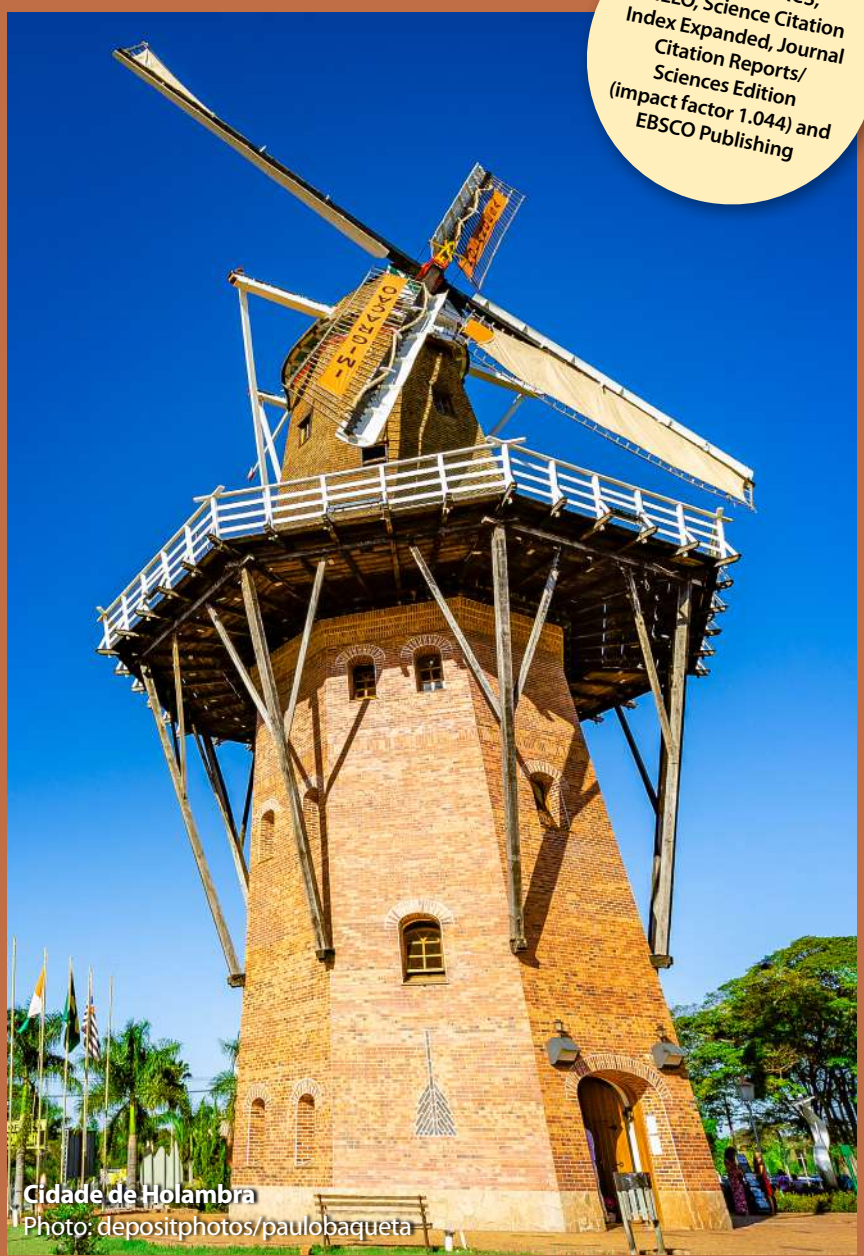

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Web of Science Journal Citation Report 2020: the Brazilian contribution to the "Medicine, General & Internal" category of the journal impact factor (JIF) ranking (SCI 2019)

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To be included in the "Medicine, General & Internal" category of the Web of Science Journal Citation Report is a distinction for a select group of 165 journals that are considered to be the most influential in this category worldwide. This means standing shoulder-to-shoulder with giants like the New England Journal of Medicine, Lancet, JAMA, BMJ and Annals of Internal Medicine. Here, we wish to highlight the Brazilian presence among these journals.

The Web of Science (WoS) is a multidisciplinary database that provides access to 12,171 scientific journals, and it is edited under the responsibility of the company Clarivate Analytics. It is made available in Brazil through the journals portal of the Brazilian government's funding agency CAPES, to all institutions that are members of this portal.

The Web of Science Journal Citation Report (JCR) identifies and evaluates the most important science and social science journals worldwide and offers analysis on journal performance. It thus reflects the scientific and academic literature of the highest quality**.** The information that the JCR provides includes the total numbers of articles and citations, and data on the journals cited and those citing them, along with other analyses.[1]

The journal impact factor (JIF), published annually, has been eagerly awaited by researchers and journal editors around the world for the last 40 years. Its bibliometric mission has steered the scientific community towards editorial rigor and its results have influenced policies, partnerships, classifications and scientific analyses.

How is the JIF calculation made? The JIF of a given periodical for any given year (for example, 2020) is calculated from citations made during the previous year (2019, in this example) for items published in the two preceding years (2017 + 2018, in this example), divided by the number of citable items in these two years (2017 + 2018), published in that periodical.

The core collection of the Web of Science is composed of ten indexes containing thousands of periodicals. Three main citation indexes are responsible for the JIFs calculated from authors' citations, namely: Science Citation Index Expanded (SCI-Expanded), covering the years from 1900 to today (in which the São Paulo Medical Journal is included); Social Sciences Citation Index (SSCI), covering the years from 1900 to today; and Emerging Sources Citation Index (ESCI), covering the years from 2005 to today.[1] A fourth major index, the Arts & Humanities Citation Index (A&HCI), covering the years from 1975 to today, is not used to generate an impact factor.

"MEDICINE, GENERAL & INTERNAL" CATEGORY (SCI 2019)

The "Medicine, General & Internal" category of the SCI is formed by a total of 165 journals that are considered to be the group of periodicals within this field that are most influential worldwide. **Table 1** shows the top ten of these 165 journals and also highlights the three Brazilian journals that also form part of this very select list, together with their respective JIFs.[-2]

The São Paulo Medical Journal is ranked 116th in terms of its JIF, and the Cochrane Database of Systematic Reviews is ranked 10th, among the journals in which there is Brazilian participation. To plant its flag in the land of giants, the São Paulo Medical Journal has, since 1932, taken the firm stance of placing value on its authors and editors and has traced out clear aims in analyzing the international trends of major journals. Through this initiative, it has over recent years been attaining the desired recognition among its peers, in terms of JIF. The calculation is shown below.[2]

Journal impact factor (JIF) calculation for the São Paulo Medical Journal (SPMJ)

JIF calculation for SPMJ

$$\text{2019 JIF} = \frac{166}{159} = 1.044$$

How is the JIF calculated?

$$\text{JIF} = \frac{\text{Citations in 2019 of items published in 2017 (108) + 2018 (58)}}{\text{Number of citable items in 2017 (75) + 2018 (84)}} = \frac{166}{159}$$

In the 2020 edition of the JCR, among the 12,171 journals that it encompasses, 1,658 journals are classified as gold open access journals. **Table 2** shows that the São Paulo Medical Journal is in this category, which means that all its articles are made public and accessible free-of-charge. This enables immediate use of them, thus contributing to the worldwide movement advocating open access.[2]

The Cochrane Database of Systematic Reviews is the periodical that is ranked tenth regarding its JIF. This ranking was achieved with participation from Brazil. **Table 3** demonstrates that Brazil was in 16th place as a contributor to its JIF, with 62 citations.

The Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) was the only Brazilian institution to contribute citations to the JIF of the Cochrane Database of Systematic Reviews. In the 2018 edition of the JCR, it was one of the top 50 institutions contributing to the JIF of this periodical, occupying 44th place (**Table 4).**

For journals to be accepted into this database, they are evaluated in terms of 28 criteria relating to quality, impact and editorial assessment. Thus, these journals have met these rigorous standards (**Table 5**).[3]

There is no doubt that Brazilian science is well disseminated through several international databases and through the best journals. The São Paulo Medical Journal is proud to be among them.

It can also be asked, "Is being part of this scenario significant?" The response has to be affirmative. The São Paulo Medical Journal and the other two Brazilian periodicals (Clinics and Revista da Associação Médica Brasileira) that form part of this group are among the most influential journals in the world, with a JIF that can reach 74.699, which is very considerable and highly important.

The São Paulo Medical Journal provides an international window for health science results produced mostly by Brazilian researchers, with support from the recent and previous boards of directors of the São Paulo Medical Association (Associação Paulista

Table 1. "Medicine, General & Internal" category rankings (SCI 2019)[2]

Ranking	"Medicine, General & Internal" journals	Journal impact factor
1.	New England Journal of Medicine	74.699
2.	Lancet	60.392
3.	JAMA – Journal of the American Medical Association	45.540
4	Nature Reviews Disease Primers	40.689
5.	BMJ – British Medical Journal	30.223
6.	Annals of Internal Medicine	21.317
7.	JAMA Internal Medicine	18.652
8.	PLOS Medicine	10.500
9.	Journal of Cachexia Sarcopenia and Muscle	9.802
10.	Cochrane Database of Systematic Reviews	7.890
.....	**Three Brazilian journals are included among the 165 journals in this category:**	
96.	**Clinics**	**1.435**
116.	**São Paulo Medical Journal**	**1.044**
128.	**Revista da Associação Médica Brasileira**	**0.915**

Table 2. Articles published in the São Paulo Medical Journal (SPMJ) in 2017 that were most cited in 2019; and the number of citations of each of these articles that were counted towards the journal impact factor. The arrow highlights the open padlock symbol that signifies that the SPMJ is a gold open access journal

Article	Number of citations
Comparison of machine-learning algorithms to build a predictive model for detecting undiagnosed diabetes ELSA-Brasil: accuracy study By: Olivera, Andre Rodrigues; Roesler, Valter; Iochpe, Cirano; Schmidt, Maria Ines; Vigo, Alvaro et al. Volume 135 Page: 234-246 Accession number: WOS:000406339500006 Document type: Article	9
Mortality due to noncommunicable diseases in Brazil, 1990 to 2015, according to estimates from the Global Burden of Disease study By: Malta, Deborah Carvalho; Naghavi, Mohsen; Franca, Elisabeth; Xavier Abreu, Daisy Maria; Perillo, Rosangela Durso et al. Volume 135 Page: 213-221 Accession number: WOS:000406339500003 Document type: Article	8
The role of dietary fatty acid intake in inflammatory gene expression: a critical review By: Rocha, Daniela Mayumi; Bressan, Josefina; Hermsdorff, Helen Hermana Volume 135 Page: 157-168 Accession number: WOS:000402009700011 Document type: Review	6
Potential mechanisms linking probiotics to diabetes: a narrative review of the literature By: Miraghajani, Maryam; Dehsoukhteh, Somayeh Shahraki; Rafie, Nahid; Hamedani, Sahar Golpour; Sabihi, Sima et al. Volume 135 Page: 169-178 Accession number: WOS:000402009700012 Document type: Review	5
Non-invasive brain stimulation and computational models in post-stroke aphasic patients: single session of transcranial magnetic stimulation and transcranial direct current stimulation. A randomized clinical trial By: dos Santos, Michele Devido; Simis, Marcel; Bikson, Marom; Gagliardi, Rubens Jose; Cavenaghi, Vitor Breseghello et al. Volume 135 Page: 475-80 Accession number: WOS:000417223700010 Document type: Article	5
Liver failure following biliopancreatic diversions: a narrative review By: Cazzo, Everton; Pareja, Jose Carlos; Chaim, Elinton Adami Volume 135 Page: 66-70 Accession number: WOS:000398127000010 Document type: Review	5
Sensory-motor training versus resistance training among patients with knee osteoarthritis: randomized single-blind controlled trial By: Gomiero, Aline Bassoli; Kayo, Andrea; Abraao, Marcelo; Peccin, Maria Stella; Grande, Antonio Jose et al. Volume 135 Page: 44-50 Accession number: WOS:000428567400007 Document type: Review	4

Table 3. Citations contributing to the journal impact factor (JIF) of the Cochrane Database of Systematic Reviews, according to country

Rank	Country	Citation count
1.	England	932
2.	Australia	416
3.	United States	358
4.	Canada	272
5.	Netherlands	157
6.	Scotland	142
7.	China Mainland	129
8.	Italy	126
9.	Germany (Fed Rep Ger)	122
10.	New Zealand	117
11.	Denmark	86
12.	Switzerland	86
13.	India	71
14.	Ireland	68
15.	Spain	65
16.	Brazil	62

Table 4. Citations contributing to the journal impact factor (JIF) of the Cochrane Database of Systematic Reviews, according to institutions and organizations. The arrow highlights the participation of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP)

Rank	Institution/organization	Citation count
41.	Queens University Belfast	29
42.	World Health Organization	29
43.	Hospital for Sick Children (SICKKIDS)	28
44.	Universidade Federal de São Paulo (UNIFESP)	27
45.	University College London Hospital NHS Foundation Trust	27
46.	NHS Blood & Transplant	26
47.	University of Aberdeen	26
48.	South Australian Health & Medical Research Institute (SAHMRI)	25
49.	Vrije Universiteit Amsterdam	25
50.	Harvard University	24
51.	Norwegian Institute of Public Health (NIPH)	24
52.	Radboud University Nijmegen	24
53.	University of Milan	24

Table 5. Quality, impact and editorial evaluation criteria that journals need to meet in order to be included in the Web of Science

Quality criteria	Impact criteria
ISSN	Comparative analysis on citations
Title	Analysis on authors' citations
Journal publisher	Analysis on editorial board's citations
URL (online journals)	Significance of published content
Content access	
Presence of a peer review policy	
Contact details	
Academic content	**Editorial evaluation criteria**
Article titles and abstracts in English	Editorial board structure
Bibliographic information	Validity of declarations
Clarity of language	Peer review
Punctuality and publication volume per year	Content relevance
Website functionality/journal format	Funding details (acknowledgements)
Presence of ethics declarations in the journal	Adherence to community standards
Details of editorial board affiliations	Author distribution
Details of author affiliations	Auto-citations of the journal

de Medicina). We also send our compliments to the editors of the journals Clinics and Revista da Associação Médica Brasileira.

It is important to highlight the major contributions that have been made from Brazil to the Cochrane Library, which equal those of more-developed countries. Free-of-charge access to the Cochrane Library has been available for all Brazilians since 2001 (https://www.cochranelibrary.com/). This was achieved thanks to yearly efforts made by Cochrane Brazil's Director, with support from the Pan-American Health Organization (PAHO) via BIREME in the beginning and from CAPES and the CAPES portal more recently.

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Does Enoxaparin treatment have any effects on the placenta in women with unexplained histories of habitual abortion? A case control study

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Heparin, low-molecular-weight.
Apoptosis.
Placenta.

AUTHORS' KEY WORDS:
Livebirth rate.
Trophoblast proliferation.
Vascularization.

ABSTRACT

BACKGROUND: It is very common to offer low molecular weight heparin (LMWH) medications to women with unexplained habitual abortion, to increase the livebirth rate. Although no benefit from LMWH has been clearly demonstrated, examination of the effects of enoxaparin on placental structure is lacking.

OBJECTIVE: To assess placental structural changes in pregnancies treated with enoxaparin, compared with controls.

DESIGN AND SETTING: Case-control study in an obstetrics and gynecology unit of a tertiary-level university hospital in Turkey.

METHODS: Forty patients who had had term pregnancies and live births but also histories of habitual abortion were recruited for this study. Placentas were sampled using a systematic random sampling method. Tissue samples were obtained, embedded and sectioned for routine histological analyses. Hematoxylin and eosin staining was used. Surface area and length estimates from placental components were evaluated by using Image J. Cell proliferation and apoptosis were also assessed via immunohistochemistry.

RESULTS: There were no significant differences between the groups regarding maternal age, abortion rate, birth weight or gestational age. Comparison of the enoxaparin and control groups showed that there were no significant differences in terms of surface area and ratios of placental components. We found that Bcl-2 was generally expressed at high levels in the enoxaparin group, while there was no difference in terms of Ki-67 between the groups.

CONCLUSIONS: This study demonstrates that enoxaparin did not show any significant effect on the placental structure of cases that had histories of habitual abortion.

INTRODUCTION

Habitual abortion is defined as the loss of three or more consecutive pregnancies prior to 20 weeks of gestation or a fetus weighing less than 500 g.[1] Approximately 1%-2% of all women are affected.[2] The etiology of habitual abortion is multifactorial and may include genetic, anatomical, infectious, thrombotic, autoimmune and endocrine causes.[3] Although there is no established therapy for treatment of this patient group, it has been reported in several studies that use of progesterone and low-dose aspirin may be effective.[4-6] Antenatal genetic consultations and psychological support are very important. Even though most published reports in the literature have failed to show any beneficial effect from low molecular weight heparin (LMWH) in enhancing the livebirth rates among women with unexplained habitual abortion,[7-9] some other studies have suggested that the use of LMWH is beneficial.[10] The mechanisms through which enoxaparin might have an effect during pregnancy are unclear.

The development of the placenta, starting with invasion of fetal trophoblast cells into the decidua in the early phase of pregnancy, is very important for the continuation of pregnancy. This process involves division, migration and differentiation of many cells and creates a dense vascular network. The placenta has been evaluated in many studies on patients with habitual abortion and some pathological conditions have been thought to cause abortion.[11]

Apoptosis is seen more frequently in the placenta of patients with habitual abortion than in that of patients with spontaneous abortion.[12] In addition, it has been shown that perivillous fibrin deposition, chronic villitis, chronic histiocytic intervillositis, and plasma cell deciduitis are higher in chromosomally normal habitual abortions than in spontaneous abortions.[13,14,15] Previous studies

have also shown that placental invasion disorder is high, rather than thrombosis, in patients with habitual abortion.[16,17]

OBJECTIVE

The aim of this study was to investigate placental changes in pregnancies with and without enoxaparin treatment, among patients who reached term and delivered healthy newborns.

METHODS

Ethical approval

The study was approved by the ethics committee of the Ondokuz Mayıs University, Samsun, Turkey, under the number 2019/725 on September 25, 2019. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

An informed written consent was obtained from patients or their relatives after the purpose of the study had been fully explained.

Study design

All placental samples were obtained with local ethics committee approval, and informed consent was obtained from each patient. All the participants recruited were pregnant women with a history of miscarriage and they delivered live babies in the third trimester of this pregnancy. Before the start of the experiment, the reason for habitual abortion was investigated and no uterus anomaly, genetic pathology or antiphospholipid syndrome was detected in any of the patients. Patients with maternal diabetes, hypertension, kidney and liver disease, preeclampsia, intrauterine growth restriction and gestational diabetes were excluded. Furthermore, patients with a history of abortion due to antiphospholipid syndrome, identified uterine anomaly or known genetic pathological condition were also excluded from the study.

Placental samples were collected between September and December 2019, from 40 cases with or without enoxaparin treatment between January and September 2019. Twenty patients with a history of abortion and who were taking enoxaparin (Clexane 4000 anti-Xa IU/0.4 ml; Sanofi Aventis) during pregnancy were included in the enoxaparin group. Twenty patients with a history of abortion and who did not use any medications and then delivered live births at the third trimester were included in the control group. None of the patients had heparin-related complications, such as bleeding or allergies. All placentas were collected at delivery for the histological examination. Age, parity, previous abortions and weight were all recorded in relation to these forty patients.

Placental sampling

After removing blood coagula and membranes, all placental samples were immersed in buffered formalin at least 72 hours. Two tissue samples were collected from each placenta. The fetal side of each placenta, in relation to the umbilical cord, was located and the tissue was marked by cutting 3 cm into the tissue on the right and left sides of the insertion of the umbilical cord. Full-depth columns of placental tissue were sampled as previously described.[18]

The tissue samples were washed overnight under a tap, dehydrated through a graded ethanol series (50, 70, 90 and 100%) (Sigma-Aldrich, USA), cleared in xylene (Merck, Darmstadt, Germany) and embedded in paraffin wax blocks. These paraffin-embedded tissue blocks were cut at a nominal section thickness of 5 μm using a microtome (RM2125RT; Leica, Nussloch, Germany). The sections were then dewaxed, rehydrated and stained with hematoxylin and eosin.

Three sections from each placental block were randomly selected and twelve microscope fields per section were captured (20x objective) by means of systematic random sampling.[19] A total of 72 fields were analyzed from each patient's samples. Images were collected using an Olympus BH2 microscope (Olympus, Tokyo, Japan) coupled to an F10 CCD digital camera (Panasonic, Osaka, Japan), and using the Pinnacle imaging software (Studio MovieBox Plus 710, Netherlands). The images thus acquired were analyzed using the ImageJ (NIH Software, Bethesda, MD, USA).

Microscopic analyses

To measure placental differences, we estimated the mean cross-sectional areas of the stem (primary villus), secondary and tertiary villi and blood vessels, together with measurements of villus vascularization (vessel area to villus area ratios). In addition to measuring villus vascularization, we also estimated the diameter and thickness of the arteries within the stem villi. The ratios between the villus surface areas were used to monitor placental growth. To estimate the intervillous spaces, the total surface area of all the villi was summed up and then subtracted from the total surface area. In addition, we assessed the mean area of fibrin deposits on the peripheral surface of the villi, along with the mean area of syncytial knots and the thickness of syncytial trophoblasts.

Immunohistochemical analyses

The avidin-biotin-peroxidase method was used for immunostaining. To detect Ki-67 and Bcl-2 antigen staining, 5 μm sections of placental samples were mounted on poly-l-lysine-coated slides and were separately incubated in the following antibodies: Ki-67 (SP6) rabbit monoclonal antibody (RM-9106-S1; NeoMarkers, CA, USA; diluted 1:50 in PBS),[20] overnight at 4 °C;

mouse anti-human Bcl-2 monoclonal antibody (Oncogene, Boston, MA, USA; diluted 1:20 in PBS),[21] overnight at 4 °C; and biotinylated goat anti-polyvalent secondary antibody (TP-125-BN; Thermo Scientific, Fremont, CA, USA), for 25 minutes at 25 °C. Sections were also incubated with the avidin-biotin-peroxidase complex (Vectastain Elite ABC kit; Vector, Burlingame, CA, USA; diluted 1:50 in PBS) for 45 minutes at 25 °C. Peroxidase activity was detected using 3-amino-9-ethylcarbazole (AEC) chromogen (TA-125-SA; Thermo Scientific, Fremont, CA, USA) and these sections were lightly counterstained in Mayer's hematoxylin (Merck, Darmstadt, Germany).

Fifteen fields were selected randomly in regions with Ki-67 positive nuclei and were examined at 100x magnification. Immunoreactivity was scored in more than 500 cells in villus cytotrophoblasts and in villus stromal cells, fetal endothelial cells and cells in the chorionic and basal plates of the placenta, for each case. For semiquantitative analysis of immunoreactivity, H-scores were used in this study, as previously described.[22]

Statistics

Means and standard errors of the means were calculated for each group. Data distribution was tested using the Shapiro-Wilk normality test. The independent-sample t-test was used to compare normally distributed data between the enoxaparin and control groups. The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc, Chicago, IL, USA). Significance was accepted at $P < 0.05$.

RESULTS

The mean maternal age, abortion rate, birth weight and gestational age did not differ between the two groups ($P > 0.05$) (**Table 1**). Comparison of placental area between the enoxaparin and control groups showed that there was no overall statistical difference. There was no significant difference between any groups regarding intervillous space area (**Table 2**). Comparison of stem, secondary and terminal villus areas between the enoxaparin and control groups did not show any statistical difference ($P > 0.05$).

While there was no significant difference between the groups in terms of the area of placental vascularization, the area of the tertiary blood vessels in the women treated with enoxaparin was slightly smaller than that of the controls (**Table 3**). There was no significant difference in stem villus artery thickness and diameter between the enoxaparin group and the control group ($P > 0.05$).

Table 1. Comparisons of the mothers' demographic characteristics between the enoxaparin and control groups

	Enoxaparin group	Control group	P-value
Age	28.2 ± 5.7	29.9 ± 5.1	0.294
Abortion rate	2.8 ± 1.1	3.1 ± 1.1	0.283
Birth weight (g)	3253.9 ± 396.4	3241.9 ± 374.8	0.918
Gestational age (weeks)	37.8 ± 1.3	37.7 ± 1.3	0.775

Table 2. Surface area and ratios of placental components

	Enoxaparin group	Control group	P-value
Total villus surface area (μm^2)	3420463.6 ± 316931.8	3311996.6 ± 314831.2	0.284
Intervillous space area (μm^2)	1638872.7 ± 362628.8	1779039.4 ± 314831.2	0.200
Fibrotic area (μm^2)	183088.9 ± 113711.5	167556.2 ± 113984.4	0.669
Stem villus surface area (μm^2)	1381308.5 ± 415346.7	1313494.8 ± 458938.9	0.627
Stem villus/total villus surface area	0.27132168	0.25800148	
Secondary villus surface area (μm^2)	766550.1 ± 277585.1	767964.9 ± 359767.6	0.989
Secondary villus/total villus surface area	0.15056859	0.15084648	
Tertiary villus surface area (μm^2)	1089516.2 ± 369572.6	1046972.6 ± 301399.7	0.692
Tertiary villus/total villus surface area	0.21400677	0.20565021	
Syncytial trophoblast thickness (μm)	26.5 ± 3.5	28.3 ± 5.2	0.196
Syncytial knot surface area (μm^2)	28311.8 ± 10335	23265.4 ± 10810.1	0.140

Table 3. Surface area and ratios of blood vessels

	Enoxaparin group	Control group	P-value
Stem villus artery surface area (μm^2)	137781.2 ± 106295.9	95878.2 ± 39147.7	0.106
Stem villus artery/stem villus surface area	0.10347815	0.08566299	
Secondary villus blood vessel surface area (μm^2)	95942.1 ± 56797.6	114429.3 ± 77698.8	0.396
Secondary villus blood vessel/ secondary villi surface area	0.12667177	0.11121584	
Tertiary villus blood vessel surface area (μm^2)	198576.9 ± 126475.7	218740.5 ± 86191.5	0.559
Tertiary villus blood vessel/ tertiary villus surface area	0.18101836	0.21258895	
Stem villus artery diameter (μm)	218.7 ± 87.7	195.4 ± 67.4	0.351
Stem villus arterial wall thickness (μm)	72.9 ± 27	68 ± 32.9	0.610

Syncytial trophoblast thickness was slightly decreased in the enoxaparin group, compared with controls but without any statistically significant difference. Syncytial knot areas were increased in the enoxaparin group, compared with the controls (**Table 2**).

Cell proliferation was assessed using the Ki-67 assay and was apparent in the nuclei of the villus trophoblasts in both groups. Immunoreactivity of syncytial trophoblasts was also found in the syncytial knots. Statistically, there were no significant differences between the groups in terms of Ki-67 immunoreactivity ($P > 0.05$) (**Figure 1**). Immunoreactive Bcl-2 protein was detected immunoenzymatically in all groups, to assess apoptosis. Immunopositive cells were located especially in the syncytial trophoblast cytoplasm of the intermediate and terminal villi and were seen as a strong, brown, cytoplasmic stain (**Figure 2**). In the enoxaparin group, the trophoblasts lining the villi exhibited positive cytoplasmic areas that were continuous with non-labeled cytoplasm. A significant increase in the mean number of Bcl-2 immunoreactive cells was found in the placental villi of the enoxaparin group, compared with the control group ($P \leq 0.01$).

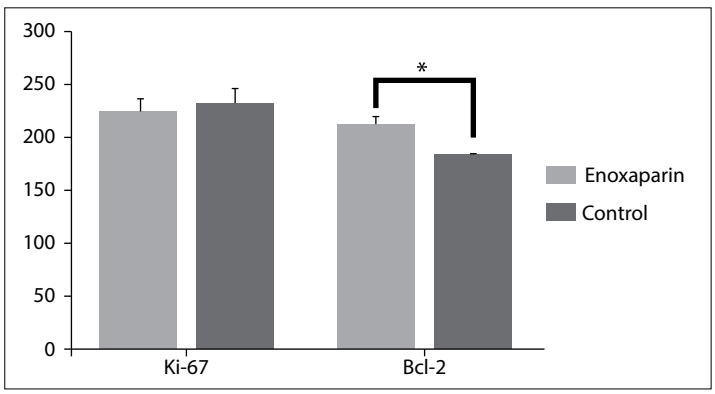

Figure 1. Average H-scores for Ki-67 and Bcl-2 in the enoxaparin and control groups. *Represents the statistical difference between the groups, $P \leq 0.01$.

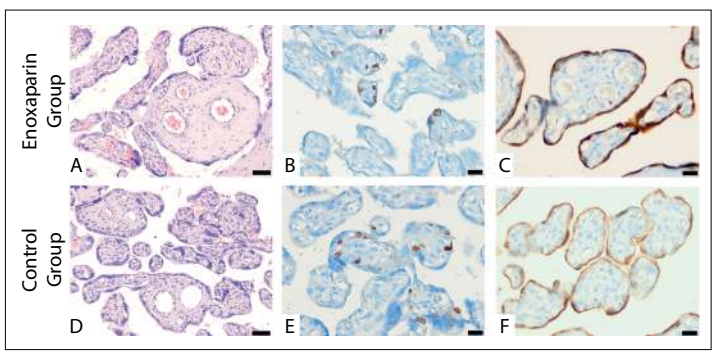

Figure 2. Stained sections from term placentas in the enoxaparin and control groups: hematoxylin-eosin (H&E) staining (A and D, obj. 10x) and immunoreactivity for Ki-67 (B and E, obj. 40x) and Bcl-2 (C and F, obj. 40x). Expression of Ki-67 and BCL-2 in normal-term villous cytotrophoblast tissue was viewed by means of rabbit monoclonal Ki-67 antibody and mouse anti-human Bcl-2 respectively. The specimens were counterstained with Mayer's hematoxylin. Bar (A and D): 50 µm; bar (B, C, E and F): 20 µm.

DISCUSSION

The placenta is an important organ for the continuation of pregnancy. Morphometric investigation of the placenta is crucial for understanding the pathogenesis of disorders affecting the fetus. The placental villus area changes depending on the level of placental ischemia.[23] The intervillous space decreases through invasion of syncytial trophoblasts, accumulation of fibrous tissue and syncytial degeneration due to deepithelization.[24] Syncytial knots emerge through accumulation of syncytial nuclei, and the number of knots increases with rising malperfusion and hypoxia levels.[25] Perivillous fibrin storage takes place in the eosinophilic fibrin conglomeration around the villi.[26] The fibrin accumulation disrupts oxygenation around the villi and causes ischemic necrosis.[15]

We did not notice any differences regarding villus area, intervillous area, syncytial knot area and fibrotic area between the patients who underwent enoxaparin treatment and those who did not, in investigating the placentas belonging to pregnancies with term live births that were obtained from our patients with previous histories of unexplained habitual abortion. It had already been observed that the levels of placental perivillous fibrin, chronic villitis and plasma cell deciduitis were higher in patients with recurrent abortion who presented normal karyotypes, compared with patients with spontaneous abortion.[14]

It was also previously seen that there was more infarct, fibrin deposition, syncytial knot development and fibrosis in the placenta of patients with antiphospholipid antibody syndrome (APS) and antiphospholipid antibody-like syndromes (APS-like), compared with normal patients. Moreover, when patients with APS and APS-like syndromes who underwent either normal birth or abortion were compared, their placental histological findings were similar between the two populations.[27] In comparing APS-positive and negative patients, patients with chromosome anomalies and patients in a control group, it was noted that there was no significant difference among the groups regarding intervillous thrombus.[17]

In another study, it was postulated that chronic histiocytic intervillositis was associated with recurrent abortion.[13] In placental studies, it was noticed that placental trophoblast invasion disorder is more common than placental thrombosis among thrombophilic patients.[13,16,17] In our study, it was found that the syncytial trophoblast thickness decreased but that the stem villus artery diameter was increased in the patients who underwent heparin treatment, compared with those who did not receive any treatment. However, these findings did not present any statistically significant difference.

Recent studies focusing on usage of low molecular weight heparin have suggested that there is insufficient evidence for application of this treatment among patients with unexplained habitual abortion.[7] In a study conducted by Lu X et al., aspirin was given to the patient groups with habitual abortion and abnormal prenatal thrombocyte aggregation, while low molecular weight heparin was used for patients with high levels of d-dimer. It was seen that thrombocyte aggregation was lowered, and that the d-dimer level was also lowered throughout the period of pregnancy. A live birth rate of 89.2% was obtained in the group with unexplained recurrent spontaneous abortion.[10]

In a 2010 randomized controlled study, patients with unexplained habitual abortion were included in the study. One group received aspirin and heparin, one group received only aspirin and the third group received placebo. There was no statistically significant difference among the groups regarding the rate of live births. In a study by Doliztky et al., 50 of the patients with unexplained abortion received aspirin treatment and 54 of them received enoxaparin treatment. It was found that the live birth rates of the two groups were similar. Moreover, the placental doppler flow was also found to be similar among the groups.[8] In a study conducted by Maged et al., on patients with unexplained habitual abortion, one group received low-dose aspirin (75 mg) and heparin (5000 IU) and the other group did not receive any medication. The evaluation criteria were that the first trimester was completed and that there was no statistically significant difference among the groups.[9]

During the development of the placenta, trophoblastic cells proliferate and the placenta becomes remodeled through apoptosis.[28] Thus, apoptosis continues as a dynamic process in placental development. In this process, proapoptotic and antiapoptotic factors should be in balance.[29] Bcl-2 is an antiapoptotic marker that inhibits apoptosis. Several studies have shown that antiapoptotic Bcl-2 levels are lower in the placenta of patients with habitual abortions than in the normal population.[12,29,30]

Furthermore, it has been indicated that Bcl-2 expression, which is low in the early weeks of normal pregnancy, increases during late weeks of pregnancy. This increase may provide continuity for the placenta.[31] In addition, decreases in Bcl-2 levels are thought to be a process that reduces chorionic villus survivability.[30] In our study, antiapoptotic Bcl-2 levels were found to be higher in the enoxaparin group than in the control group. This suggests that enoxaparin may decrease the effect of placental apoptosis.

However, in the current study, there was no difference between the groups regarding Ki-67 expression, which was measured to demonstrate placental proliferation. These results may be taken as fairly representative of what may be expected of the placenta at the end of full-term pregnancy, in comparison with the placenta at the early stage of pregnancy. Ki-67 expression has been shown to be relatively high in the placenta during early pregnancy but that it decreases over subsequent weeks.[32] On the other hand, previous studies indicated that the profile of Ki-67 expression was lower in the placentas of patients with habitual abortion.[33] Therefore, we believe that investigation of the effect of enoxaparin in placental samples taken in the early weeks of gestation may be more meaningful for evaluating the Ki-67 expression profile.

In our study, we did not notice any histomorphological alterations in placental histopathology due to enoxaparin usage, among the patients with term pregnancies. One of the limitations of our study was the absence of a group without habitual abortion. Because of this, no comparison could be made between a group without habitual abortion and a group with term pregnancy placenta. Moreover, the low number of patients included in our study was another limitation. However, it is important that the patient groups are comprised of individuals with idiopathic abortion that is investigated in terms of genetics, thrombophilia and APS.

CONCLUSION

This study is important in that it investigates the effects of enoxaparin usage, which is a costly and difficult treatment, among patients with unexplained habitual abortion, in terms of placental morphology. However, for clearer understanding of this subject, prospective studies with larger populations are needed.

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Quality of life and psychometric evaluation of patients diagnosed with irritable bowel syndrome: an observational cohort study

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Psychosomatic disorders.

ABSTRACT

BACKGROUND: Very few data are available for evaluating health-related quality of life among people with irritable bowel syndrome (IBS) and even fewer data are available in relation to anxiety and depression status among these patients.

OBJECTIVES: To evaluate the quality of life, anxiety and depression status of patients with IBS.

DESIGN AND SETTING: Observational cohort study conducted in a tertiary-care university hospital.

METHODS: Patients who had recently been diagnosed with IBS and who had been followed up for IBS-specific treatment for at least three months were included. A quality of life (QoL) survey, the Beck Anxiety Index (BAI) and the Hamilton Depression Index (HAM-D) were applied to the patients.

RESULTS: In total, 274 patients with IBS were included in the study cohort. These patients presented very high baseline scores for anxiety and depression, and very poor QoL results.

CONCLUSION: Our study showed that IBS had a very high impact on these patients, regarding their anxiety and depression levels, alongside very poor results relating to quality of life.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder that gives rise to deterioration of quality of life (QoL). The global prevalence of IBS has been estimated to be 11.2%.[1] IBS is the second most common cause of productivity loss in the United States.[1,2] The pathogenesis of IBS is multifactorial, and the diagnosis is made based upon the presenting symptoms and on ruling out organic diseases.[3-5]

OBJECTIVE

The main question and aim of this study was to demonstrate the psychometric status of patients with IBS as a functional chronic disease. Hence, the aim was therefore to evaluate the QoL and psychological profile of patients with concurrent IBS within current medical practice.

METHODS

This observational cohort study was conducted retrospectively between March 2016 and January 2019. The subjects were adult patients who had been referred to the general surgery clinic with gastrointestinal symptoms and were diagnosed and treated as IBS cases, in accordance with the Rome-IV criteria.

The patients were asked to complete a QoL survey and the questionnaires of the Beck Anxiety Index (BAI) and Hamilton Depression Index (HAM-D) before their IBS treatment and three months afterwards. The aim of this was to monitor the patients' psychological condition. The severity of IBS was then re-evaluated using the Rome IV criteria, with the aim of documenting any occurrence of remission following the treatment regimen, at the end of the three-month period.

For this study, the files of 614 IBS patients were evaluated. Out of these 614 patients, 274 who completed all questionnaires both before and three months after the treatment were enrolled in this retrospective study.

All the patients were assessed by means of upper gastrointestinal endoscopy, rectosigmoidoscopy, routine laboratory tests and abdominal ultrasonography. Patients with unstable systemic

diseases or previous psychiatric disorders were excluded. Patients who had been taking proton pump inhibitors for at least three months for other reasons (because of chronic use of anti-inflammatory drugs due to orthopedic conditions or chronic use of acetyl salicylic acid due to neurological conditions, etc.) were included the study. However, patients with late onset of proton pump inhibitors (less than three months) were excluded from the study.

Newly diagnosed IBS patients were treated with a combination product consisting of otilonium bromide (40 mg) and simethicone (80 mg), administered orally three times per day at mealtimes.

We had already recorded data on treatment outcomes for supportive reasons, and so we report these data here. Nonetheless, because the present study had a retrospective design, these data were insufficient for evaluating treatment efficacy.

Statistics

The SPSS 25.0 software (IBM Corporation, Armonk, New York, United States) was used in the analysis on the variables. The variables were analyzed at a 95% confidence level, and a P-value of less than 0.05 was considered significant. The Mardia (Doornik and Hansen omnibus) test was used to test whether the data conformed to a multivariate normal distribution, while the homogeneity of variance was evaluated using Box's M test. The Mann-Whitney U test was used with Monte Carlo scores to compare before-and-after differences in the measurements of fibromyalgia symptom severity scores and in the BAI, quality-of-life and HAM-D scales, in relation to each other, according to whether individuals achieved complete recovery or did not.

The Wilcoxon signed-rank test was used with Monte Carlo results to compare before-and-after measurements of fibromyalgia symptom severity scores and the BAI, quality-of-life and HAM-D scales. The marginal homogeneity test was used with the Monte Carlo simulation method to compare before-and-after measurements of the classified BAI and HAM-D scores. The Pearson chi-square test was used with the exact and Monte Carlo simulation methods, and the Fisher-Freeman-Halton exact test was used with the Monte Carlo simulation method, to compare the BAI and HAM-D scales. The subjects were classified according to whether complete recovery had been achieved or not. Column ratios were compared and expressed in accordance with the Benjamini-Hochberg corrected P-value results. Quantitative variables were expressed in the tables as median (minimum/maximum) and categorical variables were shown as n (%). This retrospective study received local ethics committee approval under the registration number VDH.271010/1124, approved on October 27, 2010.

RESULTS

The present study was carried out with a total cohort size of 274 patients with irritable bowel syndrome. Among these patients, 219 were female and 55 were male. The patients' mean age was 44.1 ± 5.5 years; the oldest was 84 and the youngest was 18 years of age. Out of the 274 patients included in the study, 99 (36.1%) did not have complete recovery, while 175 (63.9%) had complete recovery from irritable bowel syndrome (**Table 1**).

There were no statistically significant differences in the quality-of-life scores before the pharmacotherapy or after the pharmacotherapy or in the before-to-after difference in scores, between

Table 1. Psychometric score results from the two groups

	Total	Complete recovery (absent)	Complete recovery (present)	P-value for complete recovery
	(n = 274)	(n = 99)	(n = 175)	
	Median (minimum/maximum)	Median (minimum/maximum)	Median (minimum/maximum)	
Beck Anxiety Inventory				
Before	10 (1/58)	5 (1/16)	22 (1/58)	**< 0.001**[U]
After	6 (1/33)	6 (1/9)	8 (1/33)	**0.001**[U]
Difference (before-to-after)	-4 (-44/8)	0 (-12/8)	-7 (-44/7)	**< 0.001**[U]
P-value for before-to-after[W]	**< 0.001**	**0.364**	**< 0.001**	
Quality-of-life scale				
Before	3 (14/58)	43 (14/ 8)	43 (14/58)	**0.992**[U]
After	88 (51/104)	88 (51/104)	88 (51/104)	**0.665**[U]
Difference (before-to-after-)	45 (2/90)	43 (2/90)	46 (3/82)	**0.511**[U]
P-value for before-to-after[W]	**< 0.001**	**< 0.001**	**< 0.001**	
Hamilton Depression Rating Scale (HAM-D)				
Before	6 (5/22)	5.5 (5/6)	7.5 (5/22)	**< 0.001**[U]
After	2 (1/21)	2 (1/6)	4 (1/21)	**< 0.001**[U]
Difference (before-to-after)	-4 (-17/4)	-4 (-5/0)	-4 (-17/4)	**0.971**[U]
P-value for before-to-after[W]	**< 0.001**	**< 0.001**	**< 0.001**	

[U]Mann-Whitney U test (Monte Carlo); [W]Wilcoxon signed-rank test (Monte Carlo).

patients who achieved complete recovery (P = 0.781, 0.304 and 0.395, respectively) and those who did not (P = 0.992, 0.665 and 0.511, respectively), i.e. P > 0.05 for all comparisons. However, on the HAM-D scale, there was no significant difference between those who had complete recovery and those who did not, in terms of before-to-after difference (P = 0.971).

The median values on the Beck Anxiety Inventory (BAI) scale before pharmacotherapy and after pharmacotherapy and the before-to-after difference of those who achieved complete recovery (median (minimum/maximum)) were 9 (7/12), 3 (1/8) and -6 (-11/-1), respectively. These were statistically significantly higher than the median values of those who did not reach complete recovery (median (minimum/maximum)), which were 9 (7/12), 3 (1/9) and -6 (-11/1), respectively (P < 0.001, 0.001 and < 0.001, respectively).

The median values on the HAM-D scale before pharmacotherapy and after pharmacotherapy of those who had complete recovery (median (minimum/maximum) were 7.5 (5/22) and 4 (1/21), respectively. These were statistically significantly higher than the median values of those who did not reach complete recovery (median (minimum/maximum)), which were 5.5 (5/6) and 2 (1/6), respectively (P < 0.001).

Among all the patients, and among those who had complete recovery, there were statistically significant decreases in the median BAI and HAM-D scores after the pharmacotherapy (all P-values < 0.001), while the median values on the quality of life scale increased after the pharmacotherapy, compared with the values before the pharmacotherapy (P < 0.001).

However, among the patients without complete recovery, there were statistically significant decreases in median HAM-D scores after the pharmacotherapy, compared with before it (all P-values < 0.001), while the median values on the quality of life scale increased after the pharmacotherapy, compared with before it (P < 0.001). There was no statistically significant difference in relation to the BAI scale (P = 0.364) (**Table 1**).

There were statistically significant differences in the distribution ratios of the classified BAI and HAM-D scales from before to after the pharmacotherapy, in a comparison according to the complete recovery situation (all P-values < 0.001).

On the BAI scale, before the pharmacotherapy, presence of a low anxiety ratio among the patients without complete recovery (100%) was greater than among those with complete recovery (48%). On the other hand, presence of medium anxiety ratios (33.1%) and high anxiety ratios (18.9%) was greater among patients with complete recovery (P < 0.05). Presence of a low anxiety ratio (100%) after the pharmacotherapy was greater among the patients without complete recovery than among those with complete recovery (84.6%), while presence of a medium anxiety ratio was greater among those with complete recovery (15.4%) (P < 0.05).

Among all the patients, and among those with complete recovery, there were decreases in the numbers of patients presenting medium and high anxiety levels both before and after the pharmacotherapy, while there was an increase in the number of patients with low anxiety (all P-values < 0.001). However, among those with complete recovery, there was no significant difference (P = 0.999)

Among those without complete recovery (100%), the rate of incidence of normal HAM-D scores before the pharmacotherapy was higher than among those without complete recovery (51.4%). However, mild (17.7%), medium (33.1%), severe (21.7%) and very severe (9.1%) depression levels were higher among those with complete recovery (P < 0.05). The rate of incidence of normal scores among patients without complete recovery after the pharmacotherapy (100%) was higher than among those with complete recovery (67.4%), while mild (24%) and medium (6.3%) depression ratios were higher among those with complete recovery (P < 0.05).

Among all the patients, and among those with complete recovery, there were decreases in the depression ratios after the pharmacotherapy among the patients with mild, medium, severe and very severe depression, compared with their ratios before the pharmacotherapy, while there was an increase in the rate among normal patients (all P-values < 0.001). However, there was no significant change among those with complete recovery (P = 0.999) (**Table 2**).

DISCUSSION

The relationship between functional somatic syndromes and IBS remains unclear, but co-occurrence of IBS and fibromyalgia has been reported to be high in the literature. In a study investigating separate groups of IBS patients, 65% of IBS patients were found to suffer from other psychosomatic disorders and 70% of psychosomatic disorders patients had IBS symptoms,[6,7] which suggests that these conditions have a common etiology. General anxiety disorder, depression and/or depressive symptoms have also been found to be consistently higher in IBS patients than in healthy controls.[8-10]

It is known that bowel habits change, and IBS is seen frequently in the course of major depressive disorder (MDD). Tollefson et al.[11] reported that the IBS criteria were met in 30% of patients with MDD, whereas the IBS rate in the psychiatrically healthy control group remained at 11%. Masand et al.[12] found that the incidence of IBS in MDD patients was similar to that of Tollefson (27%), whereas the IBS rate in the control group remained at 3%. In another study, the incidence of IBS in patients with major depressive disorder (double depression) that developed on the basis of dysthymia reached 58%, while the rate in the control group was again limited to 3%.[11,12]

Mayer et al.[13] reported that IBS was accompanied by anxiety in the early period and depression in the late period. Despite the epidemiological data available, they suggested that IBS, which is seen with depression and anxiety disorders, leads patients to seek

help more frequently and that the rates determined in studies may be misleading because of these characteristics. In fact, they claimed that more than 50% of patients seeking treatment for IBS also had depression and anxiety disorders.[13]

The following questions need to be considered: Why does IBS not develop in anyone who has inflammation or visceral hypersensitivity in the colon mucosa? and, Why is depression not seen in all patients with IBS? The possible answers to these questions include individual dietary differences, genetic causes, frequency of bowel infections and susceptibility to anxiety and depression.[11-15] If the pathophysiological link between IBS and MDD is summarized, a pathway extending from the colon mucosa to the anterior cingulate cortex may be suggested.[14] Mucosal inflammation triggered by stress or infections increases cytokine levels and visceral sensory conduction mediated by neurokinins.[14,15]

Therefore, IBS treatment is expected to be effective for treating comorbid depression. The fact that the accompanying depression is more severe in IBS patients, which leads to higher levels of seeking help and appointments with doctors, makes the importance of our results greater. From this point of view, although IBS treatment can be thought to be helpful for these patients, our results regarding high anxiety and depression levels suggest that it would be very useful to take into account the results from this study. It seems that use of psychotherapy methods can also be beneficial.[11,14,16,17]

This study was designed as a real-world observational study and did not apply randomization or blind administration of medication. A high number of patients were lost to follow-up or did not complete the surveys correctly, and therefore were excluded from the analysis group. These are the weaknesses of our study. Moreover, although we reported the psychometric results subsequent to treatment, these results from a retrospective study design are insufficient for any kind of evaluation of treatment efficacy.

Our primary aim with this study was to demonstrate the levels of anxiety and depression, which were higher than expected, and the effect of irritable bowel syndrome on the patients' quality of life. Therefore, we did not discuss the efficacy of the medication that was used in this study. In addition, we think that further prospective randomized controlled trials evaluating the effect of medication on improvement of quality of life and diminution of anxiety and depression levels are needed.

Table 2. Detailed psychometric values for the patients, according to subgroups

	Total	Complete recovery (absent)	Complete recovery (present)	P-value for complete recovery
	(n = 274)	(n = 99)	(n = 175)	
	n (%)	n (%)	n (%)	
Beck Anxiety Inventory				
Before				
Low	183 (66.8)	99 (100)[B]	84 (48)	
Moderate	58 (21.2)	0 (0)	58 (33.1)[A]	**< 0.001**[PM]
Severe	33 (12)	0 (0)	33 (18.9)[A]	
After				
Low	247 (90.1)	99 (100)[B]	148 (84.6)	
Moderate	27 (9.9)	0 (0)	27 (15.4)[A]	
Severe	0 (0)	0 (0)	0 (0)	**< 0.001**[PE]
P-value for before-to-after[MH]	**< 0.001**	**0.999**	**< 0.001**	
Hamilton Depression Rating Scale (HAM-D)				
Before				
Normal	189 (69)	99 (100)[B]	90 (51.4)	
Mild	31 (11.3)	0 (0)	31 (17.7)[A]	
Moderate	38 (13.9)	0 (0)	38 (21.7)[A]	**< 0.001**[PM]
Severe	16 (5.8)	0 (0)	16 (9.1)[A]	
Very severe	0 (0)	0 (0)	0 (0)	
After				
Normal	217 (79.2)	99 (100)[B]	118 (67.4)	
Mild	42 (15.3)	0 (0)	42 (24)[A]	
Moderate	11 (4)	0 (0)	11 (6.3)[A]	
Severe	4 (1.5)	0 (0)	4 (2.3)	**< 0.001**[FF]
Very severe	0 (0)	0 (0)	0 (0)	
P-value for before-to-after[MH]	**< 0.001**	**0.999**	**< 0.001**	

[P]Pearson chi-square test (Exact, Monte Carlo), [FF]Fisher-Freeman-Halton test (Monte Carlo), [MH]marginal homogeneity test (Monte Carlo), [A]expressed significance for the group without complete recovery, [B]expressed significance for the group with complete recovery.

CONCLUSION

This study showed that the great majority of IBS patients have very high levels of anxiety and depression and very poor levels of quality of life. In the light of our study, it can be suggested that in considering IBS treatment, both the physiological and the psychological aspects should be addressed, so as to maintain optimal results and enhance the quality of life of individuals with IBS.

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Cross-cultural adaptation, validity and reproducibility of the Back Beliefs Questionnaire among older Brazilians with acute low back pain. A cross-sectional study

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KEY WORDS (MeSH terms):
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Reproducibility of results.
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Validity.
Reliability.
Psychosocial factors.
Older adults.

ABSTRACT

BACKGROUND: Low back pain (LBP) has emerging as an epidemic, multifactorial and multidimensional condition in older age. Assessment of attitudes and beliefs of patients with back pain is necessary for understanding the impact of psychosocial factors on pain perception and management.

OBJECTIVES: To cross-culturally adapt and examine the validity and reproducibility (intra and interrater reliability and agreement) of the Back Beliefs Questionnaire (BBQ) in older Brazilians with acute LBP.

DESIGN AND SETTING: Cross-sectional methodological report conducted at the Department of Physical Therapy of the Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

METHODS: The present study was conducted for translating, adapting, and examining the psychometric properties of a questionnaire. Participants aged ≥ 60 years experiencing an acute episode of LBP were recruited. Coefficients of internal consistency, reliability and agreement were obtained using Cronbach's α, intraclass correlations, and standard error of measurement and the smallest detectable change, respectively.

RESULTS: Twenty-six participants aged between 60-84 years and reporting a mean of 9.8 (4.3) years of schooling completed the study. The Brazilian Portuguese-language version of the BBQ (BBQ-Brazil) was proposed and presented with adequate conceptual, semantic, operational, and measurement equivalence from the original version. Intra and interrater evaluations showed moderate (0.74) and excellent (0.91) intraclass correlation coefficients, respectively, with small standard error of measurement for both evaluations. Internal consistency was considered adequate (0.70).

CONCLUSION: BBQ-Brazil had consistent measurements of validity and reproducibility, and proved to be a valuable tool in clinical practice for addressing attitudes and beliefs of older patients with acute LBP.

INTRODUCTION

Low back pain (LBP) has been a challenge for gerontology in relation to promoting healthy aging. Population-based surveys have attested that LBP gives rise to enormous epidemiological, clinical and economic burdens in the older population, with high prevalence and disability rates worldwide.[1,2] A recent systematic review showed that one in four Brazilians aged ≥ 60 years was suffering from LBP at any given moment.[3] More importantly, longitudinal studies have shown that about 40% of older individuals do not recover within 12 months of pain onset.[4] Their pain may evolve towards chronic pain, thus leading to severe functional impairment, social deprivation, depression and permanent incapacity.[1,5]

The transition from acute to persistent LBP among older patients can be explained in terms of psychosocial factors that significantly influence their functional status.[6] Psychosocial factors known as "yellow flags" increase the risk of long-term disability, and early screening for these factors is needed in order to prevent chronic LBP. In this regard, patients' attitudes and beliefs about pain should be highlighted.[7] The domains of these factors result from customs, ideologies, values and religious, and spiritual experiences, and they influencing individual behavior and social life at all levels, from interpersonal to political, economic and legal relationships.[8] Negative beliefs are associated with poor recovery among older adults, after an acute episode of LBP.[6,7]

The Back Beliefs Questionnaire (BBQ) was developed by Symonds et al.[8] to assess attitudes and beliefs among patients with back pain and those for whom future back problems are

unavoidable. It was previously shown to have high validity/reliability coefficients (e.g. internal consistency ≥ 0.70 and test-retest reliability ≥ 0.80) when used for the general population in clinical settings.[8-11] However, even though LBP has now emerged as an epidemic, multifactorial and multidimensional condition in older age,[1,2,6,7] no study has, to the best of the authors' knowledge, investigated the psychometric properties of the BBQ among older adults with acute back complaints.

OBJECTIVE

The purpose of the present study was to cross-culturally adapt and examine the validity and reproducibility (intra and interrater reliability and agreement) of the BBQ in older Brazilians with acute LBP.

METHODS

Study design and participants

This was a methodological report using data from a subsample of the Brazilian cohort "Back Complaints in the Elders" (BACE-Brazil). This formed part of an international multicenter study including Brazil, the Netherlands and Australia that was designed to investigate the clinical course and prognostic factors of LBP among older individuals. The BACE protocol has been published in detail elsewhere.[12]

For this report, a convenience sample of 42 individuals was recruited through advertisements in local newspapers, radio and the internet, and through active searching or referrals from healthcare professionals at public and private primary care services. BACE-Brazil was approved by the local ethics committee on February 24, 2016, under the approval number ETIC 0100.0.203.000-11, and all participants signed an informed consent form.

The inclusion criteria were that the participants needed to be community-dwelling people aged ≥ 60 years who presented with a new (acute) episode of LBP, i.e. any pain between the lower ribs and inferior gluteal folds, with or without leg symptoms, which had occurred for a period shorter than six weeks. An episode of LBP was considered new if the participant had not sought medical care due to this condition during the preceding six months before the time of data collection.[12]

The exclusion criteria were the presence of severe diseases (e.g. infectious diseases, malignant tumors and cauda equina syndrome); severe visual, hearing, or motor loss; and cognitive impairment detectable through the Mini-Mental State Examination (MMSE), using the Brazilian cutoff points according to schooling level, as follows: 13 for illiterate individuals, 18 for those with < eight years of schooling, and 26 for those with ≥ eight years of schooling.[13]

Instruments and measurements

Sociodemographic and clinical data were collected by trained researchers using a standardized multidimensional questionnaire that included age (years), sex (female/male), schooling (years), pain intensity (0-10) and "sought medical care due to LBP over the past 6 weeks?" (yes/no). Pain intensity was assessed using an 11-point visual numerical rating scale ranging from 0 ("no pain") to 10 ("worst possible pain") (**Figure 1**). The question on pain intensity was asked in relation to two times: "at the present time" of data collection and "over the past week" before data collection.

The BBQ is composed of nine statements, including five questions that are used as distractors, totaling 14 items. Respondents report their level of agreement on a Likert scale ranging from 1 (completely agree) to 5 (completely disagree). The total score is calculated by inverting the sum of scores from the 9 affirmations and can range from 9 to 45 points. The smaller the score is, the more negative the respondent's attitudes and beliefs are.[8] The BBQ exhibits good internal consistency and reliability estimates, with Cronbach's α between 0.70 and 0.81 and intraclass correlation coefficient (ICC) between 0.80 and 0.87, respectively.[8-11]

Translation and cross-cultural adaptation

Language adaptation was performed in five steps: (i) conceptual equivalence: presentation of the same concepts; (ii) item equivalence: adjustment of elements from the original scale to represent the concepts of the language in question; (iii) semantic equivalence: transfer of meaning from one language to the other; (iv) operational equivalence: checking the possibility of using a similar format of questionnaire, instructions and application form; and (v) measurement equivalence: examining whether the different versions of the questionnaire reach similar levels of validity and reliability as in the original questionnaire.[14]

Semantic equivalence was assessed in accordance with the stages proposed by Beaton et al.:[15] (1) translation: the instrument was translated to the Brazilian Portuguese language by two independent professional translators (T1 and T2) who were both native

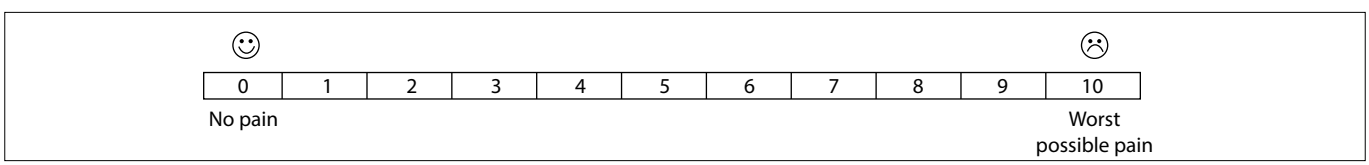

Figure 1. A model of the 11-point visual numerical rating scale that was used to assess pain intensity in the present study.

speakers of Brazilian Portuguese and proficient in the English language; (2) translation synthesis: a third person arranged a final version (T12); (3) back-translation: another two individuals (R1 and R2), who were independent from the previous two translators, back-translated the T12 version into the English language without having had any contact with the original version; (4) experts' analysis: a committee of experts in the field (e.g. physicians, physiotherapists and occupational therapists) was created to review the final version; and (5) pre-testing: application of the pre-final version (pilot test) to a sample of older persons, to assess the comprehension and adequacy of the final questionnaire.

Statistical analysis

The participants' characteristics were described using means (with standard deviation) for numerical variables and absolute numbers (with percentage) for categorical variables. The normality of numerical data distribution was tested using the Kolmogorov-Smirnov test. Internal consistency was assessed by means of interrater measurements using Cronbach's α coefficient. A value of $\alpha \geq 0.70$ was considered to be an acceptable level of internal consistency.[16]

The intrarater (test-retest) reliability was estimated using ICC type 3.1 with a two-way mixed-effects model.[17] The consistency of each examiner's measurement (model 3) was evaluated in duplicate during the comparison of single measurements. For the intrarater assessment, the BBQ was applied twice to the same participant by the same examiner, within an interval of 7 to 14 days.[15]

The interrater reliability was estimated using ICC type 2.1 with a two-way random-effects model.[17] Two different examiners (model 2) were evaluated by simple comparison of two measurements. For the interrater assessment, the BBQ was applied by two examiners to one participant on the same day.[15] The ICC was classified as poor (< 0.40), moderate (between 0.40 and 0.75), substantial (between 0.75 and 0.90) or excellent (> 0.90).[16] All questionnaires were applied under supervision to avoid bias in cases of subjects with poor educational level.

Agreement was assessed using the standard error of measurement (SEM) and the smallest detectable change (SDC), which were calculated for the intra and interrater reliability coefficients. The SEM was calculated as the ratio between the standard deviation of the mean difference and two squared. The SDC was calculated using the following formula: $SDC = 1.96 \times \sqrt{2} \times SEM$.[16] Lower SEM and SDC values indicated less error and higher concordance between measurements. The dispersion of the results from both measurements was examined through agreement analysis using Bland-Altman plots, and it was checked whether the intra and interrater estimates were encompassed within the "agreement limits" (established as 1.96 times the standard deviation of the measurements).[18]

Significant differences were inferred to exist at the level of a two-tailed $P < 0.05$. All the analyses were conducted using the SPSS software package, version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Sample characterization

The participants' descriptive data are presented in **Table 1**. Twenty-six of the 42 individuals recruited (who were all aged between 60 and 84 years) attended both the first and the second time-points of data collection, and their data were analyzed. The other 16 individuals were excluded from the analysis because they did not complete the entire data collection process. Most of the participants included were female (88.5%), had a medium-to-high schooling level (≥ 9 years), reported moderate pain intensity (scoring between 4 and 7 on the 0-10 scale), and had not sought medical care due to LBP over the past 6 weeks (69.2%).

BBQ adaptation, validity and reproducibility

Conceptual and item equivalence

The expression "attitudes and beliefs about LBP" was universally accepted as reviewed in the literature, thus showing that there was conceptual equivalence between the English and Brazilian Portuguese languages. Other terms among the BBQ questions were also adequate for different cultures and countries, i.e. these items showed equivalence. The title of the questionnaire was kept as in the original English-language version, in order to preserve the internationally used language: *Brazilian Portuguese version of the Back Beliefs Questionnaire* (BBQ-Brazil).

The term "back trouble" ("back problem") was translated and replaced by "back pain". The original author of the BBQ was contacted about this, and it was clarified that this term could also refer to back pain. Indeed, the term "back pain" is very often used in Brazil, regardless of sociocultural factors such as age group, schooling and region of the country, and thus might correspond more accurately to the presence of LBP.

Table 1. Descriptive sample characteristics (n = 26)

Variables	Mean (SD) or n (%)
Age (years)	67.4 (5.8)
Female	23 (88.5%)
Schooling (years)	9.8 (4.3)
Pain intensity "at the present time" (0-10)	5.0 (3.1)
Pain intensity "over the past week" (0-10)	7.4 (2.2)
Sought medical care due to LBP[1] (yes)	8 (30.8%)

[1]Variable referring to "sought medical care due to LBP over the past six weeks?" (yes/no).
SD = standard deviation; LBP = low back pain.

Semantic equivalence

After a critical review, the experts' committee decided on the best meanings and arrangements of the BBQ items. A literal translation was possible, except in relation to the following expressions. In item 2, "Back trouble will eventually stop you from working", the expression "stop you from working" was translated into "*make you stop working*", and so "*Back pain will eventually make you stop working*". In item 5, "bad back should be exercised", the question was adapted into "*A bad back should be exercised (for the back)*". In item 10, "Back trouble means long periods of time off work", the expression "time off work" makes the meaning more specific indicating that it is a time of absence from work due to pain and not any time different from work time, and so this question in Brazilian Portuguese is "*Back pain means long periods of time out off work*".

In item 12, "Once you have had back trouble there is always a weakness", it was suggested the addition of the term "*difficulty*" in the end of the question, which was used as an anchor for a better understanding of the expression "weakness"; this word was substituted by the expression "*weak point*" to make it clear that it is not a matter of muscle weakness, but a condition of vulnerability, concluding: "*Once you have had back pain there is always a weak point (difficulty)*". In item 13, "Back trouble must be rested", the word "*needs*" (instead of "must") in Brazilian Portuguese was the one that best expressed this question: "*Back pain needs to be rested*". Lastly, in item 14, "Later in life back trouble gets progressively worse", the expression "later in life" was adapted to "*with aging*", which indicates the same condition: "*With aging back pain gets progressively worse*". An examiner's manual addressing the application of the BBQ-Brazil was proposed and used during data collection (**Appendix 1**).

Operational equivalence

The BBQ-Brazil was applied to 26 participants, who exhibited adequate comprehension of the items (**Appendix 1**). Therefore, there was no need for a new experts' committee meeting.

Measurement equivalence

Intra and interrater assessments revealed, respectively, moderate (ICC = 0.74) and excellent (ICC = 0.91) reliability coefficients for the BBQ-Brazil. Likewise, agreement estimates only showed small error between intrarater measurements (SEM = 4.03 and SDC = 11.05) and interrater measurements (SEM = 2.44 and SDC = 6.74) (**Table 2**). The Bland-Altman limits of agreement ranged from -10.50 to 12.00 for intrarater measurements (**Figure 2**), and from -5.50 to 7.50 for interrater measures (**Figure 3**). The internal consistency of the adapted questionnaire was adequate (Cronbach's α coefficient = 0.70).

DISCUSSION

BBQ was translated, adapted, and tested in a Brazilian Portuguese-language version for older adults with acute LBP. The new questionnaire exhibited satisfactory performance regarding cross-cultural equivalence and psychometric properties and may be clinically useful for assessing the psychosocial behavior of older patients facing back pain symptoms. The original BBQ in the English-language version includes adaptation to a great number of different cultures.[8] Other methodological studies conducted on general populations in Canada,[11] Australia, Singapore and Taiwan,[10] and China[19] attest to the construct validity of this tool.

The original version was validated using a sample of workers from a biscuit factory located in northern England, where 70% of the sample were less than 45 years old.[8] The study including participants from Australia, Singapore and Taiwan was conducted among physiotherapy and nursing students of mean ages 20.3 (1.3) and 20.5 (1.0) years, respectively.[10] The study with the Chinese sample was conducted among healthcare professionals (i.e. physiotherapists, osteopaths and nurses) with a mean age of 40.3 (11.1) years.[19]

On the other hand, the present study was performed using a sample of older participants of mean age 67.4 (5.8) years and mean schooling of 9.8 (4.3) years. People of advanced age and lower schooling level tend to present poorer health outcomes and more negative complaints about back pain that impacted on their activities of daily living, while younger persons tend to have more positive beliefs regarding back pain, which thus led to better functional status.[6,7] Likewise, lower schooling reduces the rate of seeking healthcare and is associated with negative beliefs and lower functional performance.[8,10,19]

Pain intensity "at the present time" of data collection was moderate, since most participants scored between 4 and 7 on the 0-10 scale, but pain intensity "over the past week" before data collection was moderate to severe (i.e. score > 7 on the 0-10 scale). Burnett et al.[10]

Table 2. Intra and interrater reliability and agreement results from the Brazilian Portuguese version of the Back Beliefs Questionnaire (n = 26)

Examiner	1st measurement Mean (SD)	2nd measurement Mean (SD)	ICC	95% CI	SEM	SDC
1	23.81 (7.46)	22.92 (8.16)	0.74	0.49 to 0.87	4.03	11.05
2	-	22.27 (8.44)	0.91	0.81 to 0.96	2.44	6.74

SD = standard deviation; ICC = intraclass correlation coefficient; 95% CI = 95% confidence interval; SEM = standard error of measurement; SDC = smallest detectable change.

found mild pain among physiotherapist and nursing students, whereas the Chinese sample reported mild pain while resting and in the last week, moderate pain intensity in the last acute pain episode, and severe pain intensity in the worst pain episode.[19]

The majority of the participants did not seek healthcare services to treat LBP. This can be explained by difficulties in accessing healthcare services, low levels of physical capacity, attitudes of waiting for spontaneous recovery from pain, self-medication, use of resting or lack of interest because of repetitive pain episodes.[20] In addition, unpreparedness among healthcare professionals still exists with regard to dealing with psychosocial outcomes such as negative attitudes and beliefs. The focus is only on physical

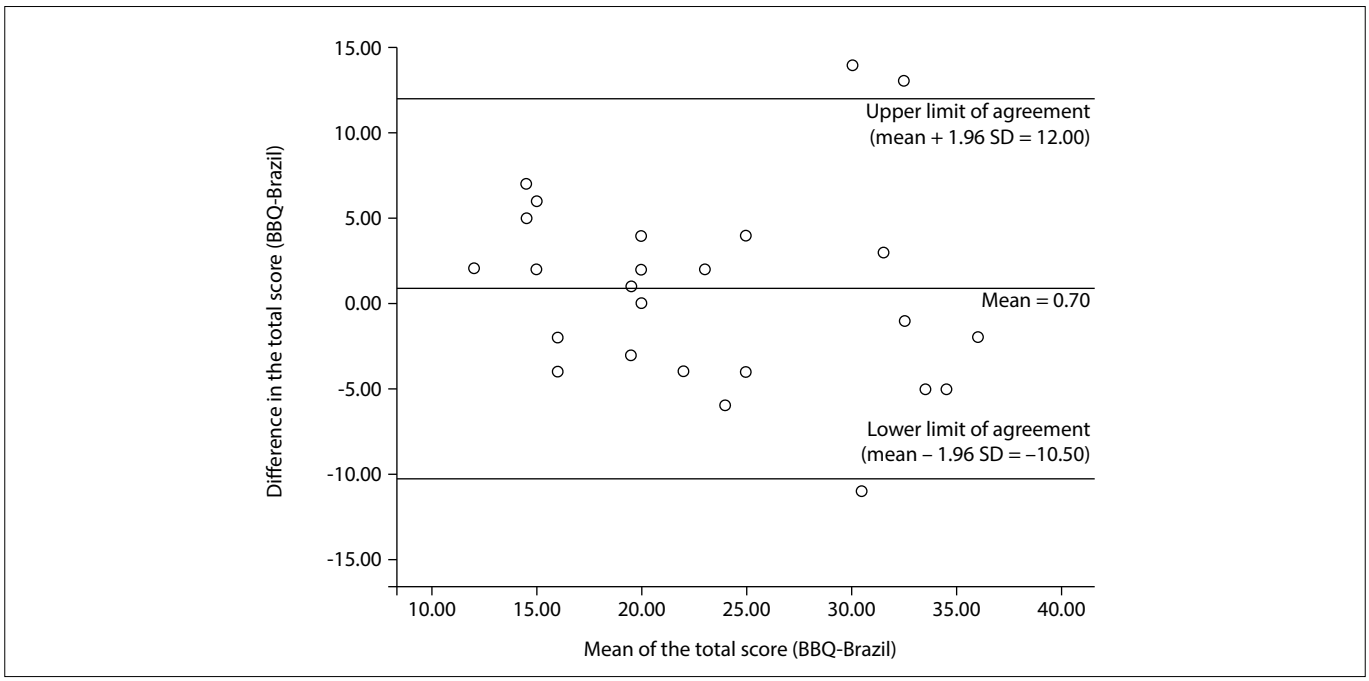

Figure 2. Bland-Altman plot for intrarater measurements demonstrating the mean differences ± 1.96 standard deviation (SD) limits of agreement using the Brazilian Portuguese version of the Back Beliefs Questionnaire (n = 26).

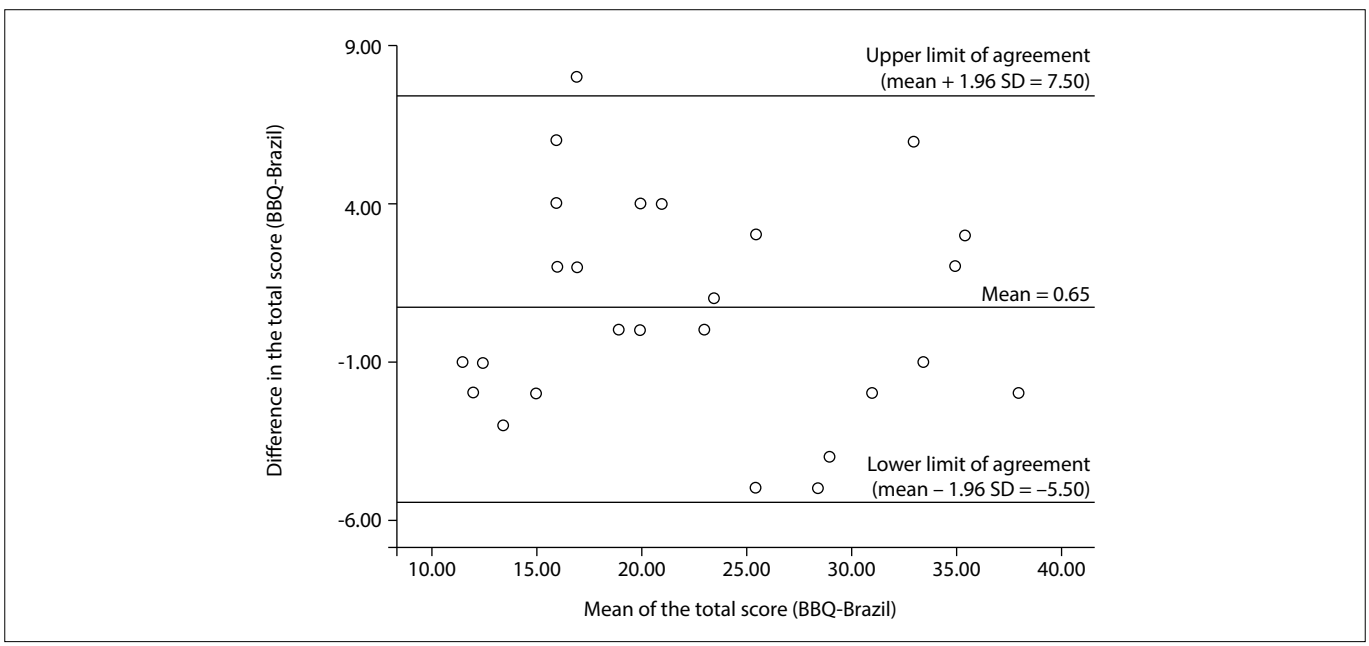

Figure 3. Bland-Altman plot for interrater measurements demonstrating the mean differences ± 1.96 standard deviation (SD) limits of agreement using the Brazilian Portuguese version of the Back Beliefs Questionnaire (n = 26).

symptoms that tend to persist, which leads to demotivation among patients in relation to the need for LBP treatment to be continuous.[7]

The mean BBQ score among these older Brazilians indicated that they had negative attitudes and beliefs, compared with the means from the Australian[10] and Canadian[11] studies, which were higher. Assessments made during the crisis period may have contributed to reports of negative attitudes and beliefs in relation to LBP. In the original validity study, the mean BBQ score tended to be more positive among the office workers than among the factory workers.[8] Burnett et al.[10] found positive beliefs among the subjects in Australia and Taiwan, and the participants in the Chinese study also showed positive attitudes and beliefs, in two evaluations.[19]

The BBQ was originally developed to assess attitudes and beliefs about back problems that caused absenteeism.[8] However, it is important to validate and assess the applicability of this questionnaire in different populations and cultures. The process of cross-cultural validation among Brazilians and in other populations[10,11,19] was based on similar standardized proposals and on consolidated references.[15,16,21]

During the cross-cultural adaptation to the Brazilian Portuguese language, the concept of "back problem" was adapted through cultural-semantic analysis into "back pain" because of the similarity between these concepts, as used in the Brazilian study population. In the Chinese version of the BBQ, few participants had difficulties in understanding the expression "back problem" and just a brief explanation of the term "back pain" was included.[19]

Semantic adaptation was necessary in some questions of the BBQ-Brazil and in other versions of the BBQ. For example, in the Chinese version, item 10 ("Back trouble means long periods of time off work") was adapted to mean formal or paid work.[19] Differently, in Brazil, a number of older people still continue to do formal work even after retirement, and many older people who have retired still working informally and/or at home. Because of this wide diversity of work possibilities, item 10 was kept and adapted according to the participants' need during application of the questionnaire. Another question that required to semantic adaptation, which was highlighted both in the Brazilian and in the Chinese[19] versions was item 12: "Once you have had back trouble there is always a weakness". Some Brazilian and Chinese[19] participants understood the word "weakness" as physical disability in general. Thus, in these both languages, "weakness" was replaced by "weak point" or "difficulty", because the authors considered these expressions to be more appropriate for preserving cultural equivalence.

The assessment of measurement equivalence showed that the test-retest (ICC = 0.74) and interrater (ICC = 0.91) coefficients for the BBQ-Brazil were at adequate levels. The time interval between questionnaire applications regarding test-retest measurements may have compromised the similarity between responses because fluctuations in pain intensity can differentiate attitudes and beliefs about LBP. In contrast, the application between examiners was done on the same day, which will have reduced the influence of changes in pain perception and patients' beliefs. No clinical changes in pain levels relating to the timing of questionnaire application were observed in other studies,[10,19] and this was probably because they did not include participants' reports of the acuteness of their pain. Lastly, Cronbach's $\alpha = 0.70$ indicates acceptable internal consistency, meaning that the questionnaire items measured the same construct and provided similar results between examiners.

Other instruments that are used for investigating psychosocial factors among patients with LBP had previously been adapted and validated for use in the Brazilian Portuguese language. Lopes et al.[22] adapted the Pain Catastrophizing Scale for older Brazilians with acute LBP and found substantial coefficients of reliability (ICC = 0.88) and internal consistency (Rasch analysis = 0.95). Abreu et al.[23] adapted the Fear Avoidance Beliefs Questionnaire for Brazilians aged 20 to 75 years with chronic LBP and also reported excellent coefficients of reliability (ICC = 0.91) and internal consistency (Cronbach's $\alpha = 0.90$). Although these instruments were used in different contexts of back pain, it may be interesting to combine them with the BBQ-Brazil, in order to obtain additional information about the psychological expectations and experiences of older patients with back complaints. The use of such instruments should be encouraged both in clinical and in research settings.[6,24]

The present study had certain strengths and limitations. The BBQ was translated, adapted and validated for use among older Brazilians with acute LBP through rigorous methodological approaches that included carefully applied face-to-face interviews with elderly people in order to control for the influence of low schooling levels. Therefore, the BBQ-Brazil might help healthcare professionals to manage LBP and thus reduce the epidemiological and clinical burden of this condition in the older population of Brazil. On the other hand, there was great difficulty in recruiting participants in accordance with the inclusion and exclusion criteria of this study, which meant that it was only possible to include a convenience sample with small number of participants (among whom 88.5% were women), thereby limiting the generalizability of the results.

CONCLUSION

The BBQ was successfully translated and adapted for use among older Brazilians with acute LBP. Good validity/reproducibility coefficients were obtained for the BBQ-Brazil using intra and interrater measurements. The attitudes and beliefs of patients with back pain are important factors regarding the development of disabling chronic pain. They relate to coping behavior and treatment expectations, which can be positively modified

through public health strategies. Psychosocial screening is essential, in order to encourage healthcare professionals to motivate their older patients to have an active life, avoid immobility and maintain independence and autonomy.

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LF, Diz JBM, Silva SLA, Viana JU and Dias RC were involved in acquisition, analysis and interpretation of data. Teixeira LF, Silva SLA, Pereira LSM and Dias RC provided inputs for statistical analysis and interpretation of data. Teixeira LF wrote the first draft of the manuscript and all the other authors were involved in revising it critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, so as to ensure that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Appendix 1. Brazilian Portuguese version of the Back Beliefs Questionnaire (BBQ-Brazil).

Version of the BBQ-Brazil in the English language

We are trying to discover what people think of back pain problems. Please indicate your general opinions about back pain. Please answer ALL the statements and indicate if you agree or disagree with each affirmation, by circling the appropriate number on the scale. The responses range from 1 (completely disagree) to 5 (completely agree).
1 = Completely disagree
2 = Disagree
3 = Neither agree nor disagree
4 = Agree
5 = Completely agree

1	*There is no real treatment for back pain.*	1 2 3 4 5
2	*Back pain will eventually make you stop working.*	1 2 3 4 5
3	*Back pain means periods of pain for the rest of one's life.*	1 2 3 4 5
4	***Doctors cannot do anything for back pain.***	1 2 3 4 5
5	***A bad back should be exercised (for the back).***	1 2 3 4 5
6	*Back pain makes everything in life worse.*	1 2 3 4 5
7	***Surgery is the most effective way to treat back pain.***	1 2 3 4 5
8	*Back pain may mean you end up in a wheelchair.*	1 2 3 4 5
9	***Alternative treatments are the answer to back pain.***	1 2 3 4 5
10	*Back pain means long periods of time out off work.*	1 2 3 4 5
11	***Medication is the only way of relieving back pain.***	1 2 3 4 5
12	*Once you have had back pain there is always a weak point (difficulty).*	1 2 3 4 5
13	*Back pain needs to be rested.*	1 2 3 4 5
14	*With aging back pain gets progressively worse.*	1 2 3 4 5
Total score:		

The score is calculated by inverting individual values (i.e. 5, 4, 3, 2 and 1) and then summing all nine affirmations. Total scores range from 9 to 45 points (higher scores indicate less negative beliefs). Questions 4, 5, 7, 9 and 11 (in bold) are considered to be a "treatment" subscale and are not computed in the final score.
Symonds TL, Burton AK, Tillotson KM, Main CJ. Do attitudes and beliefs influence work loss due to lower back trouble? Occup Med (Lond). 1996;46(1):25-32. ©1993 University of Huddersfield, UK. Used with permission.

BBQ-Brazil examiner's manual
I. The instrument can be self-administered or through interviews with participants.
II. Score: "inevitability" measurement consists of a scale that uses nine subgroups of affirmations (i.e. items 1, 2, 3, 6, 8, 10, 12, 13 and 14).
III. The remaining questions (i.e. items 4, 5, 7, 9 and 11) are considered to be a "treatment" subscale and are not computed in the final score.
IV. The score is calculated by inverting individual values (i.e. 5, 4, 3, 2 and 1) and then summing all nine affirmations. Total scores range from 9 to 45 points (higher scores indicate less negative beliefs).
V. Examples of back exercises indicated in item 5: stretching, strengthening, core stabilization, Pilates and yoga exercises.
VI. "Alternative treatments" indicated in item 9 would be complementary interventions, except for surgery, medication and physiotherapy. Examples of alternative treatments: massage, acupuncture, shiatsu, reflexology and arnica gel, among others.

Appendix 1. Continuation

Version of the BBQ-Brazil in the Brazilian Portuguese language

Estamos tentando descobrir o que as pessoas pensam sobre problemas na coluna lombar. Por favor, indique suas opiniões gerais sobre a dor na coluna. Por favor, responda TODAS as afirmações e indique se você concorda ou discorda com cada afirmação, circulando o número apropriado na escala. As respostas variam de 1 (discordo completamente) a 5 (concordo completamente).
1 = Discordo completamente
2 = Discordo
3 = Nem concordo nem discordo
4 = Concordo
5 = Concordo completamente

1	*Não existe tratamento real para a dor na coluna.*	1 2 3 4 5
2	*A dor na coluna fará você parar de trabalhar.*	1 2 3 4 5
3	*Dor na coluna significa períodos de dor para o resto da vida.*	1 2 3 4 5
4	***Médicos não podem fazer nada para a dor na coluna.***	1 2 3 4 5
5	***Uma pessoa com coluna ruim deve fazer exercícios (para coluna).***	1 2 3 4 5
6	*Dor na coluna torna tudo na vida pior.*	1 2 3 4 5
7	***A cirurgia é o modo mais eficaz para tratar a dor na coluna.***	1 2 3 4 5
8	*Dor na coluna pode fazer você terminar a vida em uma cadeira de rodas.*	1 2 3 4 5
9	***Tratamentos alternativos são a melhor resposta para a dor na coluna.***	1 2 3 4 5
10	*Dor na coluna significa longos períodos de tempo afastado do trabalho.*	1 2 3 4 5
11	***Medicação é a única maneira de aliviar a dor na coluna.***	1 2 3 4 5
12	*Depois de ter tido dor na coluna, você sempre terá um ponto fraco (dificuldade).*	1 2 3 4 5
13	*Dor na coluna necessita de repouso.*	1 2 3 4 5
14	*A dor na coluna fica progressivamente pior com o envelhecimento.*	1 2 3 4 5
Escore total:		

A pontuação é calculada invertendo-se os valores individuais (i.e. 5, 4, 3, 2 e 1) e, em seguida, somam-se todas as 9 afirmações. A pontuação total varia de 9 a 45 pontos (pontuações mais altas indicam menos crenças negativas). As questões 4, 5, 7, 9 e 11 (em negrito) são consideradas como uma subescala "tratamento" e não são computadas no escore final.
Symonds TL, Burton AK, Tillotson KM, Main CJ. Do attitudes and beliefs influence work loss due to lower back trouble? Occup Med (Lond). 1996; 46(1):25-32. ©1993 University of Huddersfield, UK. Usado com permissão.

Manual de instrução da versão brasileira do Questionário *Back Beliefs* (BBQ-Brasil)
I. O instrumento pode ser aplicado de forma autoadministrada ou por meio de entrevista com o participante.
II. Pontuação: a medida de "inevitabilidade" consiste em uma escala que utiliza um subgrupo de 9 afirmações (***i.e.*** itens 1, 2, 3, 6, 8, 10, 12, 13 e 14).
III. As questões restantes (***i.e.*** itens 4, 5, 7, 9 e 11) são consideradas como uma subescala "tratamento" e não são computadas no escore final.
IV. A pontuação é calculada invertendo os valores individuais (***i.e.*** 5, 4, 3, 2 e 1) e, em seguida, somando-se todas as 9 afirmações. A pontuação total varia de 9 a 45 pontos (pontuações mais altas indicam menos crenças negativas).
V. Exemplos de exercícios para coluna indicados no item 5: alongamento, fortalecimento, estabilização do core, Pilates e yoga.
VI. Os "tratamentos alternativos" indicados no item 9 seriam intervenções complementares, exceto cirurgia, medicamento e fisioterapia. Exemplos de tratamentos alternativos: massagem, acupuntura, shiatsu, reflexologia, gel de arnica, entre outros.

Evaluation of ionizing radiation as a risk factor for the incidence of breast cancer: long-term analysis after the cesium-137 accident in Goiânia, Brazil. An ecological study

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Breast neoplasms.
Incidence.
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Brazil.
Risk factors.

AUTHORS' KEY WORDS:
Breast cancer.
Goiânia.
Goiás.

ABSTRACT

BACKGROUND: The largest radiological accident to occur in any urban area happened in Goiânia, Brazil, in 1987.

OBJECTIVE: To evaluate the association between breast cancer incidence and ionizing radiation levels.

DESIGN AND SETTING: Ecological study among residents of the city of Goiânia, Brazil.

METHODS: The central region of Goiânia, with seven major sources of contamination from cesium-137, was defined as the study area. The addresses of women diagnosed with breast cancer were identified between 2001 and 2010. The data were geographically referenced and, using census data, the annual averages of crude incidence rates were estimated. The existence of clusters of new cases was ascertained by means of the Moran index. Correlations of radiometric measurements with the incidence were assessed using unconditional linear regression.

RESULTS: A total of 4,105 new cases were identified, of which 2,233 were in the study area, and of these, 1,286 (57.59%) were georeferenced. The gross rates of total and referenced cases were 102.91 and 71.86/100,000 women, respectively. These were close to the average for Brazilian state capitals, which is 79.37/100,000 women. The cluster analysis showed slight correlations in three small sets of census tracts, but these were far from the sources of contamination. The scatter plot of points and the R^2 value close to zero indicated that there was no association between the variables.

CONCLUSION: This study reinforces the hypothesis that the ionizing radiation levels to which women living in Goiânia are now exposed to are not associated with the onset of new cases of breast cancer.

INTRODUCTION

Breast cancer is a public health problem in both developed and developing countries.[1-3] According to the International Agency for Research on Cancer (IARC), there were two million new cancer cases and 626,000 deaths from breast cancer worldwide in 2018.[1] In Brazil, breast cancer accounts for about 30% of all new cancer cases in women, annually.[2] In this context, studies on risk factors are important for understanding the problem and for developing disease prevention policies.

Exposure to ionizing radiation is a well-known risk factor for the development of breast cancer. The risk is highest among young women at the time of exposure and is directly proportional to the radiation dose.[4] In this context, there are several associations with genetic factors, which suggest that certain variations in deoxyribonucleic acid (DNA) damage-response genes can make it difficult for radiation-induced damage to be repaired.[5] On the other hand, little is known about the impact of major radiological accidents on breast cancer incidence. The data from Japan and Chernobyl remain inconclusive, despite the increased risk of several other pathological conditions.[4,6]

In September 1987, a radiological accident of major proportions occurred in Goiânia, which affected both the population and the environment. The accident was caused by the removal and dismantling of a sealed source containing cesium-137, in an abandoned radiotherapy unit in Goiânia.[7,8] The source was in the form of cesium chloride salt, which exhibited high solubility and was easily dispersible. The weather conditions at the time of the accident comprised heavy rain and a temperature of 26.4 °C. These conditions facilitated dispersion of the initial cesium-137 in the environment, around seven main spots in the central region of the city of Goiânia.[8,9]

It has been recognized that the greatest degree of contamination of the environment occurred in the areas of the main sources of contamination.[9] It has therefore been speculated that the population neighboring these areas will have been subject to higher incidence of cancer than the general population. Hence, it is important to assess the temporal trends and possible existence of cancer clusters in these areas.[7]

Long-term and low-intensity environmental exposure is called chronic exposure. In such cases, knowledge of both the territorial distribution of emissions and the dynamics of the population transiting through the region enables calculation of the annual dose typically absorbed by an individual.[11]

OBJECTIVE

Considering the cesium-137 accident and the increasing rates of breast cancer incidence in Goiânia, this study aimed to evaluate the spatial autocorrelation (clusters) of the addresses of women who had been diagnosed with breast cancer and ascertain the association between the incidence of breast cancer and the ionizing radiation levels to which the population was subjected.

METHODS

An ecological study was conducted using the databases of new cases of breast cancer from the Population-Based Cancer Registry of Goiás (Registro de Câncer de Base Populacional de Goiás, RCBPGO) and radiometric measurements obtained with support from the National Nuclear Energy Commission (Comissão Nacional de Energia Nuclear, CNEN). To assess the existence of clusters and the association between the variables defined in this study, it was necessary to geographically locate the addresses of the women diagnosed with breast cancer. From this point, the crude incidence rates were calculated using the female population census data.

Ethical issues

The study protocol was reviewed and approved by the internal review board of the Goiás Anticancer Association (number 31068514.43001.0031) and by the internal review board of the Universidade Federal de Goiás (UFG) (number 27742214.4.0000.5078). There was no need for informed consent.

Study area

The city of Goiânia is the capital of the state of Goiás and, according to the 2010 census of the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatistica, IBGE), the total population is 1,302,001. The territorial area of Goiânia is 733.116 km², with a population density of 1,776.74 inhabitants/km², and the city is divided into census tracts, which are the territorial units used for controlling collection of the census data.[12]

The local government also uses these territorial divisions in administrative and geographical units called healthcare districts, which are composed of a set of neighboring census tracts.

The central region of Goiânia, comprised of the Campinas-Center and South healthcare districts, which contained the seven major sources of contamination of the cesium-137 accident and the majority of new cases of breast cancer, was defined as the study area, as shown in **Figure 1**.

Data collection

Radiometric survey

The radiometric survey data and estimates of the doses to which the population of Goiânia was exposed were obtained from a previous study, conducted between 2010 and 2014.[13] To conduct this survey, a mobile system for measuring gamma radioactivity in the environment, the Thermo Eberline FHT model 1376 MobiSys, was used. This system consisted of a high-sensitivity detector (five-liter plastic scintillator) coupled to a global positioning system (GPS) device and a microcomputer. The assembly was installed on a motor vehicle such that the height of the detector was one meter from the ground. The detector was configured to make absorbed dose rate measurements in the air every second. The data collected were the absorbed dose rate in the air, geographical coordinates, altitude and date and time of acquisition.[13]

Breast cancer incidence

From the RCBPGO database, information about new cases of breast cancer in the urban area of Goiânia that occurred between 2001 and 2010 was collected. The eligibility criteria for the records followed the RCBPGO methodology, comprising all cases of breast cancer diagnosed annually in women living in the city. To avoid inclusion of cases of women from other locations, the diagnosis of cancer needed to have been after the individual had settled in the city for a minimum period of six months. The consistency of the addresses in the records identified in the study area was checked and, whenever possible, they were confirmed from other public databases, with the aim of enabling their geographical referencing.

Crude incidence rate

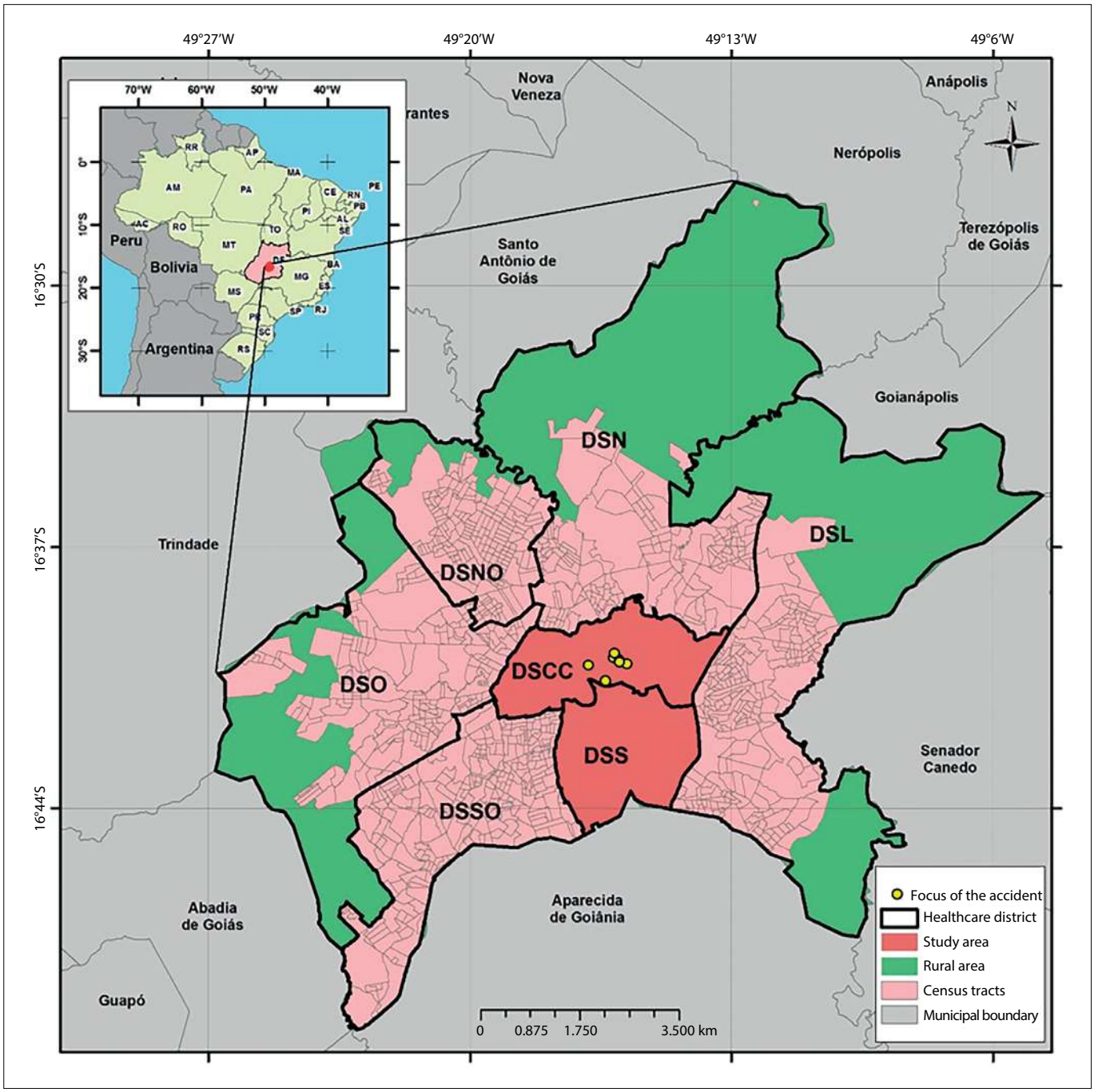
To calculating the crude incidence rate of breast cancer, the number of new cases and the female population located in a specific geographical region were considered. Data from 2000 and 2010 demographic censuses were used, in accordance with the period covered by the survey. As defined by the IBGE, the census tract data comprised private households and people who were investigated as part of the entire population; these were, by convention, called universal results. The population data referred to the

numbers of residents, in total and according to sex, in private and collective households.[12]

For comparison of the results between specific regions of Goiânia and even with other locations in Brazil, the indexes obtained from all cases were separated, considering the whole city, the study area and areas outside the study area. Moreover, for geographically referenced cases, the results were presented considering the study area and, in isolation, the two healthcare districts involved. From the number of new cases of breast cancer and the average number of women living in each specific geographical region, the annual crude breast cancer incidence rate (IR) per 100,000 women could be calculated, in accordance with equation (1).

$$IR = [(N /10) / P] \times 100{,}000 \quad (1)$$

IR – Crude incidence rate of breast cancer.
N – Number of new cases of breast cancer in the period from 2001 to 2010.



Healthcare districts: DSN = North; DSL = East; DSNO = Northeast; DSCC = Campinas-Center; DSO = West; DSSO = Southwest; DSS: South.

Figure 1. Division of the urban area of Goiânia into healthcare districts and respective census tracts, Goiânia, Goiás, Brazil, 2015.

10 – Number of years covered by the survey.
P – Average female population, considering the 2000 and 2010 censuses.

To calculate the crude incidence rate, considering all the cases identified in the survey, the estimate of the average female population (P) was obtained by reducing the 2010 population by half the population change that was observed between 2000 and 2010 in the IBGE censuses, which was 19%; therefore, the reduction factor used was 9.5%. In addition, for the sample of geographically referenced cases, the average female population was also obtained by using a 9.5% reduction factor on the female population ascertained through the 2010 IBGE census and, in this case, only the census tracts in which there was at least one geographically referenced case were considered.

Cluster analysis

The complete addresses and their geographical coordinates that were identified as being within the study area were geographically referenced. We used a geographical information system (GIS), the ArcGIS 10.0 software, which was developed by the American company ESRI (Environmental Systems Research Institute) for spatial analyses and breast cancer incidence maps. A database was also generated per census tract in the study area, using the data on the number of women diagnosed with breast cancer.

Thus, it was possible to perform a spatial assessment of the incidence of new cases of breast cancer in a particular region within a defined period, and thus, to identify possible clusters. Such clusters are gathered from events that are not merely random and, from this, it is possible to draw comparisons between specific geographical areas.[14]

Using the database with the geographically referenced crude breast cancer incidence rates, the spatial autocorrelations in the census tracts within the study area were analyzed by means of the Moran index. This index is a correlation coefficient that measures the overall spatial autocorrelation, which is multidirectional and multidimensional. However, while other coefficients measure correlations ranging from perfect to no correlation, Moran's is different: "-1" is a perfect clustering of dissimilar values (perfect dispersion); "0" is no autocorrelation (perfect randomness); and "+1" indicates perfect clustering of similar values (the opposite of dispersion).

Association between quantitative variables

The strength of the linear relationship between the continuous variables can be quantified using geographically weighted regression analyses. The main objective of this study was to analyze the association between the geographically referenced crude breast cancer incidence rates and the radiation dosimetry measurements according to census tract in the study area. We used linear regression analysis and calculation of R^2, which indicated the strength of the linear relationship between the variables using geographical weighted regression (GWR).

RESULTS

Breast cancer incidence

Total number of new cases

Between 2001 and 2010, 4,105 new cases of breast cancer were identified, among which 2,233 were in the study area and 1,872 were outside it. From the total number of new cases of breast cancer during the period of the survey, and the estimated average female population, the crude incidence rates were obtained and compared among specific regions and with estimates for 2016, as shown in **Table 1**.

Number of geographically referenced new cases

In the study area, 2,233 new cases of breast cancer were identified in the period covered by the survey and, of these, 1,286 were geographically referenced, representing 57.59% of the total sample. The other cases did not present the necessary information for

Table 1. Comparison of the crude incidence rates per 100,000 women over the period from 2001 to 2010, in specific regions of Goiânia and other locations in Brazil

Geographical region	New cases of breast cancer	% of new cases in the sample	Average female population	Incidence rate per 100,000
Goiânia	4,105	100	616,435	66.59
Study area	**2,233**	**54.40**	**216,981**	**102.91**
Campinas-Center HD	1,053	25.65	108,108	97.40
South HD	1,180	28.75	108,873	108.38
Outside of study area*	1,872	45.60	399,454	46.86
Brazil**				56.20
State of Goiás**				52.09
Goiânia**				76.07

HD = healthcare district.
*In healthcare districts in Goiânia, other than those in the study area; **Estimates for 2016.[3]

geographical referencing. The number of new cases of breast cancer ranged from one to 12 cases per census tract.

Considering only the sample of geographically referenced new cases and the average female population in each census tract (i.e. in tracts with at least one identified case), the crude incidence rates per 100,000 women were estimated. These are presented as aggregates in **Table 2**.

The crude incidence rate in the sample of geographically referenced cases, in each census tract in the study area, ranged from 16.25 to 310.39 cases per 100,000 women in the Campinas-Center healthcare district and from 17.43 to 295.97 cases per 100,000 women in the South healthcare district.

Analysis of spatial clusters

Through the statistical analysis on the spatial clusters considering the number of geographically referenced new cases of breast cancer, and from the crude incidence rates in each census tract, it was observed that most of the census tracts in the study area did not present any spatial autocorrelation. The crude incidence rates obtained in these tracts were statistically and geographically heterogeneous. There were three small sets of tracts, one in the southern region and two in the western region of the study area, where the cancer occurrence rate was high in several neighboring tracts, as seen in **Figure 2**.

Association between quantitative variables

From the geographically referenced databases of breast cancer crude incidence rates and radiometric measurements per census tract in the study area, it was possible to quantify the strength of the linear relationship between these variables.

Breast cancer incidence and ionizing radiation

In order to evaluate the association between the variables studied, a linear regression analysis showing the dispersion of the points and R^2 values was performed, as displayed in **Figure 3**.

In the graph of **Figure 3**, the dispersion of the points does not follow any geometric pattern (line or curve) that would indicate any association between the variables. This can also be confirmed from the trend line, which is practically horizontal. The low R^2 values also indicate that there was a lack of association per census tract.

Table 2. Description of the crude incidence rates of new cases of breast cancer, geographically referenced per 100,000 women, according to sanitary district in the study area

Geographical region	New cases of breast cancer	Average female population (2000-2010)	Crude incidence rate per 100,000
Study area	**1,286**	**178,950**	**71.86**
Campinas-Center HD	569	84,009	67.73
South HD	717	94,941	75.52

HD = healthcare district.

DISCUSSION

All practices using ionizing radiation should observe the basic principles of radiation protection, including the principle of optimization. This concept dictates that all exposures should be kept as low as reasonably achievable (ALARA), since radiobiological and epidemiological studies on low doses have shown that there is no way to determine a dose threshold for the onset of stochastic biological effects.[15]

Evaluating a possible association between the incidence of breast cancer and the ionizing radiation levels existing in Goiânia is relevant, considering that both people and the environment in this area were seriously affected by the cesium-137 accident.[7,8] This was the largest radiological accident that has occurred in any urban area and, therefore, it provides a rare opportunity to investigate the effects of ionizing radiation on occurrences of malignancies. In this context, this study reinforces the hypothesis that the radiological accident in Goiânia was not associated with the appearance of new cases of breast cancer.

The classical studies observed high cesium concentration at the incident site[16] and indicated that exposure to ionizing radiation could be detected in descendants of the exposed individuals.[17,18] Nevertheless, population-based studies with almost 30 years of follow-up have also suggested that was no association between the radiological accident and the incidence of cancer in the city.[19,20] One possible explanation for this is that the genetic changes induced in the exposed population were not pathogenic or did not translate into increased cancer risk.[21]

In the overall analysis on breast cancer incidence in Goiânia, the peak incidence of the disease would have been expected in 1997, i.e. after a ten-year latency period following the accident. However, a recent study showed that the increase in the incidence of breast cancer in Goiânia was gradual between 1988 and 2004, with a tendency to stabilize after 2005.[20] In this context, analysis on the incidence associated with the geospatial distribution pattern may identify points of higher concentration of the disease (clusters) and assist in constructing hypotheses about neoplasm behavioral change at that particular location.[22-24]

For the city of Goiânia, the estimates for 2016 showed that there were 250 new cases of breast cancer and a crude incidence rate of 76.07 cases per 100,000 women. Among the Brazilian state capitals, Goiânia presents an intermediate rate, close to the national average among the capitals, which is 79.37 new cases per 100,000 women.[2] In addition, no abnormal pattern in the breast cancer incidence curve was observed in Goiânia over the past 30 years, compared with other Brazilian state capitals.[2,20]

Considering the total number of new cases of breast cancer identified in this study within the period between 2001 and 2010,

the crude incidence rates per 100,000 women were much higher in the study area (102.91 cases per 100,000) than outside the study area (46.86 cases per 100,000), and higher than the average in Goiânia (66.59 cases per 100,000 women). Moreover, with regard to the absolute number of new cases, the study area presented a concentration of 54.40%, although the proportions in the Campinas-Center (25.65%) and South (28.75%) healthcare districts were similar.

Previous studies also identified higher concentrations of breast cancer cases in the Campinas-Center (39.95%) and South (20.48%) healthcare districts. These districts of Goiânia have populations with higher socioeconomic status, older women and easier access to healthcare services.[3] Thus, the difference in the incidence rate may be due to greater adherence to screening programs and expression of other risk factors for the disease, such as age, obesity and hormone exposure.

Considering only the geographically referenced new cases of breast cancer in the study area and their respective healthcare districts, the crude incidence rates per 100,000 women were 71.86 in the study area overall, i.e. 67.73 in the Campinas-Center healthcare district, and 75.52 new cases per 100,000 women in the South healthcare district. Because the sample of geographically referenced cases represented 57.59% of the total identified, it was expected that the crude incidence rates obtained in the geographically referenced sample would be proportionately lower than the rates found for all the new cases identified in the survey, and this was confirmed.

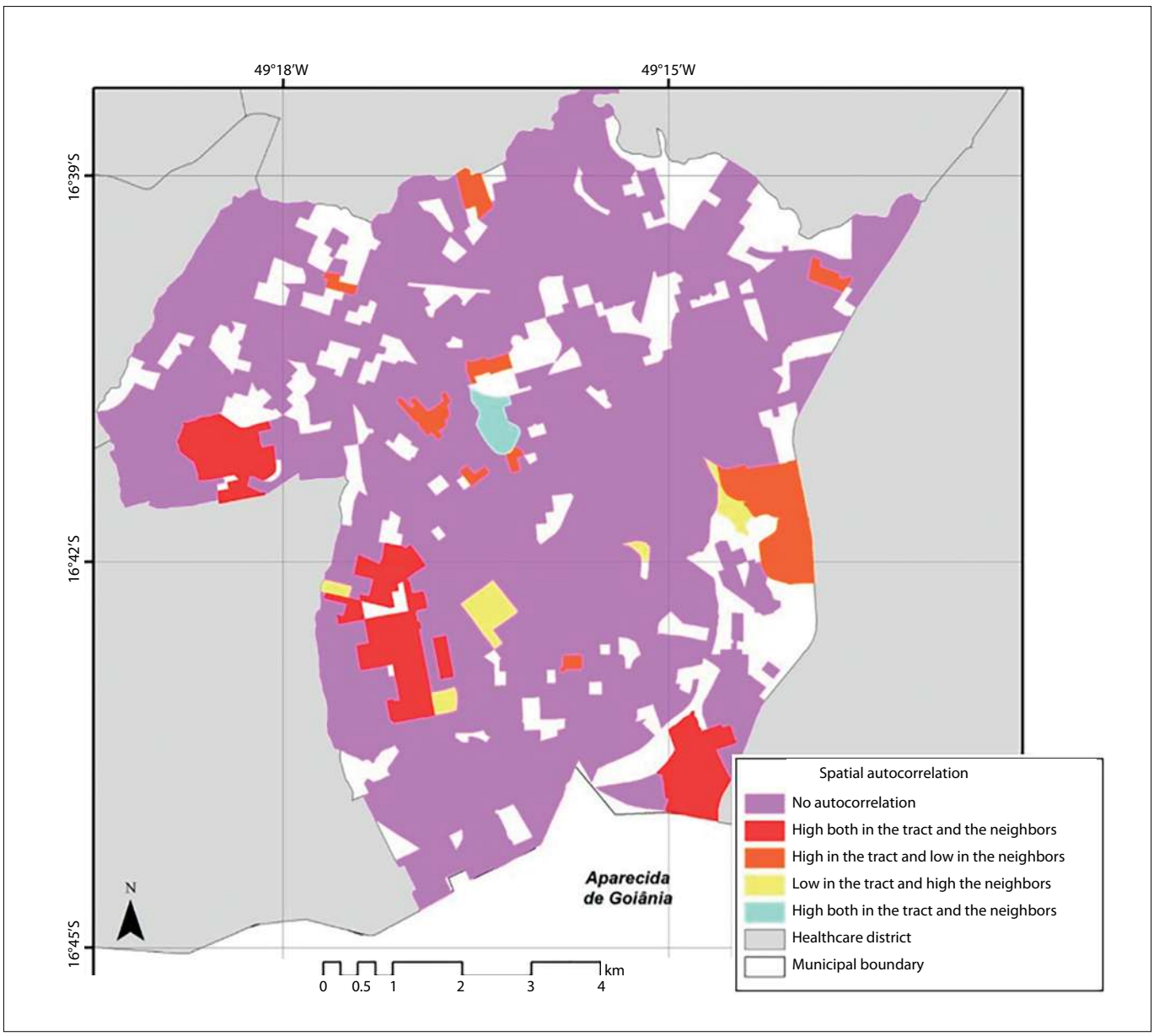


Figure 2. Spatial autocorrelation of the crude incidence rates of breast cancer (clusters) from 2001 to 2010, in each census tract of the Campinas-Center and South healthcare districts.

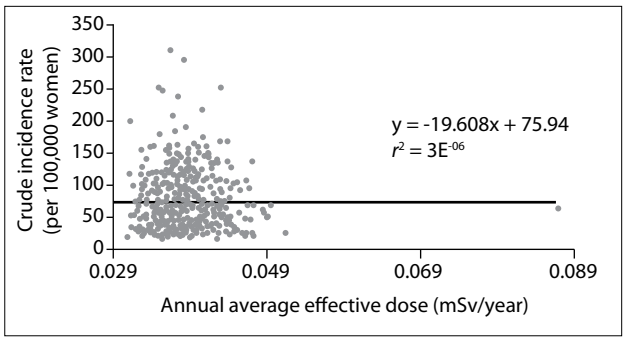


Figure 3. Association between the crude incidence rate of breast cancer and the annual average effective dose (mSv/year) in the census tracts of the study area (Campinas-Center South healthcare districts).

For the cluster analysis, we considered the crude incidence rates that took into account both the number of new cases and the female population living in each census tract. Thus, one possible source of bias was eliminated, because if the absolute number of new cases of breast cancer were considered, a focus on more densely populated areas would be expected.

The data from this study add population-based information and geographical referencing involving breast cancer and exposure to cesium-137. In an individualized analysis on the direct victims of the accident, there was no difference in the overall incidence of cancer cases.[21] By means of regression analysis, and considering the breast cancer crude incidence rate and the average dose of ionizing radiation, we found that there was no statistical association between these variables. However, new studies are needed in order to continue the evaluation of other risk factors associated with this neoplasm.

CONCLUSIONS

This study reinforces the hypothesis that the ionizing radiation levels to which women living in Goiânia are exposed to are not associated with the onset of new cases of breast cancer. Discrete clusters were observed in specific regions away from the sources of contamination from the cesium-137 accident, which were the areas with the highest levels of ionizing radiation in Goiânia.

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Evaluation of patients undergoing emergency surgery in a COVID-19 pandemic hospital: a cross-sectional study

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ABSTRACT

BACKGROUND: The COVID-19 pandemic is threatening healthcare systems and hospital operations on a global scale. Treatment algorithms have changed in general surgery clinics, as in other medical disciplines providing emergency services, with greater changes seen especially in pandemic hospitals.

OBJECTIVES: To evaluate the follow-up of patients undergoing emergency surgery in our hospital during the COVID-19 pandemic.

DESIGN AND SETTING: Cross-sectional study conducted in a tertiary-level public hospital.

METHODS: The emergency surgeries carried out between March 11 and April 2, 2020, in the general surgery clinic of a tertiary-care hospital that has also taken on the functions of a pandemic hospital, were retrospectively examined.

RESULTS: A total of 25 patients were included, among whom 20 were discharged without event, one remained in the surgical intensive care unit, two are under follow-up by the surgery service and two died. Upon developing postoperative fever and shortness of breath, two patients underwent thoracic computed tomography (CT), although no characteristics indicating COVID-19 were found. The discharged patients had no COVID-19 positivity at follow-up.

CONCLUSION: The data that we obtained were not surgical results from patients with COVID-19 infection. They were the results from emergency surgeries on patients who were not infected with COVID-19 but were in a hospital largely dealing with the pandemic. Analysis on the cases in this study showed that both the patients with emergency surgery and the patients with COVİD infection were successfully treated, without influencing each other, through appropriate isolation measures, although managed in the same hospital. In addition, these successful results were supported by 14-day follow-up after discharge.

INTRODUCTION

The first case of COVID-19 (new type of coronavirus, 2019-nCoV) in Turkey was identified on March 11, 2020, which was also the date on which the World Health Organization declared the outbreak to be a pandemic.[1-3] As COVID-19 has spread around the world and across Turkey, the hospitals that have been used to treat the disease have become locations where there is a high risk of infection.[4,5]

Between this first case in Turkey on March 11, 2020, and a survey on April 2, 2020, a further 18,135 cases were identified. Approximately 60% of these cases were seen in the city of Istanbul where our hospital is located.[6,7] Thus, Istanbul alone accounts for more than half of all patients among the 81 cities of this country. Moreover, the hospital in which we work was the first and is now one of the four officially declared pandemic hospitals in the city. The intensity of patient demand is higher around these hospitals, which gave us a responsibility to report our data because of the high reliability of our results.[7]

With the increasing incidence rate of the disease in our country, the number of patients diagnosed with or suspected of having COVID-19 infection entering our emergency service and inpatient services has also rapidly increased. It has therefore been recommended that elective surgeries should be postponed wherever possible, in regions to which the pandemic has spread.[8,9]

However, this is not possible with emergency surgeries, and so it has become necessary to carry out such surgeries while taking the maximum of precautions. Healthcare professionals are at increased risk of exposure to COVID-19 and its infection, given their involvement in treatment of this disease. This has brought to light the risk that the healthcare workforce for fighting

against the COVID-19 pandemic may become diminished through illness. Given the way in which this disease has spread and affected healthcare systems around the world, it can be understood that hospitals must provide services for individuals who have been diagnosed with or are suspected of having COVID-19 infection, while also treating emergency surgery patients. After our institution was declared a pandemic hospital, emergency surgeries continued to be performed there, in a controlled manner. The COVID-19 pandemic is affecting healthcare systems and treatment approaches through its new and unknown features.

OBJECTIVE

In this study, we aimed to evaluate the follow-up of patients who underwent emergency surgery in our hospital during the COVID-19 pandemic.

METHODS

This study consisted of a cross-sectional evaluation of the emergency surgeries performed in the general surgery clinic of a tertiary- care hospital between March 11, 2020, when the first official COVID-19 case in Turkey was reported, and April 2, 2020. Elective and semi-elective surgeries were excluded from this study. The parameters examined included the patients' demographic data, comorbidities, indications for surgery, preoperative patient assessment environment, preoperative imaging methods, infection parameters, surgical procedures, anesthetic procedures, postoperative intensive care requirement, length of hospital stay, status of postoperative COVID-19 suspicion and postoperative morbidity and mortality rates. All patients were evaluated with regard to whether there was any suspicion of or a diagnosis of COVID-19 before they were admitted to the hospital and after discharge,

Our approaches in the process of adaptation to the pandemic

Pursuant to a decision by the COVID-19 Scientific Advisory Board at the start of the outbreak, all suspected COVID-19 cases were evaluated in isolated areas, and were diagnosed and treated in separate areas within the emergency service. Thus, patients presenting for surgery at the emergency service were considered to have been prevented from coming into contact with suspected COVID-19 patients.[8]

The initial examinations on the surgical patients were made using personal protective equipment, initially using masks and gloves. However, as the number of COVID-19 cases rapidly increased, all surgical patients were assumed to have contracted this disease, and N95 or filtering facepiece (FFP) masks, protective googles and protective gowns started to be used as routine. Patients who were scheduled for surgery and admitted to the service were taken into individual rooms. They were then moved to the operating room wearing a mask, and without spending any time in the preoperative room.

In order to avoid bringing the patient into contact with too many people prior to anesthesia, the anesthesia care team consisted only of an anesthesiologist and an anesthetic technician. Under the assumption that the patient was COVID-19 positive, the anesthetic procedures were carried out with the operative wearing an N95 protective mask with a surgical mask over it, a surgical box gown and protective googles.

Intubations were made by specialist physicians using a videolaryngoscope, with rapid induction and without mask ventilation. Complete nasal oxygenation was ensured. During wakening, oxygen was administered through a nasal cannula in order to avoid post-extubation masking. Recovery and wakening occurred in the operating room when possible, and the patient was transferred directly to the surgical service without entering the postoperative room. Patients requiring intensive care were transferred to the intensive care negative-pressure isolation room, accompanied by the anesthesiologist, via a different corridor. The same personal protective equipment was used for patients receiving spinal anesthesia. The surgical team used liquid-tight gowns, surgical masks over N95, protective googles and gloves (double), as personal protective equipment.

Postoperative visits to patients were conducted with a minimum of personnel (one physician and one nurse), wearing N95 masks and a surgical box gown upon each entry to and exit from the room, and using hand disinfectant. At the time of discharge, the patients were given the recommendation that they should adhere to a 14-day isolation period. On the 14th day after discharge, these patients were called by phone, to gain information.

Ethical approval

Board of ethics approval for this study was obtained from the ethics commission of the Health Sciences University, Haseki Training and Research Hospital, under approval number 40-2020, dated April 17, 2020.

Statistical analysis

Descriptive statistics were calculated, including means, standard deviations, medians, minimums, maximums, frequencies and ratios. The SPSS 22.0 software was used for the analyses.

RESULTS

This study included a total of 25 patients, of whom nine were male and 16 were female, with a mean age of 50 years. The nine male patients all had comorbidities. **Table 1** shows the patients' comorbidities, preoperative laboratory values, preoperative imaging, anesthetic procedure, duration of operation, length of hospital stay, postoperative complications and mortality. Among all

the patients, six of them had more than one comorbidity, and none presented any suspicion of preoperative COVID-19 or had any history of contact.

Upon developing postoperative fever and shortness of breath, two patients underwent a thoracic computed tomography (CT), which did not reveal any imaging suggestive of COVID-19. Material was sent for COVID-19 polymerase chain reaction (PCR) tests and the results were negative. These two patients were discharged upon regression of their fever and cough.

Mortality occurred in the cases of two other patients who had undergone operations due to ischemia. During the 14-day follow-up on the patients who had been discharged, there was no suspicion of COVID-19 and findings of the disease.

Table 2 shows the operations and indications of the patients. The most common cause of admission was acute appendicitis. Three patients were operated on to treat findings of diffuse peritonitis due to leakage of an anastomosis. Three patients were operated on due to mesenteric ischemia because of late admission with acute abdominal and necrotic findings. Two patients were operated on to treat rectal malignancies due to mechanical colon obstruction. In one patient, bleeding did not stop despite endoscopic intervention to treat upper gastrointestinal system bleeding, and hemodynamic deterioration was observed. One patient was operated on to treat mechanical intestinal obstruction due to adhesions, since there was no intestinal passage despite follow-up for 72 hours. In one patient, intestinal evisceration occurred during postoperative mobilization. In one patient, retraction of the intestinal stoma into the abdomen occurred on the postoperative third day. In one patient who had undergone an inguinal hernia repair because of anticoagulant usage, widespread postoperative hematoma and active blood leakage was observed. One patient was operated on due to abundant hemorrhage following failure of endoscopic gastrostomy revision, by means of endoscopic therapeutic intervention.

All the patients were operated on under emergency conditions. None of the patients presented suspected COVID or any diagnostic history before hospital admission, and none of these patients had any signs or symptoms of COVID-19 over the 14-day follow-up after discharge.

DISCUSSION

In the present study, the changes in approaches to general surgery and emergency practices resulting from the COVID-19 pandemic were examined. The pandemic continues to spread rapidly, and has affected all healthcare service units and operations around the world, and Turkey has not been an exception.

We demonstrated that necessary surgeries can still be performed in COVID-19 pandemic hospitals if the measures and precautions required are taken. Despite research into the epidemiology, pathophysiology, treatment and practices relating to patients infected with

Table 1. General characteristics and demographic data

Characteristics	Range (min-max)	Median	Mean ± SD or n and %
Age (years)	19.0-87.0	58	50.0 ± 22.3
Over 65 years old			9 (36%)
Sex			
Female			16 (64.0%)
Male			9 (36.0%)
Duration of operation (minutes)	35.0-180.0	60	84.8 ± 44.7
Length of hospital stay (days)	2.0-21.0	3	6.7 ± 6.8
Comorbidity			9 (36.0%)
Preoperative chest x-ray			25 (100%)
Preoperative chest CT			11 (44.0%)
Preoperative CT suspected positive for COVID-19			0 (0%)
Anesthesia type (general)			22 (88.0%)
Need for postoperative intensive care			7 (28.0%)
Postoperative intubation			6 (24.0%)
Wound infection			4 (16.0%)
Suspected postoperative COVID-19			2 (8.0%)
Postoperative COVID-19 test			2 (8.0%)
Current status:			
Intensive care unit			1 (4%)
General surgery service			2 (8%)
Postoperative mortality			2 (8%)
Discharged without problems			20 (80%)
Preoperative laboratory parameters			
Preoperative WBC	3-39	13.0	14.4 ± 8.1
Preoperative lymphocyte	1-4	1.0	1.6 ± 0.8
Preoperative neutrophil	2-37	11.0	12.9 ± 7.8
Preoperative CRP	1-265	100.0	104.9 ± 83.6
Preoperative albumin	1.9-5	3	3 ± 0.9

Min-Max = minimum-maximum; CT = computed tomography; WBC = white blood cell; CRP = C-reactive protein; SD = standard deviation.

Table 2. Patient diagnoses and types of surgery

Indication for operation	Procedures	Patient Number
Acute appendicitis	Appendectomy (open)	3
Acute appendicitis	Appendectomy (laparoscopic)	7
Anastomosis leak	Feeding jejunostomy, loop ileostomy, Hartman colostomy	3
Mesenteric ischemia	Subtotal colectomy, segmental ileum resection, diagnostic laparoscopy	3
Malignancy rectum	Sigmoid loop colostomy	2
Bleeding in the upper gastrointestinal tract	Pyloroplasty	1
Adhesive ileus	Adhesiolysis	1
Postoperative evisceration	Postoperative exploration	1
Stoma retraction	Stoma revision	1
Unreduced umbilical hernia	Hernia repair	1
Postoperative hematoma	Hematoma drainage	1
Gastrostomy obstruction	Gastrostomy revision	1
Total		**25**

COVID-19, and the respective effects on public health, algorithms for surgical treatment on individuals with a suspicion or diagnosis of COVID-19 infection have been deemed of secondary importance.[9] Earlier in the pandemic, anesthesiologists published various recommendations for the equipment and protection that was required to protect themselves during intubation.[8,11,12] Subsequently, recommended approaches to surgery were suggested for patients with a suspicion or diagnosis of COVID-19.[3,5,10]

Although a considerable proportion of COVID-19 patients are asymptomatic, it is an infectious disease. Therefore, all our surgical patients in our pandemic hospital were approached under the assumption that they were positive, from the earliest days. Since the virus is mainly transmitted through droplets, it is accepted that the virus will remain on contact surfaces for hours, or even days, as a potential source of infection through transmission by contact.[11] This constitutes a risk for healthcare professionals, who may come into contact with these contaminated surfaces, thus transmitting the virus to themselves or others.[13] All surfaces were disinfected, and efforts were made to leave as much time as possible between two operations. Both the anesthesia care team and the surgical team tried to have the minimum number of staff present in the room during induction of anesthesia.

The use of laparoscopy in emergency surgery on patients suspected of or diagnosed with COVID-19 is a matter of controversy, given that there is still no clear information in this regard. Yu et al.[14] reported that SARS-CoV-2 spreads through droplets and contact, although fecal-oral and aerosol transmissions cannot be ignored. They therefore stated that laparoscopic surgeries could be performed on colon cancer patients infected with COVID-19, although there would be a need for good management of laparoscopic gases. Likewise, Morris et al.[15] suggested that the laparoscopic approach could be used for gynecological cases, and that the risk of COVID-19 had yet to be proven. In the present study, seven patients underwent laparoscopic appendectomy and one patient underwent diagnostic laparoscopy with a diagnosis of mesenteric ischemia. No problems were encountered during the postoperative follow-up on the seven patients. Considering that use of laparoscopy reduces the length of hospital stay, we conclude that its use should be preferred in emergency surgery when performed by experienced surgeons.

Some studies have recommended follow-up at home using antibiotics, with communication via telephone or other means, for cases of non-complicated acute appendicitis.[16] Such patients, however, were scheduled for surgery, even though there was no perforation, considering that there might not have been sufficient ways means of communication and access in the pandemic area, with poor access to healthcare facilities. A total of ten patients who underwent appendectomy were discharged without event.

In a review by Di Saverio et al.,[3] it was recommended that all patients who were to undergo surgery should be tested for COVID-19. Such tests were not requested in the earliest of our cases, given that the test results would not be available immediately, and the surgical decision would be unaffected anyway. With increasing numbers of COVID-19-positive patients and tests (PCR), we started to seek tests in new cases, as the routine. In a similar vein, no thoracic CT was requested in the earliest days, but came to be sought even if the patient was asymptomatic, in line with the latest recommendations.[5] Thoracic CT was requested in the cases of 11 patients, along with abdominal CT (44%).

Protective measures were also taken in relation to cases operated on previously in our hospital that were admitted for surgery due to complications during the process. Such patients were considered to be at risk because of their contact with visitors and healthcare personnel. Furthermore, two patients with rectal tumors underwent emergency surgery for a temporary protective loop colostomy.

Given that all elective surgery and diagnostic endoscopy procedures have been postponed because of the extended duration of the pandemic, there is growing concern about the increasing the frequency of presentations to the emergency services with a clinical picture of ileus due to colon and rectal tumors. The limitations of the present study are the limited number of patients, the single-center design, the lack of randomization and the retrospective nature of the study.

CONCLUSION

We believe that the risk of dissemination of COVID-19 will be reduced through isolating the emergency surgery services from the pandemic services, by means of using personal protective equipment, carrying out preoperative abdominal CT simultaneously with thoracic CT (when required) and ensuring the minimum of contact between healthcare staff and the patient. The data that we obtained were not surgical results from patients with COVID-19 infection. They were the results from emergency surgeries on patients who were not infected with COVID-19 but were in a hospital largely dealing with the pandemic. Analysis on the cases in this study showed that both the patients with emergency surgery and patients with COVİD infection were successfully treated, without influencing each other, through appropriate isolation measures, although managed in the same hospital. In addition, these successful results were supported by 14-day follow-up after discharge.

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Diagnostic accuracy of preoperative magnetic resonance imaging for detecting subscapularis tendon tears: a diagnostic test study

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Intra-observer agreement.

ABSTRACT

BACKGROUND: The accuracy of magnetic resonance imaging (MRI) for making the diagnosis of subscapularis tears presents wide variation in the literature and there are few prospective studies.

OBJECTIVE: To compare the findings from MRI and arthroscopy for diagnosing subscapularis tears.

DESIGN AND SETTING: Diagnostic test study performed in a tertiary care hospital.

METHODS: We included patients who underwent arthroscopic rotator cuff repair and who had firstly undergone high magnetic field MRI without contrast. The images were independently evaluated by a shoulder surgeon and two musculoskeletal radiologists. Sensitivity, specificity, positive and negative predictive values, accuracy and inter and intra-observer agreement were calculated.

RESULTS: MRIs on 200 shoulders were evaluated. The incidence of subscapularis tears was 69.5% (41.5% partial and 28.0% full-thickness). The inter and intra-observer agreement was moderate for detection of subscapularis tears. The shoulder surgeon presented sensitivity of 51.1% to 59.0% and specificity of 91.7% to 94.4%. The radiologists showed sensitivity of 83.5% to 87.1% and specificity of 41% to 45.9%. Accuracy ranged from 60.5% to 73.0%.

CONCLUSION: The 1.5-T MRIs without contrast showed mean sensitivity of 70.2% and mean specificity of 61.9% for detection of subscapularis tears. Sensitivity was higher for the musculoskeletal radiologists, while specificity was higher for the shoulder surgeon. The mean accuracy was 67.6%, i.e. lower than that of rotator cuff tears overall.

INTRODUCTION

Although the biomechanical importance of the subscapularis tendon has been recognized in biomechanical[1] and clinical studies,[2] it has long received little attention in the medical literature,[3] and has been called the "forgotten tendon".[4] Only 1% of rotator cuff tears affect only the subscapularis,[5,6] but more than half of all patients with supraspinatus tears present an associated tear of this tendon.[7,8]

The accuracy of magnetic resonance imaging (MRI) is usually lower for detection of subscapularis tears than for rotator cuff tears overall,[9,10] with sensitivity ranging from 25% to 94%[5,11] and specificity from 67% to 100%.[12-14] Studies evaluating the diagnosis of subscapularis tears are important for clinical practice, with implications for prognosis and surgical planning. Among the published studies, some have included low magnetic field MRI,[7,13,15,16] small samples,[15,17] diagnosis not restricted to rotator cuff disorders,[7,12,14-16,18-21] and use of intra-articular[11,14,19] or intravenous[15,20] contrast. These factors can generate bias in data interpretation.

OBJECTIVE

The objective of the present study was to evaluate the accuracy of preoperative high magnetic field MRI without the use of contrast, compared with arthroscopic inspection, for identifying subscapularis tears, in cases undergoing rotator cuff repair.

METHODS

This was a diagnostic test study comparing the findings from preoperative MRI (index test) with those from shoulder arthroscopy (reference standard) for diagnosing subscapularis tears. Operative data were collected in a standardized manner from consecutive patients between January 2013 and August 2017, by three surgeons at the same institution.

The study included patients undergoing arthroscopic surgery for rotator cuff repair who had firstly undergone preoperative 1.5-T MRI without the use of intra-articular or intravenous contrast. Patients were excluded if the interval between MRI and surgery was longer than one year, or if MRI was not available in digital format. Patients who refused to participate were also excluded, as were cases of reoperations. Examinations with moving artifacts were also excluded.

The local institutional review board approved the study (Comissão de Ética para Análise de Projetos de Pesquisa, CAPPesq), in a session on August 19, 2015, under research protocol number 12952.

Index test - magnetic resonance imaging

All MRI scans were performed using a 1.5-T unit (HDxt, GE Medical Systems, Milwaukee, Wisconsin, United States) and a dedicated three-channel shoulder coil. The patients were placed in a supine position with their arms in a neutral position. Neither intra-articular nor intravenous gadolinium was used for any of the examinations. The protocol used was as follows: axial, oblique coronal and oblique sagittal fat-suppressed intermediate-weighted images (TR: 2717-3784 ms; TE: 42-46 ms; FOV 15 cm; slice thickness 3-4 mm; matrix 288 x 192); and oblique coronal and oblique sagittal T1-weighted images (TR: 350-517 ms; TE: minimum; FOV 14-15 cm; slice thickness 3-4 mm; matrix 288 x 192).

The examinations were blindly evaluated using Osirix 9.0 (Pixmeo SARL, Bernex, Switzerland) by two musculoskeletal (MSK) radiologists (5 and 10 years of experience) and a shoulder surgeon with 12 years of experience. The shoulder surgeon reassessed the examinations after three months, with the MRIs randomly rearranged.

Reference standard - arthroscopy

Arthroscopic surgery was carried out with the patients placed in a beach chair position under general anesthesia and interscalene block. The integrity of the subscapularis tendon was evaluated with the 30º optic positioned in the posterior portal while an auxiliary performed the posterior lever-push maneuver.[22] When the biceps tendon impaired visualization of the subscapularis, it was debrided or tenotomized. Arthroscopies were performed by three shoulder surgeons with 10 to 12 years of experience. The surgeons were not blinded to the MRI findings, but were blinded to the results from the study observers.

Subscapularis evaluation

In the MRI evaluation, the subscapularis tendon was classified in one of the following categories: intact tendon, partial-thickness tear or full-thickness tear. In the arthroscopic evaluation, the same categories were used. The tendon was considered intact when no signs of tear were present, independent of presenting normal or high signals in T2. Tears were considered partial when articular, intra-substantial or longitudinal tears were present, without complete discontinuity. Full-thickness tears included those affecting the upper third, upper two-thirds or entire extent of the tendon.

Other variables analyzed

The following clinical and demographic data were evaluated: sex; age; preoperative function, as measured on the American Shoulder and Elbow Surgeons (ASES) scale; University of California Los Angeles (UCLA) shoulder rating scale; and time between MRI and surgery. Data regarding the other tendons were collected by means of arthroscopy: supraspinatus (intact, partial tear or full-thickness tear); infraspinatus (intact or torn); and biceps (intact or torn). Biceps stability was also evaluated. For the variables visualized by means of MRI, the mean from the four evaluations of the continuous data (coracohumeral interval, measured in mm) was used. For the categorical data, a consensus reached among the evaluators regarding the following was used: fatty degeneration as described by Fuchs et al.,[23] categorized as I or ≥ II; and presence of cysts in the lesser tuberosity, categorized as absent or present.

Statistical analysis

Continuous data were described using means and standard deviations. Categorical data were described using absolute and proportional frequencies. Accuracy was described using the diagnosis from arthroscopy as its reference and was determined through analyses on sensitivity, specificity, positive and negative predictive value and positive and negative likelihood ratio, with their respective confidence intervals. The intra and inter-observer analyses were performed using the kappa test and the modified Fleiss kappa test, respectively. The data were presented as absolute values and were categorized in accordance with the criteria of Landis and Koch: ≥ 0.81 almost perfect; 0.61 to 0.80 substantial; 0.41 to 0.60 moderate; 0.21 to 0.40 fair; and ≤ 0.20 slight.[24] The value set for statistical significance was ≤ 5%. The software used was SPSS® for Mac 23.0 (Chicago, IL, United States). There was no need to impute data.

RESULTS

Between January 2013 and August 2017, 411 shoulders with rotator cuff tears were operated on. The following cases were not included: 57 open repairs, 70 cases with an interval between the MRI and surgery longer than one year, 6 cases with movement artifacts, 12 cases with previous surgery and 66 cases in which MRI was not available in digital format. Thus, MRIs for 200 shoulders (195 patients) were analyzed.

Table 1 shows the general characteristics of the sample according to subscapularis tendon condition. Supraspinatus and subscapularis fatty degeneration, biceps instability, gender and age differed between the groups. The other variables did not present statistically significant differences.

The comparison of subscapularis appearance among the five different evaluations is shown in **Table 2**. The shoulder surgeon detected fewer tears than those observed through arthroscopy (41.0% to 47.5% versus 69.5%). Radiologists, on the other hand, detected more tears than were observed through arthroscopy (74.5% to 78.5%). In the arthroscopic views, 30.5% of the sample presented intact tendons; 41.5%, partial tears; and 28.0%, full-thickness tears.

The inter-observer agreement was substantial for full-thickness tears (kappa 0.631; 95% confidence interval, CI 0.556-0.700; P < 0.001). For overall tears (partial or full-thickness), the results were moderate (kappa 0.463; 95% CI 0.383-0.534; P < 0.001). Intra-observer agreement was almost perfect for detection of full-thickness tears (kappa 0.809; 95% CI 0.696-0.923; P < 0.001). For overall tears, the results were moderate (kappa 0.546; 95% CI 0.430-0.662; P < 0.001). These data are shown in **Table 3**.

The accuracy measurements are detailed in **Table 4**. The shoulder surgeon presented sensitivity of 35.7% to 39.3% (mean 37.5%) for full-thickness tears and 51.1% to 59.0% (mean 55.1%) for overall tears. The specificity was 91.7% to 94.4% (mean 93.1%) and 78.7% to 82.0% (mean 80.4%), respectively. For the MSK radiologists, the sensitivity ranged from 57.1% to 71.4% (mean 64.3%) for full-thickness tears and 83.5% to 87.1% (mean 85.3%) for overall tears, while the specificity was 85.4%

Table 1. General sample characteristics according to the presence or absence of the different subscapularis tendon conditions

	Subscapularis tear			
	No tear (n = 61)	Partial tear (n = 83)	Full-thickness tear (n = 56)	P
Supraspinatus tear [n (%)]				
None	5 (41.7)	2 (16.7)	5 (41.7)	
Partial	19 (43.2)	18 (40.9)	7 (15.9)	0.139
Full-thickness	37 (25.7)	63 (43.8)	44 (30.6)	
Infraspinatus tear [n (%)]				
No	40 (32.3)	53 (42.7)	31 (25)	0.472
Yes (partial + full-thickness)	21 (27.6)	30 (39.5)	25 (32.9)	
Supraspinatus fatty degeneration [n (%)]**				
I	51 (32.1)	73 (45.9)	35 (22.0)	0.001*
≥ II	10 (24.4)	10 (24.4)	21 (51.2)	
Infraspinatus fatty degeneration [n (%)]**				
I	48 (33.3)	61 (42.36)	35 (24.3)	0.372
≥ II	13 (23.2)	22 (39.3)	21 (37.5)	
Subscapularis fatty degeneration [n (%)]**				
I	59 (33.1)	77 (43.3)	42 (23.6)	< 0.001*
≥ II	2 (9.1)	6 (27.3)	14 (63.3)	
LHB stability [n (%)]				
Stable	43 (41.0)	45 (44.6)	13 (12.9)	
Unstable	13 (16.5)	25 (46.3)	17 (31.5)	< 0.001*
NA	5 (29.4)	5 (29.4)	7 (41.2)	
LHB tear [n (%)]				
Not torn	34 (38.6)	34 (38.6)	20 (22.7)	0.071
Torn	27 (24.1)	49 (43.8)	36 (32.1)	
Gender [n (%)]				
Male	31 (31.3)	33 (33.3)	35 (35.4)	0.031*
Female	30 (29.7)	50 (49.5)	21 (20.8)	
Cysts in the lesser tuberosity [n (%)]				
Yes	10 (28.6)	16 (45.7)	9 (25.7)	0.855
No	51 (30.9)	67 (40.6)	47 (28.5)	
Age, years (mean ± SD)	54.97 ± 16.42	56.53 ± 10.87	58.72 ± 6.77***	0.005*
Coracohumeral interval, mm (mean ± SD)	8.19 ± 1.72	8.43 ± 2.01	8.01 ± 8.72	0.507
Time between MRI and arthroscopy, days (mean ± SD)	123.97 ± 86.68	138.01 ± 86.94	160.61 ± 106.71	0.192
ASES score (mean ± SD)	45.64 ± 21.98	43.76 ± 21.5	45.61 ± 19.05	0.608
UCLA score (mean ± SD)	15.67 ± 5.47	15.07 ± 5.44	15.66 ± 5.44	0.644

LHB = long head of the biceps; SD = standard deviation; ASES = American shoulder and elbow surgeons; UCLA = University of California Los Angeles; NA = Not applicable.

to 86.1% (mean 85.8%) and 41.0% to 45.9% (mean 43.5%), respectively. Considering the average of the four evaluations, the sensitivity for overall tears was 70.2%, while the specificity was 61.9%. The accuracy of the four evaluations ranged from 77% to 81.5% (mean 78.6%) for full-thickness tears and 60.5% to 73% (mean 67.6%) for overall tears.

Table 2. Comparison of the integrity of the subscapularis tendon between findings from magnetic resonance imaging and arthroscopy

Subscapularis tear	Shoulder surgeon (1st evaluation)		Shoulder surgeon (2nd evaluation)		MSK radiologist 1		MSK radiologist 2		Arthroscopy	
	n	%	n	%	n	%	n	%	n	%
No	118	59.0%	105	52.5%	51	25.5%	43	21.5%	61	30.5%
Yes	82	41.0%	95	47.5%	149	74.5%	157	78.5%	139	69.5%
Partial	48	24.0%	67	33.5%	88	44.0%	105	52.5%	83	41.5%
Full-thickness	34	17.0%	28	14.0%	61	30.5%	52	26.0%	56	28.0%

MSK = musculoskeletal.

Table 3. Inter-observer and intra-observer reliability results

Parameter	K	95% CI		P-value
		Inferior	Superior	
Inter-observer reliability results				
Subscapularis tear (full-thickness + partial)	0.463	0.383	0.534	< 0.001
Full-thickness tear	0.631	0.556	0.700	< 0.001
Intra-observer reliability results				
Subscapularis tear (full-thickness + partial)	0.546	0.430	0.662	< 0.001
Full-thickness tear	0.809	0.696	0.923	< 0.001

CI = confidence interval.

Table 4. Values relating to sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and accuracy of magnetic resonance imaging, compared with arthroscopy (gold-standard), for each evaluator

	Subscapularis full-thickness tear			Subscapularis tear (full-thickness + partial)		
	Mean	95% CI		Mean	95% CI	
		Inferior	Superior		Inferior	Superior
Shoulder surgeon (1st evaluation)						
Sensitivity	39.3%	27.2%	52.1%	51.1%	43.2%	59.1%
Specificity	91.7%	87.5%	96.3%	82.0%	72.4%	92.3%
Positive predictive value	64.7%	49.2%	81.4%	86.6%	79.1%	94.3%
Negative predictive value	79.5%	73.1%	86.7%	42.4%	33.4%	51.7%
Accuracy	77.0%	71.2%	83.5%	60.5%	53.2%	67.3%
Shoulder surgeon (2nd evaluation)						
Sensitivity	35.7%	23.2%	48.3%	59.0%	51.0%	67.1%
Specificity	94.4%	91.2%	98.5%	78.7%	68.3%	89.8%
Positive predictive value	71.4%	55.1%	88.4%	86.3%	79.7%	93.2%
Negative predictive value	79.1%	73.2%	85.2%	45.7%	36.6%	55.5%
Accuracy	78.0%	72.7%	84.4%	65.0%	58.3%	72.3%
MSK radiologist 1						
Sensitivity	71.4%	60.1%	83.4%	83.5%	77.7%	90.0%
Specificity	85.4%	80.2%	91.1%	45.9%	33.4%	58.1%
Positive predictive value	65.6%	53.1%	77.2%	77.9%	71.6%	84.7%
Negative predictive value	88.5%	83.2%	94.7%	54.9%	41.1%	69.3%
Accuracy	81.5%	76.2%	87.7%	72.0%	66.3%	78.2%
MSK radiologist 2						
Sensitivity	57.1%	44.2%	70.2%	87.1%	82.7%	93.3%
Specificity	86.1%	80.1%	92.1%	41.0%	29.5%	53.6%
Positive predictive value	61.5%	48.4%	75.3%	77.1%	70.2%	84.1%
Negative predictive value	83.8%	78.5%	90.2%	58.1%	43.7%	73.2%
Accuracy	78.0%	72.5%	84.1%	73.0%	67.3%	79.4%

CI = confidence interval; MSK = musculoskeletal.

DISCUSSION

Subscapularis tears, which rarely occur in isolation,[5,6] are present in the majority of arthroscopies for rotator cuff repair.[7,8] The accuracy of magnetic resonance imaging for tear detection presents wide variation in the literature.[5,11-14] Studies published to date have presented some weaknesses, such as use of low magnetic field MRI,[7,13,15,16] small samples[15,17] and evaluation of diagnoses not restricted to rotator cuff disorders.[7,11,14-16,18-21] Further studies on this subject are justified, in the effort to search for more accurate results.

In the present study, the sensitivity observed regarding subscapularis tear detection ranged from 51.1% to 87.1%, with an average of 55.1% for the shoulder surgeon, 85.3% for the radiologists and 70.2% in general. Other studies evaluating 1.5-T MRI without contrast have found sensitivity values ranging from 63.6% to 82.2%.[8,21,25]

The specificity ranged from 41.0% to 82.0%, with an overall average of 61.9%. It was 80.4% for the shoulder surgeon and 43.5% for the radiologists. These values were lower than those found in other studies with the same field strength and without contrast, from which the reported values have ranged from 86.1% to 92.1%.[8,21,25] On the other hand, they were similar to those found by Choo et al.,[18] who used 3.0-T MRI with contrast.

Most studies in the literature have demonstrated a pattern in which specificity is superior to sensitivity with regard to detection of subscapularis tears.[5-8,12,13,16,17,21,25-28] This pattern was also observed in an analysis on rotator cuff tears overall,[9] but with higher percentages, thus suggesting that making the diagnosis of posterosuperior tears is less complex than that of subscapularis tears. One possible explanation for our finding is that the evaluators were aware of the objective of the study, which may have generated observation bias.

In evaluating accuracy, less pronounced differences were observed between the different observers, ranging from 60.5% to 73.0%, with an overall mean of 67.6%. It should be noted that the accuracy was higher when only full-thickness tears were analyzed, mainly due to higher specificity, ranging from 77.0% to 81.5%.

We observed an antagonistic pattern regarding the evaluations by the radiologists and the shoulder surgeon, such that sensitivity predominated in the former and specificity in the latter, but with similar accuracy. Halma et al.[29] observed that radiologists showed greater agreement with each other, compared with orthopedists, although they did not specifically assess the subscapularis tendon.

The correlation in the intra-observer analysis was almost perfect (0.809) with regard to detection of full-thickness tears. However, in evaluating overall tears, kappa fell to a moderate level (0.546). This can be explained by the difficulty in differentiating partial tears from tendinopathy, as reported by other authors.[26,28] To our knowledge, the present study is the first to calculate intra-observer agreement in relation to detection of subscapularis tears by means of MRI.

The inter-observer agreement found in the present study was substantial in relation to full-thickness tears (0.631), but lower than that reported by Choo et al.[18] (0.78). Regarding overall detection of tears, considering both partial and full-thickness tears, the concordance observed in the present study was moderate (0.463), and lower than the values reported by most other authors.[16,17,19,20,26] Only Lee et al.[20] reported similar results. It is noteworthy that all of these authors analyzed MRI with contrast, applied intra-articularly[16,18,19] or intravenously;[17,20,26] and that most utilized 3.0-T devices,[17,18,20,26] which may explain the results.

The arthroscopic inspection was performed without 70º optics, which could make it difficult to detect tears intraoperatively, according to other authors.[7,12] In spite of this, use of standard inspection and the posterior lever-push maneuver allowed clear visualization of the subscapularis tendon in all the arthroscopies.

The inter-observer concordance analysis was performed for the two MSK radiologists and one shoulder surgeon; however, the analysis on intra-observer agreement assessed the latter only. The three evaluators knew the purpose of the study, which may have influenced the detection of tears. The surgeon had access to the MRI, both the images and the report, before performing the procedure. However, all the evaluators in the present study (MSK radiologists and shoulder surgeon) were blinded to the intraoperative findings and the surgeons were blinded to the results from the study observers.

Lastly, the time that elapsed between examinations and arthroscopy was 140 days on average, with a maximum of one year. Structural change to the tendon may have occurred during this period, although this is considered acceptable and was even used in a systematic review on this subject.[30] Another possible criticism is that general sensitivity and specificity values were not obtained by reaching a consensus among the evaluators. However, the present authors believe that such consensuses have little practical applicability, since they are not routinely used in clinical practice.

One strong point of this study was the analysis on inter and intra-observer agreement, especially the latter. This study was the first to do this in relation to making a diagnosis of subscapularis tears. The design used, which was prospective and included consecutive cases, had only previously been used in a few articles on the same line of research.[16,27] The large sample in the present study only involved patients undergoing arthroscopy to treat rotator cuff tears, thus increasing the internal validity of the data.

The findings from the present study have practical implications for both radiologists and orthopedists. For radiologists, they should emphasize the need for thorough evaluation of the subscapularis tendon and highlight that the differences between tears and tendinopathy may be the cause of false positives and negatives. New imaging protocols that optimize the analysis on this tendon could also be studied. For orthopedists, the findings show that

cautious inspection is necessary, including actively searching for subscapularis tears, even when MRI shows no lesions. Lastly, the data presented may be useful for future meta-analyses, which would more clearly elucidate the limitations of MRI for detection of subscapularis tears.

CONCLUSION

The 1.5-T MRI without contrast showed a mean sensitivity of 70.2% and a mean specificity of 61.9% in relation to detection of subscapularis tears. The sensitivity was higher for the MSK radiologists, while specificity was higher for the shoulder surgeon. The mean accuracy was 67.6%, which was a performance rate inferior to that for posterosuperior tears of the rotator cuff.

Level of evidence: Level III, Diagnostic Study.

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Evaluation of knowledge and attitudes among intensive care physicians during the COVID-19 pandemic: a cross-sectional survey

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ABSTRACT

BACKGROUND: The novel coronavirus (COVID-19) emerged in Wuhan, China, in December 2019.

OBJECTIVES: To evaluate the knowledge of intensive care physicians in Turkey about COVID-19 and their attitudes towards the strategies and application methods to be used for COVID-19 cases that need to be followed up in an intensive care unit, and to raise awareness about this issue.

DESIGN AND SETTING: The population for this descriptive study comprised clinicians working in a variety of healthcare organizations in Turkey who provide monitoring and treatment within the intensive care process for COVID-19 patients.

METHODS: Data were collected online using a survey form on the SurveyMonkey website between April 20 and April 25, 2020.

RESULTS: The mean age of the 248 intensive care clinicians participating in the study was 37.2 ± 13.7 years and 49.19% were female. High rates of classical laryngoscope use were observed, especially among clinicians employed in state hospitals. Among all the participants, 54.8% stated that they were undecided about corticosteroid treatment for patients who had been intubated due to COVID-19.

CONCLUSIONS: Many medications and methods are used for COVID-19 treatment. All national science committees are attempting to create standard treatment protocols. For intensive care treatment of COVID-19 patients, many factors require management, and clinicians' experience is guiding future processes. We believe that this study will create awareness about this topic and contribute to the creation of standard treatment algorithms and the provision of better and safer healthcare services for this patient group.

INTRODUCTION

Coronaviruses are single-chain, positive-polarity, enveloped ribonucleic acid (RNA) viruses. Their surfaces have rod-like extensions.[1] In December 2019, it was understood that the agent causing a pneumonia epidemic in Wuhan city in China was the newly-identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was then defined as coronavirus disease 2019 (COVID-19). Patients in Wuhan with SARS-CoV-2 infection exhibited clinical symptoms over a broad spectrum from asymptomatic disease and mild tableau with mild upper respiratory tract infection to accompanying respiratory failure and severe viral pneumonia resulting in death. As a result, while some patients could be treated as outpatients, other patients required intensive care treatment.[2,3]

Currently, there is no specific treatment with proven safety and efficacy for COVID-19. Additionally, because of the urgency of the situation and the limited scientific data, treatments are commonly being chosen based on data that only show possible efficacy, for these patients around the world. Severe COVID-19 infection initially begins with flu-like complaints and is a situation that progresses to hypoxemic respiratory failure in 7-10 days. These critical patients require intensive care and this necessity is assessed by intensive care clinicians.[4]

OBJECTIVE

In this study, we aimed to investigate the experience of clinicians who have been participating in treatments for COVID-19 patients within intensive care and their observations during the critical monitoring process for this patient group.

METHODS

The population in this descriptive study comprised clinicians working in a variety of healthcare organizations in Turkey who provide monitoring and treatment within the intensive care process for COVID-19 patients. Permission for the study was granted by the clinical research ethics committee of Çanakkale Onsekiz Mart University (date: April 14, 2020; approval no. 2020/116). The sample size for the study was calculated using Minitab 16.0 (Minitab LLC, PA, United States). With a 95% confidence interval, 5% type 1 error and 90% power, and based on data from similar studies in terms of the parameters investigated, the power analysis determined that at least 244 people should be contacted. Data were collected online using a survey form on the SurveyMonkey website (SurveyMonkey, San Mateo, CA, United States) between April 20, 2020, and April 25, 2020. Members of the Turkish Anesthesiology and Reanimation Association were asked to participate in the study, via the Twitter, LinkedIn and WhatsApp social media platforms and through e-mail. Those who agreed to participate completed the above-mentioned survey. The researchers prepared survey questions that were in line with recommendations within the COVID-19 guidelines that were published by the General Directorate of Public Health of the Turkish Ministry of Health and the World Health Organization (WHO).[5-7] The survey contained 21 items: these questions related to sociodemographic characteristics, workplace features and treatment processes within intensive care that would be used in the event of a diagnosis of COVID-19.

RESULTS

The mean age of the 248 intensive care clinicians who participated in the study was 37.2 ± 13.7 years, and 49.19% were female. Regarding the length of time for which the participants had worked in the field of anesthesia, 32.7% had worked for 1-5 years, while 24.3% had worked for 6-10 years. Evaluation of the participants' titles showed that 56.4% were specialist doctors, while 26.6% were residents. Among the doctors who participated, 41.1% were working in universities, 30.6% in state hospitals and 16.1% in education-research hospitals. Some sociodemographic characteristics and professional information about the participants are shown in **Table 1**.

Among the clinicians working in intensive care, 50.8% stated they had received education about the COVID-19 disease from their organization. While 48.8% worked in university or education-research hospitals involved in education, 41.1% worked in state hospitals and 10.1% worked in private hospitals. Among all the participants, 87.1% worked in pandemic hospitals, and 84.6% of the clinicians considered that they had come into contact with COVID-19-positive patients. The proportion who thought that their workload had increased since the pandemic began was 59.6%. Among all the clinicians included in this study, 50.8% stated that COVID-19-positive patients were admitted to intensive care from the emergency service, while 44.3% stated that COVID-19-positive patients were admitted from the wards where they were being monitored.

In this study, it appeared that 45.1% of the intensive care physicians were using a videolaryngoscope, 13.7% were using an aerosol box and 41.1% were using classical laryngoscope for the intubation procedures. The proportion of intensive care clinicians stating that extubation procedures were completed at the patient's bedside was 62.1%, while 22.5% said that extubation was done in isolated areas within intensive care and 15.3% said that extubation was done after transfer to another intensive care area. The treatment approaches and relevant opinions of the clinicians participating in the study, relating to patients who developed acute respiratory distress syndrome(ARDS) during COVID-19 treatment are shown in **Table 2**.

When asked about the time at which favipiravir treatment (2 x 600 mg) should be used within intensive care, 63.7% of the participants stated that it should begin immediately upon the patient's admission to intensive care, 21.7% stated that it should begin when chloroquine (2 x 200 mg) and azithromycin (4 x 250 mg) treatments were unsuccessful and 14.52% stated that it should begin when ARDS was noted in patients. The participants' attitudes

Table 1. Sociodemographic and professional characteristics of the participants (n = 248)

Variable	n (%)
Gender	
Female	126 (50.8)
Male	122 (49.1)
Age groups (years)	
21-30	40 (16.1)
31-40	96 (38.7)
41-50	84 (33.8)
51-60	26 (10,7)
61 and over	2 (0.8)
Titles	
Specialist doctor	140 (56.4)
Resident	66 (26.6)
Professor	8 (3.2)
Associate Professor	10 (4.0)
Assistant Professor	12 (9.6)
Length of time working in the field of anesthesia (years)	
1-5	80 (32.2)
6-10	72 (29)
11-15	60 (24.1)
16-20	28 (11.2)
21 or longer	8 (3.2)
Organization	
University hospital	102 (41.1)
State hospital	76 (30.6)
Education-research hospital	40 (16.1)
Private hospital	30 (12.1)

towards the interventions that are performed in intensive care units on patients infected with COVID-19 are shown in **Table 3**.

DISCUSSION

In this study, the clinicians participating in intensive care monitoring and treatment of COVID-19-positive patients abided by the routine treatment protocols. However, different approaches were observed for some topics. When the clinical progression of COVID-19 is examined, fever, cough and dyspnea are initially observed, while in advanced cases pneumonia, respiratory failure, ARDS tableau and death are observed. Development of respiratory failure requiring intensive care in individuals infected with COVID-19 leads to a need for treatment under intensive care conditions.[5,8] Because of the close contact between intensive care doctors and infected patients and these doctors' potential exposure to respiratory droplets or aerosols from the patient's respiratory tract, they are among healthcare workers with highest risk of infection.[9]

All studies have emphasized the importance of personal protective equipment (PPE) in terms of preventing transmission of infection. Especially during intubation, which produces droplets, use of N95/FFP2 or equivalent respiratory masks along with other PPE is recommended. In addition, intubation should be performed by experienced people in a single attempt if possible, using a videolaryngoscope.[10] In our study, 45.1% of the intensive care workers used a videolaryngoscope, 13.7% used an aerosol box and the remaining 41.9% used a laryngoscope. It appeared that the clinicians with high rates of classical laryngoscope use were those working mostly in state hospitals. In a study by Dost et al.,[11] in which the attitudes of anesthesiologists and their assistants towards patients infected with COVID-19 were investigated, theoretical and applied training that was given before they encountered the infected patients reportedly made it easier to protect both patient and healthcare worker safety, and to prevent situations of panic that would interfere with the calmness that is needed for this work.

Nearly half of the survey participants stated that high-flow oxygen and noninvasive mechanical ventilation support reduced the need for intubation. One-third of the participants stated that they were undecided about this topic. This situation may be considered to be linked to the greater chance of transmission to intensive care physicians with noninvasive ventilation. One study included a weak recommendation regarding use of noninvasive mechanical ventilation; however, it was emphasized that intubation should not be delayed.[12]

The doctors participating in our study used high positive end-expiratory pressure (PEEP) administration, suitable recruitment maneuvers and the prone position. They stated that the mean PEEP values were 8-12 cmH_2O in ARDS cases requiring mechanical ventilation, which was in accordance with the literature. While corticosteroid treatment is not recommended for non-ARDS cases, it is recommended for cases that develop ARDS.[13] Among all the participants, 54.8% stated that they were undecided about corticosteroid treatment for intubated patients treated in intensive care due to COVID-19.

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an anti-viral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. It is probably

Table 2. Treatment approach used in relation to COVID-19 ARDS patients (%)

	Yes		No	
Do you use prone position?	77.4%		23.6%	
Do you use recruitment maneuver?	65%		35%	
Mean PEEP (cmH_20)	0-5	5-8	8-12	12-16
%	2.4%	32.2%	52.4%	13%

ARDS = acute respiratory distress syndrome.

Table 3. Participants' attitudes towards the interventions that are performed in intensive care units on patients infected with COVID-19

For suspected/confirmed COVID-19 patients, noninvasive mechanical ventilation removes the need for intubation	
Variables	**%**
Definitely agree	8.06
Agree	37.9
Undecided	29.8
Disagree	19.3
Definitely disagree	4.8
For suspected/confirmed COVID-19 patients, a reservoir mask is the most appropriate method for oxygen support	
Variables	**%**
Definitely agree	24.3
Agree	47.1
Undecided	17
Disagree	9.7
Definitely disagree	1.6
For suspected/confirmed COVID-19 patients, N95/FFP2 or N99/FFP3 masks should definitely be used during procedures that may cause aerosolization	
Variables	**%**
Definitely agree	94.3
Agree	4
Undecided	1.7
Disagree	0
Definitely disagree	0
For suspected/confirmed COVID-19 patients, the intubation procedure should be performed by the most experienced person	
Variables	**%**
Definitely agree	80.6
Agree	16.1
Undecided	1.6
Disagree	1.6
Definitely disagree	0

Continue...

Table 3. Continuation

For suspected/confirmed COVID-19 patients, tracheostomy should be performed under planned operating room conditions	
Variables	**%**
Definitely agree	22.5
Agree	19.3
Undecided	26.6
Disagree	22.5
Definitely disagree	8.8
Suspected/confirmed COVID-19 patients benefit from steroid treatment	
Variables	**%**
Definitely agree	10.4
Agree	23.3
Undecided	54.8
Disagree	10.4
Definitely disagree	0.8
Suspected/confirmed COVID-19 patients have more incidence of super-infection during monitoring, compared with other patients	
Variables	**%**
Definitely agree	14.5
Agree	49.1
Undecided	22.5
Disagree	12.9
Definitely disagree	0.8
For suspected/confirmed COVID-19 cases, there is a direct correlation between mortality and advanced age for patients on mechanical ventilation	
Variables	**%**
Definitely agree	54.9
Agree	34.4
Undecided	5.7
Disagree	4.1
Definitely disagree	0.8

effective against the RNA virus of SARS-CoV-2. Preliminary results from a study on 80 patients showed that favipiravir had a stronger antiviral effect than lopinavir/ritonavir. The favipiravir group had significantly fewer side effects than lopinavir/ritonavir. Among COVID-19 patients, favipiravir did not significantly improve clinical amelioration rates on the seventh day, compared with arbidol.[14,15] The intensive care doctors participating in the present survey stated that favipiravir treatment for COVID-19 critical patients was effective if it was begun upon first admission to intensive care.

CONCLUSION

The COVID-19 pandemic has spread rapidly around the world. Concerns about a second wave have been expressed worldwide. The incidence of COVID-19 cases around the world and in Turkey is increasing every day, and these cases may result in death. Patients developing moderate and advanced respiratory failure are admitted to intensive care units for close monitoring and treatment and require mechanical ventilation. Many drugs and methods are being used with the aim of treating the disease. National scientific committees in all countries are trying to create standard treatment protocols. Many factors require management during intensive care treatment for COVID-19 patients, and clinicians' experience in relation to this topic will guide future procedures.

Through this study, we believe that awareness of the topic of standardization of treatment algorithms will be raised, with the aim of providing better and safer healthcare services for this patient group.

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Reasons for non-vaccination against influenza among older adults with hypertension in Brazil: a cross-sectional study

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ABSTRACT

The aim of this study was to estimate the prevalence of non-vaccination against influenza among Brazilian older adults with systemic arterial hypertension and determine the main reasons for non-adherence. A cross-sectional study was conducted using data from older adults (≥ 60 years of age) with hypertension who participated in the 2013 National Health Survey and reported not having been vaccinated against flu over the previous 12 months (n = 1,295). The analyses were performed using the Stata 14.0 software. The data were weighted because of the sampling design. An estimated 3,026,080 older adults with hypertension had not received a flu vaccine over the 12 months prior to the survey (22.6%). No significant associations were found with sex, age group or schooling. The prevalence of unvaccinated older adults was lower in the southern and southeastern regions of Brazil than in the northern and northeastern regions, even after adjusting for age. The prevalence was higher among individuals without private health insurance. The main reasons for non-vaccination were *fear of a reaction, rarely having the flu and not believing in the protection of the vaccine*. The present findings underscore the need for healthcare professionals to explain to the population the benefits of the vaccine for preventing severe influenza (protective effect and possible reactions) and for secondary prevention of cardiovascular events. Increasing the prevalence of vaccination in older adults with hypertension and other cardiovascular diseases is of fundamental importance within the realm of public health as a strategy for reducing occurrences of complications and deaths associated with influenza.

INTRODUCTION

Systemic arterial hypertension is a major risk factor for other cardiovascular diseases[1] and is highly prevalent in both adults and elderly people.[2,3] Data from the Brazilian National Health Survey revealed rates of 44.4%, 52.7% and 55.0% among Brazilian elderly people aged 60-64, 65-74 and ≥ 75 years, respectively,[4] and the prevalence increased with age (71.7% of individuals aged ≥ 70 years had high blood pressure or reported taking antihypertensive medication).[3]

Individuals with cardiovascular disease are at greater risk of complications from influenza.[5,6] Besides the risk factors described in the literature (hypertension, obesity, physical inactivity, smoking, etc.), influenza contributes to cardiovascular morbidity and mortality.[6] The American Heart Association and American College of Cardiology indicate the flu vaccine for individuals with atherosclerotic disease.[7] The United Kingdom National Clinical Guideline Centre[8] and the Brazilian Cardiology Society[9] indicate the vaccine for individuals with heart failure.

Studies have shown that in individuals with cardiovascular disease, the flu vaccine reduces occurrences of cardiovascular events and mortality.[6,10] Among individuals with hypertension, vaccination prior to the flu season has been significantly associated with reduction of the risk of death due to acute myocardial infarction, stroke and all causes.[10]

In Brazil, the flu vaccine is offered through the public healthcare system to groups that are at risk (elderly people and individuals with chronic respiratory, heart, neurological, liver, kidney and metabolic diseases), as a strategy for prevention of the disease, its severe forms and complications.[11] Higher rates of vaccination among individuals with hypertension have been observed since these campaigns began.[12,13]

Since hypertension is a chronic disease that requires follow-up and treatment, most older adults in Brazil are dependent on the public healthcare system[14] and primary care is the main source of antihypertensive medications.[15] Thus, it can be hypothesized that this group is more attentive to information on vaccination campaigns and other offers from public healthcare services. However, after two decades of vaccine campaigns, approximately 20% of elderly people

with hypertension are not receiving the vaccine, and this percentage has remained stable over the years.[12,16]

OBJECTIVE

The aim of the present study was to estimate the prevalence of non-vaccination against influenza among older Brazilians with hypertension and determine the main reasons for non-adherence.

METHODS

A cross-sectional study was conducted using public domain data on elderly people (≥ 60 years) who participated in the 2013 National Health Survey,[17] reported having hypertension (n = 5,524) and reported having not been vaccinated against influenza over the previous 12 months (n = 1,295). We estimated the absolute number and proportion of non-vaccinated elderly people with hypertension and the respective 95% confidence intervals, according to sociodemographic characteristics, and determined the reasons for non-vaccination.

All estimates were made using the Stata 14.0 software and took the sampling design into consideration. The National Health Survey had received approval from the National Ethics Committee of the Health Ministry (certificate number: 328.159; June 26, 2013).

RESULTS

The mean age of the elderly people with hypertension was 70.3 years (95% confidence interval, CI: 70.0-70.7), and 61.0% (95% CI: 58.8-63.2) were women. It was estimated that 3,026,080 elderly people with hypertension had not been vaccinated against influenza (22.6%; 95% CI: 20.9-24.5). No significant associations were found in relation to sex (P = 0.373), age group (P = 0.456) or schooling (P = 0.138). In comparison with the northern region of the country (27.9% not vaccinated), the prevalence of non-vaccinated elderly people was lower in the southern and southeastern regions (16.7% and 20.8%, respectively), even after adjusting for age. The prevalence of non-vaccination was higher among individuals without private health insurance P = 0.026 (**Table 1**).

Table 1. Vaccination against influenza among older Brazilians with hypertension, according to sociodemographic characteristics. National Health Survey, 2013

Variables	n	Unvaccinated		Vaccinated	
		%	95% CI	%	95% CI
Region					
North	751	27.9	22.0-34.6	72.1	65.4-78.0
Northeast	1,620	29.0	25.7-32.5	71.0	67.5-74.3
Center-West	653	25.1	20.5-30.4	74.9	69.6-79.5
Southeast	1,659	20.8	18.1-23.8	79.2	76.2-81.9
South	841	16.7	13.5-20.4	83.3	79.6-86.4
Sex					
Male	1,908	21.5	18.7-24.7	78.5	75.3-81.3
Female	3,616	23.3	21.1-25.7	76.7	74.2-78.9
Age group					
60 to 69	2,917	22.0	19.8-24.3	78.0	75.6-80.2
70 to 79	1,810	23.6	20.4-27.2	76.4	72.8-79.6
80 or more	797	22.8	18.0-28.5	77.2	71.5-82.0
Race/skin color					
White	2,609	21.2	18.7-24.0	78.8	76.0-81.3
Nonwhite	2,914	24.2	21.8-26.8	75.8	73.2-78.2
Lives with spouse/partner					
Yes	2,453	20.4	17.7-23.3	79.6	76.7-82.2
No	3,071	25.5	23.0-28.2	74.4	71.8-77.0
Schooling					
None/incomplete primary school	3,977	23.5	21.3-25.7	76.5	74.3-78.6
Complete primary and high school	1,040	20.6	17.0-24.7	79.4	75.3-83.0
Incomplete/complete university	507	19.8	14.5-26.4	80.2	73.6-85.5
Can read and write					
Yes	4,114	21.3	19.3-23.5	78.7	76.5-80.7
No	1,410	27.1	23.5-31.0	72.9	69.0-76.5
Private health insurance					
Yes	1,676	19.7	16.8-22.9	80.3	77.1-83.2
No	3,848	24.0	21.9-26.3	76.0	73.7-78.1

CI = confidence interval (α = 0.05), considering the study design effect.

The main reasons for non-vaccination were *fear of a reaction* (28.6%; 95% CI: 24.9-32.6), *rarely having the flu* (22.0%; 95% CI: 18.9-25.4) and *not believing in the protection of the vaccine* (12.3%; 95% CI: 9.5-15.8) (**Figure 1**).

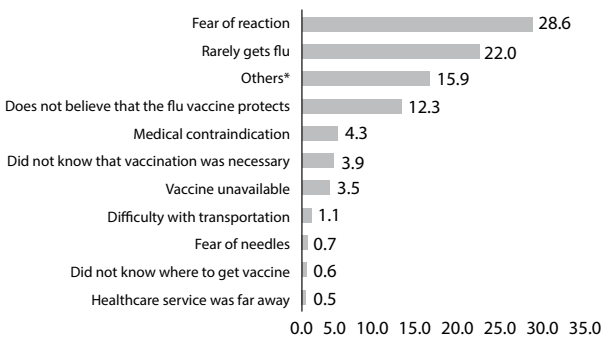
The prevalence of non-vaccination among elderly people with hypertension was lower than the rates found for elderly people in general and for those who reported not having hypertension (27.4% and 31.9%, respectively).

DISCUSSION

In the present study, the prevalence of vaccination against influenza among elderly people with hypertension was lower than what was expected for the general population of elderly people, given that the goal in 2013 was to vaccinate at least 80% of all individuals ≥ 60 years of age.[11] Considering the greater contact of this group with healthcare services,[12,15] the absolute number of unvaccinated individuals was high. Previous studies also found that there were no associations between the vaccination rate and sex,[12,16,18,19] age group[18] or schooling.[18,19] Sato et al.[19] found that the chance of having been vaccinated was greater among elderly people registered with the Family Health Program.

Regarding regional differences, the southern and southeastern regions of Brazil present socioeconomic differences in relation to the northeastern region. This may be reflected in access to healthcare services and, consequently, to information and counseling regarding the importance of vaccination. Moreover, the seasonality of influenza is more pronounced in the more southerly regions. In contrast, in northeastern Brazil, the peaks of the disease occur prior to the period when vaccination campaigns have been run,[20] and this may have had an impact on the effectiveness of such campaigns as well as on the perceptions of elderly people regarding the protection offered by the vaccine, which thus will have had a negative influence on adherence.

The reasons for non-vaccination given by these elderly people with hypertension were similar to those found for the older population in general.[18,19] Fear of side effects falsely attributed to the vaccine, not considering it important and having insufficient information regarding the benefits were the main reasons given.[12,21] Counseling by healthcare professionals has been positively associated with vaccination and should be used as a strategy for improving knowledge among elderly people regarding both the disease and the vaccine.



**Others:* Did not have anyone to accompany him/her to healthcare service, had financial difficulties and other reasons not detailed in National Health Survey.

Figure 1. Distribution of reasons for non-adherence to vaccination against influenza among elderly people with hypertension. National Health Survey, 2013.

CONCLUSION

The main reasons for non-vaccination (fear of a reaction, belief that influenza is a rare event, belief that the vaccine does not offer protection and fear of needles) accounted for more than 60% of the reasons given by these elderly people. These findings underscore the need for health professionals to explain to the population what the benefits of the vaccine are, regarding prevention of severe influenza (its protective effect and possible reactions) and secondary prevention of cardiovascular events. Increasing the prevalence of vaccination among elderly people with hypertension and other cardiovascular diseases is of fundamental importance within the realm of public health, as a strategy for reducing occurrences of complications and deaths associated with infection by the influenza virus.

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Clinical profile of individuals with bisphosphonate-related osteonecrosis of the jaw: an integrative review

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Drug-induced osteonecrosis of the jaw.

ABSTRACT

BACKGROUND: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is still the most prevalent type of osteonecrosis with clinical relevance. In Brazil, bisphosphonate use is high but there is a lack of epidemiological studies on BRONJ.

OBJECTIVE: To determine the clinical profile of BRONJ in a Brazilian population through an integrative review.

DESIGN AND SETTING: Integrative review of BRONJ in a Brazilian population.

METHODS: Cases and clinical research on Brazilians with BRONJ between 2010 and 2019, indexed in PubMed/MEDLINE, Scopus, Web of Science and LILACS were reviewed. Age, sex, type and time of bisphosphonate intake, administration route, related diseases, region of the BRONJ, diagnostic criteria, staging, triggering factor and type of treatment were analyzed.

RESULTS: Fifteen articles on 128 subjects were included. Most patients were women (82.03%); the mean age was 63 years. Intravenous zoledronic acid was mostly used (62.50%), for breast cancer treatment (46.87%). The main localization of BRONJ was the mandible (54.68%), associated mainly with tooth extractions (45.98%). The diagnostic criteria were clinical (100%) and radiographic (89.06%), mostly in stage II (68.08%). The surgical treatments were sequestrectomy (37.50%) and platelet-rich plasma (PRP) (36.71%). Microbial control was done using chlorhexidine (93.75%) and infection control using clindamycin (53.90%).

CONCLUSIONS: BRONJ had higher prevalence in Brazilian women receiving treatment for breast cancer and osteoporosis. The mandible was the region most affected with a moderate stage of BRONJ, particularly when there were histories of tooth extraction and peri-implant surgery. Sequestrectomy with additional drugs and surgical therapy was the treatment most accomplished.

INTRODUCTION

Bisphosphonates (BPs) are drugs with oncological indication that have been used since 1960.[1] They are currently indicated as therapy for multiple myeloma, malignant hypercalcemia, prevention of bone metastases and pathological fractures.[2] BPs may also be prescribed for other diseases such as rheumatoid arthritis, osteoporosis and osteopenia.[3-5]

The mechanism of action of BPs consists of decreasing local vascular support and regulating bone metabolism, thereby reducing the action of osteoclasts and decreasing angiogenesis. Therefore, bone remodeling and deposition of physiological bone matrix are also affected.[6,7] These effects on bone metabolism associated with local triggering factors, such as infection and tissue inflammation in the mouth, are named bisphosphonate-related osteonecrosis of the jaw (BRONJ).[8] Among the main triggering factors of BRONJ are the following: exodontia, peri-implant surgery and traumas in the buccal mucosa.[1,9-11] The clinical characteristics of BRONJ can include asymptomatic manifestations, severe pain, presence of infections and bone exposure.[6]

In 2014, there was a change in the nomenclature for this disease, to take into account its relationship with other drugs. The names currently used follow the pattern [medication]-related osteonecrosis of the jaw. This relates to the use of anti-resorptive and antiangiogenic medications,[8,12-14] and more recent studies also mention the use of tyrosine kinase-inhibitor drugs and mammalian-target inhibitors of rapamycin.[8-14]

Although, as mentioned before, other medications relating to maxillary osteonecrosis do exist, BPs are still the most relevant drugs in relation to osteonecrosis of the jaws.[8] The Brazilian

population has high rates of breast and prostate cancer,[15] and for this reason, BPs are highly indicated, which exposes these individuals to the risk of BRONJ.

The clinical profile of BRONJ and treatment protocols can vary according to specific demographic factors. Therefore, there is a need for population-specific studies. However, there are no studies in the literature reporting on the features of BRONJ and its treatment in Brazil.

OBJECTIVE

This integrative review aimed to determine the clinical profile of osteonecrosis of the jaw exclusively associated with bisphosphonate therapy in the Brazilian population.

METHODS

The guiding question of this review was: What are the clinical features of BRONJ in the Brazilian population that determine its clinical profile?

The inclusion criterion for this integrative review was that publications relating to Brazilian individuals would be included: these could include case reports, case series and clinical studies. Over the last decade, the nomenclature, staging and treatment method for BRONJ have undergone changes. This review considered articles either in English or in Portuguese that were published between January 2010 and April 2019. Articles that comprised review of the literature, laboratory analyses, letters to the editor, studies conducted on animal studies and research that did not involve Brazilians were excluded.

The variables selected were the following: age, sex, type of bisphosphonate used, duration of use of bisphosphonates until disease manifestation, route of administration, underlying disease that led to indication for drug use, oral region affected by BRONJ, clinical criteria for diagnosis of BRONJ, clinical staging according to the American Association of Oral and Maxillofacial Surgeons (AAOMS),[8] local triggering factor and type of treatment. When data on any of these variables were absent, the study was not included in this review.

Four online databases were searched for articles: PubMed, Scopus, Web of Science and LILACS. PubMed, Scopus and Web of Science are international databases that have a search filter for the nationality of the articles, and this was used after the initial search. LILACS is a Latin American database with descriptors in the English and Portuguese language. We used the country identification tool for the Scopus, Web of Science and LILACS, and for PubMed we add the descriptor "Brazil". The descriptors entered in the databases are described below.

1. "osteonecrosis" and "bisphosphonate" and "Brazil" for PubMed.
2. "osteonecrosis" and "bisphosphonate" for Web of Science and Scopus
3. "osteonecrosis" and "bisphosphonate" and "bisphosphonate or "diphosphonate" and "osteonecrosis" for Lilacs.

The selection of the articles that were assessed in full for the analysis on each of the variables of this review is described in **Figure 1**.

RESULTS

Fifteen studies were included (**Figure 1**).[4,5,9,16-26] A total of 141 different areas of BRONJ were reported in 128 individuals, of whom 105 (82.03%) were female[4,9,10,12,21,16-21,24,25] and 23 (17.97%) were male.[5,9,10,16-19,25] The subjects' minimum age was 38 years and maximum age was 90 years, with a mean of 63.34 ± 34.87 years.

The commonest diagnoses relating to BRONJ were: breast cancer, in 60 individuals[9,10,12,16,17,19,21] (46.87%); osteoporosis,[10,17-19,23-26] in 25 (19.53%); multiple myeloma,[5,9,16,17,20] in 16 (12.50%); and prostate cancer,[9,10,16,18,19] in 16 (12.50%) (**Table 1**).[4,5,9,10,12,16-21,23-26]

The types of BPs most related to BRONJ were: zoledronic acid [9,10,12,16-21,26] (ZOE), in a dose of 4 mg intravenously, in 80 cases (62.50%); and alendronate[4,10,17-19,23-26] (ALE) in a dose of between 70 and 90 mg orally, in 26 cases (20.31%). However, other BPs such as pamidronate[5,9,10,16,19] (PAM) (10.93%), an association of ZOE and PAM[10,19,26] in six cases (4.68%) and an association of ZOE and ALE[10,26] in two cases (1.56%) were also used. The duration of BP use until a manifestation of BRONJ ranged from 5 to 15 months, with a mean of 45.8 ± 39.7 months.[4,5,9,16-26]

Regarding the location of the BRONJ, the mandible was the most affected by BRONJ,[4,9,10,16-20,25] in 70 cases (54.68%), followed by the maxilla[9,10,12,16-19,21,23-26] in 52 cases (40.62%). Less frequent

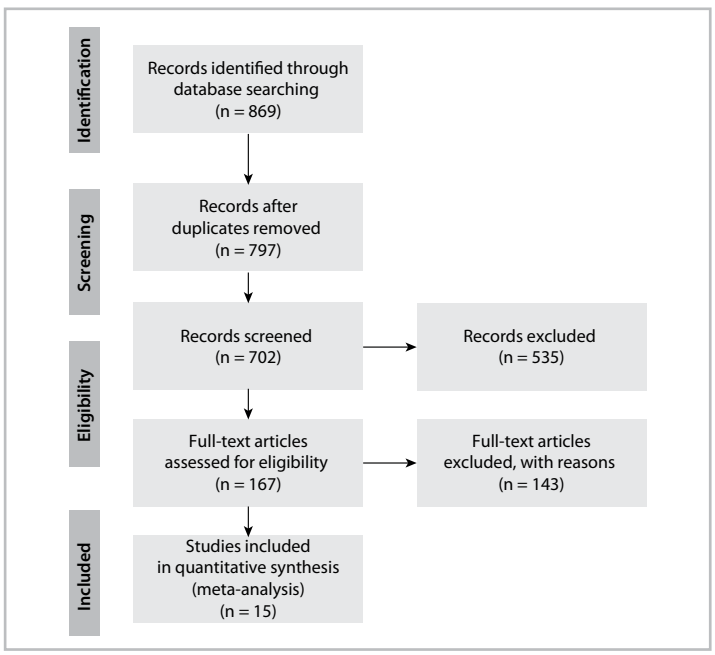

Figure 1. Flow diagram of the studies included in the integrative review

Table 1. Reports on Brazilian individuals with bisphosphonate-related osteonecrosis of the jaw

Authors	Title	Type of bisphosphonate	No. of individuals	Gender	Age	Duration of bisphosphonate intake (months)	Related diseases
Antonini et al.[21]	Management of osteonecrosis of the jaws in patients with history of bisphosphonates therapy.	ZOE (1/1)	1	Female	72	36	BC
Conte-Neto et al.[4]	Oral bisphosphonate-related osteonecrosis of the jaws in rheumatoid arthritis patients: a critical discussion and two case reports.	ALE (2/2)	2	Female (2/2)	58-68	84-96	RA (2/2)
Curi et al.[9]	Bisphosphonate-related osteonecrosis of the jaws--an initial case series report of treatment combining partial bone resection and autologous platelet-rich plasma.	ZOE (21/25) PAM (4/25)	25	Female (20/25) Male (5/25)	42-85	12 - 84	BC (14/25) MM (7/25) PC (4/25)
Martins et al.[16]	Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: a preliminary study.	ZOE (18/22) PAM (4/22)	22	Female (16/22) Male (6/22)	42-90	12- 48	BC (13/22) PC (6/22) MM (2/22) LC (1/22)
Farias et al.[17]	Clinical and image findings in bisphosphonate-related osteonecrosis of the jaws.	ZOE (5/7) ALE (2/7)	7	Female (6/7) Male (1/7)	42-76	36 - 156	BC (2/7) OP (2/7) MM (1/7) LVC (1/7) GCC (1/7)
Rabelo et al.[18]	Bisphosphonate-Related Osteonecrosis of the Jaws and Its Array of Manifestations.	ZOE (4/8) ALE (4/8)	8	Female (6/8) Male (2/8)	53-76	5 – 72	OP (4/8) BC (2/8) PC (1/8) PD (1/8)
Mathias Duarte et al.[19]	Bisphosphonate-related osteonecrosis of the jaws: analysis of a case series at a dental school.	ZOE (7/13) PAM (2/13) ZOE + PAM (1/13) ALE (3/13)	13	Female (12/13) Male (1/13)	48-84	36	BC (9/13) OP (3/13) PC (1/13)
Zanata et al.[5]	Bisphosphonate-related osteonecrosis of the jaw in patient affected by multiple myeloma: A case report.	PAM (1/1)	1	Male	55	48	MM
Lopes et al.[10]	Surgical Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw: Six-Year Experience of a Single Institution.	ZOE (22/33) ZOE + PAM (5/33) PAM (3/33) ALE (2/33) ZOE + ALE (1/33)	33	Female (25/33) Male (8/33)	39-83	26 - 120	BC (18/33) MM (4/33) PC (4/33) LC (4/33) OP (2/33) KC (1/33)
Heggendorn et al.[20]	Bisphosphonate-related osteonecrosis of the jaws: Report of a case using conservative protocol.	ZOE (1/1)	1	Female	52	22	MM
Maluf et al.[12]	Surgery Combined with LPRF in Denosumab Osteonecrosis of the Jaw: Case Report.	ZOE (1/1)	1	Female	79	36	BC
Momesso et al.[23]	Successful use of lower-level laser therapy in the treatment of medication-related osteonecrosis of the jaw.	ALE (1/1)	1	Female	65	60	OP
de Oliveira Ruellas et al.[24]	Managing bisphosphonate-related osteonecrosis of the jaws with xenografts: a case report.	ALE (1/1)	1	Female	69	120	OP

Continue...

Table 1. Continuation

Authors	Title	Type of bisphosphonate	No. of individuals	Gender	Age	Duration of bisphosphonate intake (months)	Related diseases
Fernando de Almeida Mourão et al.[25]	The use of Platelet-rich Fibrin in the management of medication-related osteonecrosis of the jaw: A case series.	ALE (11/11)	11	Female (9/11) Male (2/11)	38-84	36-84	OP
Santos et al.[26]	Extensive osteonecrosis of the maxilla caused by bisphosphonates: Report of a rare case.	ZOE + ALE (1/1)	1	Female	52	144	OP
Total		**ZOE 80 (62.50%) ALE 26 (20.31%) PAM 14 (10.93%) ZOE + PAM 6 (4.68%) ZOE + ALE 2 (1.56%)**	**128 (100%)**	**Female 105 (82.03%) Male 23 (17.97%)**	**63.34 (mean)**	**45 months (mean)**	**BC 60 (46.87%) OP 25 (19.53%) MM 16 (12.50%) PC 16 (12.50%) LC 5 (3.90%) RA 2 (1.56%) KC 1 (0.78%) PD 1 (0.78%) GCC 1 (0.78%) LVC 1 (0.78%)**

ZOE = zoledronate; PAM = pamidronate; ALE = alendronate; BC = breast cancer; MM = multiple myeloma; PC = prostate cancer; OP = osteoporosis, LC = lung cancer; RA = rheumatoid arthritis; KC = kidney cancer; PD = Paget's disease; GCCA = giant-cell cancer; LVC = liver cancer.

manifestations were in both jaws,[16,17,19] the palatine torus[10] and the mylohyoid region[17] (**Table 2**).[4,5,9,10,12,16-21,23-26]

The main diagnostic criterion was clinical evaluation of bone exposure,[4,5,9,16-26] which was found to be present in 100% of the cases. The most common complementary examinations were panoramic radiographs,[4,5,9,10,16-20,23,25] in 114 cases (89.06%); and cone-bean computed tomography,[4,5,12,16,19,21,24-26] in 52 cases (40.62%). In contrast, the histopathological evaluation[4,21] was present only in three cases (2.34%) (**Table 2**).[4,5,9,10,12,16-21,23-26]

The local trigger factors for BRONJ were the following: tooth extraction,[5,9,10,12,16-19,25,26] in 63 individuals (45.98%); implant placement,[9,17,19,23,25] in 19 (13.86%); prosthetic trauma,[9,10,16,20] in 19 (13.86%); and spontaneous manifestation,[9,10,16-19,21] in 19 (13.86%). Other local factors are considered in **Table 2**.[4,5,9,10,12,16-21,23-26]

According to the AAOMS classification, three individuals (2.12%) presented stage 0[17,18] of BRONJ; 16 cases (11.34%) had stage I;[9,16-18] 96 cases (68.08%, i.e. the majority) presented stage II;[4,5,9,10,16-20,23,25] and 26 cases (18.43%) had stage III[9,10,12,16,18,21,24,26] (**Table 2**).[4,5,9,10,12,16-21,23-26]

There was a lack of detailed information about the types of treatment and management used in these cases reported from Brazilian populations. The treatment most reported was sequestrectomy,[4,5,10] in 48 cases (37.50%); while platelet-rich plasma[9,16,19,21,25] was used to complement surgery, in 47 cases (36.71%). Other treatments, such as bone resection with or without curettage,[9,16,19,21,24-26] tooth extractions with debridement of the necrotic bone,[4,9] debridement alone[12,17,18] or even low power laser therapy, are described in **Table 2**.[4,5,9,10,12,16-21,23-26]

The topical medication most used for treatment of BRONJ was chlorhexidine solution,[4,5,9,16,17,19-26] in 120 individuals (93.75%). The systemic medication used consisted of antibiotic therapy with clindamycin in 69 cases (53.90%) and amoxicillin in four cases (3.12%).[12,17,26] Other antibiotics were also reported to have been used as part of BRONJ treatments but without any detailed description. Thus, for this reason, they were not included in this review.

DISCUSSION

The cases of BRONJ in Brazil showed that 103 individuals (80.47%) received BPs intravenously as part of their cancer treatment. The other 25 (19.53%) received BPs orally as osteoporosis treatment. In North American populations, similar results were observed, i.e. BRONJ developed mainly in individuals who were undergoing oncological treatment intravenously.[27,28] Use of this administration route increases the risk of BRONJ one hundredfold, compared with the oral route.[8]

The oral route for BPs is more used for controlling osteoporosis: not only in Brazil[4,5,9,16-26] but also in the United States.[27,28] Among BPs, ALE is the BP that is most associated with BRONJ.[4,5,9,16-2] In Europe, individuals with rheumatoid arthritis have higher incidence of BRONJ than individuals with osteoporosis, since ALE is the treatment of choice and its use is prolonged.[29-31]

In addition to the type of diagnosis of the disease and type of BP, surgical manipulation of the jaws[19,32] accounts for 60% of the local trigger factors for developing BRONJ.[32-34] Thus, in these Brazilian cases, the triggering factor most reported was tooth dental extraction (45.98%),

Table 2. Clinical features of bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Authors	Title	Region of BRONJ	No. of cases of BRONJ	Triggering factor	Diagnostic criteria	AAOMS classification (stage)	Type of treatment
Antonini et al.[21]	Management of osteonecrosis of the jaws in patients with history of bisphosphonates therapy.	Post. right reg. maxilla	1	Spontaneous	CLN, TOMO and HPT	III (1/1)	HBO therapy, RES, PRP, CFLX, CHX, DH
Conte-Neto et al.[4]	Oral bisphosphonate-related osteonecrosis of the jaws in rheumatoid arthritis patients: a critical discussion and two case reports.	Right reg. mandible; left reg. mandible	2	Trauma; periodontitis	CLN, TOMO, and HPT; CLN, RAD and TOMO	II (2/2)	AT Clin. CHX, IR, SEQ, AdDEB; CHX, AT Clav. EXT, AdDEB.
Curi et al.[9]	Bisphosphonate-related osteonecrosis of the jaws--an initial case series report of treatment combining partial bone resection and autologous platelet-rich plasma.	Mandible (8/25); maxilla (7/25)	25	Extraction (14/25); prosthetic trauma (7/25); implant (2/25); spontaneous (2/25)	CLN and RAD	I (3/25) II (15/25) III (7/25)	CHX, AT; AT Clin, RES, AdDEB, PRP; EXT AdDEB, PRP
Martins et al.[16]	Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: a preliminary study.	Mandible (17/22); maxilla (3/22); both jaws (2/22)	22	Extraction (12/22); prosthetic trauma (3/22); spontaneous (2/22); periodontitis (1/22)	CLN, RAD and TOMO	I (9/22) II (10/22) III (3/22)	CHX + AT (3/22); RES + AdDEB (5/22); PRP + LLT (14/22)
Farias et al.[17]	Clinical and image findings in bisphosphonate-related osteonecrosis of the jaws.	Post. bilateral reg. mandible (2/7); right myeloid reg. (1/7); both post. reg. jaws (1/7); both post. left reg. jaws (1/7); ant. reg. maxilla (2/7)	7	Extraction (4/7); Extraction + Implant. (1/7); spontaneous (2/7)	CLN and RAD	0 (2/7) I (1/7) II (4/7)	DEBL + AT Amox + CHX
Rabelo et al.[18]	Bisphosphonate-Related Osteonecrosis of the Jaws and Its Array of Manifestations.	Post. reg. mandible (3/8); post. reg. maxilla (2/8); ant. reg. mandible (1/8); ant. reg. maxilla. (1/8); ant. and post. reg. maxilla (1/8)	8	Extraction (6/8); spontaneous (2/8)	CLN and RAD	0 (1/8) I (3/8) II (1/8) III (3/8)	AT + DEBL; AT + SURG; AS + AT; AT + AS + DEBL/ AT + DEBL
Mathias Duarte et al.[19]	Bisphosphonate-related osteonecrosis of the jaws: analysis of a case series at a dental school.	Mandible (8/13); maxilla (4/13); both jaws (1/13)	13	Extraction (7/13); implant (2/13); periodontitis (2/13); spontaneous (2/13)	CLN, RAD and TOMO	II (13)	CHX, AT Clin. (3/13); RES (4/13); PRP (6/13)
Zanata et al.[5]	Bisphosphonate-related osteonecrosis of the jaw in patient affected by multiple myeloma: A case report.	Post. reg. mandible	1	Extraction	CLN, RAD and TOMO	II (1/1)	OH + CHX +SEQ + AdDEB
Lopes et al.[10]	Surgical Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw: Six-Year Experience of a Single Institution.	Post. reg. mandible. (19/46); post. reg. maxilla (16/46); Ant. reg. mandible (5/46); Ant. reg. maxilla. (3/46); mandibular torus (2/46); both jaws (1/46)	46	Extraction (16/46); periodontitis + periimplantitis (9/46); prosthetic trauma (8/46); spontaneous (8/46); implant (3/46); palatine torus trauma (2/46)	CLN and RAD	II (37/46) III (9/46)	Ad DEB; SEQ; AT Clin + AT + CHX

Continue...

Table 2. Continuation

Authors	Title	Region of BRONJ	No. of cases of BRONJ	Triggering factor	Diagnostic criteria	AAOMS classification (stage)	Type of treatment
Heggendorn et al.[20]	Bisphosphonate-related osteonecrosis of the jaws: Report of a case using conservative protocol.	Post. left. reg. mandible	1	Prosthetic trauma	CLN and RAD	II (1/1)	CHX + LLLT
Maluf et al.[12]	Surgery Combined with LPRF in Denosumab Osteonecrosis of the Jaw: Case Report.	Ant. reg. maxilla	1	Extraction	CLN and TOMO	III (1/1)	DEB, LPRF, CHX, Amox + CLV, MTZ, DH
Momesso et al.[23]	Successful use of lower-level laser therapy in the treatment of medication-related osteonecrosis of the jaw.	Post. right reg. maxilla.	1	Implant	CLN and RAD	II (1/1)	LLLT + CHX + Clin
de Oliveira Ruellas et al.[24]	Managing bisphosphonate-related osteonecrosis of the jaws with xenografts: a case report.	Post. right reg. maxilla.	1	Odontogenic infection	CLN and TOMO	III (1/1)	Ress, EXT, graft, AdDEB, CFLX, MTZ, CHX
Fernando de Almeida Barros Mourão et al.[25]	The use of Platelet-rich Fibrin in the management of medication-related osteonecrosis of the jaw: A case series.	Ant. reg. maxilla (1/11); post. right reg. maxilla (3/11); post. left reg mandible (3/11); post. right reg. mandible (4/11)	11	Implant (10/11); extraction (1/11)	CLN, RAD and TOMO	II (11/11)	RES, PRP, AdDEB, CHX
Santos et al.[26] 2019	Extensive osteonecrosis of the maxilla caused by bisphosphonates: Report of a rare case.	Ant. and post. bilateral reg. maxilla (1/1).	1	Extraction	CLN and TOMO	III (1/1)	CHX, Amox + CLV, RES, AdDEB
Total		**Post. reg. mandible 33 (25.78%); post. reg. maxilla 24 (18.75%); ant. reg. maxilla 7 (5.46%); ant. reg. mandible 6 (4.68%); post. reg. both jaws 2 (1.56%); palatine torus 2 (1.56%); myeloid reg. 1 (0.78%); post. and ant. reg. both jaws 1 (0.78%)**	**141 (100%)**	**Extraction 63 (45.98%); implant 19 (13.86%); prosthetic trauma 19 (13.86%); spontaneous 19 (13.86%); periodontitis 13 (10.65%); palatine torus trauma 2 (1.45%); trauma 1 (0.73%); odontogenic infection 1 (0.72%) 137 (100%)**	**CLN 128 (100%); RAD 114 (89.06%); TOMO 52 (40.62%); HPT 3 (2.34%) 128 (100%)**	**Stage 0: 3 (2.12%); stage I: 16 (11.34%); stage II: 96 (68.08%); Stage III: 26 (18.43 %) 141 (100%)**	**CHX 120 (93.75%); Clin 69 (53.90%); AT 54 (42.18%); SEQ + adDEB 48 (37.50%); PRP 47 (36.71%); EXT + adDEB 26 (20.31%); LLLT 16 (12.50%); RES + AdDEB 13 (10.15%); Amox 4 (3.12%); AD 3 (2.34%); DH 2 (1.56%); IR 1 (0.78%); LPRF 1 (0.78%); HBO 1 (0.78%) 128 (100%)**

AT = other antibiotics; CHX = chlorhexidine; Ext = extraction; AdDEB = additional debridement; SEQ = sequestrectomy; RES = resection; IR = implant removal; CLN = clinical; RAD = radiographic; TOMO = tomographic; HPT = histopathologically; DEBL= local debridement; Reg. = region; PRP = platelet-rich plasma; LLLT = low-level laser therapy; Post. = posterior; Ant = anterior; OH = oral hygiene guidance; Clin = clindamycin; AD = abscess drainage; Amox = amoxicillin; MTZ = metronidazole; CFLX = cefalexin; DH = drug holiday; HBO = hyperbaric oxygen therapy; LPRF = leukocyte-platelet-rich fibrin.

especially in individuals using ZOE (62.50%). Tooth extraction was also reported to be the main local factor that triggered BRONJ in North American,[27] European[31,34-39] and Asian [40-43] populations.

Among the triggering factors for BRONJ, implant surgery still remains a matter of controversy in the literature.[8] A systematic review found that there was no evidence to demonstrate safety in performing dentoalveolar surgical procedures such as placement of dental implants in individuals exposed to BPs. Therefore, such procedures should be considered to be local risk factors.[44] In one Brazilian population, implant placement was considered to be the

second most prevalent trigger factor (13.86%), with epidemiological values similar to those of a European population (13.50%).[35] Placement of dental implants in individuals who are using BPs presents local and systemic risk factors for development of BRONJ, regardless of the route of BP administration. Hence, these patients should not be treated in a conventional manner. The imminent risk of BRONJ and the risk of failure of peri-implant treatment should be always considered in drawing up the treatment plan. Patients should always be made aware of their systemic and dental condition.

Among the jaw bones, the chance of developing BRONJ is twice as high in the mandible as in the maxilla.[8,32,42,45] In the present review, we observed greater involvement of the mandible, i.e. similar to the findings in North American,[27,30,46] European[31,34,35,37-39,47,48] and Asian[40-43] populations. Despite the lack of detailed information regarding the location of BRONJ that was seen in the present review, we found that the posterior region of the mandible was the most involved, which coincided with findings from the rest of the world's population.[31,34,35,37-43,47,48] Therefore, in all cases, bone manipulation must be done in a precise, fast and atraumatic manner.

The fact that women have been found to be more affected by BRONJ, both in Brazil and in the rest of the world,[27-31,34-43,47-50] may be related to administration of BPs after the menopause and to high incidence of breast cancer and osteoporosis. In Brazil, under these two conditions, there is an indication for using BPs. In the present study, breast cancer and osteoporosis were the underlying diseases that led to the highest prevalence of BRONJ, and similar results were found in European populations.[36,38] Although the prevalence of BRONJ has mainly been associated with occurrences of breast cancer in the United States, multiple myeloma is the second most prevalent disease related to this oral complication.[27,34,38,46] The South Korean population is the only population in which BRONJ is more related to osteoporosis than to other underlying diseases.[42,43]

Therefore, it is important for medical specialists such as mastologists and/or gynecologists to be aware that patients who use BPs are at greater risk of developing BRONJ. One preventive measure could be to refer patients for dental assessment, before or during the first months of prescription of BPs, in order to eliminate some foci of infection that can expose these patients to the risk of developing BRONJ.

This integrative review identified that the majority of the Brazilian cases were diagnosed during stage 2 of BRONJ, and this is similar to findings from other countries.[30,31,36-38,41-43,46,48] High prevalences of other stages are unusual, but when this occurs, it is usually stage 3, in which there is involvement of adjacent structures such as the maxillary sinus or occurrence of pathological fracture of the mandible.[35,47-49] In the present review, stage 3 had the second highest prevalence, affecting 18.43% of this Brazilian population.

The diagnosis of BRONJ in these Brazilian cases was clinical in all of them. Since 2014, AAOMS has recommended the use of complementary imaging tests to finalize the staging and evaluate possible bone alterations that can precede BRONJ. Despite this recommendation for concomitant use of computed tomography (CT) as the most appropriate examination, the present review identified that only 40.62% of the cases were diagnosed by means of cone beam computed tomography (CBCT). This suggests not only that there is probably a lack of knowledge of indication of 3D imaging such as CBCT to perform better examinations, but also that there is a lack of local resources or else that these examinations have a high cost. The radiographic evaluation criterion was not included in this integrative review because of the lack of detailed information in the studies selected.

In addition, it is important to mention that, although AAOMS recommends that BRONJ should be diagnosed using clinical and imaging methods, we would emphasize that there is a need to make differential diagnoses in relation to other lesions with clinical signs of bone exposure, such as bone metastases and clinical manifestations of multiple myeloma in the jaw through histopathological analysis.[50-52] Nonetheless, such lesions have been found to be very scarce, accounting for only 2.34%.

The etiology and progression of BRONJ are related to infection and inflammation.[8] In these Brazilian cases, sequestrectomy, resection and curettage were used, almost always in association with chlorhexidine mouthwashes and antibiotic therapy when necessary. In this last case, clindamycin was the main antibiotic selected, while other antibiotics like amoxicillin, tetracycline and metronidazole were also used but less frequently. Some studies have reported that the penicillin group was the first choice among antibiotics in Europe,[34,35,47] and clarithromycin in Asia.[40]

Among the types of treatment mentioned earlier, surgical treatment is widely used in different populations around the world.[29,34,41,46,47,53] Regardless of the type of surgical approach used, debridement or sequestrectomy until accessing the bleeding bone is recommended for improving the chances of success in the treatment.[38]

The limitation of the present study was its inability to provide detailed information about the location of BRONJ, type and dose of medications, radiographic features, biopsy and follow-up because of the lack of detailed information in the studies selected. In addition, there were no randomized studies or investigations on BRONJ in Brazilian populations. For this reason, we suggest that such studies need to be conducted and need to provide detailed information, as mentioned earlier.

CONCLUSION

The manifestation of BRONJ in this Brazilian population was greatest in the mandibles of younger females, with greater associations with breast cancer and osteoporosis. The major risk factor was previous exodontia, and BRONJ was diagnosed mainly

in the intermediate staging (II). Surgical intervention was the treatment most commonly used among these Brazilian patients. This review identified greater use of chlorhexidine solution and prescription of clindamycin as the first-choice antibiotic therapy. PRP was the complementary therapy most used.

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Evidence from Cochrane systematic reviews for controlling the dissemination of COVID-19 infection. A narrative review

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AUTHORS' KEY WORDS:
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Evidence synthesis.
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ABSTRACT

BACKGROUND: COVID-19 infection has high transmissibility and several measures have been adopted for controlling its dissemination.

OBJECTIVE: To identify and summarize the evidence from Cochrane systematic reviews (SRs) regarding measures for controlling the dissemination of COVID-19 infection.

DESIGN AND SETTING: This review of Cochrane SRs was carried out in the Division of Vascular and Endovascular Surgery and in the Division of Emergency Medicine and Evidence-Based Medicine of Universidade Federal de São Paulo, Brazil.

METHODS: A comprehensive search in the Cochrane Database of Systematic Reviews retrieved all Cochrane SRs directly related to measures for controlling COVID-19 dissemination. The main characteristics and results of all the SRs included were summarized and discussed.

RESULTS: Three Cochrane SRs were included in the qualitative synthesis. These evaluated population-based and individual measures for controlling the dissemination of COVID-19.

CONCLUSION: Low-certainty evidence shows that quarantine for people exposed to confirmed or suspected COVID-19 cases prevented 44% to 81% of incident cases and 31% to 63% of deaths, compared with situations of no measures. Moreover, the sooner the quarantine measures were implemented, the greater the cost savings were. High-confidence evidence showed that clear communication about infection control and prevention guidelines was vital for successful implementation. Low-certainty evidence showed that healthcare professionals with long gowns were less exposed to contamination than were those using coveralls. In addition, coveralls were more difficult to doff. Further SRs on controlling the dissemination of COVID-19 infection are desirable.

INTRODUCTION

COVID-19 is a disease caused by a new type of coronavirus (SARS-CoV-2), which was identified in December 2019 in Wuhan province, China. Many patients develop only moderate symptoms without complications. However, approximately 14% of infected people develop a severe form of the disease that requires hospitalization and oxygen support and 5% of patients need treatment in intensive care units. SARS-CoV-2 disseminates among people mainly through the respiratory route, through coughing and sneezing, but it can also be transmitted by means of contaminated surfaces. Although the incubation time varies from 5 to 6 days in most cases, this time can reach up to 14 days. The infection period is not precise, varying from 24 hours to 48 hours before the manifestation of the symptoms. The viral load detected in the upper respiratory tract at the onset of the disease is high.[1]

When a new respiratory infection becomes widespread, as has occurred with the COVID-19 pandemic, healthcare professionals must adhere to prevention protocols in order to avoid contamination and infection. The prevention protocols recommend a variety of strategies: both personal measures, relating to the professionals, and measures that concern the environment. For the professionals, the protocols suggest that a mask, face shields, gloves and aprons, known as personal protective equipment (PPE), should be used. Concerning the environment, the protocols suggest that patients with respiratory diseases should be isolated and that cleaning routines should be more rigorous. Given that, in practice, adherence to these strategies can be challenging, healthcare authorities and facilitators need to support their professionals in implementing them.[2]

In epidemics and pandemics of highly infectious diseases such as Ebola, COVID-19 and severe acute respiratory syndrome (SARS), healthcare professionals' contact with the body fluids of contaminated patients means that these professionals are the group at the highest risk of infection.[3]

The World Health Organization (WHO) recommends quarantine and isolation, in association with other public health measures, as measures for controlling the spread of infection. Both quarantine and social isolation are epidemiological interventions to mitigate infectious disease and reduce the potential for transmission. However, the effects of these and other measures for controlling the pandemic still generate discussion.[4]

Different countries have been using both individual and collective interventions for controlling the dissemination of infection, such as use of PPE, social isolation and compulsory quarantine, but the impact of these measures still needs to be studied in order to bring out robust evidence.

OBJECTIVE

The aim of this study was to identify and summarize the evidence from Cochrane systematic reviews (SRs) regarding measures for controlling the dissemination of COVID-19 infection, in an overview.

METHODS

Design and setting

This review of Cochrane SRs was carried out in the Division of Vascular and Endovascular Surgery and the Division of Emergency Medicine and Evidence-Based Medicine of Universidade Federal de São Paulo, Brazil.

Inclusion criteria

Types of study

We included full Cochrane SRs published in the Cochrane Database of Systematic Reviews (CDSR), with no restrictions on the date of publication. Withdrawn or outdated versions of SRs and protocols for SRs were considered not relevant.

Types of participants

All participants at risk of contagion, with suspected or confirmed clinical status of COVID-19 infection were considered relevant, i.e. males and females of all ages, with no restrictions as to the severity of the condition or place of treatment (outpatient or hospital setting).

Types of interventions

We considered SRs that evaluated any intervention to control the spread or reduce the contagion of COVID-19 infection, compared with standard care or another intervention, in at least one arm of the study.

Types of outcomes

Any epidemiological, clinical or laboratory results relevant to patients were considered, as assessed by the authors of the SRs included.

Search for reviews

We performed a sensitive systematic search in the CDSR, via Wiley, on April 26, 2020, using the MeSH terms 'Coronavirus Infections' and 'Coronavirus', and all related variants, along with free terms in 'titles, abstracts and keywords'. The detailed electronic search strategy is shown in **Table 1**.

Selection of reviews

Two researchers (LCUN and RLGF) independently assessed the titles and abstracts to analyze whether the SRs met the inclusion criteria, using the Rayyan software (rayyan.qcri.org/welcome).[5] Any disagreement was resolved in consultation with two other authors (CDQF and PIFP) or through discussion. Two authors (PIFP and RLGF) selected and summarized the SRs that were included.

Presentation of results

We presented the search results and the SRs that were included as a qualitative synthesis (descriptive approach).

Table 1. Electronic search strategy and results in the Cochrane Database of Systematic Reviews

Line	Searched terms	Number of results
#1	MeSH descriptor: [Coronavirus Infections] explode all trees	38
#2	MeSH descriptor: [Coronavirus] explode all trees	11
#3	(severe acute respiratory syndrome coronavirus 2) or (Wuhan coronavirus) or (Wuhan seafood market pneumonia virus) or (COVID19 virus) or (COVID-19 virus) or (coronavirus disease 2019 virus) or (SARS-CoV-2) or (SARS2) or (2019 novel coronavirus)	68
#4	COVID-19 or (2019 novel coronavirus infection) or (COVID-19 pandemic) or (coronavirus disease-19) or (COVID19) or (2019 novel coronavirus disease) or (coronavirus disease 2019)	69
#5	Coronavirus* or Deltacoronavirus* or Deltacoronavirus* or (Munia coronavirus* HKU13) or (Coronavirus* HKU15) or (Coronavirus* Rabbit) or (Bulbul coronavirus* HKU11) or (Thrush coronavirus* HKU12)	154
#6	#1 or #2 or #3 or #4 or #5	172
#7	Filter: Cochrane Reviews	19

RESULTS

Search results

Nineteen references were retrieved from our search strategy and, after screening the titles and abstracts, six SRs were preselected. After evaluating the full texts, three reviews were found to meet the inclusion criteria and were included in the qualitative summary.[2-4]

Comments included

The most recent versions of all the SRs included were published in April 2020 in the CDSR. Details regarding the review design, characteristics of the interventions, comparisons, results and the certainty or confidence of evidence are presented in **Table 2**.[2-4]

1. Quarantine alone or in combination with other public health measures for controlling COVID-19: a rapid review [4]

A rapid review was carried out to support WHO quarantine-related measures that were implemented subsequent to WHO's declaration of the COVID-19 pandemic in March 2020. Nussbaumer-Streit et al. conducted a SR with abbreviated methods (rapid review) in order to evaluate two key questions (KQ): 1) the effects of quarantine (alone and in association with other public health measures) for individuals who had been in contact with confirmed cases of COVID-19; and 2) the effects of quarantine on individuals who had travelled from countries with a declared pandemic or who were living in regions with high transmission of the disease.

Main results

The authors of this SR included 29 studies as follows: 15 modelling studies on SARS and Middle East respiratory syndrome (MERS), four observational studies and 10 modelling studies on COVID-19 (**Table 2**). Because of the different measurement and analysis methods among the results of interest, it was not possible to carry out a meta-analysis, and the authors of this SR summarized the data in a narrative synthesis. Using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, the certainty of evidence ranged from low to very low due to the type of evidence found through this SR.[6]

Simulated quarantine measures showed a benefit, as reported through the modelling studies. Quarantine measures for people exposed to confirmed or suspected cases prevented 44% to 81% of incident cases and 31% to 63% of deaths, compared with no measures. This low-certainty evidence was based on four modelling studies on COVID-19 in SARS (incident cases), and two modelling studies on COVID-19 in SARS (mortality). Two modelling studies on SARS suggested that the earlier the quarantine measures were implemented, the greater the cost savings would be (low-certainty evidence). Two modelling studies on SARS indicated that the effect of quarantine measures for travelers from a country with a reported outbreak was small, with regard to reducing deaths and the incidence of the disease (low-certainty evidence). Other prevention and control measures used in combination with quarantine, including travel restrictions, social distancing and school closures, showed a more significant effect in reducing deaths, transmissions and new cases, than did individual measures alone. Modelling studies on COVID-19 provided this low-certainty evidence: four studies relating to incident cases, two relating to subsequent transmission and another two relating to mortality. The studies on SARS and MERS were consistent with the results from studies on COVID-19.

Adverse effects

This SR focused on transmission, reduction of mortality and use of quarantine resources because WHO selected these as outcomes of interest. The authors of this SR did not include any consideration of the psychological impact of quarantine on individuals. There may be other adverse economic and health effects resulting from quarantine that were not assessed by this review (for example, domestic violence, unemployment and quality of life). For these reasons, this SR was unable to address the issue of when quarantine and other public health measures aimed at reducing the dissemination of COVID-19 should be relaxed or limited. It is also important to note that the authors of this SR did not subject the two modelling studies that reported on use of resources to specific critical economic assessments and did not attempt to come to any conclusions regarding the relative costs or efficiency of quarantine alone or in combination with other measures, compared with these public health interventions or measures in isolation.

Review conclusions

Although the evidence was limited to modelling studies, this SR showed that quarantine was essential for reduction of the incidence of COVID-19 and consequent mortality. Early implementation of quarantine and combination of quarantine with other public health measures seemed to be essential for ensuring effectiveness. Decision-makers should continuously keep the outbreak situation and the impact of the measures implemented under surveillance. To assess the true prevalence of infection and reduce the uncertainty of modelling assumptions, testing representative samples in different contexts might be of some help.

2. Barriers and facilitators to healthcare workers' adherence with infection prevention and control (IPC) guidelines for respiratory infectious diseases: a rapid qualitative evidence synthesis[2]

This was a rapid review to synthetize the evidence relating to factors that influence healthcare professionals to follow infection control and prevention (ICP) protocols for respiratory diseases.

Table 2. Details of review design, characteristics of interventions, comparisons, participants, main results and certainty of evidence, assessed by means of GRADE

Reference / Review design Types of primary studies analyzed in the review	Interventions	Comparisons	Participants	Main Results	GRADE
Nussbaumer-Streit et al.[4]/rapid review • Cohort • Case-control • Time series • Interrupted time series • Case series • Mathematical modelling studies	Different types and quarantine locations for individuals. They included studies combining isolation and quarantine.	• No quarantine. • Different types and quarantine locations. • Public health measures without quarantine to reduce the spread of the virus (isolation, social distancing, personal protective equipment, hand hygiene and others).	• (KQ1) contacts of a confirmed or suspected case of COVID-19 (SARS or MERS) or individuals living in areas with high rates of transmission; • (KQ2) individuals returning from countries with a declared outbreak of COVID-19 (SARS or MERS), defined by WHO as an 'occurrence of cases of disease above normal expectations'.	• Quarantine of people exposed to confirmed or suspected cases prevented 44% to 81% of incident cases and 31% to 63% of deaths, compared with no measures (incident cases: four modelling studies on COVID-19 and SARS; mortality: two modelling studies on COVID-19 and SARS).	• Low certainty
				• The earlier the quarantine measures are implemented, the greater the cost savings (two modelling studies on SARS).	• Low certainty
				• The effect of quarantining travelers from a country with a reported outbreak was small with regard to reducing the incidence of illness and deaths (two modelling studies on SARS).	• Low certainty
				• When the models combined quarantine with other prevention and control measures, including school closures, travel restrictions and social distancing, modelling studies demonstrated a greater effect with regard to reducing new cases, transmissions and deaths than individual measures alone (incident cases: four modelling studies on COVID-19; subsequent transmission: two modelling studies on COVID-19; mortality: two modelling studies on COVID-19).	• Low certainty
Houghton et al.[2]/ rapid review (synthesis of evidence) • Mixed method designs (qualitative aspect)	• Early recognition and source control (screening and breathing hygiene). • Administrative controls (isolation, spatial separation and cohort of patients). • Environmental and engineering controls (cleaning and disinfection; and ventilation). • PPE (dressing and undressing), aprons, gloves, masks and glasses). • Hand hygiene.	Control group is not evident from the nature of the review.	Most of the studies included involved nurses (14 studies) or doctors (9 studies). Other types of healthcare professionals included in the studies were occupational therapists, respiratory therapists and physical therapists; auxiliary personnel responsible for patient care, such as porters and domestic workers; laboratory technicians; infection control professionals; and managers.	• Healthcare professionals felt insecure about how to follow local guidelines when they were lengthy and ambiguous or did not reflect national or international guidelines.	• Moderate confidence
				• Clear communication about ICP guidelines was considered vital for its implementation.	• High confidence
				• Sufficient space to isolate patients was also considered essential for the implementation of the guidelines.	• Moderate confidence
				• The lack of PPE and poor quality equipment were serious concerns for healthcare workers and managers.	• Moderate confidence
				• Healthcare professionals believed that they followed ICP guidelines more closely when they saw their value.	• Moderate confidence
				• Healthcare professionals pointed out the importance of including all employees (cleaning, doormen, kitchen and other support staff) when implementing ICP guidelines.	• Low confidence

Continue...

Table 2. Continuation

Reference / Review design Types of primary studies analyzed in the review	Interventions	Comparisons	Participants	Main Results	GRADE
Verbeek et al.[3]/ traditional systematic review • RCT • Non-randomized controlled trial • Cohort • Case-control • Prospective and retrospective controlled field studies	• Different types of full body protection (PPE), different compositions or amounts of PPE (body protection, such as aprons, overalls; eye and face protection in glasses, goggles, face mask visors or masks or hoods that cover the entire head; hand protection: gloves; and foot protection: boots). • Different parts of PPE or different procedures or protocols for placing and producing PPE. • Effectiveness of training to increase compliance with existing guidelines on the selection or use of PPE, including, but not limited to: education (courses); practical training; information only (such as posters, guidance leaflets, etc.); audit and feedback, or monetary or organizational incentives.	Comparisons were grouped according to similarity. Studies without a comparator group were not included.	• For simulation studies, any type of participant (volunteer or health professional) using PPE designed for Ebola virus disease or highly infectious diseases comparable with serious consequences was included. • For field studies, only studies carried out on healthcare professionals or auxiliaries exposed to patients' body fluids in the form of splashes, droplets or aerosols contaminated with particles of highly infectious diseases that have serious health consequences, such as Ebola virus, SARS or COVID-19. Studies carried out on the laboratory team were excluded because the preventive measures in the laboratories are more detailed and easier to comply with.	• Using a respirator and energized air purifier with overalls can protect against the risk of contamination better than an N95 mask and gown (RR 0.27; 95% CI 0.17 to 0.43), but it was more difficult dressing (non-conformity: RR 7.5; 95% CI 1.81 to 31.1).	• Very low certainty
				• In an RCT (59 participants), people with a long gown had less contamination than those with a coverall, and the coverall was more difficult to wear	• Low certainty
				• The following modifications to the PPE design can lead to less contamination, compared with the standard PPE: combination of sealed gown and glove (RR 0.27; 95% CI 0.09 to 0.78), a more suitable fit around the neck, wrists and hands (RR 0.08; 95% CI 0.01 to 0.55), additional tags to grip, to facilitate the use of masks (RR 0.33; 95% CI 0.14 0.80) or gloves (RR 0.22; 95% CI 0.15 to 0.31).	• Very low certainty
				• better coverage of the wrist-cuff interface can lead to less contamination, compared with standard PPE (RR 0.45; 95% CI 0.26 to 0.78)	• Low certainty
				• Using the CDC recommendations can lead to less contamination, compared with no guidance (small spots: MD -5.44; 95% CI -7.43 to -3.45).	• Very low certainty
				• The use of additional computer simulation can lead to fewer errors in the process (MD -1.2; 95% CI -1.6 to -0.7).	• Very low certainty

GRADE: Grading of Recommendations, Assessment, Development and Evaluation; RCT = randomized controlled trial; PPE = personal protective equipment; KQ1 = key question 1; KQ2 = key question 2; SARS = severe acute respiratory syndrome; MERS = Middle East respiratory syndrome; WHO = World Health Organization; IPC = infection control and prevention; RR = relative risk; CI = confidence interval; CDC = Centers for Disease Control and Prevention; MD = mean difference.

These strategies include the use of PPE such as masks, face shields, gloves and aprons; isolation of patients with infectious respiratory disease; and stricter cleaning routines. The review authors searched only the MEDLINE database via OVID and included all types of primary studies, with no limits on date or language of publication. The review authors used the GRADE-CERQual approach (Trust in Evidence from Qualitative Research Reviews) to assess the level of confidence in each result.

Main results

The authors of this SR found 36 relevant studies, and 20 studies were included in the qualitative analysis of this review. There was no meta-analysis, and the results were reported narratively (**Table 2**). Two of the studies included were from Australia, four from America, four from Africa, and ten from Asia. The studies demonstrated the vision and experience of doctors, nurses and other health professionals who deal with SARS, influenza A (H1N1), MERS, tuberculosis (TB) or seasonal influenza. Most of the participating healthcare professionals were working in hospitals and primary care communities.

The following factors (barriers or facilitators) that were ascertained were based on results that were assessed as presenting a moderate to high level of confidence.

Lengthy and ambiguous guidelines or those that did not reflect national or international guidelines made the healthcare professionals insecure about how to follow local

guidelines. Continual changes to the local guidelines left the healthcare professionals feeling overwhelmed. They also described how ICP strategies led to increased workloads and fatigue; for instance, because they had to wear PPE and do additional cleaning. The level of support that the healthcare professionals felt that they received from their management team was described as a point that influenced their responses to ICP guidelines.

Clear communication about ICP guidelines was considered vital. The healthcare professionals pointed out that there was a lack of training on how to use PPE and on the infection itself. They also considered it to be a problem when training was not mandatory.

Sufficient space to isolate patients was also considered essential. The lack of isolation rooms, antechambers and showers was a problem. Other critical practical measures described by the healthcare professionals included rapid screening of infected patients, minimization of overcrowding, easy access to handwashing facilities and restrictions on visitors.

The healthcare workers and managers pointed out that the lack of PPE and inadequate quality equipment were serious concerns, and that there was a need to adjust the volume of supplies as outbreaks of infection continued.

The healthcare professionals believed that they followed ICP guidelines more carefully when they understood their value. Some of the healthcare professionals felt motivated to follow the guidelines because they felt responsible for their patients or because they were afraid of infecting themselves or their families. The healthcare workers identified that there was some trouble in using masks and related PPE when it made patients feel isolated, scared or stigmatized. The healthcare professionals also found that the masks and other equipment were unpleasant to use. The culture of the workplace also possibly influenced whether the healthcare professionals followed ICP guidelines or not.

In many of the conclusions, the healthcare professionals pointed out the importance of including all employees, including cleaning, doorkeeping, kitchen and other support staff, when implementing ICP guidelines.

Adverse effects

Some factors possibly constitutes barriers against infection control and prevention strategies, such as lack of alignment between national and international protocols, which led to insecurity among health professionals with regard to following these protocols. Another critical factor was the lack of personal protective equipment or the availability only of inferior material, which caused discomfort among professionals. In some situations, although healthcare professionals were aware of the regulations, it could be challenging to adhere to the protocols, especially when working under critical conditions.

Review conclusions

The review authors pointed out several factors that influenced the ability and willingness of healthcare professionals to follow ICP guidelines when managing respiratory diseases. Those factors included points associated with the guidelines themselves and how they were disclosed, support from managers, training, workplace culture, physical space, access to and confidence in PPE and the intention to provide excellent patient care. The review also highlighted the importance of including all staff at the facility, including the support team, when implementing the ICP guidelines.

3. Personal protective equipment for preventing highly infectious diseases due to exposure to contaminated body fluids in healthcare staff[3]

In situations of outbreaks of epidemics or pandemics, there is an increased risk of infection for healthcare professionals due to greater exposure to body fluids from infected patients. Use of PPE can reduce this exposure. This study was a SR that assessed which type of full-body PPE and which method of dressing and undressing presented the lowest risk of contamination and infection for healthcare professionals. The study also addressed training methods that had the capacity to increase adherence to protocols.

Main results

The authors of this SR included 24 studies with 2,278 participants: 14 of these studies were randomized controlled trials (RCTs), nine had a non-randomized design and one was a quasi-RCT. Among the 24 studies included, eight compared dressing and undressing processes, eight compared types of PPE, three evaluated types of training and six evaluated adapted PPE. In 18 simulation studies on harmless microbes or fluorescent markers, the average contamination rates were 25% for the intervention group and 67% for the control group.

The certainty of the evidence for all the results was very low, except when mentioned otherwise, because it was based on only a few studies, because it used indirect evidence (simulation) and because of the risk of bias in the studies included (**Table 2**).

Use of an energized respirator and air purifier with coveralls can better protect against the risk of contamination than a N95 mask and gown (relative risk (RR) 0.27; 95% confidence interval (CI) 0.17 to 0.43), but it was more difficult to wear (non-conformity: RR 7.5; 95% CI 1.81 to 31.1). In an RCT (59 participants), long aprons (gowns) were better able to protect against contamination than overalls, and the overalls were more difficult to wear (evidence of low certainty). Long aprons (gowns) were also better able to protect against contamination than short aprons (small spots: mean difference (MD) -10.28; 95% CI -14.77 to -5.79). PPE made of more breathable material led to a similar number of stains

on the trunk (MD 1.60; 95% CI -0.15 to 3.35), compared with water-repellent material, but user satisfaction was possibly higher (MD -0.46; 95% CI -0.84 to -0.08, scale from 1 to 5).

The following modifications to the design of the PPE had the capacity to lead to less contamination, compared with the standard PPE: 1) a more suitable fit around the neck, wrists and hands (RR 0.08; 95% CI 0.01 to 0.55); 2) a combination of sealed gown and gloves (RR 0.27; 95% CI 0.09 to 0.78); 3) better coverage of the wrist interface (RR 0.45; 95% CI 0.26 to 0.78; low-certainty evidence); and 4) additional tags to grab to facilitate the use of masks (RR 0.33; 95% CI 0.14 0.80) or gloves (RR 0.22; 95% CI 0.15 to 0.31).

Use of the recommendations of the Centers for Disease Control and Prevention (CDC) had the capacity to lead to less contamination, compared with no guidance (small spots: MD -5.44; 95% CI -7.43 to -3.45). One-step removal of gloves and gown did not enable lower contamination with fluorescence (RR 0.98; 95% CI 0.75 to 1.28) than separate removal. However, this one-step removal strategy led to less bacterial contamination (RR 0.20; 95% CI 0.05 to 0.77). Use of double gloves had the capacity to lead to less viral or bacterial contamination, compared with simple gloves (RR 0.34; 95% CI 0.17 to 0.66), but not less contamination with fluorescence (RR 0.98; CI 95 % 0.75 to 1.28). Additional spoken instructions had the capacity to lead to fewer errors in execution (MD -0.9; 95% CI -1.4 to -0.4) and fewer points of contamination (MD -5; 95% CI -8.08 to - 1.92).

Computer simulation in addition to other measures had the capacity to lead to fewer errors in the process (MD -1.2; 95% CI -1.6 to -0.7). A video lecture on PPE placement had the capacity to lead to better skill scores (MD 30.70; 95% CI 20.14 to 41.26) than a traditional lecture. Face-to-face instructions had the capacity to reduce non-compliance with guidelines, compared with just providing folders or videos (odds ratio (OR) 0.45; 95% CI 0.21 to 0.98).

Adverse effects

The use of various elements of PPE created discomfort regarding its use, which gave rise to possibly higher risk of contamination of the healthcare professional at the time of undressing.

Use of an energized respirator and air purifier with overalls was more challenging to wear (non-compliance: RR 7.5; 95% CI 1.81 to 31.1).

Review conclusions

This SR found very low to low-certainty evidence that covering more parts of the body enabled better protection, but that protection covering more of the body was generally more difficult to wear or make and was associated with less user comfort and, therefore, would perhaps even lead to more contamination. More breathable types of PPE could lead to similar contamination but could also lead to greater user satisfaction. Modifications to the design of the PPE, such as incorporation of gripping tags, had the capacity to decrease the risk of contamination. Placement and manufacturing procedures that followed the CDC guidelines, the ability to remove the gloves and gown in one step, use of double gloves, use of verbal instructions during execution and disinfection of gloves had the capacity to reduce contamination and increase compliance. Face-to-face training in the use of PPE had the capacity to reduce errors more than training based on printed material such as folders.

The authors of this SR concluded that there was a lack of RCTs with long-term follow-up; a lack of simulation studies with large numbers of participants to find out which PPE combinations and which procedures gave better protection; and a lack of evidence from real life. They considered that a consensus regarding simulation of exposure and evaluation of the results was necessary. Therefore, they considered that the use of PPE by healthcare professionals who would be exposed to highly infectious diseases needed to be recorded, and that these professionals should be followed up prospectively regarding the risk of infection.

DISCUSSION

The COVID-19 pandemic is right now the most significant global health threat. Its dissemination has been rapid, with at least 146 countries affected.[7]

One of the WHO guidelines for disease control is quarantine, which means separation of healthy people who might be infected by the virus and have the potential to spread the disease. Other similar recommendations are isolation (similar to quarantine, but including people with symptoms of COVID-19) and social distancing (when healthy people keep a physical distance away from other people).[1]

In massive pandemics with a highly infectious disease such as COVID-19, there is higher contamination among healthcare professionals. These individuals may develop infectious conditions earlier, due to their more significant contact with infected people. Therefore, it is a matter of urgency to determine strategies and develop protocols for these professionals so that there is greater adherence to safety regulations. When PPE such as masks, glasses, face shields, gloves, aprons and coveralls is routinely used within the care provided for these infected patients and the guidelines for dressing and undressing are followed, cases of contamination will be more significantly mitigated. However, these strategies often become difficult to follow in practice, and so there is a need for more significant support for these professionals, for them to be implemented.

Several measures have been taken in the light of this pandemic. These have included combinations of case isolation, domestic quarantine and social distancing among at-risk groups (the elderly and individuals with comorbidities). These are the most effective combined policies for reducing the epidemic curve.

Through these Cochrane SRs, it was possible to identify the effects of the strategies that have been used to clarify how PPE should be best used among healthcare professionals and how valuable this is. When the care protocols for avoiding contamination were used correctly, these professionals were safer. Also, it was possible to determine the effects of quarantine (alone and in association with other public health measures) for reducing the incidence of COVID-19 and the resultant mortality. Early implementation of quarantine was found to be essential for the effectiveness of this action.

Nonetheless, the success of these approaches comes not only from the effectiveness of their implementation, but also especially from the natural and biological history of the COVID-19 pathogen, its transmissibility and the feasibility of interventions within the context of the country's public health organizations.[8]

The number of Cochrane systematic reviews that directly address the COVID-19 pandemic is still limited, but efforts are being made to rapidly produce high-quality syntheses of evidence that are of interest for decision-makers within healthcare and healthcare policies.[9]

CONCLUSION

After a comprehensive systematic search, three Cochrane SRs were included in this review. They contributed evidence regarding population-based measures (such as quarantine and isolation) and individual measures (such as use of PPE, type of PPE, etc.) for controlling the spread of COVID-19.

Low-certainty evidence showed that quarantine for people who had been exposed to suspected or confirmed cases prevented 44% to 81% of incident cases and 31% to 63% of deaths, compared with no measures. Moreover, the earlier that the quarantine measures were implemented, the higher the cost savings were.

Evidence with high confidence showed that clear communication about ICP guidelines was considered vital for their implementation. In addition, evidence of moderate confidence showed that healthcare professionals felt insecure about how to follow local guidelines when these did not reflect national or international guidelines or when they were lengthy and ambiguous. Sufficient space to isolate patients was also seen as essential for the implementation of the guidelines.

Low-certainty evidence showed that people with long aprons received less contamination than those with coveralls, and that the coveralls were more challenging to wear. Furthermore, there was low-certainty evidence that better coverage of the wrist cuff interface had the capacity to lead to less contamination, compared with standard PPE. Uncertainty remained regarding the best use of PPE for controlling COVID-19 dissemination because the evidence relating to this was of very low certainty.

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Contamination risk in urology operating room during the COVID-19 pandemic

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Dear Editor,

The novel coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus is a highly transmittable and pathogenic newly emerging human infectious disease.[1] Healthcare workers are at increased risk of coronavirus infection but they have to manage to provide optimum care to patients.

With the number of cases expected to increase in the coming weeks, we think that efficiently prioritizing surgical procedures is the first step towards facing up to the increased risks during the COVID-19 pandemic. Benign urological surgeries should be postponed until the pandemic is over.[2] However, oncology and emergency activities should be maintained in the hospital, and healthcare teams need to become more proactive regarding respiratory hygiene, since SARS-CoV-2 spreads primarily through droplets.

The data concerning this disease that are available at this date remain limited. Notably, asymptomatic SARS-CoV-2 infected individuals play a role in disseminating the infection.[2] Human-to-human spreading of SARS-CoV-2 occurs in situations of close contact with an infected person, through exposure to this person's coughing, sneezing, respiratory droplets or aerosols.[1]

However, other routes of potential transmission are highly suspected. Viral ribonucleic acid (RNA) has now been detected in feces, thus suggesting the possibility of a fecal-oral route of transmission.[3] Some studies have found patients that had persistently positive rectal swabs, even after their nasopharyngeal tests were negative.[3] Moreover, Xia et al. speculated that SARS-CoV-2 may be detected in the tears and conjunctival secretions of COVID-19 patients presenting conjunctivitis.[4] Also, viral RNA has been detected in blood, thus suggesting that infection may sometimes be systemic.[5] SARS-CoV-2 has not been detected yet in urine, except in one study in which SARS-CoV-2 was found in urine specimens from of 6.9% of the patients and remained positive even after throat swabs turned negative.[3,6]

These potential transmission routes, i.e. both respiratory and extra-respiratory routes, may explain the rapid spread of COVID-19. Consequently, urologists should be careful in the operating room, especially with patients who are potentially infected with COVID-19.

All staff need to be specifically trained to don, doff and dispose of personal protective equipment (PPE), including masks (FFP2 or 3), eye protection, double non-sterile gloves, gowns, suits, caps and socks.[7]

Suspected or confirmed patients should be managed in a dedicated operating room equipped with a negative pressure environment, to reduce dissemination of the virus.[7]

There is a significant risk of SARS-CoV-2 dissemination due to pneumoperitoneum-associated aerosolization of particles in laparoscopic surgery. Thus, lowering electrocautery power settings as much as possible is recommended.[8] Also, intraperitoneal CO_2 should be extracted using the active smoke evacuation mode.[9] Moreover, some authors have suggested that use of laparoscopy should be reserved for COVID-19 negative patients, except for cases in which the risks of laparotomy far outweigh the risks of laparoscopy.[10]

For endoscopic surgery in suspected or confirmed COVID-19 patients, complete protection against infection is recommended.[2,9] The same precaution needs to be taken when the anus is accessible in the operating field.[9] Healthcare workers in contact with such patients must also wear a double pair of gloves and long shoe covers.[7]

Bowel utilization, such as in enterocystoplasty, should also be careful and kept to minimum because of the presence of SARS-CoV-2 in feces.[2,3]

In conclusion, facing up to COVID-19 is challenging, and protecting both healthcare workers and patients is mandatory. Urologists need to adopt sufficient protective strategies and develop internal protocols for their operating room teams, to minimize infection risks.

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COVID-19 threatens to cause collateral delay in cancer diagnosis

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Dear editor,

In December 2019, a novel coronavirus disease termed COVID-19 emerged in Wuhan, China. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Because COVID-19 is able to spread through respiratory droplets, the number of cases has rapidly increased in many countries throughout the world, including Brazil.[1] The World Health Organization (WHO) has declared COVID-19 to be the first worldwide pandemic involving a coronavirus disease, which classifies this outbreak as an international emergency.[1] In order to reducing the peak incidence of infections and hospitalizations and thus avoid overloading of healthcare systems, restrictive measures have been adopted all over the world. In an effort to conserve resources and reduce the risk of transmission, non-urgent laboratory and imaging tests, along with scheduled procedures, have been suspended across the world to help healthcare facilities in dealing with the COVID-19 outbreak. Thus, elective procedures may be delayed for an indeterminate period of time.[2]

In May 2020, the American Society of Clinical Oncology (ASCO) published a special report recommending postponement of any visits to clinics and any cancer screening or diagnosis and staging-related procedures if this postponement does not pose a risk for disease progression or worsening of the prognosis.[3] It is reasonable to limit procedures and imaging or laboratory investigation for patients whose disease is only suspected clinically to present low risk of rapid progression or low risk of recurrence.[3] On the other hand, delaying all screening, diagnostic and staging procedures will probably lead to an unprecedented elevation of cancer diagnoses at late stages in subsequent months.

There is a need to propose new screening strategies to avoid delay in recognition of cancer caused by postponement of diagnostic investigations due to prolonged COVID-19 containment measures. At this unusual phase of the pandemic, there needs to be careful evaluation of the risks and benefits of pursuing each procedure. One suggestion would be to incorporate alternatives such as self-collection of specimens for the fecal occult blood test (FOBT) or human papillomavirus (HPV) test.[4] Health diagnostic centers could also have a specific day and/or location for performing preventive procedures, such as mammography and colonoscopy. Requests for imaging and laboratory tests could be sent directly to the diagnostic center, thus avoiding the need for patient consultation.

Through adopting such measures, in addition to those recommended by the World Health Organization (WHO) for the general population, screening and diagnostic activities can be made safer. Healthcare providers should also be alert to, and be trained to investigate, the presence of any symptom of COVID-19 infection in all patients who are referred for screening or diagnosis procedures.[5]

The return to normalcy may be slow. Strategies to ensure that cancer screening and prevention measures can be implemented need to be discussed within the major international medical societies. Through such strategies, a significant increase in late-stage disease at diagnosis and, consequently, higher cancer morbidity and mortality rates in the near future may be avoided.

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Pulmonary embolism in patients with COVID-19 and its treatment based on low-molecular-weight heparin

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Dear Editor,

In late 2019, a large number of pneumonia patients were diagnosed as having a disease of unknown cause in Wuhan, China. Following this outbreak of human symptoms and infections, a novel coronavirus was identified as the pathogen. In February 2020, the World Health Organization (WHO) named this novel coronavirus COVID-19.[1] In studies on patients, fever, coughing, myalgia or fatigue were identified as common symptoms, and production of sputum, headache, hemoptysis and diarrhea as less common symptoms. Dyspnea was also reported in about half of the patients. Patients' blood tests showed normal or low white blood cell counts (25%) and lymphopenia (65%). Highlights of radiological images in patients with severe coronavirus pneumonia also included a ground-glass appearance and lung consolidation that could affect both lungs. Gradually, in a general classification, patients were placed into four categories: mild, moderate, severe and critical, based on the severity of symptoms.[1,2]

However, one of the clinical findings that has been reported to be relatively higher than expected, in patients with COVID-19 in intensive care units, is pulmonary embolism. Studies conducted around the world have now shown a link between COVID-19 and occurrences of pulmonary embolism and its prevalence.[3] In a study in France, this clinical finding was estimated to be twice as high in patients with COVID-19 as in those with influenza. That study also reported that out of the 107 patients admitted to the intensive care unit (ICU), 22 (20.6%) patients had pulmonary embolism.[4] Another study in France reported a rate of 30%.[5] Zotzmann showed that the laboratory D-dimer levels were elevated in a large number of patients.[6] Cellina et al. also highlighted the importance of identifying and managing pulmonary embolism in patients with COVID-19.[7] In a case study conducted by Danzi et al., the possibility of a link between severe infections in these patients and pulmonary embolism was noted.[8] The results from their study were in line with what had been reported by Grillet et al.[3] regarding this relationship. The prevalence of pulmonary embolism among hospitalized COVID-19 patients in the latter study was 23%.[3]

Pulmonary embolism is defined as an obstruction in the pulmonary vasculature caused by air, fat, tumor growth or, the most common cause, thrombosis. This condition is known to be life-threatening, and is a cause of death among patients admitted to intensive care units. The main risk factor for this condition is vascular thromboembolism in the lower extremities, which can eventually lead to pulmonary embolism, followed by mechanical and chemical events. Obstruction of the pulmonary vasculature can increase vascular resistance and pressure, and right-sided heart failure. If the pulmonary vascular pressure increases, chemicals are released and this ultimately causes ventilation-perfusion mismatch.[9]

In COVID-19 infection, endothelial cell dysfunction develops, leading to increased thrombin production and cessation of fibrinolysis. This indicates an increase in coagulation status (one of the main risk factors for vascular thromboembolism) in infected patients. In addition, in COVID-19 infection, hypoxia (especially the acute form) can facilitate thrombosis not only through increasing blood viscosity but also through activation of a hypoxia-inducible transcription factor-dependent signaling pathway. This results in obstruction and formation of microthromboses in patients' small pulmonary arteries, in critical forms of COVID-19.[10]

Oxygen exchange in the lungs can also be disrupted through a reaction between the coronavirus spike (S) protein and the angiotensin-converting enzyme 2 (ACE 2) receptor in the lungs, thereby increasing ACE 2 expression. Studies have shown that ACE 2 has a greater tendency to bind to coronaviruses. This can eventually destroy the alveoli and reduce oxygen exchange.[11] Injury to alveolar cells can, in turn, cause a series of systemic reactions and even death.[12]

Respiratory and hemodynamic support, along with anticoagulant therapy, are the mainstay of pulmonary embolism treatment. The American College of Chest Physicians guidelines now emphasize treatment of acute pulmonary embolism as soon as possible, using parenteral anticoagulants. These can include unfractionated heparin, fondaparinux or subcutaneous low-molecular-weight heparin (LMWH).[9] LMWH is preferred in these patients because of its cost, availability and authorization for use.[13] Use of heparin as an experimental anticoagulant in patients with COVID-19 and high D-dimer levels has reportedly been associated with lower mortality.[6] Experts have recently emphasized the desirability of management of coagulopathy in all COVID-19 patients using prophylactic doses of LMWH.[14]

Poissy et al. pointed out that heparin can have positive effects in patients with COVID-19, but noted that uncertainties remained regarding the heparin dose that would be most effective, and regarding monitoring of complications.[4] Treatment with heparin reduces inflammatory biomarkers and may, therefore, be effective in reducing the inflammatory status of COVID-19. Heparin is essential for limiting fibrin deposition and microthrombus formation, and for treating systemic prothrombotic complications in patients. However, it is ineffective for clearing fibrin clusters in the alveolar space.[15]

It seems that further studies are needed in order to justify prescription of LMWH as prophylaxis for prevention of pulmonary embolism in patients with COVID-19.

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Trends in Peruvian scientific publications on COVID-19: A bibliometric analysis

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This study was conducted using the researchers' personal computers during quarantine, Lima, Peru

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Dear Editor,

The coronavirus disease 2019 (COVID-19), which was declared to be a pandemic by the World Health Organization (WHO) on March 11, 2020, is an important issue worldwide.[1] Because of the importance of increasing knowledge about COVID-19, some initiatives have been set up to encourage scientific research in this field in Peru. The National Council for Science, Technology and Technological Innovation (CONCYTEC) generated calls for funding on COVID-19 research. Similarly, the Peruvian Journal of Experimental Medicine and Public Health (Revista Peruana de Medicina Experimental y Salud Pública, RPMESP) called for manuscripts on COVID-19 to be included in its next issues. However, no bibliometric study on Peruvian scientific production relating to COVID-19 has yet been conducted. Therefore, we resolved to perform a bibliometric analysis in this field.

We conducted a systematic search for Peruvian scientific articles on COVID-19 in the PubMed/MEDLINE and SciELO databases, and directly in the RPMESP archives up to May 21, 2020. The search strategy for PubMed/MEDLINE was (COVID-19 [MeSH] OR COVID-19 diagnostic testing [MeSH] OR COVID-19 drug treatment [MeSH] OR COVID-19 serotherapy [MeSH] OR COVID-19 vaccine [MeSH] OR severe acute respiratory syndrome coronavirus 2 [MeSH] OR COVID-19 [Title/Abstract] OR SARS-CoV-2 [Title/Abstract] OR coronavirus disease 2019 [Title/Abstract] OR Wuhan coronavirus [Title/Abstract]) AND (Peru [MeSH] OR Peru [Title/Abstract] OR Peruvian [Title/Abstract] OR Andean [Title/Abstract]). For SciELO, it was (COVID-19) OR (infections coronavirus) OR (coronavirus disease 2019) OR (SARS-CoV-2). Articles that did not provide scientific knowledge were excluded.

We included 24 articles (**Figure 1**). Eleven articles (45.83%) were published in RPMESP. Only 12.50% were published in Q1 journals; 29.17% were original and/or brief reports; and 66.67%

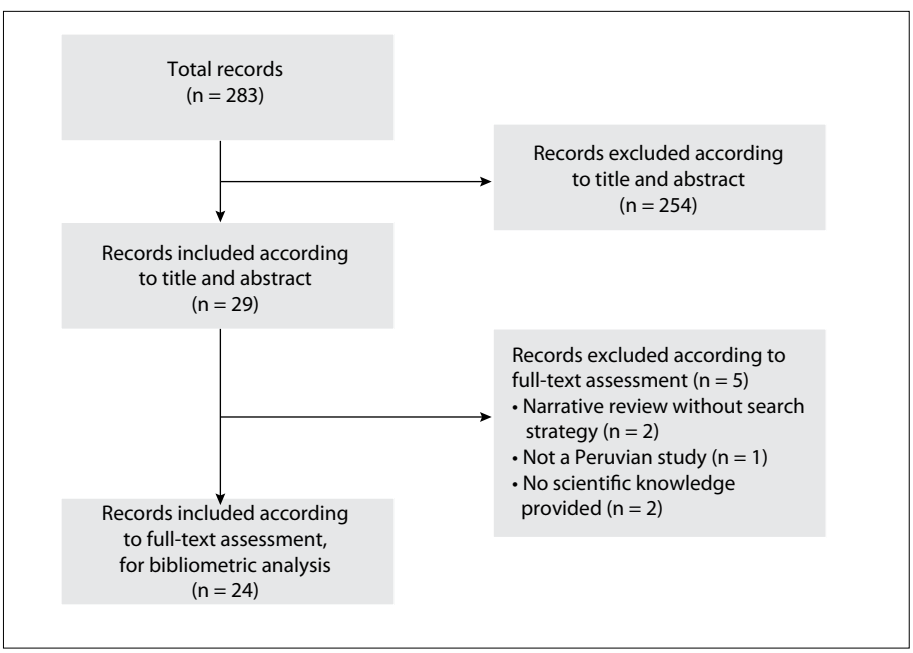

Figure 1. Flowchart of study selection.

were indexed in PubMed/MEDLINE and Scopus (**Table 1**). Most of the authors (91.70%) had affiliations with institutions in Lima, Peru. The highest numbers of publications were attributed to Universidad Nacional Mayor de San Marcos (UNMSM) (25.00%) and to Universidad Peruana Cayetano Heredia (UPCH) (20.83%).

Table 1. Bibliometric characteristics of Peruvian scientific articles on COVID-19

	n (%)
Journal name	
Psychiatry Research	1 (4.17)
Travel Medicine and Infectious Disease	1 (4.17)
AIDS and Behavior	1 (4.17)
Revista de la Facultad de Ciencias Médicas de Córdoba	1 (4.17)
Revista de Gastroenterologia del Perú	1 (4.17)
Microbiology Resource Announcements	1 (4.17)
Revista Peruana de Medicina Experimental y Salud Pública	11 (45.83)
Pre-print	6 (25.00)
Quartile	
Q1	3 (12.50)
Q2	0 (0.00)
Q3	11 (45.83)
Q4	2 (8.33)
NA	8 (33.33)
Language	
Spanish	19 (79.17)
English	5 (20.83)
Foreign collaboration	
Yes	5 (20.83)
No	19 (79.17)
Number of participating institutions per article (M ± SD)	2.75 ± 1.54
Type of article	
Original	6 (25.00)
Brief report	1 (4.17)
Case report	1 (4.17)
Letter to editor/correspondence	7 (29.17)
Review article	3 (12.50)
Editorial	5 (20.83)
Other	1 (4.17)
Indexing databases	
PubMed/MEDLINE	
Yes	16 (66.67)
No	8 (33.33)
Scopus	
Yes	16 (66.67)
No	8 (33.33)
SciELO	
Yes	18 (75.00)
No	6 (25.00)

NA = not available; M = mean; SD = standard deviation.

The topics addressed mostly were related to epidemiology, with emphasis on the probability of effectiveness or failure regarding pandemic control measures. The technological contribution of telemedicine and tele-education was also addressed. In addition, research on mental health in the era of COVID-19 pointed out the possibility of undesired outcomes such as development of psychotic symptoms due to inadequate management of anxiety caused by COVID-19.

We found that around 10% of the articles were published in Q1 journals. Scientific publication in higher-quartile journals increases the likelihood of citation because of higher impact factors and h-indexes, which are important indicators of scientific-academic publication.[2] Therefore, Peruvian researchers should aim to publish more frequently in those journals. Moreover, about 30% of the articles were original. This is the main type of publication in scientific journals, and forms an important indexing criterion in different databases.

In Peru, UNMSM and UPCH provide the highest scientific production within medicine.[3] Accordingly, the largest proportion of COVID-19 publications was also attributed to those universities.

In conclusion, Peruvian scientific production on COVID-19 has emphasized epidemiological research, and has mainly been produced within institutions located in Lima. Therefore, there is a need to decentralize collaborative networks and promote clinical studies in order to generate more evidence with which to combat the pandemic.

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project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal). Both authors actively contributed to the discussion of the results of the study, and reviewed and approved the final version to be released

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal does not charge authors any "open access fees" and submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

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Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

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São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;

2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports;
4. a brief description of the contributorship of each author;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number 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. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
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. Each author should indicate a valid, up-to-date email address for contact;
7. 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);
8. Place or institution where the work was developed, city and country.
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.

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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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