SÃO PAULO Medical Journal

EVIDENCE FOR HEALTH CARE

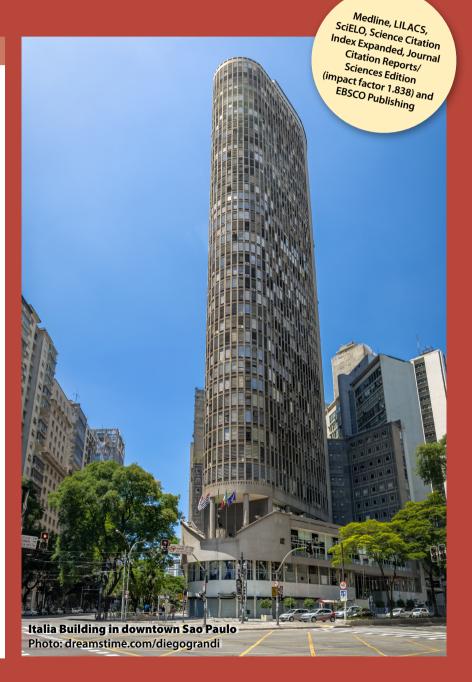### September 1 - Volume 140 - Number 5

Editorial:

• Biobank – the key to personalized medicine

Cross-sectional and exploratory study:

• Can medical residency keep young specialists in the place where they graduate?

Cross-sectional study:

• Baseline laboratory parameters for preliminary diagnosis of COVID-19 among children

Italia Building in downtown Sao Paulo
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APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Federada da

AMB Associação Médica Brasileira

I Jornada de DOR no Homem

5.NOV **8h às 17h**

Sede da APM: Av. Brigadeiro Luís Antônio, 278 - Bela Vista- São Paulo/SP

Com o intuito de aprofundar o olhar sobre as condições dolorosas comuns à população masculina, o Comitê de Dor da APM promoverá a 1ª edição da jornada.

Serão abordadas as principais queixas masculinas que comprometem a qualidade de vida dos homens.

O evento terá a participação de especialistas na área e permitirá interação e ampla troca de pontos de vista e experiências clínicas.

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Particularidades da dor masculina

Ansiedade, medo e dor

Particularidades psicológicas da dor

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APOIO

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SUPERA

ORGANIZATION

Biobank – the key to personalized medicine

Flavio Pola dos Reis[I], Paulo Manuel Pêgo-Fernandes[II]

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

[I]MD. Attending Physician, Thoracic Surgery Service, Lung Transplant Group, Instituto do Coração, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.
 http://orcid.org/0000-0002-4510-1070

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

Personalized medicine can be defined as a medical approach based on individualized information that allows planning and treatment considering the patient's clinical and genetic characteristics. Despite the great advance since the creation of the Human Genome Project aimed at identifying all the genes of human beings, the transcription of the gene was found to be not solely responsible for the result of our organism's responses. Therefore, the investigations of proteomics and metabolomics projects were also initiated, considering the transcription from deoxyribonucleic acid (DNA) to ribonucleic acid (RNA), its production of proteins and products of cellular metabolism.[1] Moreover, this data set needs to be associated with the patient's clinical information. The collection and storage of biological material enable a series of studies that will allow the distinction between the healthy and pathological tissues and the genotype and associated phenotypes.[2]

The biobank is an organized collection of human biological material and associated information, collected and stored for research purposes, according to regulations or pre-defined technical, ethical, and operational standards, under the institutional responsibility and management of the stored materials, with no commercial purposes. In other words, it is the democratic storage of biological materials for research on patients, guaranteed by an institution. Contrarily, the biorepository is the storage of biological material during a specific research project, under institutional responsibility and the researcher's management.[3]

Motivations for building a biobank are related to new goals of modern medicine and multidisciplinary practice, such as personalized medicine, early diagnosis of specific diseases like cancer or genetic diseases, and response prediction to targeted therapy with the principles of pharmacogenetics.[4,5]

Biobank's biological materials are valued in terms of the digital traceability of information and presence of clear consent and assent of participants and their guardians (in case of minors), in addition to the technique of sample acquisition, storage, quality control, data collection, correlation to clinical data, data security and access.[6] Ischemia time clearly changes gene expression. Furthermore, the method of tissue fixation can change the results of laboratory tests, resulting into false positives or negatives. Therefore, in the biobank, best practices must be strictly followed.

Several specimens allow storage, like organs, solid tissues, tumors, umbilical cord, feces, blood and its derivatives, urine, cerebrospinal fluid, teeth, saliva, bronchoalveolar lavage fluid, and perfusates (samples from organ perfusion). Samples must be stored based on the objective to be studied with fresh frozen tissue; since specific preparations are required for extracting DNA, RNA, mitochondria, specific proteins, among others.[2]

However, the biobank is not restricted to the acquisition and storage of biological materials. The progressive use of artificial intelligence and databases, with the possibility of intersecting the collected materials, retrospectively or prospectively, with associated donor information, pushes new frontiers of knowledge. Additionally, the participants can include their own data using the biobank's websites or Apps, and can be notified about the usage of their information and material.[7]

One of the main biobanks in the world is the United Kingdom (UK) Biobank, managed by England. Currently, it has more than 500,000 participants. Since 2014, magnetic resonance imaging and other images are also being collected. This biobank assesses genetics, physical activities, imaging tests, biomarkers, physical measurements, cognition, and hearing, in addition to

prospective questionnaires. Although this large biobank is not compatible with the representation of the general population, as it is a cohort of healthy people, evaluation of public health outcomes can be ideally performed.[8]

Franklin Delano Roosevelt, former United States President, died in 1945 after an acute myocardial infarction. He encouraged his successor Harry Truman to develop the National Heart, Lung, and Blood Institute. In 1948, Truman included the first patient in the institute from one of the main cohorts in the world: the Framingham Heart Study. This cohort allowed several publications and guided the consensus on cardiovascular risk and its prevention. This was possible because of the integration of information and storage of biological materials. This is the concept of a biobank.[9]

In 2021, 89 biobanks in Brazil had been authorized by the National Research Ethics Commission for the most diverse purposes of collecting biological materials. Based on this tool in the arsenal of translational research, worldwide and in Brazil, the Heart Institute of the Medical School of the University of São Paulo (Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo [InCor HCFMUSP]) created the Institutional Biobank, with a capacity for more than 84,000 samples, including the cardiopulmonary department, in which groups can store samples of selected lines of action, such as lung transplantation.[10]

Presently, the concept of evidence-based medicine is developing into medicine based evidence, which means, with the acquisition of new information from large databases, associated with materials collected from biobanks and the integration of artificial intelligence, either by deep learning, neural network, or other forms of algorithms. The evidence, that is, the data, will be able to better predict the treatment, target therapy, specific diagnoses, and others. Evidence-based medicine supports personalized medicine, and the biobank plays a key role in this regard. The collection of biological materials and the reproducibility of the technique in different general and specific populations will allow these studies.

Specific institutions created for biobank such as the UK Biobank or well-structured educational institutions such as the InCor, with the capacity to store information and biological materials, will be able to collect and provide researchers and the population with answers that is lacking at present, especially focused on the patient's individuality.

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Highlights of clinical and laboratory parameters among severe COVID-19 patients treated with tocilizumab: a retrospective observational study

Melahat Uzel Şener[I], Tuğba Çiçek[II], Ayperi Öztürk[III]

Pulmonary Medicine Department, Health Sciences University Faculty of Medicine, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey; and Pulmonary Medicine Department, Konya Numune Hospital, Konya, Turkey

[I]MD. Physician, Pulmonary Medicine Department, Health Sciences University Faculty of Medicine, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey.
https://orcid.org/0000-0001-8309-9517

[II]MD. Physician, Pulmonary Medicine Department, Konya Numune Hospital, Konya, Turkey.
https://orcid.org/0000-0002-1049-6877

[III]MD. Associate Professor, Pulmonary Medicine Department, Health Sciences University Faculty of Medicine, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey.
https://orcid.org/0000-0003-0692-4784

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ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) can cause cytokine release syndrome (CRS), which leads to high mortality rates. Tocilizumab suppresses CRS by blocking the signal transduction of interleukin-6 (IL-6).

OBJECTIVE: To evaluate the clinical and laboratory parameters associated with mortality among patients receiving tocilizumab treatment.

DESIGN AND SETTING: Retrospective observational study conducted in the chest disease departments of two different training and research hospitals in the center of Ankara, Turkey.

METHODS: Patients who were hospitalized and treated with tocilizumab in September 2020 were retrospectively analyzed. Their laboratory parameters and clinical characteristics were obtained from the hospital information system database. Comparative analyses were performed between the patients who died and the ones who survived.

RESULTS: A total of 58 patients who received tocilizumab treatment were included in this study, among whom 35 (60.3%) died. There was no difference between the mortality and survival groups in terms of white blood cell (WBC), neutrophil, lymphocyte, ferritin or C-reactive protein (CRP) levels detected on admission. WBC, lymphocyte, neutrophil and CRP levels measured on the third and fifth days after tocilizumab administration were found to be significantly lower in the survival group (P < 0.05). In multiple logistic regression analysis, age and oxygen saturation were determined to be independent risk factors for mortality.

CONCLUSION: Persistently high WBC, CRP and neutrophil levels and low lymphocyte levels could be considered to be valuable indicators of mortality among COVID-19 patients treated with tocilizumab. Age and low oxygen saturation are independent risk factors for mortality among patients receiving tocilizumab treatment.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which originated in China in December 2019, has become a pandemic affecting the entire world.[1] It is a matter of grave public health concern because of its rapid spread and associated mortality. COVID-19-associated pneumonia may lead to development of respiratory distress syndrome and, thus, respiratory failure is the most important cause of mortality related to this disease.[2,3]

In the first report of death due to the causative agent of COVID-19, i.e. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was stated that a pathologically high concentration of proinflammatory cytokines was detected.[4] Cytokine release syndrome (CRS) can occur because of infection, the action of some drugs or other factors and is characterized by sudden increases in the levels of many proinflammatory cytokines.[5,6]

CRS is more common in diseases related to the immune system, immune system-related treatments such as chimeric antigen receptor T-cell therapy, organ transplant sepsis and viral infections.[7] Its clinical symptoms can range from a flu-like syndrome to circulatory disorders, pulmonary edema, hypoxia, peripheral edema, hypotension and multiorgan system failure.[6]

Interleukin 6 (IL-6) is an important member of the cytokine system and plays a critical role in acute inflammation, autoimmune cell differentiation and disease treatment.[8] Tocilizumab is a recombinant, humanized, antihuman IL-6 monoclonal antibody of the immunoglobulin GI (IgG1) subtype. It binds to membrane-bound and soluble IL-6 receptors specifically and provides blockade of signal transduction. It was developed to treat rheumatoid arthritis and systemic juvenile idiopathic arthritis.[9,10]

COVID-19 is severe in approximately 14% and critical in approximately 5% of patients.[11] This has led to rapid application of various treatments around the world during the pandemic. Many drugs have been tested over the course of treatment of severe COVID-19.

There are a lot of studies in the literature with diverse results regarding the effect of tocilizumab. In an observational study, tocilizumab was shown to contribute to survival.[12] However, randomized studies on tocilizumab have shown mixed results among patients with varying degrees of severity of COVID-19 and populations with various care standards.[13,14] Rosas et al. found that clinical status and mortality in the tocilizumab arm of their study were not superior to placebo.[13] On the other hand, a meta-analysis including six randomized controlled trials showed that tocilizumab treatment reduced the need for mechanical ventilation and/or the rates of all-cause mortality among hospitalized patients.[15]

In a meta-analysis that included 30 studies, older age, male gender, chronic kidney disease, chronic obstructive pulmonary disease, cancer, hypertension, diabetes and laboratory findings such as lymphopenia, thrombocytopenia and high C-reactive protein (CRP), D-dimer, alanine aminotransferase and creatine kinase levels were found to be associated with poor prognosis.[16] CRP, ferritin, platelet, leukocyte and erythrocyte counts have been recommended as markers showing the severity of hyperinflammation.[15]

In Turkey, severe cases of COVID-19 have always been treated in hospital settings, up to the present day. Therefore, through this study, we planned to evaluate our experiences of administering tocilizumab to patients with severe COVID-19 who were treated outside of the intensive care unit and the clinical characteristics that affected the mortality rate among these patients receiving tocilizumab treatment.

OBJECTIVE

In this study, we aimed to evaluate the clinical features and laboratory parameters associated with mortality among patients receiving tocilizumab treatment.

METHODS

Approval for this study was obtained from our hospital's local ethics committee (approval number and date: 707/31.12.2020). Data were collected retrospectively from the hospital information system database. Patients who were hospitalized and followed up in the department of chest disease at two advanced-level educational and training hospitals, during September 2020, and who received tocilizumab treatment, were eligible for inclusion. Those older than 18 years with COVID-19-positive reverse transcription polymerase chain reaction (RT-PCR) test results and full data availability from the database were included in the study. These patients were divided into two groups: (I) mortality and (II) survival.

Clinical features such as age, gender, body mass index (BMI, kg/m^2), major comorbidities and symptoms at the time of admission (including coughing, shortness of breath, fever, diarrhea, loss of taste and myalgia) were recorded. Oxygen saturation (sO$_2$) and high fever (with body temperature > 38.2 °C) were recorded.

Laboratory parameters such as white blood cell (WBC), lymphocyte, neutrophil, platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, D-dimer, troponin and CRP levels were recorded. Tocilizumab was administered once at a dose of 8 mg/kg (in accordance with the guidelines of the Ministry of Health[17]), to all the patients. The courses of the WBC, lymphocyte, neutrophil, CRP and ferritin levels measured on the first, third and fifth days after tocilizumab administration were evaluated. Differences in these values between the mortality and survival groups were analyzed.

The chest X-ray findings on admission were classified as normal, unilateral infiltration, or bilateral infiltration. The pathological findings from computed tomography (CT) were categorized as ground glass, consolidation or a combination of these two. In addition, all radiological findings were classified as unilateral, bilateral, central, peripheral or diffuse localization, according to the location. Among CT findings evaluated using axial sections, if ground glass and/or consolidation was detected in less than 25% of all areas, the case was recorded as "mild involvement," while if this was detected in 25% to 50%, it was recorded as "moderate involvement" and if over 50%, as "severe involvement." Subsequent radiological findings during the follow-up were not taken into account. Differences were analyzed in terms of radiological findings between the groups.

Treatment protocols were applied in accordance with the guidelines of the Ministry of Health.[17] Drug treatments and duration, and supportive oxygen treatments (initial and advanced), were recorded. Tocilizumab, high-dose steroid (HDS) and convalescent plasma (CP) were classified and recorded as advanced medical treatments. These advanced treatments were used in patients who did not gain clinical benefit from their initial treatment.

Statistical analysis

The statistical analysis was performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, Illinois, United States). A normality analysis on continuous data was conducted using the Shapiro-Wilk test. It was accepted that a P-value of less than 0.05 in the Shapiro-Wilk test did not provide an assumption of normality. For normally distributed variables, the independent-sample t test was used to carry out comparisons of means between pairs of independent groups, and these variables were expressed as means, standard deviations and 95% confidence intervals. For variables that were assumed to be not normally distributed, the Mann-Whitney U-test was used for comparisons between

pairs of independent groups, and these variables were expressed as medians and interquartile ranges (IQRs). Chi-square tests were performed to compare the frequency distributions of categorical variables, and these variables were expressed as counts and percentages. Multiple logistic regression analysis was performed for parameters that had been evaluated to be significant, in terms of survival, in univariate analyses. In this analysis, odds ratios were presented with 95% confidence intervals for the potential predictors of mortality. P-values of less than 0.05 were taken to be statistically significant.

RESULTS

A total of 58 patients who received tocilizumab treatment were included in the study. Of these, 17 (29.3%) were females. Thirty-five (60.3%) of the patients died. The average age was determined to be statistically different between the survival and mortality groups (P = 0.030; 64 [range: 50-68] and 69 [range: 59-72] years, respectively). Although the median BMI was 30 kg/m² (IQR: 28-30) in both groups, there was no difference in terms of BMI.

Median sO$_2$ on admission was 89% and 85% in the survival and mortality groups, respectively (P = 0.036). There were no statistically significant differences between the two groups in terms of comorbidities and symptoms (**Table 1**).

There were no differences between the two groups in terms of WBC, neutrophil, lymphocyte, AST, ALT, D-dimer, ferritin, troponin or CRP levels. However, a significant difference was found between the survival and mortality groups regarding the WBC, lymphocyte, neutrophil and CRP levels detected on the third and fifth days after tocilizumab treatment (P < 0.05; **Table 2**). The course of WBC, neutrophil, lymphocyte, CRP and ferritin levels over the days after tocilizumab treatment is shown in **Figure 1**. There were no differences between the groups in terms of the chest X-ray and CT findings (**Table 3**).

The initial treatment modalities are presented in **Table 4**. At the beginning, nine (15.5%) of the patients did not receive any steroids. Dexamethasone was administered at a dose of 8 mg/day and methylprednisolone at a dose of 40 or 80 mg/day. However, methylprednisolone was given at a high dose of 250 mg/day for

Table 1. Demographics and symptoms

Variables		Total n = 58 (100.0%)		Survival n = 23 (39.7%)		Mortality n = 35 (60.3%)		P-value
		n (%)	Med (IQR)	n (%)	Med (IQR)	n (%)	Med (IQR)	
Gender	Male	41 (70.7)		16 (39.0)		25 (61.0)		0.879*
	Female	17 (29.3)		7 (41.2)		10 (58.8)		
Age			66.5 (57-71)		64 (50-68)		69 (59-72)	0.030**
BMI			30 (28-30)		30 (28-32)		29 (27.8-30)	0.196**
Admission sO$_2$			86.5 (75-90)		89 (80-91)		85 (75-89)	0.036**
BT > 38.2 °C		9 (15.5)		1 (11.1)		8 (88.9)		0.073***
Comorbidity		43 (74.1)		16 (37.2)		27 (62.8)		0.519*
HT		36 (62.1)		13 (36.1)		23 (63.9)		0.480*
DM		19 (32.8)		9 (47.4)		10 (52.6)		0.402*
CAD		12 (20.7)		3 (25.0)		9 (75.0)		0.329***
CHF		3 (5.2)		1 (33.3)		2 (66.7)		1.000***
COPD		7 (12.1)		2 (28.6)		5 (71.4)		0.692***
Asthma		3 (5.2)		0 (0.0)		3 (100.0)		0.270***
Malignancy		0 (0.0)		0 (0.0)		0 (0.0)		-
CKD		1 (1.7)		0 (0.0)		1 (100.0)		1.000***
ILD		0 (0.0)		0 (0.0)		0 (0.0)		-
Rheumatological		2 (3.4)		0 (0.0)		2 (100.0)		0.513***
Cough		54 (93.1)		21 (38.9)		33 (61.1)		1.000***
Dyspnea		58 (100.0)		23 (39.7)		35 (60.3)		-
Sore throat		30 (51.7)		11 (36.7)		19 (63.3)		0.630*
Fever		20 (34.5)		8 (40.0)		12 (60.0)		0.969*
Diarrhea		7 (12.1)		1 (14.3)		6 (85.7)		0.226***
Taste-smell disorder		8 (13.8)		2 (25.0)		6 (75.0)		0.458***
Myalgia		30 (51.7)		9 (30.0)		21 (70.0)		0.120*

Med = median; IQR = interquartile range; BMI = body mass index; sO$_2$ = oxygen saturation; BT = body temperature; C = Celsius; HT = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; ILD = interstitial lung disease.
*chi-square test; **Mann-Whitney U test; ***Fisher's exact test.

Table 2. Laboratory test data

	Total	Survival	Mortality	P-value
	Median (IQR) or Mean ± SD	Median (IQR) or Mean ± SD	Median (IQR) or Mean ± SD	
WBC	8455 (5690-10560)	8430 (6206-10420)	8480 (5580-10880)	0.733*
WBC 1st day	10800 (8910-14580)	10420 (7680-13230)	11925 (9070-15115)	0.408*
WBC 3rd day	12108 ± 5400	10264 ± 4729	13476 ± 5530	0.029†
WBC 5th day	11681 ± 6127	9275 ± 4866	13484 ± 6429	0.016†
Lymphocyte	840 (570-1220)	1080 (690-1660)	720 (490-980)	0.025*
Lymphocyte 1st day	601 ± 321	731 ± 387	507 ± 226	0.018†
Lymphocyte 3rd day	525 (380-860)	650 (450-1100)	440 (350-580)	0.005*
Lymphocyte 5th day	620 (460-930)	900 (780-1200)	485 (415-670)	< 0.001*
Neutrophil	6625 (3890-8940)	5700 (3600-7420)	6990 (3900-9050)	0.262*
Neutrophil 1st day	10013 ± 3718	9240 ± 4008	10568 ± 3452	0.194†
Neutrophil 3rd day	10920 ± 5231	8983 ± 4437	12357 ± 5375	0.018†
Neutrophil 5th day	10245 ± 5885	7450 ± 3738	12340 ± 6371	0.002†
Monocyte	445 (300-660)	540 (350-720)	370 (270-580)	0.107*
Eosinophil	1 (0-1)	1 (0-10)	0 (0-1)	0.193*
Hemoglobin	13.6 ± 1.6	13,9 ± 1,4	13,5 ± 1,6	0.319†
Platelet	228000 (176000-273000)	238000 (182000-305000)	226000 (168000-273000)	0.645*
Creatinine	0.91 (0.74-1.1)	0.87 (0.75-1.1)	0.93 (0.73-1.1)	0.679*
ALT	35 (24-50)	30 (22-56)	36 (25-49)	0.460*
AST	43 ± 19	41 ± 16	45 ± 20	0.387†
Na	137 (135-139)	137 (134-139)	137 (135-140)	0.949*
Ca	8.8 (8.5-9)	8.8 (8.4-8.9)	8.8 (8.5-9)	0.774*
D-dimer	0.6 (0.4-0.7)	0.5 (0.3-0.7)	0.6 (0.4-0.9)	0.289*
Troponin	8.7 (5.6-16.2)	8.5 (4.4-12.6)	9 (6.4-17)	0.195*
CRP	102.5 (48.5-143)	102 (44.9-144)	103 (69-139)	0.899*
CRP 1st day	111.7 ± 49.4	93.4 ± 42.4	124.8 ± 50.4	0.018†
CRP 3rd day	65 (40-100)	50 (22-85)	90 (51-118)	0.019*
CRP 5th day	21 (13-61)	20 (10-26)	27.5 (16.5-86.5)	0.031*
CRP TOCI day	177.8 ± 62.2	155.3 ± 53.4	192.6 ± 63.7	0.024†
Ferritin	311.3 (88-536)	280 (124-432)	357 (76.9-595.3)	0.874*
Ferritin 1st day	615 (350-1250)	600 (234-1036)	678 (400-1387)	0.656*
Ferritin 3rd day	599 (350-1100)	480 (345-869)	700 (389-1200)	0.278*
Ferritin 5th day	504 (333-1133)	400 (333-699)	621.5 (361.5-1300)	0.074*

IQR = interquartile range; SD = standard deviation; WBC = white blood cell; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Na: sodium; Ca = calcium; CRP = C-reactive protein; TOCI = tocilizumab.

*Mann-Whitney U test; median (IQR); †independent-sample t test; mean ± SD.

three days to three patients (**Table 4**). There were no significant differences between the survival and mortality groups in terms of broad-spectrum antibiotics, low-molecular-weight heparin (LMWH), supportive oxygen treatments or the time of transition to advanced treatments (P > 0.05; **Table 4**).

With regard to advanced medical treatments, seven patients (12.1%) received only tocilizumab, two (3.4%) received tocilizumab and HDS, 48 (82.8%) received tocilizumab and CP, and one received tocilizumab, HDS and CP. There were no differences between the groups in terms of these treatment modalities (P > 0.05).

The mortality rate was found to be higher among patients with initial supportive oxygen treatment, such as a Venturi/reservoir mask or high-flow nasal oxygen (78.6% and 62.5%, respectively).

Increasing the oxygen support was not found to be associated with mortality during the follow-up (P = 0.804; **Table 4**).

Age and sO_2 levels on admission were found to be independent risk factors for mortality in the multiple logistic regression analysis (**Table 5**).

DISCUSSION

There are still many uncertainties surrounding COVID-19 treatment, and differing results have been obtained among patients treated with tocilizumab. The aim of this study was to investigate clinical features that might predict different outcomes from tocilizumab treatment among similar patients. It was found that some inflammation markers could be used for such predictions.

WBC = white blood cell; CRP = C-reactive protein.

Figure 1. Predictors levels during follow-up.

One of the cytokines responsible for CRS is IL-6. Cardiomyopathy, complement activation, coagulation cascade activation and hyperinflammation-like disseminated intravascular coagulation develop because of IL-6 release.[18] Tocilizumab reduces the harmful effects of hyperinflammation by decreasing IL-6 signal transmission in cases of severe CRS.[19] Therefore, patients diagnosed with COVID-19 should be followed up regarding hyperinflammation.[20]

In this study, there were no significant differences between the mortality and survival groups in terms of WBC, neutrophil, CRP, D-dimer or ferritin levels. However, significantly higher CRP, WBC and neutrophil levels and lower lymphocyte levels were detected in the mortality group on the first, third and fifth days after tocilizumab administration. Therefore, it can be thought that the course followed by inflammation markers after treatment may be associated with mortality.

In one study, ferritin was shown to be a marker for macrophage activation syndrome.[20] In another study involving 150 patients, ferritin and IL-6 levels (which are inflammatory factors) were found to be associated with mortality.[21] In the current study, no significant difference in ferritin levels was found between the mortality and survival groups. However, looking at the first, third and fifth days of follow-up after tocilizumab treatment, there were persistent high ferritin levels in the mortality group (**Figure 1**). Considering that all the patients had severe COVID-19, no difference was expected

Table 3. Imaging data

Variables		Total	Survival	Mortality	P-value
		n (%)	n (%)	n (%)	
Chest X-ray	None	7 (12.1)	3 (42.9)	4 (57.1)	0.758*
	Unilateral	13 (22.4)	4 (30.8)	9 (69.2)	
	Bilateral	38 (65.5)	16 (42.1)	22 (57.9)	
CT type	HRCT	7 (12.5)	4 (57.1)	3 (42.9)	0.429†
	Thorax CT	49 (87.5)	19 (38.8)	30 (61.2)	
CT signs	Ground glass	32 (57.1)	10 (31.3)	22 (68.8)	0.051*
	Consolidation	21 (37.5)	10 (47.6)	11 (52.4)	
	Ground glass + Consolidation	3 (5.4)	3 (100.0)	0 (0.0)	
Lobe involvement	< 25%	19 (33.9)	8 (42.1)	11 (57.9)	0.823*
	25-50%	29 (51.8)	11 (37.9)	18 (62.1)	
	> 50%	8 (14.3)	4 (50.0)	4 (50.0)	
CT unilateral/ bilateral	Unilateral	2 (3.6)	2 (100.0)	0 (0.0)	0.164†
	Bilateral	54 (96.4)	21 (38.9)	33 (61.1)	
CT lobes	Upper lobes	2 (3.6)	0 (0.0)	2 (100.0)	0.482*
	Lower lobes	31 (55.4)	13 (41.9)	18 (58.1)	
	All	23 (41.1)	10 (43.5)	13 (56.5)	
CT central/ peripheral	Central	0 (0.0)	0 (0.0)	0 (0.0)	0.183‡
	Peripheral	35 (62.5)	12 (34.3)	23 (65.7)	
	Diffuse	21 (37.5)	11 (52.4)	10 (47.6)	

CT = computed tomography; HRCT = high-resolution computed tomography.
*chi-square test (insufficient sample counts); †Fisher's exact test; ‡chi-square test.

Table 4. Treatment and follow-up

Variables		Total		Survival		Mortality		P-value
		n (%)	Median (IQR) or Mean ± SD	n (%)	Median (IQR) or Mean ± SD	n (%)	Median (IQR) or Mean ± SD	
Hospitalization duration			20 (15-29)		23 (18-30)		20 (14-25)	0.063*
Plaquenil		43 (74.1)		15 (34.9)		28 (65.1)		0.208†
Favipiravir		56 (96.6)		23 (41.1)		33 (58.9)		0.513‡
Steroid	None	9 (15.5)		6 (66.7)		3 (33.3)		0.096†
	Dexamethasone	35 (60.3)		14 (40)		21 (60)		
	M-prednisolone	14 (24.1)		3 (21.4)		11 (78.6)		
LMWH		58 (100)		23 (39.7)		35 (60.3)		-
Antibiotics		57 (98.3)		23 (40.4)		34 (59.6)		1.000‡
C-vit		39 (67.2)		14 (35.9)		25 (64.1)		0.402†
Dexamethasone dose			8 (0-8)		8 (0-8)		8 (0-8)	0.780*
M-prednisolone dose (mg/day)	0	39 (67.2)		18 (46.2)		21 (53.8)		0.294**
	40	6 (10.3)		0 (0)		6 (100)		
	80	10 (17.2)		3 (30)		7 (70)		
	250	3 (5.1)		2 (66.7)		1 (33.3)		
Wide-spectrum AB	None	2 (3.4)		1 (50)		1 (50)		0.700§
	Admission	24 (41.4)		8 (33.3)		16 (66.7)		
	Follow-up	32 (55.2)		14 (43.8)		18 (56.3)		
AB change time			5 (5-7)		5 (5-7)		5 (4-7)	0.526*
Initial O$_2$ therapy	None	10 (17.2)		8 (80)		2 (20)		0.174**
	Nasal	26 (44.8)		9 (34.6)		17 (65.4)		
	Venturi-reservoir	14 (24.1)		3 (21.4)		11 (78.6)		
	HF	8 (13.8)		3 (37.5)		5 (62.5)		
Advanced O$_2$ therapy	None (additional)	26 (44.8)		11 (42.3)		15 (57.7)		0.804†
	Venturi-reservoir	14 (24.1)		6 (42.9)		8 (57.1)		
	HF/CPAP	18 (31)		6 (33.3)		12 (66.7)		
O$_2$ therapy change time			5 ± 2		5 ± 2		5 ± 2	0.304¶
Therapy change time			5 (3-6)		5 (3-7)		5 (4-6)	0.846*
Advanced medical therapy	Toci	7 (12.1)		1 (14.3)		6 (85.7)		0.311§
	Toci + HDS	2 (3.4)		1 (50)		1 (50)		
	Toci + plasma	48 (82.8)		20 (41.7)		28 (58.3)		
	Toci + HDS + plasma	1 (1.7)		1 (100)		0 (0)		

IQR = interquartile range; SD = standard deviation; M = methyl; AB = antibiotic; LMWH = low-molecular-weight heparin; O$_2$ = oxygen; HF = high-flow oxygen therapy; CPAP = continuous positive airway pressure; Toci = tocilizumab; HDS = high-dose steroid; *Mann-Whitney U test; †chi-square test; ‡Fisher's exact test; §chi-square test (insufficient sample counts); ¶independent-sample t test; **Bonferroni correction used in the analysis on multiple groups, with adjusted P-values.

Table 5. Multiple logistic regression analysis

		B	Sig.	Exp(B)
Step 1[a]	Age	0.080	0.014	1.083 (1.016-1.154)
	sO$_2$ (admission)	-0.063	0.048	0.939 (0.882-1.000)
	Constant	0.567	0.850	1.764

sO$_2$ = oxygen saturation; [a]variable(s) entered in step 1: age and sO$_2$ (admission); Sig. = significance.
Equation: logit (P) = 0.567 + (0.08 x age) + (-0.063 x sO$_2$).

between the two groups. Therefore, persistently high ferritin levels during the follow-up may be an indicator of poor prognosis.

In a study conducted on 21 patients in China, it was found that lymphocyte and CRP levels returned to normal after tocilizumab treatment. After tocilizumab administration, the need for oxygen support decreased in 15 of the patients, and there was no need for oxygen support in one.[14] In the current study, a statistically significant decrease in CRP levels was observed in the survival group after tocilizumab treatment. CRP is thought to be a suitable surrogate marker that reflects IL-6 bioactivity. In another study on 15 cases, a significant decrease in CRP levels was seen after tocilizumab treatment.[22] This suggests that mortality was lower in the group in which the IL-6 effect decreased faster after tocilizumab treatment.

In a study on 63 severe cases of COVID-19, the patients received intravenous and subcutaneous tocilizumab, and no difference between these drug administration methods was

found after treatment. In addition, improvements in CRP, ferritin, D-dimer and lymphocyte levels were observed in all 63 patients.[23]

The decrease in lymphocyte levels in COVID-19 is an important marker for diagnosis and disease severity.[24] In a meta-analysis, it was reported that tocilizumab treatment had no effect on lymphocyte and neutrophil levels.[25] However, in the current study, lower lymphocyte levels on admission and in the follow-up during tocilizumab treatment were detected in the mortality group. Although an improvement in lymphocyte levels after tocilizumab treatment was observed in the mortality group, these levels were found to still be low.

Zhao et al. reviewed 13 retrospective studies and reported that use of tocilizumab significantly reduced mortality rates, compared with standard therapy (odds ratio, OR = 0.44; 95% confidence interval, CI: 0.36-0.55).[25] In another study, it was stated that use of tocilizumab in severe cases of COVID-19 was safe and had a positive effect regarding improvement of many laboratory parameters.[26] In a meta-analysis that examined the causal relationships between interventions and outcomes and included reference randomized controlled studies, it was stated that administering tocilizumab to patients who had been hospitalized due to COVID-19 did not reduce the risk of all-cause mortality in these patients, but it reduced the possibility of needing mechanical ventilation.[15]

In our study, the mortality rate was 60.3%, but all the patients were diagnosed with severe COVID-19. Among the hospitalized patients who needed a Venturi mask and high-flow oxygen, the resultant mortality rates were 78.6% and 62.5%, respectively. These data corroborated that notion that tocilizumab administration has no effect on mortality among patients using mechanical ventilation, as determined in the meta-analysis.[25]

In our study, no difference in radiological signs in either chest X-rays or computed tomography (CT) images was found between the survival and mortality groups. It can be said that the patients were a homogeneous group in terms of their radiological involvement. Therefore, it was not logical to evaluate the relationship between radiological findings and mortality in this study.

There were several limitations to our study. First, it was retrospective and had a limited number of patients. Second, IL-6 levels could not be studied in these patients in relation to hospital conditions.

Furthermore, the patients were recruited from two different hospitals. The Ministry of Health treatment guidelines were used in both hospitals, but the optional treatment approaches, especially high-dose steroids and convalescent plasma, were administered according to the individual preferences of the doctors. Lastly, all the patients who received tocilizumab treatment were severely ill, and the lack of comparison with a control group that did not receive tocilizumab can be considered to be a limitation. However, tocilizumab was used according to its availability during the pandemic and, therefore, it was not possible to compare the laboratory parameters of the group not given tocilizumab with those of patients with similar disease severity.

Through prospective studies in which the severity of the disease can be scored in terms of clinical, radiological and laboratory parameters, treatment arms can be better standardized and changes in all parameters after treatment can be revealed more clearly.

CONCLUSION

A few laboratory findings that could predict mortality among COVID-19 patients receiving tocilizumab treatment were detected. High WBC, neutrophil and CRP levels and persistently low lymphocyte levels may be indicators of mortality. In addition, age (> 65 years) and low sO_2 on admission are independent risk factors for mortality among patients receiving tocilizumab treatment. However, we need to state that, because of the retrospective design of our study, selection of the patients for tocilizumab treatment may have affected the results.

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Address for correspondence:

Melahat Uzel Şener

Pulmonary Medicine Department, Health Sciences University Faculty of Medicine, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey

Keçiören — Ankara — Turkey

Tel. (+ 90) 505 649 74 38

E-mail: melahatuzeldr@yahoo.com.tr

Clinical and epidemiological aspects of victims of maritime accidents on the Mar Grande-Salvador crossing, Bahia, Brazil: a case series study

Danyelle de Souza Mendonça[I], Paloma Fernandes Carneiro[II], Adriana Conceição de Mello Andrade[III], Kátia de Miranda Avena[IV]

School of Medicine, Centro Universitário UniFTC, Salvador (BA), Brazil

[I]Undergraduate Student, School of Medicine, Centro Universitário UniFTC, Salvador (BA), Brazil.
https://orcid.org/0000-0002-0886-2188

[II]Undergraduate Student, School of Medicine, Centro Universitário UniFTC, Salvador (BA), Brazil.
https://orcid.org/0000-0002-2820-5089

[III]MD, MSc. Full Professor, Department of Life Sciences, School of Medicine, Centro Universitário UniFTC, Salvador (BA), Brazil.
https://orcird.org/0000-0002-7654-9273

[IV]PT, PhD. Full Professor, Department of Scientific Research, School of Medicine, Centro Universitário UniFTC, Salvador (BA), Brazil.
https://orcid.org/0000-0002-2179-3893

ABSTRACT

BACKGROUND: Maritime transportation is an activity of vital importance for societies. The Mar Grande-Salvador crossing is an intercity waterway transport line in Brazil that transports 3,500 passengers/day, including residents and tourists. In 2017, an accident on this crossing was considered to be the biggest maritime tragedy in Bahia in the last decade.

OBJECTIVE: To describe the clinical and epidemiology characteristics of victims of this maritime accident, with analysis on bodily injuries, causes of death and means/instruments that caused the fatal injuries.

DESIGN AND SETTING: Case-series study at the Forensic Medical Institute of Bahia, Brazil.

METHODS: Reports on 73 victims who were examined for bodily injury or were necropsied by the Forensic Medical Institute were analyzed. This study was approved by the institution's Research Ethics Committee (protocol 04012218.1.0000.5032).

RESULTS: The victims' mean age was 33.0 years [95% confidence interval, CI, 26.3-47.0]. The mean age of those who died was 43.0 years [95% CI, 30.5-53.5]. Bodily injuries were found in 74% of the victims. The most frequent bodily injuries were ecchymoses among females (69.7%) and abrasions among males (76.2%). Blunt instruments produced most bodily injuries (85.2%). Among the victims who died, 68.4% were female. Mechanical asphyxiation through drowning was the leading cause of death (89.4%). The overall lethality rate was 26%, and this was higher among females (28.2%).

CONCLUSION: Women were the main victims of this maritime accident. Bodily injuries occurred more frequently than death, but these injuries proved to be quite significant, thus demonstrating the importance of measures to improve the safety of navigation.

INTRODUCTION

Maritime transportation is an activity of vital importance to societies.[1] However, this activity is associated with several risks, among them the possibility of accidents, which can cause marine pollution and loss of life.[2]

According to the Brazilian Navy, between January and August 2017, 107 shipwrecks were recorded in the country, a number 12.6% higher than the number of cases that occurred in the same period of 2016.[3]

Among the maritime accidents recorded in 2017, the one that occurred on the Mar Grande-Salvador crossing can be considered to have been the biggest maritime tragedy in Bahia in the last decade and the second biggest in Brazil that year, second only to the accident in the Xingu River, in the state of Pará, which left 21 dead. The Mar Grande-Salvador crossing is an intercity waterway transport line in Brazil that crosses the bay known as "Baía de Todos os Santos" to connect the island of Itaparica to the mainland. On average, 3,500 passengers are transported per day, including both residents and tourists.[4]

Over the years, measures have been taken to improve safety in shipping, such as regulations and crew training. However, navigation accidents remain a source of concern[5] due to the number of events and fatalities.[6]

In shipwrecks, one of the concerns is the drowning of passengers and crew members. About 500,000 people per year die worldwide as a result of such events.[7] Drowning can happen in several circumstances, and the cases most often reported occur in fresh water. However, in coastal areas, accidents involving navigation and water sports are common.[8]

In Brazil, deaths due to drowning exceed 5,700 cases/year, and most of the victims are children. In 2016, about 89% of drownings in Brazil had unintentional causes. Of these, 1.1% were due to boating accidents.[9]

Death due to drowning is a three-phase process: defense, resistance and exhaustion. The defense phase can be further divided into surprise and dyspnea. In the resistance phase, as a form of defense, breathing movements are interrupted. This is followed by the exhaustion phase, when resistance ceases and the victim starts breathing deeply and then loses consciousness and dies.[10] Individuals who survive the submersion episode may develop late complications resulting from water aspiration, such as severe infections and pulmonary edema, which may later result in the victim's death.[11]

In accidents in fluvial or marine waters, when an unconscious person is found in shallow waters, it needs to be considered that spinal cord injury, head trauma or sudden illness may have occurred. These can be caused by acute myocardial infarction, convulsion, lipothymia, hydrocution (thermal shock) or primary drowning in which the victim ends up in shallow waters.[12] Given that head trauma is responsible for 25% of trauma deaths, this should be evaluated among individuals who are victims of accidents involving water.[13]

Maritime accidents can result not only in drowning, but also in other injuries to the human body. According to the Brazilian Penal Code, these may be classified as mild, serious or very serious, and may also involve intentional injuries.[14] From the medical-legal point of view, intentional injuries are consequences of a violent act that is capable of directly or indirectly producing damage to someone's physical integrity or health, or that is responsible for worsening or continuation of an already existing disturbance. These injuries therefore consist of alterations to the biopsychosocial balance. Violence should be understood not simply as the consequence of mechanical action, but as the means of action, whether physical, chemical, physicochemical, biochemical, biodynamic or mixed.[15]

Given the large number of shipwrecks recorded over recent years and the need for research describing maritime accidents that occurred in Brazilian territory, it is relevant evaluate the possible causes of death and bodily injury among the victims. Drowning may or may not have been the ultimate cause. Thus, there is a need to assess whether drowning is, in fact, what kills the most during this type of accident.[16]

OBJECTIVE

In this context, considering the proportions of this accident on the Mar Grande-Salvador crossing, the aim of the present study was to describe the clinical and epidemiological characteristics of the victims and to analyze their bodily injuries, the cause of death and the means or instrument of action that produced the fatal injuries.

METHODS

This was a case series study conducted through analysis on reports from the Forensic Medical Institute of Bahia, Brazil. These were obtained through the Integrated System for Forensics Administration of the Technical Police Department of Bahia.

The study population was composed of the 116 passengers and four crew members of the express ferry "Cavalo Marinho I", which suffered a maritime accident during the Mar Grande-Salvador crossing on August 24, 2017. This express ferry departed from the Mar-Grande Maritime Terminal, on the island of Vera Cruz, heading for Salvador. Its capacity was 160 passengers.

The study population included people of both sexes and all ages (children, young people, adults and elderly people) who had suffered bodily injuries or died as a result of this maritime accident. There were no exclusion criteria in this study since the objective was to characterize the epidemiology of all the victims of the shipwreck.

The variables of the study were age, sex and the existence of bodily injury or death. Among the victims who suffered bodily injury, we also evaluated: (I) types of bodily injury; (II) whether the injury resulted in harm to the bodily integrity or health of the victim; (III) what the instrument or means that produced the injury was; (IV) whether the injury caused incapacity for normal activities for more than thirty days; and (V) whether the injury resulted in danger to life, permanent debilitation of a limb or impairment of its sensation or function, acceleration of labor, permanent incapacity to work, incurable disease, loss or disablement of a limb or loss of its sensation or function, permanent deformity or abortion. Among the victims who died, we evaluated: (I) the cause of death; (II) the instrument or means that produced the fatal injury or injuries; and (III) whether poison, fire, explosives, asphyxiation, torture or other insidious or cruel means were used, or the means resulted in common danger, or whether any means that made it difficult or impossible to defend the victim was used.

Data analysis was performed using the IBM SPSS software, version 26.0 (SPSS Inc., Chicago, Illinois, United States). Categorical variables were presented as the frequency distribution of the categories, represented as absolute numbers (n) and percentages (%). Numerical variables were described as medians and 95% confidence levels. In addition, the lethality rate was calculated overall and according to sex.

Because this was a study involving human beings, it was submitted to and approved by our institution's research ethics committee on Dec 12, 2018, in accordance with the ethical principles of the Helsinki Declaration and with Resolution 466/2012 of

the Brazilian National Health Council. This study was registered through authorization certificate number 04012218.1.0000.5032.

RESULTS

An overview of the accident revealed that there was a total of 73 victims, who were all among the passengers on the vessel. The distribution of the victims with bodily injuries and deaths according to age and sex is shown in **Table 1**.

Among the victims, 54 people (74%) had bodily injuries, and these were predominantly females (61.1%). Their median age was 33.0 years [95% confidence interval, CI, 26.3-47.0]. By stratifying them according to sex, it was observed that the women who suffered bodily injuries were older than the men (34.0 years [95% CI, 25.0-47.0] and 31.0 years [95% CI, 27.0-47.0], respectively).

There was a mortality rate of 26%, totaling 19 fatal victims, who were predominantly female (68.4%); their median age was 43.0 years [95% CI, 30.5-53.5]. The lethality rate among females was higher than among males (28.2% versus 22.2%, respectively). In addition, the women who died were older than the men (48.0 years [95% CI, 38.0-53.0] versus 18.5 years [95% CI, 2.0-59.0], respectively).

Regarding the cause of death, it was observed that mechanical asphyxia due to drowning occurred in 89.4% of the deaths (n = 17). The remaining deaths occurred due to brain hemorrhage and mechanical asphyxia after head trauma (n = 1; 5.3%) and to an undetermined cause (n = 1; 5.3%).

From evaluating the instrument or means that produced the injury, it was found that a physical-chemical means was the main agent responsible for the deaths, totaling 84.2% of the cases (n = 16). A physical-chemical means in association with blunt instruments resulted in 10.5% of the deaths (n = 2). In 5.3% of the cases (n = 1), the analysis was impaired.

Considering the instruments or means that produced bodily injuries, the most prevalent type was blunt instruments, which accounted for 85.2% of the injuries produced (n = 46). Injuries caused by blunt/short blunt instruments and blunt instruments/physical-chemical means accounted for 3.7% (n = 2) each.

Regarding the bodily injuries presented by the victims, it was observed that among women, ecchymoses were most prevalent, in 69.7% of the cases, followed by abrasions in 66.7% and contusion wounds in 24.2%. Unlike the results found among females, abrasions were the most prevalent injuries among males, totaling 76.2% of the cases, followed by ecchymoses in 38.1% and contusion in 19.0%. The other injuries presented are described in **Table 2**. It is important to note that combinations of different types of bodily injuries were present in some of in the accident victims.

In assessing the consequences of the injuries suffered by the victims, it was found that in 1.9% of the cases there was incapacity in relation to the usual occupations for more than 30 days, while 85.2% did not suffer any such incapacity. For 92.6% of the victims, their bodily injuries did not result in any life-threatening condition. In addition, 85.2% of the victims did not suffer any permanent weakness of limb or impairment of its sensation or function, or any acceleration of labor, while 13.0% relied on further examinations to find out whether the weakness would be permanent or not (**Table 3**).

Table 2. Distribution of bodily injuries according to sex among the victims of the maritime accident on the Mar Grande-Salvador crossing, Bahia, Brazil, in 2017

Bodily injuries*	Victims**	
	Female (n = 33)	Male (n = 21)
Ecchymosis	23 (69.7)	8 (38.1)
Excoriations	22 (66.7)	16 (76.2)
Contused wound	8 (24.2)	4 (19.0)
Edema	3 (9.1)	1 (4.8)
Cutting wound	2 (6.1)	0 (0.0)
Cutaneous contusion lesion	1 (3.0)	1 (4.8)
Hemorrhagic effusion in right eye	0 (0.0)	1 (4.8)
Absence of lesion	1 (3.0)	0 (0.0)

*Presence of bodily injury in associated or unassociated form;
**frequency (percentage).

Table 1. Distribution according to age and sex among the victims with bodily injuries and the deaths due to the maritime accident on the Mar Grande-Salvador crossing, Bahia, Brazil, in 2017

Victims	n (%)	Age (years)		
		MD [95% CI]	Minimum	Maximum
Bodily injuries				
Female	33 (61.1)	34.0 [25.0-47.0]	19	75
Male	21 (38.9)	31.0 [27.0-47.0]	21	65
Total	**54 (100.0)**	**33.0 [26.3-47.0]**	**19**	**75**
Deaths				
Female	13 (68.4)	48.0 [38.0-53.0]	20	70
Male	6 (31.6)	18.5 [2.0-59.0]	0.5	68
Total	**19 (100.0)**	**43.0 [30.5-53.5]**	**0.5**	**70**

n = frequency; MD = median; CI = confidence interval.

Table 3. Distribution of the consequences of injuries suffered by victims of the maritime accident on the Mar Grande-Salvador crossing, Bahia, Brazil, in 2017

Consequences[*]	Victims (n = 54)			
	IPO	Danger to life	PWL	PDW
Yes	1 (1.9)	2 (3.7)	0 (0.0)	0 (0.0)
No	46 (85.2)	50 (92.6)	46 (85.2)	46 (85.2)
Depending on examinations	6 (11.1)	2 (3.7)	7 (13.0)	7 (13.0)
Damaged	1 (1.8)	0 (0.0)	1 (1.8)	1 (1.8)

IPO = inability to perform usual occupations for more than thirty days; PWL = permanent weakness of limb or impairment of its sensation or function, or acceleration of labor; PDW = permanent disability to work, incurable disease, loss or disablement of limb or loss of its sensation or function, permanent deformity or abortion; [*]frequency (percentage).

DISCUSSION

In this study, we present the clinical-epidemiological profile, characteristics of bodily injuries, cause of death and the means or instrument of action that produced the injuries of the 73 victims of the maritime accident that occurred during the Mar Grande-Salvador crossing, in Bahia, Brazil, on August 24, 2017.

In this maritime accident, females were more prevalent among the victims who died. This finding differed from what was reported in a study conducted by Araújo et al.,[17] who showed that most of the fatal victims of drowning were male. According to Pinheiro Júnior et al.,[18] men are more adventurous and expose themselves to greater risk than do women; and moreover, women usually have less physical conditioning. These factors favor the results presented by Araújo et al.[17] It is noteworthy that while the study by Araújo et al.[17] analyzed all the cases of drowning in the city of Ribeirão Preto, state of São Paulo, between the years 2001 and 2004, the present study analyzed the cause of death and the means or instrument of action that produced the fatal injuries, through necropsies performed on the victims of a marine accident. Thus, the circumstances of the deaths were different.

Regarding the age of the fatal victims, only three children died in this accident: two were two years old and one was six months old. Corroborating this finding, the study by Quan and Cummings,[19] carried out between 1980 and 1995, showed that children between 0 and 4 years old, when alone, tend to drown when they fall into pools or open waters (rivers or lakes), while people between 35 and 64 years old are usually sailing when drowning occurs.

In the maritime accident that occurred on the Mar Grande-Salvador crossing, the main cause of death was mechanical asphyxiation through drowning. According to Armstrong and Erskine,[20] drowning is considered, in most cases, to be an asphyxiating process that can cause systemic repercussions in several organs, and

the lungs are certainly the organ most affected during this process.[7] As a consequence of the obstruction caused either by foreign bodies or by fluid aspiration, hypoxia (decreased oxygen in the organ/tissue), hypoxemia (decreased oxygen in the blood) and asphyxia appear. Subsequently, if the obstruction is not reversed, neuronal injury and cardiorespiratory arrest ensue.

Head trauma can occur through any injury resulting from a blunt or penetrating force to the head that leads to involvement of vessels and meninges, and loss of consciousness is a possible consequence of this process.[12,21] In addition, mental confusion, convulsion and focal deficit may be symptoms associated with head trauma.[13] In our study, we found that only one passenger (5.3%) died due to brain hemorrhage and mechanical asphyxia after head trauma. Drowning can be attributed as a secondary mechanism resulting from encephalic lesion, which, through compromising the level of consciousness, makes the victim unable to remain on the water surface, thus causing subsequent drowning.

Regarding bodily injury, injuries produced by blunt instruments generate blunt injuries and these include abrasions, ecchymoses and hematomas.[22] Factors such as age, sex, location of the injury and fragility of blood vessels can influence the victim's susceptibility to contusion. These factors may explain the higher prevalence of blunt instruments in producing the bodily injuries suffered by the accident victims, as well as the higher prevalence of bruises and excoriations.

The women who were victims of the maritime accident on the Mar Grande-Salvador crossing presented more blunt injuries than did the men. According to Vanezis,[23] women commonly present greater susceptibility to developing bruises due to their greater deposition of subcutaneous fat, which favors the appearance of such findings, thus corroborating the findings of the present study.

According to the Brazilian Penal Code (item I, Paragraph 1, Article 129), serious bodily injury can produce consequences such as incapacity to do one's habitual occupations for more than 30 days, permanent weakness of the limb or impairment of its sensation or function, and acceleration of labor. On the other hand, the consequences of very serious injuries include permanent incapacity to work, incurable disease, and loss or disablement of the limb or loss of its sensation or function.

In analyzing this accident, we noticed that most of the injuries were not considered severe or very severe. This corroborates the findings of Verdan,[24] who stated that bruises and scratches are considered to be minor injuries.

The high lethality rate demonstrated in the present study highlights the severity of this maritime accident. However, despite the large number of shipwrecks that happen in Brazil, the number of studies addressing this subject is very small. Thus, there is a need to encourage further research in this field.

CONCLUSION

This study showed that injuries such as ecchymosis and abrasions were the ones most commonly found among the victims, and the main instruments that produced these injuries were blunt instruments. Moreover, it was observed that the main cause of death was mechanical asphyxiation through drowning, and that physical-chemical media were mostly responsible for causing lethal trauma.

Women were the main victims of this maritime accident, in relation to both bodily injuries and deaths. However, it was not possible to determine how many men and how many women in total were present on the boat, and this can be considered to be a limitation of this study, since women may have been more affected because they were present in larger numbers on the boat.

Accidents involving boats and ships occur widely around the world, and are responsible for large numbers of deaths through drowning. The present study is relevant in that it brings specific data from a maritime accident and thus contributes support for strategies aimed towards prevention of injuries in such accidents.

It is essential to develop measures for improving the safety of navigation, such as training for the crew, safety policies that encourage the use of life jackets and, lastly, stimulation of vessel inspections, so that the number of deaths can be minimized.

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Address for correspondence:
Adriana Conceição de Mello Andrade
Escola de Medicina, Centro Universitário UniFTC
Av. Luis Viana, 8.812
Paralela — Salvador (BA) — Brasil
CEP 41741-590
Tel. (+55 71) 3281-8000
E-mail: proctoamello@gmail.com

Can medical residency keep young specialists in the place where they graduate? Cross-sectional and exploratory study of the first seven years after implementation of medical residency programs in the State of Tocantins, Brazil

Giovanna Tandaya Grandi[I], Raquel Prudente de Carvalho Baldaçara[II], Itágores Hoffman I Lopes Sousa Coutinho[III], Leonardo Baldaçara[IV]

Universidade Federal do Tocantins, Palmas (TO), Brazil

[I]Undergraduate Student, Universidade Federal do Tocantins, Palmas (TO), Brazil.
https://orcid.org/0000-0003-2274-373X

[II]MD, PhD. Assistant Professor, Health Department of the State of Tocantins, Universidade Federal do Tocantins (UFT), Palmas (TO), Brazil.
https://orcid.org/0000-0002-7817-6319

[III]MD, PhD. Assistant Professor, Health Department of the State of Tocantins, Universidade Federal do Tocantins (UFT), Palmas (TO), Brazil.
https://orcid.org/0000-0003-4818-7073

[IV]MD, PhD. Assistant Professor, Health Department of the State of Tocantins, Universidade Federal do Tocantins (UFT), Palmas (TO), Brazil.
https://orcid.org/0000-0002-5201-8515

ABSTRACT

BACKGROUND: New medical schools and new medical residencies in Brazil, mainly in its interior, were opened under the justification of collaborating towards distribution of these healthcare professionals and specialist doctors across the national territory. However, this proposal did not guarantee that medical practitioners would become established in the place where they graduated and specialized.

OBJECTIVE: To calculate, through interviews, how many specialists who graduated in the state of Tocantins stayed there after finishing their medical residency; and to analyze the factors that made them stay or leave the place.

DESIGN AND SETTING: Cross-sectional exploratory study conducted at a Brazilian federal public higher education institution.

METHODS: All graduates from medical residencies in Tocantins, who graduated between 2013 and 2019, were contacted by telephone and, after obtaining consent, an interview was conducted. The interviews took place between June 2020 and January 2021.

RESULTS: The permanence of medical residency graduates in the state increased from 50% in an earlier study to 55.8% in the current study, thus showing a situation of stability. In addition, we detected some reasons for staying or not. In a multivariate analysis, only working in the state capital was related to staying in the state of Tocantins, showing a 5.6 times greater chance.

CONCLUSIONS: The percentage of those who remained was just over 50%, even some years after implementation of the first programs. Most specialists remained working for the state health department, with a smaller proportion in municipal health departments, and were concentrated in the state capital.

INTRODUCTION

According to the Medical Demographic Census of 2020,[1] Brazil has reached the goal of 500,000 doctors. This accelerated increase has been due to the opening of new medical graduation opportunities and increased vacancies within medicine.[1] However, the rising number of physicians in this country has not guaranteed egalitarian geographical distribution. Nor has it ensured the qualifications that are necessary for the needs of the population to be met.[1]

Medical residency is a type of postgraduate education for doctors that ensures ethical and professional qualification. It is the "gold standard" of specialization.[2] Through this qualification, residents get the title of specialist in a medical field. However, for the specialization to be considered "medical residency", it needs to be accredited by the National Committee of Medical Residency.[2,3] Despite the increase in medical graduations, the distribution of the number of residencies and the number of specialist physicians remains uneven among the various regions and states in Brazil.[2,3]

While this country has an average ratio of 2.27 doctors per thousand inhabitants, the northern region has a ratio of 1.30, i.e., 43% lower than the national average ratio. Likewise, in the northeastern region, the ratio is 1.69.[2] The same is seen in relation to the proportion of specialists over general practitioners in the northern region of Brazil, which is the smallest in the country (1.08), and the highest concentration of specialists in this region is in state capitals.[2]

New medical schools in Brazil, especially in its interior, were opened under the justification of collaborating with the distribution of these healthcare professionals and specialist doctors across the national territory. However, this proposal did not guarantee that medical practitioners would become established in the place where they graduated and specialized.[4]

A pilot study conducted in the state of Tocantins that analyzed the prevalence of remaining in the state between 2013 and 2017 revealed that 65.9% of residents stayed in Tocantins.[5] Another complete survey considering only the years 2013 and 2014 revealed that 50% of graduating residents remained in the state.[3]

These data demonstrated that medical residents' decisions on where to settle are based on numerous factors that go beyond the increase in vacancies, such as working conditions, sex, remuneration, city of origin, family and proximity to large urban and economic centers.[3] Therefore, there is a need to analyze the reasons that lead graduates to leave the state so that, in addition to expansion of opportunities, other aspects can be considered in order to increase the proportion of medical residents who stay.

Thus, the aim of the current study was to analyze how many residents who concluded their first medical residency between 2013 and 2019 remained in the state of Tocantins after finishing. We tried to find factors that related to whether they stayed or not.

OBJECTIVE

Residents who graduated in the state of Tocantins were interviewed to ask them whether they had stayed in the state after finishing medical residency, with the aim of analyzing the factors that influenced their decision to stay or leave the state.

METHODS

This was an observational and exploratory cross-sectional study in which all graduates from medical residency in Tocantins, in the years 2013 to 2019, were evaluated. The subjects were contacted by telephone to obtain consent and then to answer the questions. Subjects were excluded if they did not agree to take part or could not be found. The period over which the interviews took place was from June 2020 to December 2020.

The variables (questions asked) were the following: year of graduation; residency program attended; age; date of birth; gender; marital status; whether before the residency they had worked in Tocantins or in any municipal network in this state; whether before the residency they worked in the public network of the state of Tocantins; whether after graduation they stayed in the state of Tocantins and the reason for staying or leaving; the current state where they were living; whether they were still working in the specialty in which they graduated; whether they were currently working in a public state network in another state or in Tocantins; whether they were currently working in a municipal network and

in which city; whether they were currently working in the private network of Tocantins; whether their current income was higher than their residency income; hours worked weekly; whether the residency had improved their medical practice; and whether they had subsequently done another medical residency, and if so, in what specialty and where.

The interviews took place via telephone. Out of the 265 graduates contacted, 240 agreed to take part and completed the survey. Nine graduates were not found, fourteen were found but did not respond to the messages, and two refused to take part in the interview. This study was submitted to and approved by the research ethics committee of the Federal University of Tocantins, under the number CAAE 73833615.5.0000.5519; date: September 22, 2017.

Statistical analysis

The data are presented as numbers and percentages. We compared ages by means of the Kruskal-Wallis test and other nominal variables using the chi-square test. Significance was set at $\alpha \leq 0.05$. The main outcome was whether the doctor stayed in the state of Tocantins. We compared this outcome (dependent) with other variables as factors, using a general linear model with a logistic regression tool. In a multivariate analysis, we adjusted the significance using the Bonferroni correction for $\alpha \leq 0.0008$.

RESULTS

Details of the sample are presented in **Table 1**.

Regarding the institutions from which the subjects graduated, the number increased over the years. All of the 15 and 21 residencies available in 2013 and 2014, respectively, were at the Universidade Federal de Tocantins (UFT). In 2015, in addition to 24 residencies (91.7%) at UFT, there were two (8.3%) at the State Health Department of Tocantins (SHD-TO). In 2016, there were 34 training residencies: 28 (82.4%) at UFT, two (5.9%) at SHD-TO and 4 (11.8%) at the Municipal Health Department of Palmas (MHD). In 2017, there were 40 resident physicians: 31 (77.5%) at UFT, four (10.0%) at SHD-TO and five (12.5%) at MHD. In 2018, 51 resident physicians graduated: 34 (66.7%) from UFT, five (11.8%) from SHD-TO and 11 (21.6%) from MHD. In the last year analyzed (2019), out of a total of 55 residents, 38 (69.1%) were at UFT, three (5.5%) were at SHD-TO and 14 (25.5%) were at MHD. These data show that in comparison with 2013-2014, the number of trained resident doctors increased from 36 to 240, among whom UFT contributed 78.8% of the total, SHD-TO 7.1% and MHD 14.2%.

Considering sex, females represented 66.5% of the total. In 2013, eight residents (53.3%) were women and seven (46.7%) were men. In 2014, 12 (57.1%) were women and nine (42.9%) were men. In 2015 there was the greatest difference in all the years of this study, with 17 women (70.8%) and six men (29.2%). In 2016, there were

Table 1. Main variables according to years of conclusion of residency. Comparisons made using the Kruskal-Wallis and chi-square tests

Variable	2013 n = 15	2014 n = 21	2015 n = 24	2016 n = 34	2017 n = 40	2018 n = 51	2019 n = 55	Total	Z/χ², P
Age (mean ± standard deviation)	36.7 ± 3.4	35.5 ± 3.5	35.4 ± 4.0	35.6 ± 5.7	34.6 ± 6.9	32.3 ± 3.5	32.5 ± 4.6	**34.1 ± 5.0**	45.40, P < 0.01
Up to 30 years of age	-	-	-	1 (2.9%)	11 (27.5%)	15 (29.4%)	23 (41.8%)	**50 (20.8%)**	
From 31 to 40 years of age	13 (86.7%)	17 (81.0%)	22 (91.7%)	29 (85.3%)	23 (57.5%)	34 (66.7%)	26 (47.3%)	**164 (68.3%)**	45.30, P < 0.01
More than 40 years of age	2 (13.3%)	4 (19.0%)	2 (8.3%)	4 (11.8%)	6 (15.0%)	2 (3.9%)	6 (10.9%)	**26 (10.8%)**	
Gender									
Male	7 (46.7%)	9 (42.9%)	7 (29.2%)	11 (32.4%)	14 (35.0%)	16 (31.4%)	19 (34.5%)	**83 (34.6%)**	2.22, 0.90
Female	8 (53.3%)	12 (57.1%)	17 (70.8%)	23 (67.6%)	26 (65.0%)	35 (68.6%)	36 (65.5%)	**157 (65.4%)**	
Institution									
Universidade Federal do Tocantins	15 (100%)	21 (100%)	22 (91.7%)	28 (82.4%)	31 (77.5%)	34 (66.7%)	38 (69.1%)	**189 (78.8%)**	24.81, 0.02
State Health Department of Tocantins	0	0	2 (8.3%)	2 (5.9%)	4 (10.0%)	5 (11.8%)	3 (5.5%)	**17 (7.1%)**	
Municipal Health Department of Palmas	0	0	0	4 (11.8%)	5 (12.5%)	11 (21.6%)	14 (25.5%)	**34 (14.2%)**	
Marital status									
Single	3 (20%)	8 (38.1%)	5 (20.8%)	4 (11.8%)	11 (27.5%)	23 (45.1%)	22 (40.0%)	**76 (31.7%)**	25.60, 0.11
Married	11 (73.3%)	12 (57.1%)	17 (70.8%)	25 (73.5%)	28 (70.0%)	26 (51.0%)	30 (54.5%)	**149 (62.1%)**	
Divorced	1 (6.7%)	1 (4.8%)	1 (4.2%)	5 (14.7%)	1 (2.5%)	2 (3.9%)	2 (3.6%)	**13 (5.4%)**	
Widower	0	0	1 (4.2%)	0	0	0	1 (1.8%)	**2 (0.8%)**	
Worked in public network before residency									
No	5 (33.3%)	5 (23.8%)	4 (16.7%)	13 (38.2%)	12 (30.0%)	19 (37.3%)	14 (25.5%)	**72 (30.0%)**	5.41, 0.49
Yes	10 (66.7%)	16 (76.2%)	20 (83.3%)	21 (61.8%)	28 (70.0%)	32 (62.7%)	41 (74.5%)	**168 (70.0%)**	
Worked in private network before residency									
No	11 (73.3%)	19 (90.5%)	15 (62.5%)	29 (85.3%)	34 (85.0%)	39 (76.5%)	45 (81.8%)	**192 (80.0%)**	8.18, 0.22
Yes	4 (26.7%)	2 (9.5%)	9 (37.5%)	5 (14.7%)	6 (15.0%)	12 (23.5%)	10 (18.2%)	**48 (20.0%)**	
Stayed in state of Tocantins?									
No	4 (26.7%)	13 (61.9%)	11 (45.8%)	10 (29.4%)	19 (47.5%)	26 (51.0%)	23 (41.8%)	**106 (44.2%)**	8.83, 0.18
Yes	11 (73.3%)	8 (38.1%)	13 (54.2%)	24 (70.6%)	21 (52.5%)	25 (49.0%)	32 (58.2%)	**134 (55.8%)**	
If settled down in Tocantins, why?									
Family matters	4 (26.7%)	3 (14.3%)	10 (76.9%)	14 (58.3%)	12 (57.1%)	15 (60.0%)	20 (62.5%)	**78 (58.2%)**	36.29, 0.20
Opportunities in jobs	3 (20.0%)	3 (14.3%)	1 (7.7%)	5 (20.8%)	4 (19.0%)	5 (20.0%)	8 (25.0%)	**29 (21.6%)**	
Demand for specialty	2 (13.3%)	0	0	3 (12.5%)	1 (4.8%)	0	0	**6 (4.5%)**	
Local identification/quality of life	2 (13.3%)	1 (4.8%)	2 (15.4%)	1 (4.2%)	4 (19.0%)	1 (4.0%)	2 (6.3%)	**13 (9.7%)**	
Another residency in the state	0	1 (4.8%)	0	0	0	4 (16.0%)	2 (6.3%)	**7 (5.2%)**	
Work in a field other than medicine	0	0	0	1 (4.2%)	0	0	0	**1 (0.7%)**	
If did not settle down in Tocantins, why?									
Family matters	0	2 (15.4%)	3 (27.3%)	2 (20.0%)	3 (15.8%)	4 (15.4%)	1 (4.3%)	**15 (14.2%)**	16.97, 0.52
Issues related to jobs	1 (25.0%)	7 (53.8%)	4 (36.4%)	6 (60.0%)	11 (57.9%)	10 (38.5%)	15 (65.2%)	**54 (50.9%)**	
Another residency	3 (75.0%)	4 (30.4%)	4 (36.4%)	1 (10.0%)	5 (26.3%)	11 (42.3%)	5 (21.7%)	**33 (31.1%)**	
Other reasons	0	0	0	1 (10.0%)	0	1 (3.8%)	2 (8.7%)	**4 (3.8%)**	
Current municipality									
Palmas	11 (73.3%)	8 (38.1%)	7 (29.2%)	17 (50.0%)	19 (47.5%)	22 (43.1%)	29 (52.7%)	**113 (47.1%)**	18.24, 0.11
Other	1 (6.7%)	3 (14.3%)	2 (8.3%)	4 (11.8%)	3 (7.5%)	6 (11.8%)	2 (3.7%)	**21 (8.7%)**	
Out of state	3 (20.0%)	10 (47.6%)	15 (62.5%)	13 (38.2%)	18 (45.0%)	23 (45.1%)	24 (43.6%)	**106 (44.2%)**	
Still works in the field of the specialization									
No	4 (26.7%)	7 (33.3%)	10 (41.7%)	6 (17.6%)	7 (17.5%)	15 (29.4%)	7 (12.7%)	**56 (23.3%)**	11.67, 0.07
Yes	11 (73.3%)	14 (66.7%)	14 (58.3%)	28 (82.4)	33 (82.5%)	36 (70.6%)	48 (87.3%)	**184 (76.7%)**	

Continue...

Table 1. Continuation

Variable	2013 n = 15	2014 n = 21	2015 n = 24	2016 n = 34	2017 n = 40	2018 n = 51	2019 n = 55	Total	Z/χ^2, P
Hours worked weekly									
Up to 60 hours	4 (26.7%)	10 (47.6%)	4 (16.7%)	11 (32.4%)	13 (32.4%)	15 (29.4%)	17 (30.9%)	74 (30.8%)	5.29, 0.51
More than 60 hours	11 (73.3%)	11 (52.4%)	20 (83.3%)	23 (67.6%)	23 (67.6%)	36 (70.6%)	38 (69.1%)	166 (69.2%)	
Bigger salary than in residency									
No	0	0	0	0	3 (7.5%)	5 (10.0%)	7 (12.7%)	15 (6.3%)	11.50, 0.07
Yes	15 (100.0%)	21 (100.0%)	24 (100.0%)	34 (100.0%)	37 (90.0%)	46 (90.0%)	48 (87.3%)	225 (93.7%)	
Works in a municipal network in the current state									
No	13 (86.7%)	16 (76.2%)	19 (79.2%)	20 (58.8%)	26 (65.0%)	38 (74.5%)	36 (65.5%)	168 (70.0%)	15.84, 0.60
In the capital	2 (13.3%)	2 (9.5%)	2 (8.3%)	8 (23.5%)	9 (22.5%)	5 (9.8%)	12 (21.8%)	40 (16.7%)	
Another city	0	1 (4.8%)	2 (8.3%)	3 (8.8%)	0	2 (3.9%)	3 (5.5%)	11 (4.6%)	
Out of state	0	2 (9.5%)	1 (4.1%)	3 (8.8%)	5 (12.5%)	6 (11.8%)	4 (7.3%)	21 (8.8%)	
Currently works in a private network									
No	0	3 (14.3%)	2 (8.3%)	6 (17.6%)	13 (32.5%)	21 (41.2%)	21 (38.2%)	66 (27.5%)	7.64, 0.27
Yes	15 (100%)	18 (85.7%)	22 (91.7%)	28 (82.4%)	27 (67.5%)	30 (58.8%)	34 (61.8%)	174 (72.4%)	
Currently works in a state health department									
No	11 (73.3%)	15 (71.4%)	18 (75.0%)	20 (58.8%)	23 (57.5%)	35 (68.6%)	30 (54.2%)	152 (63.3%)	27.55, <0.01
Yes	4 (26.7%)	6 (28.6%)	6 (25.0%)	14 (41.2%)	17 (42.5%)	16 (31.4%)	25 (45.5%)	88 (36.7%)	
Specialty									
Internal medicine	6 (40%)	5 (23.8%)	6 (25.0%)	7 (20.6%)	10 (25.0%)	8 (15.7%)	5 (9.1%)	47 (19.6%)	89.27, 0.67
Family and community medicine	0	1 (4.8%)	0	5 (14.7%)	8 (20.0%)	17 (33.3%)	19 (34.5%)	50 (20.8%)	
Orthopedics and traumatology	0	0	0	0	0	0	2 (3.6%)	2 (0.8%)	
Anesthesiology	0	0	2 (8.3%)	2 (5.9%)	3 (7.5%)	4 (7.8%)	3 (5.5%)	14 (5.8%)	
General surgery	4 (26.7)	6 (28.6%)	6 (25.0%)	6 (17.6%)	6 (15.0%)	6 (11.8%)	5 (9.1%)	39 (16.3%)	
Vascular surgery	0	0	1 (4.2%)	1 (2.9%)	1 (2.5%)	1 (2.0%)	1 (1.8%)	5 (2.1%)	
Dermatology	0	0	0	0	0	0	1 (1.8%)	1 (0.4%)	
Gynecology and obstetrics	0	2 (9.5%)	3 (12.5%)	4 (11.8%)	2 (5.0%)	2 (3.9%)	4 (7.3%)	17 (7.1%)	
Infectiology	0	0	0	0	0	0	1 (1.8%)	1 (0.4%)	
Pediatric intensive care medicine	0	0	0	0	1 (2.5%)	0	1 (1.8%)	2 (0.8%)	
Neonatology	0	0	0	0	0	2 (3.9%)	2 (3.6%)	4 (1.7%)	
Pediatrics	5 (33.3%)	7 (33.3%)	6 (25.0%)	6 (17.6%)	6 (15.0%)	6 (11.8%)	5 (9.1%)	41 (17.1%)	
Psychiatry	0	0	0	0	1 (2.5%)	0	2 (3.6%)	3 (1.3%)	
Angioradiology	0	0	0	1 (2.9%)	1 (2.5%)	1 (2.0%)	1 (1.8%)	4 (1.7%)	
Digestive system surgery	0	0	0	1 (2.9%)	0	1 (2.0%)	1 (1.8%)	3 (1.3%)	
Intensive medicine	0	0	0	0	0	2 (3.9%)	1 (1.8%)	3 (1.3%)	
Rheumatology	0	0	0	1 (2.9%)	1 (2.5%)	1 (2.0%)	1 (1.8%)	4 (1.7%)	
Did residency improve your medical practice?									
No	0	0	0	0	0	0	1 (1.8%)	1 (1.8%)	3.38, 0.76
Yes	15 (100%)	21 (100%)	24 (100%)	34 (100%)	40 (100%)	51 (100%)	54 (98.2%)	239 (99.6%)	

23women (67.6%) and 11 men (32.4%). In 2017, 26 (65.0%) were women and 14 (35.0%) were men. In 2018, 35 (68.6%) were women and 16 (31.4%) were men. Lastly, in 2019, 36 (65.5%) were women and 19 (34.5%) were men.

Regarding marital status, the majority were married (149; 62.1%), while 76 (31.7%) were single. For more details according to year, and for other marital statuses, see **Table 1**.

The study results revealed that 168 subjects (70.0%) had worked in the public network before residency, as follows, according to year: 10 (66.7%) of the 2013 residency graduates; 16 (76.2%) from 2014; 20 (83.3%) from 2015; 21 (61.8%) from 2016; 28 (70.0%) from 2017; 32 (62.7%) from 2018; and 36 (74.5%) from 2019. In total, 72 (30.0%) had not worked in a public network before their residency.

When the subjects were asked whether they had worked in a private network before the residency, the majority answered "no" (192; 80%). The highest numbers were presented over the last three years: 45 (81.8%) from 2019, 39 (76.5%) from 2018 and 34 (85.0%) from 2017. However, 2014 presented the highest proportion that

answered "no", with 19, standing for 90.5%; while there were 11 (73.3%) from 2013, 15 (62.5%) from 2015 and 29 (85.3%) from 2016.

Regarding the subjects who stayed in the state, the majority answered "yes" (134; 55.8%). Analysis on the numbers over the years showed that these started at 11 (73.3%) in 2013 and 8 (38.1%) in 2014, and increased to 13 (54.2%) in 2015, 24 (70.6%) in 2016, 21 (52.5%) in 2017 and 25 (49.0%) in 2018, respectively. In 2019 the number rose again to 32 (58.2%).

Among those who stayed in the state, the following reasons aided the subjects in making their decision to stay: 78 (58.2%) cited family reasons, 29 (21.6%) job opportunities, six (4.55%) the demand for the specialty, 13 (9.7%) identified with the region and its quality of life, seven (5.2%) wanted to do another residence and one (0.7%) wanted to work in a field other than medicine. On the other hand, a total of 106 (44.2%) left the state, for the following reasons: 54 (50.9%) reported issues relating to job conditions, 33 (31.1%) wanted to do another residency, 15 (14.2%) cited family matters and four (3.8%) had other reasons. For more details, see **Table 1**.

Regarding the place where the subjects were currently living, 114 (47.5%) stayed in Palmas, the state capital of Tocantins. Proportionally, 2013 had the highest rate, with 11 (73.3%), but in absolute numbers 2019 had the highest number, with 29 (52.7%). In second position, 106 (44.2) were currently living in another state and 21 (8.7%) were currently living in the state of Tocantins, outside of the state capital.

Regarding the subjects' current field of work, a total of 184 (76.7%) were still working in the specialty corresponding to their medical residency, but 56 (23.3%) said that they were not. In total, 168 (70.0%) did not work in a municipal network, 40 (16.7%) were working in the municipal network of the state capital of Tocantins, 11 (4.6%) were working in the municipal network of another city in Tocantins and 21 (8.8%) were working in a municipal service outside of the state of Tocantins. Furthermore, 88 (36.7%) said that they were working in a state health department, and 174 (72.4%) said that they were working in a private network. For more details, see **Table 1**.

Considering the specialties, 50 (20.8%) chose family and community medicine, 47 (19.6%) internal medicine, 41 (17.1%) pediatrics, 39 (16.3%) general surgery, 17 (7.1%) gynecology and obstetrics, 14 (5.8%) anesthesiology, three (1.3%) psychiatry, two (0.8%) orthopedics and traumatology, four (1.7%) neonatology, five (2.1%) vascular surgery, one (0.4%) dermatology, one (0.4%) infectious diseases, four (1.7%) angioradiology, three (1.3%) digestive system surgery, three (1.3%) intensive medicine, four (1.7%) rheumatology and two (0.8%) pediatric intensive care medicine.

It is important to note that family and community medicine has increased greatly over the years, considering that in 2013 and 2015 no residents graduated in this field, and in 2014 only one. However, in 2016 the numbers started to increase. The number of
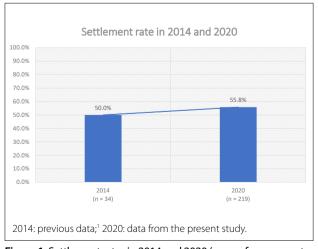
residents in general surgery did not change over the years studied, staying between four and six trained physicians, and this was also seen in relation to gynecology and obstetrics (between three and four) and pediatrics (between five and six).

Orthopedics and traumatology, dermatology, vascular surgery, infectiology, pediatric intensive care medicine and neonatology are more recent specialties in the state of Tocantins, and so the number of trained doctors is still low. Regarding the first four of these programs, the first residents only graduated in 2019, while in the penultimate program, this was in 2017 and in the last program, in 2018. Psychiatry varied over these six years, since in 2013, 2015, 2016 and 2018 there were no resident physicians, while in 2014 and 2017 there was one in each year and in 2019 there were two resident psychiatrists. It can be concluded that there was an increase in the number of specialties over these last years.

Main outcome: staying in the state of Tocantins

Figure 1 presents the percentages of settlement in Tocantins according to the year of conclusion of residency and compares these with previous data (published in 2018, comprising data relating to 2014).[3] As in the previous study, the figures have been adjusted for those who were not public-sector employees before residency.

In the multivariate logistic regression analysis using the general linear model (GLM) procedure, we used to stay in Tocantins as the dependent variable and other variables as factors. The details are presented in **Table 2**. Working in the state capital (Palmas) [B = 1.73 ± 0.44; Exp(B) = 5.66 (confidence interval, CI = 2.38-13.50); P = 0.00009] and working in the public network of Palmas [B = 1.73 ± 0.44; Exp(B) = 5.67 (CI = 2.38-13.50); P = 0.00009] were the only significant factors related to staying in the state of Tocantins after finishing medical residency.

2014: previous data;[1] 2020: data from the present study.

Figure 1. Settlement rates in 2014 and 2020 (years of assessment, i.e. one year after the respective year of occurrence).

Table 2. Multivariate analysis by logistic regression using the general linear model procedure

Variable	B (SE)	Exp(B) (CI)	Sig.
Age up to 30 years	-0.16 (0.28)	0.85 (0.49-1.49)	0.572
Age 31-40 years	-0.17 (0.16)	0.84 (0.62-1.15)	0.275
Age > 40 years	-0.81 (0.42)	0.44 (0.19-1.02)	0.056
Male	-0.17 (0.22)	0.84 (0.55-1.30)	0.443
Female	-0.27 (0.16)	0.76 (0.56-1.05)	0.095
Concluded in 2013	-1.01 (0.58)	0.36 (0.12-1.14)	0.083
Concluded in 2014	0.49 (0.45)	1.62 (0.67-3.92)	0.280
Concluded in 2015	-0.17 (0.41)	0.87 (0.38-1.89)	0.683
Concluded in 2016	-0.87 (0.38)	0.42 (0.20-0.87)	0.020
Concluded in 2017	-0.10 (0.32)	0.90 (0.49-1.68)	0.752
Concluded in 2018	0.04 (0.28)	1.04 (0.60-1.80)	0.889
Concluded in 2019	-0.33 (0.27)	0.72 (0.42-1.23)	0.227
Universidade Federal do Tocantins	-0.16 (0.15)	0.85 (0.64-1.13)	0.276
State Health Department of Tocantins	-0.61 (0.51)	0.54 (0.20-1.47)	0.232
Municipal Health Department of Palmas	-0.48 (0.35)	0.62 (0.31-1.24)	0.174
Single	0.10 (0.23)	1.11 (0.71-1.74)	0.647
Married	0.31 (0.17)	1.36 (0.99-1.89)	0.061
Divorced	-0.15 (0.56)	0.86 (0.29-2.55)	0.782
Widower	22.57 (0.71)	-	-
Worked in public network before residency			
No	0.06 (0.24)	1.06 (0.67-1.68)	0.814
Yes	0.31 (0.16)	1.37 (1.00-1.85)	0.046
Worked in private network before residency			
No	0.23 (014)	1.26 (0.95-1.67)	0.113
Yes	0.25 (0.29)	1.29 (0.73-2.27)	0.388
If settled down in Tocantins, why?			
Family matters	22.57 (0.11)	-	-
Opportunities in jobs	22.57 (0.19)	-	-
Demand for specialty	22.57 (0.41)	-	-
Local identification/ quality of life	22.57 (0.28)	-	-
Another residency in the state	22.57 (0.38)	-	-
Work in a field other than medicine	22.57 (1.0)	-	-
If did not settle down in Tocantins, why?			
Family matters	-22.56 (0.26)	-	-
Issues related to jobs	-3.13 (1.02)	-	-
Another residency	-22.57 (0.17)	-	-
Other reasons	-22.57 (0.50)	-	-
Current municipality			
Palmas	1.73 (0.44)	5.66 (2.38-13.50)	0.000090
Other	1.50 (0.78)	4.50 (0.97-20.82)	0.054
Out of state	-2.25 (0.74)	0.10 (0.02-0.45)	0.002
Still works in the field of the specialization			
No	0	1.00 (0.59-1.69)	1.000
Yes	0.31 (0.15)	1.36 (1.01-1.82)	0.040
Hours worked weekly			
Up to 60 hours	-0.27 (0.23)	0.76 (0.48-1,21)	0.246
More than 60 hours	0.47 (0.16)	1.59 (1.17-2.18)	0.003469
Bigger salary than in residency			
No	-0.13 (0.52)	0.87 (0.32-2.41)	0.796
Yes	0.27 (0.13)	1.31 (1.00-1.70)	0.046

Table 2. Continuation

Variable	B (SE)	Exp(B) (CI)	Sig.
Works in a municipal network in the current state			
No	0.12 (0.15)	1.13 (0.83-1.52)	0.440
In the capital	1.73 (0.44)	5.67 (2.38-13.50)	0.000090
Another city	1.50 (0.78)	4.50 (0.97-20.83)	0.054
Out of state	-2.25 (0.74)	0.10 (0.02-0.45)	0.002
Currently works in a private network			
No	0.43 (0.25)	1.54 (0.94-2.52)	0.087
Yes	0.16 (0.15)	1.17 (0.87-1.58)	0.289
Currently works for a state health department			
No	0.29 (0.16)	1.34 (0.97-1.85)	0.075
Yes	0.14 (0.21)	1.15 (0.75-1.74)	0.523
Specialty			
Internal medicine	-0.39 (0.30)	-	-
Family and community medicine	0.24 (0.29)	-	-
Orthopedics and traumatology	0 (1.41)	-	-
Anesthesiology	0 (0.53)	-	-
General surgery	-0.58 (0.33)	-	-
Vascular surgery	22.57 (0.44)	-	-
Dermatology	-22.57 (1.0)	-	-
Gynecology and obstetrics	1.18 (0.57)	-	-
Infectiology	22.57 (1.0)	-	-
Pediatric intensive care medicine	22.57 (1.0)	-	-
Neonatology	1.01 (1.15)	-	-
Pediatrics	0.55 (0.32)	-	-
Psychiatry	22.57 (0.58)	-	-
Angioradiology	22.57 (0.50)	-	-
Digestive system surgery	22.57 (0.58)	-	-
Intensive medicine	0.69 (1.22)	-	-
Rheumatology	1.10 (1.15)	-	-
Did residency improve your medical practice?			
No	22.56 (1.00)	-	-
Yes	0.23 (0.13)	-	-

CI = confidence interval; SE = standard error; Sig. = significance.

DISCUSSION

In the literature, some data have suggested the possibility that doctors might remain in the places where they did their training.[6] However, these data vary and the values are not high in all locations.[7-10]

In November 2020, Brazil reached a total of 500,000 doctors, a historic milestone. With this, the country now has a ratio of 2.38 doctors per 1,000 inhabitants. In January 2020, out of the total of 478,010 doctors working in the Brazil, 61.3% had one or more specialist titles, while 38.7% had no title in any specialty.[1] In absolute numbers, Brazil has 293,064 specialist physicians and 184,946 general practitioners, thus resulting in a ratio of 1.58 specialists for each general practitioner. In addition, the offer of residency vacancies, as well as the presence of specialists, is uneven across regions and states, especially in the northern region.[1]

In previously published data from Brazil, out of 107,114 doctors who graduated from residencies in places other than where they were born, 27,106 (25.31%) were living in the city where they graduated, including some major centers of attraction: approximately 60% of those who stayed where they graduated from residency remained in seven state capitals, of which five were in southeastern Brazil.[11]

Recent data showed that some medical practitioners had changed the Brazilian state in which they lived: 28% were currently in a state other than the one in which they started their careers. Moreover, some were traveling between municipalities to work: one third were working in a city other than the one in which they lived.[1] However, most doctors (72%) did not change the state at any point during their careers, such that always lived and worked in the same state. Among the other 28% who changed state, more than half (54.9%) moved permanently. The others moved temporarily, possibly for personal reasons, work or professional training.[1]

In 2019, overall in Brazil, 64.5% of doctors were working in the same city where they lived; 27.4% worked in the city where

they lived, but also traveled to work in another city; and 8.1% only worked in a city other than where they lived.[1]

Our previous survey considering only the years 2013 and 2014 revealed that 50% of graduated residents remained in the state of Tocantins.[3] Comparing this with the current data, from which we found that 55.8% remained in this state, the increase was only 5.8%. The reasons for staying that were reported included family matters, work opportunities and doing another residency, and these were like the reasons for not staying. Thus, settlement decisions among new specialists are complex and public-sector managers need to be aware not only of the demand for specialties, but also of personal issues that may influence these specialists, other than job opportunities and good salaries after completion of the residency and the offer of continuity in other local residencies. Across the seven-year period covered by our study, the increase in the settlement rate was small.

In another study, reasons why family doctors remained in their positions were evaluated. The results revealed that there was a high turnover of physicians, figured out by professional dissatisfaction, inadequate working conditions and heavy workload. Among the characteristics of the local human resources policy, distortions in relation to payment stood out, along with problems in the job, career and salary plan relating to family doctors, which limited and penalized the professional's advancement. The main reasons identified in that study that favored permanence were identification with the philosophy of the strategy, professional vocation and the possibility of serving the community.[4]

The geographical distribution and career trajectory of medical graduates and the factors associated with their choice of practice location was evaluated in another study in which a total of 563 graduates completed a questionnaire. Among these, 4.3% reported that family medicine was their medical specialty, 19.9% reported other primary care specialties (internal medicine, pediatrics, surgery and obstetrics-gynecology) and the remainder chose subspecialties. Larger cities were more likely to be chosen for practice, particularly by newly graduated doctors. The job invitations received during medical residency training increased the likelihood of choosing highly populated cities. In contrast, job invitations received during medical school increased the likelihood of choosing less populated cities. Among medical practitioners in cities with a lower population density, proximity to family members was an additional influencing factor, while those who chose more densely populated cities did so because of better infrastructure and recreational options.[12]

In another study, the results showed that the employment attribute that most affected the respondents' choice was the location of the work, followed by working conditions, payment, access to medical residency, type of contract and workload. It was found that respondents who had attended private colleges, those with higher family income and females generally showed greater resistance to moving to unsafe urban regions and to remote areas of the interior. The employment scenarios that proved to be the most plausible in terms of public intervention were those that combined intermediate wages, good working conditions and obtaining an additional 10 to 20 points in medical residency examinations.[13] Higher income, satisfaction with training decisions and board certification were also variables associated with a higher retention rate.[14]

CONCLUSIONS

We see that medical residency led to insertion of new specialists in the state of Tocantins. However, the percentage of residents who remained had only increased by 5.8%, even years after implementation of the first programs. Most specialists are still working for the state health department, with a smaller proportion in municipal health departments, and concentration of specialists in the state capital. We presented reasons for staying in the state that corroborated data in the literature. In the current study, working in the state capital was the only significant factor. Therefore, the reasons that attract specialists to priority areas continue to be diverse and, hence, a variety of measures need to be adopted by public-sector management. The decisions of physicians to stay or leave showed a cost-benefit pattern once their basic needs had been met.[15]

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Address for correspondence:
Leonardo Baldaçara
Universidade Federal do Tocantins (UFT)
Av. NS 15, Quadra 109 Norte, s/nº — Bloco Bala I
Plano Diretor — Tocantins (TO) — Brasil
CEP 77001-090
Tel. (+55 63) 3229-4658
E-mail: leonardobaldassara@gmail.com

In-hospital severe COVID-19 in a philanthropic tertiary hospital setting: is asthma a concern? A retrospective study

Gabriela Accetta Rojas[I], Flávia Nascimento Ost[II], Roberto Stirbulov[III], Ozíris Simões[IV]

Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil

[I]Medical Student, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil.
 https://orcid.org/0000-0001-5747-0474

[II]Medical Student, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil.
 https://orcid.org/0000-0002-5873-9575

[III]MD, PhD. Full Professor of Internal Medicine, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil; and Clinical Chief, Irmandade da Santa Casa de Misericórdia de São Paulo (ISCMSP), São Paulo (SP) Brazil.
 https://orcid.org/0000-0003-0841-8105

[IV]MD, PhD. Assistant Professor, Collective Health Department, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo (SP), Brazil.
 https://orcid.org/0000-0002-1608-0469

ABSTRACT

BACKGROUND: The frequency of coronavirus disease 2019 (COVID-19) cases among asthmatics has been reported to be reduced. However, the findings regarding the association between asthma and the risk of severe COVID-19 have been divergent.

OBJECTIVE: To investigate whether asthma is associated with a reduced risk of development of severe COVID-19.

DESIGN AND SETTING: Retrospective analysis on COVID-19 surveillance databases at two tertiary-level hospitals in São Paulo, Brazil.

METHODS: The medical records of patients hospitalized due to COVID-19 between March and August 2020 were reviewed in accordance with the clinical, laboratorial, radiological and epidemiological criteria for COVID-19, and for comorbidities.

RESULTS: Among the adult patients included (> 18 years of age) there were 52 asthmatics and 1,318 non-asthmatics. Their median ages and interquartile ranges (IQR) were, respectively, 54 (41-69) and 60 (44-72) years. At least one comorbidity was seen in 73% of asthmatics and 56% of the non-asthmatics. Among the asthmatics, most presented mild asthma (92%) and the prevalence of chronic obstructive pulmonary disease (COPD) was high (27%). The asthmatics presented an unadjusted odds ratio (OR) for severe COVID-19 of 0.89 (95% confidence interval, CI 0.5-1.56); and OR 0.88 (95% CI 0.5 -1.68) after multivariable adjustment. Age > 60 years, male sex, hypertension, diabetes, cancer and homelessness were covariates associated with increased odds for severe COVID-19. Kaplan-Meier estimated survival over hospitalization of up to 30 days did not differ between the groups (log-rank P = 0.09).

CONCLUSIONS: The association between asthma and decreased risk of severe COVID-19 or increased survival was statistically non-significant.

INTRODUCTION

Asthma is characterized as a disease involving chronic airway inflammation and variable limitation of airflow. In asthmatics, upper-airway viral infection is a well-known risk factor for symptom exacerbations and hospitalizations. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel virus that mainly affect the airways, has not clearly followed this pattern. Among hospitalized patients with coronavirus disease 2019 (COVID-19), the prevalence of asthma has been low and in some cohorts it has been reported that asthma was a condition that gave rise to reduced risk of severe COVID-19 presentations,[1,2] differently from other chronic lung diseases.[3]

Reduced expression of angiotensin-converting enzyme 2 (ACE2), identified as one of the key receptors for viral cellular entry,[4] has been observed in asthmatics. Use of inhaled corticosteroids and the allergic asthma phenotype seem to be the main underlying mechanisms for reduced ACE2 expression,[5,6] thus providing a plausible causal explanation for decreased risk of severe COVID-19 among asthmatics. However, to date, the findings from observational studies regarding asthma and severe COVID-19 remain divergent. Additionally, to our knowledge, no studies have addressed this relationship in the context of a highly socially vulnerable population.

OBJECTIVE

Therefore, the aim of this study was to investigate the association between asthma and development of severe COVID-19 and in-hospital mortality in a unique tertiary-level hospital complex that cares for the underserved population in the largest Latin American city.

METHODS

Study design

We conducted a retrospective study in a medical center formed by two tertiary-level hospitals, through access to the hospitals' COVID-19 surveillance databases. The electronic medical records of all hospitalized patients with acute respiratory symptoms who were suspected of having COVID-19 and who were admitted between March 1 and August 28, 2020, were reviewed. These two hospitals share the same location and staff, and differ mainly with regard to healthcare access: one is restricted to health-insured individuals, while the other is a philanthropic hospital, providing care mainly to uninsured patients. The COVID-19 surveillance database is composed of cases that were evaluated in the emergency department and were found to present suspected symptoms of COVID-19. Some of these patients required hospitalization, while others developed COVID-19 while hospitalized. This study was conducted in accordance with the ethical principles embodied in the Declaration of Helsinki and local applicable laws and regulations. It was approved by the Human Research Ethics Committee of the Irmandade da Santa Casa de Misericórdia de São Paulo (CAEE no. 36961020.9.0000.5479) on September 11, 2020.

Study population

The institutional criteria for hospital admission were two or more of the following: respiratory rate ≥ 22 breaths/minute or dyspnea, oxygen saturation < 95% in room air, fever and alterations seen on computed tomography (CT) of the chest.

The electronic medical records of individuals identified in the COVID-19 surveillance database were reviewed regarding their hospitalization. Patients ≥ 18 years of age were included if they presented at least three of the following findings: clinical criteria in accordance with the case definition of the Centers for Disease Control and Prevention (CDC),[7] epidemiological criteria, radiological criteria[8] and positive real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2. Patients with unknown clinical outcomes were excluded.

Covariates

Age was categorized into the following groups: 18 to < 40, 40 to < 50, 50 to < 60, 60 to < 70, 70 to < 80 and ≥ 80 years. Regarding comorbidities, we extracted from the records those that have been associated with higher risk of severe illness and mortality, such as hypertension, diabetes, chronic cardiac disease (heart failure, previous myocardial infarction or arrhythmias), chronic kidney disease, obesity, current smoking, active cancer, chronic obstructive pulmonary disease (COPD), chronic lung disease (other than COPD and asthma) and immunosuppression

(human immunodeficiency virus (HIV)-positive individuals and transplant recipients). In addition, we created two other binary variables: regular use of inhaled corticosteroids (ICS) and homelessness. ICS is part of the treatment therapy for asthma and COPD, and has been indicated as a possible protective factor against COVID-19 severity. Thus, in this study, it was included as an important confounder. In the context of a philanthropic hospital, we included homelessness as a proxy variable for extreme social vulnerability.

Furthermore, epidemiological week was used as a covariate to account for possible unmeasured effects regarding changes to transmission dynamics, resource availability and standard of care development, given the course of the pandemic. The first epidemiological week in the analysis was determined as the week of the first in-hospital case registered.

Asthma was categorized into two groups: either mild or moderate to severe, according to the treatment step and following current Global Initiative for Asthma (GINA) classification.[9] Patients whose medical records did not report any continuous use of medications for asthma and only use of asthma reliever therapy, and those whose daily use consisted only of low-dose inhaled corticosteroids, were considered to be mild asthmatics. Patients with at least medium to high-dose use of inhaled corticosteroids were considered to have moderate to severe asthma. Possible optimization of asthmatic therapy during hospitalization was not taken into account for this classification, which only considered previous pharmacological therapy. as reported in the medical records at the time of admission.

Outcomes

We considered that severe COVID-19 was a binary composite outcome, comprising either death or the need for intubation. In the Cox proportional-hazards model, death was considered to be the outcome.

Statistical analysis

Descriptive baseline characteristics were reported as percentages when they were categorical variables, or as medians and interquartile ranges when they were continuous variables. No sample size calculation was performed, given that the size of the database was considered fixed.

A logistic regression model was used to estimate the association between severe COVID-19 and asthma. The model was adjusted for age > 60, sex, regular ICS use, chronic cardiac disease, diabetes, hypertension, COPD, chronic lung disease, active cancer, obesity, immunosuppression, smoking and homelessness.

Kaplan-Meier curves were constructed to show the cumulative probability of survival over hospitalization of up to 30 days. The survival functions were compared using a log-rank test.

We calculated hazard ratios (HR) for death according to the duration of hospitalization for asthmatics and non-asthmatics, through use of a Cox proportional-hazards model adjusted for age, sex, regular ICS use, chronic heart disease, diabetes, hypertension, COPD, chronic lung disease, chronic kidney disease, cancer, obesity, smoking and homelessness. Testing of the proportional-hazards assumptions was performed. Statistical significance was accepted with a 95% confidence interval (CI) and P values < 0.05. GraphPad Prism version 8 (GraphPad, La Jolla, California, United States) was used to elaborate **Figure 1**. Stata version 16 (StataCorp, Texas, United States) was used for the statistical analyses and to elaborate **Figure 2**.

RESULTS

We assessed the data of all 1,529 hospitalized individuals, except for 76 individuals under 18 years of age and 83 for whom data regarding either the COVID-19 diagnosis or related death were
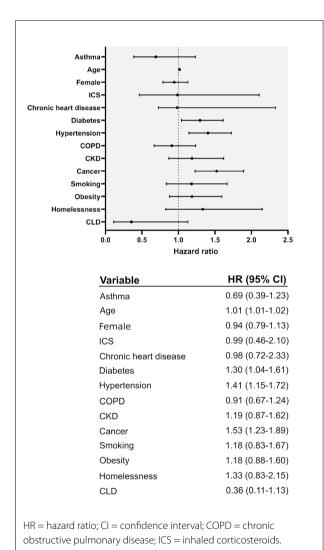
missing. Among the 58 individuals registered as asthmatics, 52 were included as asthmatics and six were considered to be non-asthmatics because of conflicting data.

The asthmatics represented 3.8% of the hospitalized patients with COVID-19. A slightly higher proportion of women (60%) was seen in the asthma group, in comparison with non-asthmatics (41.3%). The median age and interquartile range (IQR) were 54 (41-69) years among asthmatics and 60 (44-62) years among non-asthmatics. Most of the individuals in both groups were ≥ 60 years old, and the age distribution over the decades did not present any important variation between the groups. Patients < 50 years old were proportionally more prevalent in the asthma group.

The prevalence of comorbidities was remarkably high in both groups, such that 73% of the asthmatics and 57% of the non-asthmatics presented at least one comorbidity. Hypertension was the most common comorbidity in both groups (38% in the asthma group versus 31% in the non-asthma group), followed by diabetes. A minimal difference was seen regarding diabetes: 21% versus 18.6%, respectively. COPD was particularly high in the asthma group: 14 (27%) versus 103 (8%) in the non-asthma group. Use of ICS, either as reliever therapy or daily therapy, was seen in 85% of asthmatics. Mild asthma was present in 48 asthmatics (92%) (**Table 1**).

Severe COVID-19

In a sensitivity analysis considering only patients with positive RT-PCR, the unadjusted estimate for severe COVID-19 among asthmatics remained non-significant (OR 0.84; 95% CI 0.42-1.69).

The proportions of patients in the 1st to 8th, 9th to 16th and 17th to 32nd epidemiological weeks were similar between the groups. The need for mechanical ventilation was seen in 36% of the

Variable	HR (95% CI)
Asthma	0.69 (0.39-1.23)
Age	1.01 (1.01-1.02)
Female	0.94 (0.79-1.13)
ICS	0.99 (0.46-2.10)
Chronic heart disease	0.98 (0.72-2.33)
Diabetes	1.30 (1.04-1.61)
Hypertension	1.41 (1.15-1.72)
COPD	0.91 (0.67-1.24)
CKD	1.19 (0.87-1.62)
Cancer	1.53 (1.23-1.89)
Smoking	1.18 (0.83-1.67)
Obesity	1.18 (0.88-1.60)
Homelessness	1.33 (0.83-2.15)
CLD	0.36 (0.11-1.13)

HR = hazard ratio; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids.

Figure 1. Risk of death due to COVID-19.

Figure 2. Survival over 30 days of hospitalization.

Table 1. Demographic variables

Variable	Asthmatics (%) n = 52	Non-asthmatics (%) n = 1,318
Age (median, IQR)	54 (41-69)	60 (44-72)
18 - < 40	11 (21)	235 (17.8)
40 - < 50	12 (23)	220 (16.7)
50 - < 60	7 (14)	224 (16.9)
60 - < 70	10 (19)	258 (19.6)
70 - < 80	6 (11.5)	232 (17.6)
≥ 80	6 (11.5)	171 (13.0)
Female	31 (59.6)	544 (41.3)
Obesity	8 (15.4)	119 (9.0)
Smoking	3 (5.8)	83 (6.3)
Diabetes	11 (21)	245 (18.6)
Hypertension	20 (38.5)	402 (31.0)
Chronic heart disease	3 (5.8)	99 (7.5)
Chronic kidney disease	3 (5.8)	80 (6.1)
Immunosuppression	2 (3.8)	47 (3.6)
COPD	14 (27)	103 (8)
Chronic lung disease	.	19 (2)
Homelessness	2 (3.8)	49 (3.7)
Uninsured	42 (81)	1,003 (76)
Cancer	7 (13.5)	193 (14.6)
Number of comorbidities		
0	14 (27)	565 (43)
1	16 (31)	387 (29)
≥ 2	22 (42)	366 (28)
RT-PCR	49 (94)	740 (56)
Clinical features	50 (96)	1,298 (99)
Radiological criteria	35 (67)	824 (62.5)
ICS use*	44 (85)	101 (8)
Mild asthma	48 (92)	.
Severe asthma	4 (7.6)	.

IQR = interquartile range; COPD = chronic obstructive pulmonary disease; RT-PCR = real-time polymerase chain reaction; CS = inhaled corticosteroid.
*Either continuous use or as relief therapy.

Table 2. Characteristics of hospitalization and outcomes

Variable	Asthmatics (%) n = 52	Non-asthmatics (%) n = 1,318
Intubation	19 (36)	444 (34)
Death	12 (23)	504 (38)
Hospitalization (days)		
< 5	12 (23)	376 (28.5)
5 - < 10	16 (31)	391 (30)
10 - < 15	10 (19)	203 (15.4)
≥ 15	14 (27)	348 (26.4)
Epidemiological week		
1-8	18 (35)	265 (20)
9-16	21 (40)	608 (46)
17-32	13 (25)	445 (34)

Table 3. Odds ratio for severe coronavirus disease 2019 (COVID-19)

Variables	Odds ratio	[95% CI]	P value
Univariate analysis			
Asthma	0.89	[0.51-1.56]	0.69
Multivariate analysis			
Asthma	0.88	[0.5-1.68]	0.7
Age > 60	2.31	[1.8-2.96]	< 0.001
Female	0.63	[0.49-0.8]	< 0.001
Chronic heart disease	1.18	[0.75-1.88]	0.74
Diabetes	1.48	[1.06-2.06]	0.02
Hypertension	1.93	[1.40-2.50]	< 0.001
COPD	1.00	[0.64-1.56]	0.98
Chronic kidney disease	1.31	[0.80-2.16]	0.28
Cancer	2.81	[1.99-3.94]	< 0.001
Smoking	1.71	[0.72-1.90]	0.51
Obesity	1.55	[1.03-2.30]	0.03
Homelessness	2.24	[1.21-4.15]	< 0.001
Chronic lung disease	3.04	[0.69-13.33]	0.14
Epidemiological week	0.97	[0.95-0.98]	< 0.001
ICS*	0.88	[0.46-1.68]	0.71

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids.
*Regular use.

asthmatics and 34% of the non-asthmatics, while death occurred in 23% and 38%, respectively (**Table 2**).

Asthmatics, compared with non-asthmatics, presented an unadjusted estimate of severe COVID-19 risk of 0.89 (95% CI 0.5-1.56). After multivariable adjustment, the odds ratio (OR) was 0.88 (95% CI 0.5-1.68), i.e. it remained statistically non-significant. Age > 60, male sex, hypertension, diabetes, cancer and homelessness were the covariates associated with a statistically significant increased risk of severe COVID-19. Progression of epidemiological week over the 32-week period was inversely correlated with severe COVID-19 in a statistically significant manner (OR 0.97; 95% CI 0.95-0.98) (**Table 3**).

Overall mortality

Asthmatics' unadjusted HR for death, in comparison with non-asthmatics, was 0.64 (95% CI 0.7-1.1). After multivariate adjustment, asthmatics presented HR of 0.69 (95% CI 0.39-1.23), in

comparison with non-asthmatics. Sensitivity analysis showed HR of 0.68 (95% CI 0.37-1.26) (**Figure 1**).

Kaplan-Meier estimated survival over hospitalization of up to 30 days showed no difference between the groups (log-rank P = 0.09). The probability of survival among asthmatics, versus non-asthmatics, was respectively 0.88 versus 0.83 at 5 days, 0.77 versus 0.67 at 10 days, 0.65 versus 0.58 at 15 days, 0.65 versus 0.5 at 20 days and 0.65 versus 0.42 at 30 days (**Figure 2**).

The length of hospitalization was relatively similar in the two groups. 23% of the asthmatics and 28.5% of the non-asthmatics were hospitalized for less than 5 days; 31% of the asthmatics versus 30% of the non-asthmatics were hospitalized for ≥ 5 to < 10 days; and 19% versus 15.4% for ≥ 10 to < 15 days, respectively (**Table 2**).

DISCUSSION

In this study, we retrospectively evaluated all patients hospitalized in the first 32 weeks of COVID-19 cases in one of the most important tertiary-level medical centers and philanthropic emergency departments, in São Paulo and in Brazil. The prevalence of asthma was similar to what had been reported previously among COVID-19 patients and to the prevalence in the general population.[10,11] No statistically significant association was found between asthma and severe COVID-19, and differences in survival were not statistically significant between the groups.

Overall, a pronounced prevalence of comorbidities was observed. This was to be expected, considering that some of the individuals admitted to the emergency department were patients followed up at our institution's subspecialty outpatient clinics. Hypertension, diabetes and cancer were associated with increased risk of severe COVID-19 and death, as also found in other very recent reports.[11] In the asthma group, proportionally more individuals with at least two comorbidities and with at least three comorbidities were seen. In contrast, although our institution is a referral hospital for treating severe asthma, patients with this condition were underrepresented. Most of them presented mild asthma and were either in step 1 or step 2 of treatment. This observation was consistent with recent studies, in which patients with severe asthma did not seem to present increased susceptibility to severe forms of SARS-CoV-2 infection.[12]

In addition, we found a positive correlation between severe disease and homelessness, which is a condition of extreme social vulnerability. The incidence of COVID-19 incidence has been correlated with high social vulnerability,[13] but the extent to which this can affect the course of this disease remains unknown. We observed that women predominated in the asthma group, which is consistent with the epidemiology of asthma, and this contrasted with the predominance of males in the non-asthma group. This pattern has been seen in most COVID-19 cohorts.[11]

Age is a special confounder regarding asthma and worse outcomes from COVID-19. Lung function is overall reduced in elderly asthmatics[14] and the features of type 2 inflammation, which is supposedly associated with a protective effect against severe COVID-19, may be notably reduced.[15] Although we did not perform multiple age-stratification, given the relatively small number of asthmatics, we can assume that the impact of aging might give rise to a less protective relationship for asthma against SARS-CoV-2 infection.

Asthma did not have any impact on the time that elapsed until death or the duration of hospitalization, as reported from other observational studies.[11] Mortality among both asthmatics and non-asthmatics was reduced, given the course of the pandemic in the year 2020, as suggested by other reports.[16] This was also seen in the decreased odds for severe COVID-19, given the course of the epidemiological weeks.

It remains to be elucidated whether asthma has a protective effect against severe COVID-19. Even through the most recent meta-analyses, this could not be determined.[17,18] Nonetheless, despite not finding any significant association between asthma and reduced risk of severe COVID-19, we believe that the biological mechanisms associated with asthma have a small but protective role. This could occur either directly, through the phenotypic T-helper cell type 2 (Th2) immune response, or indirectly, through ICS use.

It is possible that different asthma phenotypes might account for different risk relationships with severe COVID-19. A large analysis on polygenic risk scores for asthma phenotypes found that there was a significant risk association for severe COVID-19, driven by non-allergic asthma, which remained significant after stratifying according to presence of COPD.[19] Accordingly, increased transcript levels of FURIN, a host cell enzyme that enables activation of spike proteins, were found in neutrophilic asthma.[20] In the present study, we were not able to determine asthma phenotypes, but we can hypothesize that there was high prevalence of non-allergic asthma, given the high proportion of COPD-asthma overlap. This condition is considered to be a non-type 2 inflammatory response and is driven by different cytokines such as interleukin (IL)-8 and IL-17, which are not related to atopy.[20] In addition, it is known that patients with clinical features of both asthma and COPD present increased overall mortality, in comparison with asthma or COPD alone. A large systematic review and meta-analysis revealed a high-risk association between COPD and severe COVID-19.[17] Thus, in our sample, the noticeable prevalence of COPD among asthmatics might have biased the association of asthma with severe COVID-19 towards the null hypothesis.

In allergic asthma, downregulation of ACE2 has been associated with a type 2 immune profile,[21-22] through which increased levels of IL-13 might reduce the expression of disintegrin and metalloprotease 17 (ADAM-17). This protein cleaves the ACE2 protein and facilitates endocytosis of the ACE2–SARS-CoV-2 complex.

Moreover, ICS use has been studied as another underlying mechanism associating asthmatics with reduced ACE2 expression, through suppression of type 1 interferon response[23] and decreased transcription of genes that are important for virus co-hosting. In a placebo-controlled randomized trial, it was observed that genes that were co-expressed with ACE2, particularly ADAM17 and FURIN, were underexpressed after ICS use.[24]

Our study has many limitations. First, the radiological criteria for SARS-CoV-2 infection were obtained from the medical records, which were elaborated by internists and, as needed, consulting radiologists. Furthermore, patients who were transferred to other hospitals (6% of the initially eligible sample) were excluded due to missing final outcome data. This could have biased the sample towards inclusion of more severe cases. Third, not all of the individuals included had RT-PCR results, especially at the beginning of the pandemic. However, in sensitivity analyses that included only those

with RT-PCR positivity for SARS-CoV-2, the results were not significantly altered, which indicates that our findings had good internal and external validity. Overall, the groups were not significantly heterogeneous, except mainly for sex and age. However, the small size of the asthmatics group may have accounted for the non-significant confidence intervals of the association measurements.

One of the strengths of this analysis was that it comprised an evaluation on a large and representative sample of COVID-19 hospitalized patients in São Paulo, the most populous city in Latin America. Furthermore, our main data source came from a tertiary referral hospital that has the largest philanthropic emergency department in Brazil. Thus, our study helps to provide information about severe COVID-19 in a context of a highly comorbid and socially vulnerable population.

CONCLUSIONS

In summary, asthma was not associated with either decreased odds for severe COVID-19 or increased survival. Future larger studies evaluating ICS use, as well as asthma phenotypes, might be able to point out a possible small, but protective effect of asthma against severe COVID-19. It is of the utmost importance to determine which subgroups and phenotypes are at increased risk of severe COVID-19, in order to guide public healthcare policies. In addition, future investigations of COVID-19 outcomes according to subsets of asthma might provide new insights on SARS-CoV-2 immunopathology.

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Address for correspondence:
Oziris Simões
Departamento de Saúde Coletiva da Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP)
R. Dr. Cesário Motta Jr., 61
São Paulo (SP) — Brasil
CEP 01221-020
Tel. (+55 11) 3367-7700
E-mail: gabriela.accetta.rojas@gmail.com

Barriers to physical activity among adults in primary healthcare units in the National Health System: a cross-sectional study in Brazil

Ana Luísa Kuehn de Souza[I], Letícia Pechnicki dos Santos[II], Cassiano Ricardo Rech[III], Ciro Romelio Rodriguez-Añez[IV], Claudia Alberico[V], Lucélia Justino Borges[VI], Rogério César Fermino[VII]

Universidade Tecnológica Federal do Paraná (UTFPR), Curitiba (PR), Brazil

[I]BHSc. Student, Multiprofessional Residency Program on Family Health, Sergio Arouca National School of Public Health, Fundação Oswaldo Cruz (FIOCRUZ), Rio de Janeiro (RJ), Brazil.
ⓘ https://orcid.org/0000-0001-9904-4561

[II]MSc. Researcher, Postgraduate Program on Physical Education and Research Group on Environment, Physical Activity and Health, Universidade Tecnológica Federal do Paraná (UTFPR), Curitiba (PR), Brazil.
ⓘ https://orcid.org/0000-0002-4443-5191

[III]PhD. Professor and Researcher, Postgraduate Program on Physical Education and Study Group on Urban Environment and Health, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
ⓘ https://orcid.org/0000-0002-9647-3448

[IV]PhD. Professor and Researcher, Postgraduate Program on Physical Education and Research Group on Environment, Physical Activity and Health, Universidade Tecnológica Federal do Paraná (UTFPR), Curitiba (PR), Brazil.
ⓘ https://orcid.org/0000-0001-8430-7621

[V]PhD. Researcher, Biomedical/Biotechnology Research Institute, North Carolina Central University (NCCU), Durham (NC), United States.
ⓘ https://orcid.org/0000-0001-8337-7978

[VI]PhD. Professor and Researcher, Department of Physical Education, Universidade Federal do Paraná (UFPR), Curitiba (PR), Brazil.
ⓘ https://orcid.org/0000-0002-0142-3641

[VII]PhD. Professor and Researcher, Postgraduate Program on Physical Education and Research Group on Environment, Physical Activity and Health, Universidade Tecnológica Federal do Paraná (UTFPR), Curitiba (PR), Brazil.
ⓘ https://orcid.org/0000-0002-9028-4179

ABSTRACT

BACKGROUND: Many factors may negatively impact physical activity (PA), but studies lack evidence of individual predictors of perceived barriers to PA among adults in primary healthcare units.

OBJECTIVE: To analyze associations between sociodemographic characteristics, health conditions, leisure-time physical activity (LTPA), PA counseling and perceived barriers to LTPA among adult patients in primary healthcare units of the National Health System in Brazil.

DESIGN AND SETTING: Cross-sectional study on a representative sample of adults in primary healthcare units in São José dos Pinhais, Paraná, Brazil.

METHODS: This study was conducted in 2019, among 779 adults (70% women). Barriers to LTPA, sociodemographic characteristics (sex, age, marital status, skin color, education and income), health conditions (body mass index, hypertension, diabetes, dyslipidemia, coronary disease and medications), LTPA level and PA counseling received were measured using validated, standardized procedures. The data were analyzed using chi-square and Mann-Whitney U tests.

RESULTS: The most prevalent barriers were "feeling too tired" (53%) and "lack of time" (52%). PA counseling was inversely associated with "lack of time" (45% versus 57%; P < 0.001) but positively associated with "injury or disease" (38% versus 29%; P = 0.008). There was an inverse linear trend between the number of barriers and LTPA (walking and total) (P < 0.001). Most barriers differed in comparisons of sociodemographic characteristics, health conditions, LTPA and counseling (P < 0.05).

CONCLUSIONS: The barriers vary according to the individual predictors. Counseling strategies need to be specific for each barrier and may be promising for promoting LTPA within primary healthcare.

INTRODUCTION

Around 28% of the worldwide adult population is not physically active, with higher prevalence among women (32%) and Latin American populations (39%), especially in Brazil (47%).[1] Therefore, physical inactivity has been considered to be a pandemic, with significant impact on public health and elevated economic burden with regard to healthcare, lack of productivity and premature mortality rates due to chronic disease.[2] In Brazil, the National Policy on Health Promotion is an important strategy for confronting physical inactivity that guides physical activity promotion at the community level through primary healthcare.[3]

There is strong evidence showing the protective effects of regular physical activity against major chronic diseases and for improvement of quality of life.[2,4] Leisure-time physical activity (LTPA) has higher potential for modification than physical activity at work, for example. Additionally, it is affected by psychological, biological, social and behavioral processes that operate at individual, group and social levels.[5] Many factors can affect choices and opportunities for being physically active during leisure time,[6,7] which demonstrates that LTPA is influenced by factors that go beyond motivation or the population's knowledge of its health benefits.[2] Therefore, the perception of barriers to LTPA needs to be considered with regard to the success of programs to promote physical activity,[8] since those barriers can differ according to sex, age, health conditions, social and cultural characteristics, types of LTPA and lifestyle.[9,10]

The barriers most commonly reported among the Brazilian adult population are intrapersonal and related to lack of motivation, time and physical limitations.[9] Overall, these barriers have

been identified in specific populations such as students, teachers and police officers,[9] which may not represent the demographic characteristics, health conditions and lifestyles of the adult populations who use the services available in primary care units.[9,10]

For example, counseling received by patients from professional teams in primary care units may stimulate LTPA.[11,12] Counseling is a form of orientation based on information, understanding and support that has the aim of facilitating incorporation of new attitudes as behavioral change towards health self-care, such as better dietary habits and smoking cessation, among others.[13-15] This is an effective and low-cost initiative for promoting LTPA within primary healthcare,[11,12] and it has also been recognized as a health education action that has the potential to develop individuals' autonomy to face health-related behavioral change, such as increased active commuting and reduction of sedentary behavior.[16,17]

Although the main barriers to LTPA in the Brazilian population are presented in the literature, few studies have explored them in relation to primary care unit users. Gomes et al.[18] identified the barriers to LTPA among physically active women in Rio Claro (SP); Silva et al.[19] assessed the barriers to participation in LTPA programs in Pernambuco; and Häfele and Siqueira evaluated the barriers to behavioral change after physical activity counseling among adults in Pelotas (RS).[20] From reviewing this literature, it can be seen that there is no evidence with regard to potential individual predictors of barriers in this study population, or whether physical activity counseling could affect the perception of these barriers. Exploring this association may help direct counseling strategies and support management actions for implementing LTPA promotion programs within primary healthcare.

OBJECTIVE

The aim of this study was to analyze associations between sociodemographic characteristics, health conditions, LTPA levels, physical activity counseling and perceived barriers to LTPA among adult users of primary care units in the Brazilian National Health System.

METHODS

Design, study site and ethical considerations

In 2019, a quantitative, observational, cross-sectional study was conducted on a representative sample of adult patients in primary care units (Unidade Básica de Saúde, UBS) in the urban area of São José dos Pinhais, Paraná, southern Brazil. The data used in this study were secondary to the project "Effectivity of community programs for promoting physical activity and reducing sedentary behavior".[21-23] This study was reported in accordance with the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

São José dos Pinhais is a developed city of medium size in the metropolitan region of Curitiba (state capital). The center of this

municipality is 18 km from the center of Curitiba. It is situated in an area of 946 km² (79% rural) and has a population of 329,000 inhabitants. Its Human Development (0.758) and Gini (0.459) indices are high. There are 413 healthcare establishments within the city, among which 27 are primary care units (56% in urban area). For this study, data from 15 units in urban areas were selected, since these units are accessible to 90% of the population.

The study was approved by the Research Ethics Committee of the Pontifícia Universidade Católica do Paraná (PUC-PR) (protocol #2.882.260; September 10, 2018) and the procedures used followed the recommendations of the National System for Research Ethics, issued by the National Health Council.

Sample size

The sample size was estimated from the average number of appointments registered on the website "Transparent Health" during January and February 2019 (N = 34,275). To ensure a representative sample, the proportion of patients receiving PA counseling from healthcare professionals was considered (this proportion was 30%). The confidence level was kept at 95%, the sampling error was 4% and the design effect was 1.5. With these data, the minimum number of participants was estimated as 745. However, to take into account potential losses and refusals, this estimate was increased by 10%, to yield a total of 820 patients. We also agreed to recruit at least 100 extra participants (n = 920) to allow future studies to perform multivariate analyses while avoiding estimation errors. The number of users to be recruited was calculated proportionally to the number of appointments in each primary care unit and ranged from 31 to 92 users.

Participant selection

Participants were systematically selected based on their position in the waiting room at the primary care unit, counting from one to five, from left to right, using the entrance door as a reference. The third patient was approached. If this person refused to participate or did not meet the inclusion criteria, the first person to their left was selected.

Only adults (≥ 18 years) were invited to participate in the study. Those who did not live in the city or were using the unit for the first time, had any physical limitation that would prevent LTPA (e.g. use of a wheelchair or crutches) or had a cognitive limitation that prevented them from understanding the survey (e.g. hearing loss), were excluded (n = 9).

Data collection

Ten trained surveyors administered face-to-face interviews between April and October 2019. These took place either before or after a consultation with a healthcare professional and were conducted in a private, reserved room to avoid external

influences. The average duration of the interview was 18 minutes (standard deviation, SD = 5 minutes; range = 9-55 minutes).

Outcome variables: barriers to leisure-time physical activity

The perception of barriers was assessed through an instrument developed for the Brazilian population.[24] Participants answered the question: *How often do the following affect your LTPA?* Eight individual barriers were evaluated, based on the ones most frequently mentioned in the literature:[9,25] 1) lack of money; 2) feeling tired; 3) lack of company; 4) lack of time; 5) having an injury or disease; 6) fear of injury; 7) dislike of physical activity or exercise; and 8) feeling too old. A five-point Likert scale was available for each barrier, with the following options: always, often, sometimes, rarely and never.

For analysis purposes, the options "always", "often" and "sometimes" were grouped and categorized as "yes" (code 1), thus indicating the presence of a barrier. The options "rarely" and "never" were grouped and categorized as "no" (code 0), which consequently represented the lack of a barrier. The total number of barriers was determined as the sum of the eight barriers, ranging from zero to eight.

Predictor variables

Sociodemographic characteristics

The patients' sex was noted and age was grouped into three categories (young adult: 18-39 years old; middle-aged adult: 40-59 years old; or older adult: ≥ 60 years old). Marital status was classified as single (single/divorced/widowed) or married (married/living with a partner). Skin color was self-reported as one of five categories (white, black, yellow, brown or indigenous) and was categorized as white or nonwhite (all other categories). Education was assessed through five options and was classified into three categories of education: less than elementary school, elementary school or high school or more. Socioeconomic status was assessed using a standard questionnaire[26] in seven categories (A1 [highest], A2, B1, B2, C, D and E) and was grouped as low-income (C+D+E) or high-income (A+B).

Health conditions

The body mass index (BMI) was calculated from self-reported weight and height and was classified into three categories (≤ 24.9 kg/m²; 25.0-29.9 kg/m²; or ≥ 30.0 kg/m²). Presence of chronic disease was assessed through dichotomous responses (no or yes) with regard to medical diagnoses of hypertension, diabetes, dyslipidemia and cardiovascular disease[27]. The number of disease diagnoses was categorized as 0, 1 or ≥ 2. Lastly, the participants were asked to report any continuous use of medications for chronic disease, and this was classified according to the number of prescription medications (0, 1-3 or ≥ 4).

Level of leisure-time physical activity

Weekly LTPA in a usual week was measured by means of the leisure module of the long version of the International Physical Activity Questionnaire (IPAQ).[28,29] The participants reported their weekly frequency and average duration of walking and of moderate and vigorous physical activity. The score for each activity/intensity was obtained as the number of minutes per week (min/week) by multiplying the weekly frequency by the mean daily volume. The total LTPA was obtained by summing the minutes/week of walking + minutes/week of moderate physical activity + (minutes/week of vigorous physical activity*2). Walking and total LTPA were classified in accordance with the World Health Organization guidelines (≥ 150 minutes/week).[30]

Physical activity counseling received from healthcare professionals

Physical activity counseling was assessed and recorded based on a dichotomous response (no or yes) to the following question: *During the past year (12 months), in a visit to the healthcare unit, did you receive physical activity counseling while in consultation with a healthcare professional (advice, tips or orientation on physical activity or exercise)?* This measurement had previously been used in similar studies and was adapted to the local context.[13,15,18,20]

Data quality control

Quality control was conducted in six steps. First, all research assistants received 20 hours of training on the technical procedures regarding interviews (how to: approach participants, register losses and refusals, administer surveys and code forms), based on an instruction manual that had been developed for the project. The interviewers, who were blinded to the study aims and hypothesis, followed the procedures and were supervised by the field coordinators. Second, a pilot study was conducted using a random sample of 81 participants in three healthcare units to test the procedures for data collection and the understanding of questions in the survey, especially those that had been translated or adapted to the local context. Third, all the participants in the pilot study were surveyed for a second time, after an interval of seven to 10 days, to analyze the temporal stability of the main study variables. The reliability of physical activity counseling was analyzed in terms of the percentage agreement and Cohen's kappa test. The percentage agreement was found to be 88%, and the kappa value was moderate (0.77; P < 0.001). Fourth, the field coordinator was responsible for data entry using the EpiData software (version 3.1, Odense, Denmark). Fifth, data management included an exploratory analysis using the Statistical Package for the Social Sciences (SPSS version 26.0, SPSS Inc., Chicago, Illinois, United States) to identify possible data entry errors and any presence of outliers, and to verify the distribution of all the variables. Lastly, every outlier was checked and corrected when problems were found.

Statistical analysis

The data were analyzed using descriptive statistics (average, standard deviation and median of the number of barriers) and using the absolute and relative frequency distribution of qualitative variables. The prevalence of each barrier was determined between the categories of predictor variables, and the association was analyzed using chi-square tests (χ^2) for heterogeneity and linear trend. The normality of the distribution of the number of barriers was analyzed using the Kolmogorov-Smirnov test. The data did not present normal distribution ($P < 0.001$), and the Mann-Whitney U test was used to compare the number of barriers according to physical activity counseling. Analyses were conducted using the SPSS 26 software, and the significance level was kept at 5%.

RESULTS

A total of 935 users were approached, with a refusal rate of 14% (n = 134) and loss of 2% (n = 22), thus resulting in a sample of 779 interviewed participants. Most participants were female (69.8%), aged between 18 and 39 years (45.2%), married or living with a partner (64.0%), white (73.0%), with completed high school education or more (50.4%) and of low economic level (71.2%) (**Table 1**).

Around 68% were overweight (BMI ≥ 25.0 kg/m²); 35.9% had high blood pressure; 15.7% were diabetic; 15.9% had dyslipidemia; and 6.5% had coronary artery disease. A little over half of the participants reported using medications (50.3%), and 14.8% used four or more different types of pharmacological treatments (**Table 1**).

Between 13.4% and 24.8% of the participants were active for at least 150 minutes per week, consisting of walking or doing LTPA, respectively. The prevalence of physical activity counseling from healthcare professionals was 43.0% (95% confidence interval, CI: 39.5-46.4%) (**Table 1**).

At least one barrier to LTPA was reported by 89% of the participants. The average number of barriers was 2.70 ± 0.1 (median = 3), and this was similar between the participants who reported receiving physical activity counseling and those who did not (2.73 ± 0.08 versus 2.70 ± 0.10; P = 0.822, respectively). Feeling tired (53%) and lack of time (52%) were the barriers most reported (**Figure 1**).

Physical activity counseling from healthcare professionals was inversely associated with the barrier "lack of time" (45% versus 57%; P < 0.001), but was positively associated with "having an injury or disease" (38% versus 29%; P = 0.008) (**Figure 2**).

A positive linear trend was observed between the number of barriers and < 150 minutes per week of walking (χ^2 for trend: 22.3; P < 0.001) and total LTPA (χ^2 for trend: 38.2; P < 0.001) (**Figure 3**).

Female sex was associated with the barriers "feeling tired" (56.3% versus 46.8%; P = 0.015), "lack of company" (47.6% versus 31.1%; P < 0.001) and "dislike of exercise" (29.6% versus 18.7%; P

= 0.002). Other associations between sociodemographic characteristics, health conditions, LTPA and perception of each barrier are shown in **Table 2**. Only marital status was not associated with any of the barriers (P > 0.05) (**Table 2**).
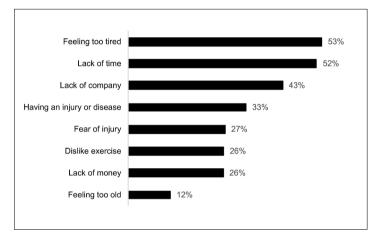
Table 1. Characteristics of adults assisted within primary healthcare. São José dos Pinhais, Paraná, southern Brazil, 2019 (n = 779)

Variable	Category	n	%
Sociodemographic characteristics			
Sex	Female	544	69.8
	Male	235	30.2
Age group (years)	18-39	346	45.2
	40-59	283	36.9
	≥ 60	137	17.9
Marital status	Single	280	36.0
	Married	497	64.0
Skin color	White	566	73.0
	Nonwhite	209	27.0
Education level	Less than elementary education	247	31.7
	Elementary education	139	17.8
	High school or more	393	50.4
Economic level	Low	555	71.2
	High	224	28.8
Health conditions			
Body mass index (kg/m²)	< 24.9	248	32.2
	25-29.9	291	37.4
	≥ 30.0	230	29.9
Hypertension	No	499	64.1
	Yes	280	35.9
Diabetes	No	657	84.3
	Yes	122	15.7
Dyslipidemia	No	655	84.1
	Yes	124	15.9
Coronary artery disease	No	728	93.5
	Yes	51	6.5
Number of chronic diseases	0	427	54.8
	1	204	26.2
	≥ 2	148	19.0
Number of prescribed medications	0	387	49.7
	1-3	277	35.6
	≥ 4	115	14.8
Leisure-time physical activity			
Walking (min/week)	< 150	675	86.6
	≥ 150	104	13.4
Total LTPA (min/week)*	< 150	586	75.2
	≥ 150	193	24.8
PA counseling received from a healthcare professional	No	444	57.0
	Yes	335	43.0

PA = physical activity; LTPA = leisure-time physical activity; *minutes/week of walking + minutes/week of moderate PA + (minutes/week of vigorous PA*2).

DISCUSSION

In this study, we sought to explore intrapersonal correlates as potential predictors of LTPA barriers perceived by adult patients in primary care units in a city in southern Brazil. The quantitative approach adopted allowed exploration of associations between sociodemographic characteristics, health conditions, LTPA, physical activity counseling and the prevalence of each barrier in a representative sample of adults. These were positive and
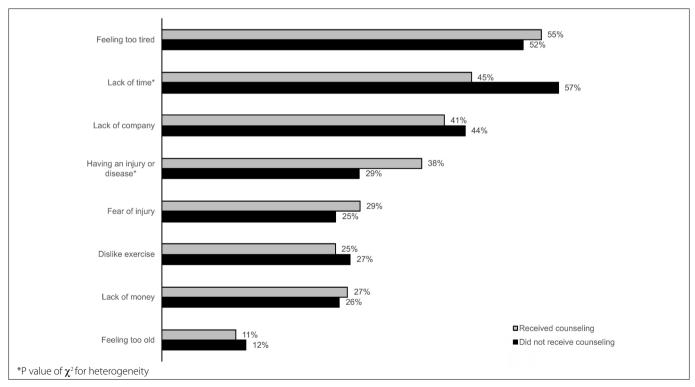
innovative aspects of this study. The analyses among users of primary care units assisted in enabling understanding of how physical activity counseling from healthcare professionals may have an impact on the barriers associated with physical inactivity in this population. Moreover, the variables were measured through valid, internationally standardized protocols and instruments, which allowed comparisons with similar studies.

This study presents a sample with an important sociodemographic characteristic, representing a population that is more vulnerable to physical inactivity in Brazil (e.g. women, low-income individuals, with chronic diseases and who depend on continuous medication). This is relevant since community programs to promote physical activity in Brazil allow free access for the population with these characteristics.[23,31]

In this study, "feeling too tired" and "lack of time" were the most prevalent barriers, and this agreed with the results from other studies.[9,20,25,32] These reports may be partially explained by the participants' daily routines (work, commuting and household activities), which would impact their liveliness and time available for LTPA. Therefore, orientations and counseling actions from healthcare professionals could include all four domains of physical activity (leisure, transportation, occupation and household), with the aim of raising awareness about the need to reduce sedentary time.[9,30]

Intrapersonal, interpersonal and environmental barriers faced by adolescents, adults and older adults have been widely

Figure 1. Barriers to leisure-time physical activity reported by adults in primary care units. São José dos Pinhais, Paraná, southern Brazil, 2019 (n = 779).

Figure 2. Association between physical activity counseling and perception of barriers reported by adults at primary care units. São José dos Pinhais, Paraná, southern Brazil, 2019 (n = 779).
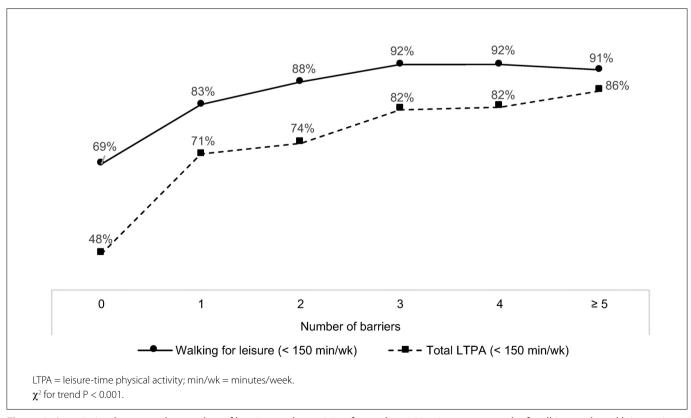
reported and identified in the literature.[9,19,32] However, these reports cannot be extrapolated for the general population. In fact, among adult patients seen at primary care units, the main barriers are health conditions and lack of appropriate locations for exercising near their homes, among others.[18,19] However, these barriers differ among individuals. For example, a healthy young single male who is university-educated and has a high income, and who plays sports regularly and intends to swim in a gym, will probably have barriers that are different to those of a middle-aged black female who is a day laborer with a low income and is physically inactive and hypertensive, and who intends or needs to participate in guided walking groups offered at the primary care unit near home.[18,19]

Physical activity counseling was inversely associated with the "lack of time" barrier but positively associated with "having an injury or disease". The time available for activities is a multifactorial issue that may not be easily changed.[9,32] However, counseling is a strategy for health promotion that involves orientation and support from professionals. This action may contribute to a more positive perception among individuals with regard to organizing their time for LTPA. In this manner, the relevance of counseling in the process of behavioral change is strengthened.[11-13] The positive association between counseling and the barrier of "having an injury or disease" may be explained by studies that have shown

that there is a higher probability that older adults and those with chronic disease are the ones receiving counseling.[20,33]

The number of barriers was associated with the prevalence of < 150 minutes per week of walking and total LTPA. Similar results were found in a population study in Pelotas (RS), another mid-sized city in the southern region of Brazil.[25] These results are essential and reiterate the idea that counseling needs to be directed at the individual level to stimulate LTPA and reduce the perception of barriers. Therefore, it is clear that reducing barriers should be at the center of healthcare professionals' actions towards increasing the level of LTPA in this population.

Multiple sociodemographic characteristics and health conditions presented associations with barriers to LTPA in the expected ways. For example, the perceptions of "feeling too tired", "lack of company" and "dislike of exercise" were also found to be more likely among women in other studies. These perceptions can be explained by double shifts, lack of support from a partner and, consequently, low motivation for activities.[9,19,25,32] Also, for example, older adults (with physical limitations, chronic disease, arthritis or arthrosis) may fear that higher-intensity LTPA could result in pain or injuries.[9,19,25,32] These results highlight the need for programs to promote LTPA in the Brazilian National Health System and the need to identify barriers to participation in the activities that are offered. Thus, healthcare teams should aim to create strategies to

LTPA = leisure-time physical activity; min/wk = minutes/week.
χ^2 for trend P < 0.001.

Figure 3. Association between the number of barriers and practicing fewer than 150 minutes per week of walking and total leisure-time physical activity, among adult patients at primary care units. São José dos Pinhais, Paraná, southern Brazil, 2019 (n = 779).

**Table 2.** Association between sociodemographic characteristics, health conditions, leisure-time physical activity and barriers to physical activity reported by adults at primary healthcare units. São José dos Pinhais, Paraná, southern Brazil, 2019 (n = 779)

	Feeling too tired (%)	Lack of time (%)	Lack of company (%)	Having an injury or disease (%)	Fear of injury (%)	Dislike of exercise (%)	Lack of money (%)	Feeling too old (%)
Sociodemographic characteristics								
Sex (p)	**0.015**[h]	0.854[h]	**< 0.001**[h]	0.699[h]	0.825[h]	**0.002**[h]	0.129[h]	0.442[h]
Female	56.3	52.2	47.6	32.9	26.5	29.6	27.8	12.1
Male	46.8	51.5	31.1	31.5	27.2	18.7	22.6	10.2
Age group (years) (p)	**0.001**[t]	**< 0.001**[t]	**0.002**[t]	**< 0.001**[t]	**0.003**[t]	0.119[t]	0.672[t]	0.052[t]
18-39	58.1	63.0	48.8	22.8	21.1	28.9	24.0	9.5
40-59	54.1	53.7	38.5	39.6	30.7	24.7	30.4	11.3
≥ 60	40.1	21.2	35.0	42.3	32.1	22.6	23.4	16.1
Marital status (p)	0.558[h]	0.137[h]	0.510[h]	0.159[h]	0.175[h]	0.385[h]	0.801[h]	0.714[h]
Single	52.1	48.6	55.7	35.7	29.6	28.2	26.8	12.1
Married	54.3	54.1	58.1	30.8	25.2	25.4	26.0	11.3
Skin color (p)	0.756[h]	0.117[h]	**0.020**[h]	0.085[h]	0.318[h]	**0.027**[h]	**0.031**[h]	0.662[h]
White	53.9	53.7	45.2	34.3	25.6	28.4	28.3	11.3
Nonwhite	52.6	47.4	35.9	27.8	29.2	20.6	20.6	12.4
Education level (p)	0.688[t]	**< 0.001**[t]	0.228[t]	0.369[t]	0.274[t]	0.181[t]	0.944[t]	**0.033**[t]
Less than elementary education	55.1	44.5	38.5	35.6	30.0	23.1	25.9	15.4
Elementary education	51.1	45.3	46.8	28.8	23.7	27.3	26.6	10.1
High school or more	53.2	59.0	43.8	31.8	25.7	28.0	26.2	9.7
Economic level (p)	0.227[h]	0.095[h]	0.382[h]	0.704[h]	0.299[h]	**0.049**[h]	0.082[h]	0.227[h]
Low	50.0	56.7	40.2	33.5	24.1	21.4	21.9	9.4
High	54.8	50.1	43.6	32.1	27.7	28.3	27.9	12.4
Health conditions								
Body mass index (p)	**0.024**[t]	0.545[t]	0.602[t]	**0.012**[t]	0.932[t]	0.778[t]	0.366[t]	0.659[t]
< 24.9 kg/m²	50.0	53.2	41.5	29.0	25.8	27.8	26.2	11.3
25-29.9 kg/m²	51.2	52.6	41.9	30.2	28.2	22.3	22.3	11.0
≥ 30.0 kg/m²	60.4	50.4	43.9	40.0	26.1	29.1	30.0	12.6
Hypertension (p)	0.937[h]	**< 0.001**[h]	0.268[h]	**< 0.001**[h]	**0.006**[h]	0.257[h]	0.257[h]	0.536[h]
No	53.5	59.1	44.1	27.3	23.4	27.7	24.8	11.0
Yes	53.2	39.3	40.0	41.8	32.5	23.9	28.6	12.5
Diabetes (p)	0.080[h]	**< 0.001**[h]	0.841[h]	**0.002**[h]	**0.006**[h]	0.273[h]	**0.042**[h]	0.069[h]
No	52.1	54.8	42.5	30.3	24.8	25.6	24.8	10.7
Yes	60.7	36.9	43.4	44.3	36.9	30.3	33.6	16.4
Dyslipidemia (p)	0.878[h]	**0.015**[h]	0.867[h]	**< 0.001**[h]	**0.008**[h]	0.598[h]	0.146[h]	0.152[h]
No	53.3	53.9	42.7	29.6	24.9	26.0	25.2	10.8
Yes	54.0	41.9	41.9	47.6	36.3	28.2	31.5	15.3
Coronary artery disease (p)	0.166[h]	0.191[h]	0.611[h]	**< 0.001**[h]	0.435[h]	0.239[h]	0.230[h]	**0.006**[h]
No	52.7	52.6	42.9	30.9	26.4	25.8	25.7	10.7
Yes	62.7	43.1	39.2	54.9	31.4	33.3	33.3	23.5
Number of chronic diseases (p)	0.646[t]	**< 0.001**[t]	0.399[t]	**< 0.001**[t]	**0.002**[t]	0.965[t]	0.142[t]	0.185[t]
0	53.2	59.5	45.4	24.4	23.4	26.9	24.8	11.0
1	52.0	47.5	35.3	39.2	25.5	23.5	25.0	9.3
≥ 2	56.1	36.5	44.6	46.6	37.8	28.4	31.8	16.2
Number of prescribed medications (p)	0.673[t]	**< 0.001**[t]	0.479[t]	**< 0.001**[t]	**< 0.001**[t]	0.700[t]	**0.040**[t]	**0.037**[t]
0	53.7	62.0	43.9	22.2	22.0	27.4	23.0	9.6
1-3	50.9	48.7	41.5	36.8	27.8	24.5	28.5	12.3
≥ 4	58.3	26.1	40.9	56.5	40.0	27.0	31.3	16.5
Leisure-time physical activity (LTPA)								
Walking (min/wk) (p)	**0.015**[h]	**< 0.001**[h]	**0.001**[h]	0.861[h]	0.510[h]	**0.003**[h]	0.083[h]	0.738[h]
< 150	55.1	55.4	45.0	32.6	27.1	28.1	27.3	11.7
≥ 150	42.3	29.8	26.9	31.7	24.0	14.4	19.2	10.6
Total LTPA (min/wk)*(p)	**< 0.001**[h]	**< 0.001**[h]	**0.001**[h]	0.314[h]	0.508[h]	**< 0.001**[h]	0.107[h]	0.102[h]
< 150	57.2	58.0	46.9	33.4	27.3	29.7	27.6	12.6
≥ 150	42.0	33.7	29.5	29.5	24.9	16.1	21.8	8.3

*min/wk = minutes/week of walking + minutes/week of moderate physical activity (PA) + (minutes/week of vigorous PA*2); [t]χ² for linear trend; [h]χ² for heterogeneity.

reduce the impact of barriers, so that program users may be more physically active.

The results from this study provide important information that needs to be considered in planning, implementing, conducting and maintaining actions integrated with counseling from healthcare professionals, to reduce barriers to LTPA. Furthermore, these results can help leverage community programs for physical activity promotion within primary care, given that such programs can affect the population's interest in, search for and involvement in these activities.[18,19,32,34]

Programs need to be developed and directed according to the barriers perceived by different groups stratified in terms of sex, age, chronic disease and LTPA levels. For example, healthcare professionals may stimulate and counsel users to seek community programs for LTPA that are available in the city, based on these perceptions of barriers. In turn, the programs need to offer pleasant group-based activities that can be performed in public open spaces and which are diversified in time, type and intensity so as to engage the population.[6,8,18,19,32,34,35]

Continuous and adequate physical activity counseling could be emphasized for people with chronic disease or fear of illness, and for people who are insufficiently active during their leisure time.[11,22] This could make it easier for primary care unit users to understand that regular physical activity is not a potential cause of injury or pain.[9] The Physical Activity Guidelines for the Brazilian Population can contribute to a better understanding of physical activity among the population and help healthcare professionals regarding the content for counseling.[36] Also, healthcare professionals could encourage users to attend public open spaces (e.g. parks, squares, sports and leisure centers and fitness zones) that are easily accessible and free, for LTPA.[19,31,32]

Some limitations of this study need to be considered in order to adequately interpret and extrapolate these results. First, the sample was limited to adult patients at primary care units in the urban area of a mid-sized city in southern Brazil. Second, these units did not have a physical education professional as part of their healthcare teams, which may have affected the perception of barriers. Third, the quantitative approach using a short, standardized survey to evaluate intrapersonal barriers did not allow much depth when exploring interpersonal or environmental matters of relevance to implementation of physical activity promotion programs in the community. Therefore, it was impossible to capture contextual information that could explain or signify feelings towards barriers. This would only have been possible through a qualitative or mixed-method approach.[10] Lastly, the cross-sectional design limited the capacity to establish causality between predictor variables and the outcomes.

CONCLUSION

The perceived barriers to physical activity that were most often reported were "feeling too tired" and "lack of time". These barriers differed in importance according to sociodemographic characteristics, health conditions and levels of LTPA. Physical inactivity increased with increasing numbers of perceived barriers. Future studies may advance the analyses and explore other interpersonal and environmental aspects of barriers through using mixed methods among patients at primary care units in larger cities or rural areas of smaller municipalities. It is also relevant to assess the effectiveness of counseling actions provided by trained professionals, using an evidence-based technical protocol to reduce the perception of barriers against LTPA.

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Address for correspondence:

Rogério César Fermino

Programa de Pós-graduação em Educação Física, Universidade Tecnológica Federal do Paraná (UTFPR)

R. Pedro Gusso, 2.601

Neoville — Curitiba (PR) — Brasil

CEP 81310-900

Tel. (+55 41) 3247-0966

E-mail: rogeriofermino@utfpr.edu.br

Severe acute respiratory syndrome and COVID-19 under the hierarchy of the urban network of municipalities in the state of Acre, western Brazilian Amazon region, 2020-2021: a cross-sectional study

Mário Ribeiro Alves[I], Erlei Cassiano Keppeler[II]

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

[I]PhD. Geographer and Associate Professor, Instituto de Saúde Coletiva (ISC), Universidade Federal de Mato Grosso (UFMT), Cuiabá (MT), Brazil.
https://orcid.org/0000-0003-3665-6821

[II]PhD. Biologist and Assistant Professor, Centro Multidisciplinar, Universidade Federal do Acre (UFAC), Rio Branco (AC), Brazil.
https://orcid.org/0000-0001-6216-9029

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ABSTRACT

BACKGROUND: The Respiratory Syndromes Surveillance System was created by the Brazilian Ministry of Health in 2000 to monitor influenza in this country. With the emergence of the new coronavirus pandemic, it became incorporated into the surveillance network for influenza and other respiratory viruses.

OBJECTIVE: To analyze the transmission of coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) in the state of Acre through its hierarchical urban network.

DESIGN AND SETTING: Cross-sectional, descriptive and ecological study, using a spatiotemporal approach and using secondary data. This study was conducted in the state of Acre, northern Brazil.

METHODS: This study used secondary data, and epidemiological weeks and municipalities were taken to be the units of analysis. Incidence rates and kernel intensities were calculated for four study periods. Spatiotemporal analysis was performed using scan statistics to identify clusters of SARS cases and considering the population of each municipality.

RESULTS: In general, it could be observed that there were higher kernel rates and intensities in municipalities located in the north and south of this state (i.e. its most populous municipalities).

CONCLUSION: Priority areas for interventions to control transmission of COVID-19 were highlighted, with the aim of reducing the risks of transmission to more distant areas in the urban hierarchy of the state of Acre.

INTRODUCTION

Coronaviruses (CoVs) belong to a taxonomic group of viruses that cause respiratory infections and can affect humans and other animals.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus belonging to the Coronaviridae family, characterized by the shape of a crown, with a particle size between 60 nm and 140 nm. It is composed mainly of internal genetic ribonucleic acid (RNA) material, external proteins and a lipid bilayer. As in other viruses, SARS-CoV-2 contains nucleocapsid (N) proteins that are responsible for camouflaging the RNA, the genetic material of the virus, which is replicated in infected cells, thereby increasing the level of infection.[2,3]

The preventive measures usually publicized by public health authorities and the media encompass the following personal recommendations: avoid crowding, keep one's distance from other people, stay at home, only go to commercial establishments in cases of extreme need, adopt social isolation, use masks and gloves and adopt use of delivery service; and traffic between cities should be blocked.[2] Such measures aim to control transmission, involving individual and collective hygiene and physical distance actions.[4]

The Respiratory Syndromes Surveillance System was created by the Brazilian Ministry of Health in 2000 to monitor influenza in this country. With the emergence of the new coronavirus pandemic, it became incorporated into the surveillance network for influenza and other respiratory viruses.[5] Data from June 24, 2021, revealed that there had been 18,243,483 confirmed cases of coronavirus 2019 (COVID-19) in Brazil, among which 16,511,701 individuals had recovered. There had been 509,141 deaths, corresponding to a mortality rate of 242.3 per 100,000 inhabitants of Brazil; death had occurred in 2.8% of the cases. In the state of Acre, there had been 85,128 cases (incidence of 9,652.4 per 100,000 inhabitants) and 1,735 deaths, with a mortality rate of 196.7 per 100,000 inhabitants of this state.[6]

OBJECTIVE

In this context, the aim of this study was to analyze the transmission of COVID-19 and severe acute respiratory syndrome (SARS) in the state of Acre, in the west of the Amazon region, according to the hierarchical urban network of its municipalities, given the significant increase in deaths from COVID-19. It was hypothesized that the geographical accessibility of the municipalities would be a factor in its transmission, since shorter distance from the state capital would tend to contribute to greater transmission.

METHODS

This was a retrospective, descriptive and ecological study, using a spatiotemporal approach and using secondary data. Epidemiological weeks and municipalities were taken to be the units of analysis. This study was conducted in the state of Acre, northern Brazil, which had a projected population for the year 2021 of 906,876 inhabitants.[7] Acre has 22 municipalities and the state capital is the municipality of Rio Branco **(Figure 1)**.

The records of weekly cases of SARS for the period from January 8, 2020, to April 19, 2021, are freely accessible and were collected on April 23, 2021, from the Ministry of Health's Respiratory Syndromes Surveillance System, which includes COVID-19 data.[5] For the present study, the SARS case registry was used as a proxy (representative) of COVID-19 incidence, which had been justified through other studies using SARS data during the pandemic period.[8,9,10] Furthermore, with the pandemic, the reinforcement of the SARS surveillance system represented an important step forward for public health, in the light of the epidemiology of respiratory agents.[11]
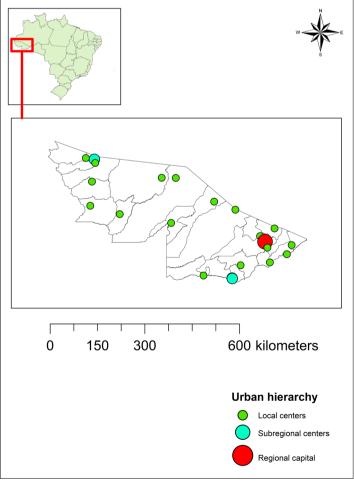
The Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE) was used as a source for data referring to the regions of influence (Regiões de Influência das Cidades, REGIC)[12,13] and accessibility of the municipalities of Acre.[14] The municipalities of this state are classified into three hierarchical levels: regional capital (Rio Branco), subregional centers (Brasiléia, Cruzeiro do Sul and Epitaciolândia) and local centers (other municipalities). In this hierarchical system, regional capitals are urban centers with a high concentration of management activities, but with a smaller reach of influence over the region than metropolises. Subregional centers are municipalities with less complex management activities, with a smaller extent of areas of influence than regional capitals (and the same is true for population size). At the last hierarchical level, local centers exert influence only within their territorial limits; they are able to attract residents from other cities in specific contexts, but are not the main destination from any other city. They have weak centrality of business and public management activities, and usually have links to other urban centers that are hierarchically higher with regard to purchasing/service activities and in relation to accessing public administration activities and business dynamics[12] **(Figure 2)**.

Estimated population data (2020) were obtained from the Ministry of Health.[15] Digital grids for the municipalities and their respective main urban areas in the state of Acre were obtained from the IBGE.[16]

SARS data were filtered in terms of residents of the state of Acre and were then organized according to the municipalities of the state. Incidence rates and kernel intensities were calculated for four study periods, organized as the following ranges of reporting weeks: weeks 3 to 18, weeks 19 to 35 and weeks 36 to 53 of the year 2020, and weeks 1 to 12 of the year 2021.

The incidence rate was calculated by dividing the number of cases of SARS per period by the estimated population for each municipality, multiplied by 100,000. Kernel intensities are statistically calculated from incidence rate data and thus were also obtained by dividing the number of cases per period by the estimated population for each municipality, multiplied by 100,000. Nine intensity and adaptive radius strata were used.

Spatiotemporal analysis was performed using scan statistics to identify clusters of SARS cases and considering the population of each municipality. A Kulldorff statistical cylindrical scan was

Figure 1. Location and hierarchy of municipalities in the state of Acre, Brazilian Amazon region.

used, with a discrete Poisson probability distribution, to identify high-risk clusters by comparing the number of cases observed with the number of cases expected. The SaTScan software, version 9.6 (Kulldorff Information Management Services Inc., New York City, United States), was used for this.
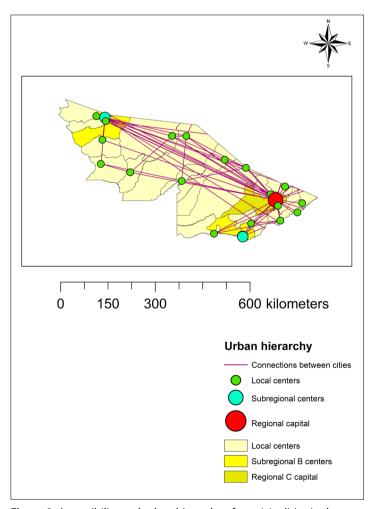
Additionally, the relative risk (RR) was calculated for each cluster, based on the underlying population. The clusters were placed in order according to their log-likelihood ratio (LLR), such that the cluster with the highest LLR was the one that was least likely to have occurred by chance. The significant clusters (P-value < 0.05) had no geographical overlap and included a maximum of 50% of the city's population.[17] A circular radius of one kilometer was used, without geographical overlap.

From the municipal digital grid of Acre, a map of the incidence rates of SARS was made, along with a map of spatiotemporal clusters of SARS data and a map of accessibility and urban hierarchy, using the QGis software, version 2.18.20.[18]
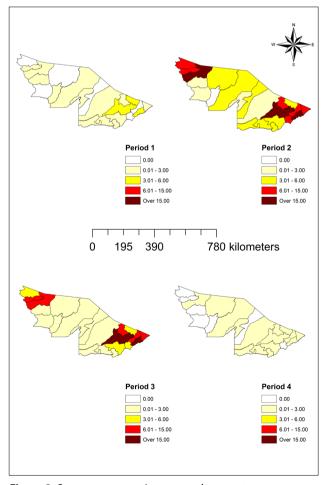
Submission to and approval by an ethics committee was not necessary, given that the present study analyzed ecological data,

without identifying the registered cases. These are open-access and freely available public secondary data.

RESULTS

From the analysis on the SARS rates, it could be observed that, in general, there were higher values in the municipalities located in the northern and southern parts of the state, especially in Cruzeiro do Sul, Rio Branco and Plácido de Castro. With lower values, the municipalities of Acrelândia, Bujari, Capixaba, Mâncio Lima, Rodrigues Alves and Senador Guiomard were highlighted. In the first study period, the highest rates of SARS were observed in Rio Branco (59.75), Plácido de Castro (35.08) and Porto Acre (31.87). In the second study period, the highest rates were observed in Plácido de Castro (451.01), Rio Branco (217.21) and Cruzeiro do Sul (163.91). During the third period, Plácido de Castro (275.62), Rio Branco (191.57) and Senador Guiomard (86.07) had the highest rates. In the last period, there was a reduction in these rates, such that all values werebelow 30.00: Bujari (28.79), Rio

Figure 2. Accessibility and urban hierarchy of municipalities in the state of Acre, Brazilian Amazon region.

Figure 3. Severe acute respiratory syndrome rates per 100,000 inhabitants in the municipalities of the state of Acre, Brazilian Amazon region, 2020-2021.

Branco (28.78), Epitaciolândia (21.39) and Xapuri (15.31) (**Figure 3**).

Regarding kernel intensities, in general, a spatial pattern similar to that of the SARS rates was observed, especially for the municipalities in the north and south of the state. In the first study period, the highest intensities were observed in the south of the state; among the municipalities with lower values, the kernel intensities in the municipalities of Assis Brasil, Jordão, Santa Rosa do Purus and Sena Madureira stood out. An increase in intensity was observed in the second period of the study, with concentration of higher values in the north and south of the state, and also in the municipalities of Brasiléia, Epitaciolândia, Feijó and Tarauacá. Similar patterns of intensity and spatial distribution were observed in the third period. In the last period of analysis, the municipalities in the south of the state were highlighted, along with the municipalities of Assis Brasil and Santa Rosa do Purus (**Figure 4**).

Initially, six spatiotemporal clusters were observed. However, two of these were not significant (P-value > 0.05) and were excluded. Each cluster was formed by only one municipality:

cluster 1 (Rio Branco), cluster 2 (Plácido de Castro), cluster 3 (Cruzeiro do Sul) and cluster 4 (Rodrigues Alves). The highest LLR value was observed in cluster 1. The highest relative risk values were observed in clusters 2 (5.30) and 4 (4.26), and the same occurred in the relationship between observed cases and expected cases (5.10 and 4.24, respectively). Longer time durations were observed in clusters 1 and 2 (32 and 27 weeks, respectively) (**Table 1** and **Figure 5**).

DISCUSSION

SARS-CoV-2 entered Brazil through the airspace, via passengers coming from Europe. Following the hierarchy of the Brazilian urban network, the disease spread through connections between airports. Later on, it spread through road transportation (which has different levels, ranging from interstate to commuting, using public transport), promoted through connections from hub cities to smaller municipalities within a given region of influence. Subsequently, transmission of the disease occurred through closer social relationships.[19]
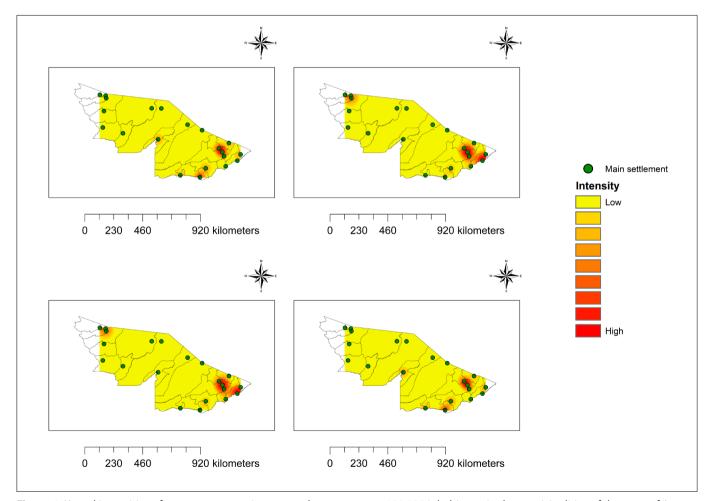
Figure 4. Kernel intensities of severe acute respiratory syndrome rates per 100,000 inhabitants in the municipalities of the state of Acre, Brazilian Amazon region, 2020-2021.

The spatial distribution of COVID-19 cases has had a pattern similar to what was seen in other epidemics. It has shown relationships with intensities, frequencies, directions, duration and the qualitative characteristics of spatial interactions; and it has varied according to the stages of social relations, the population size and the technological standards of society (highlighting transportation itself). The international spread of the disease initially occurred through commercial passenger aviation, and this followed the configuration and logic of the urban hierarchy, air transportation and population arrangement of cities, such that its spread was faster and more spatially diffused in the most populous cities and capitals of countries and provinces.[19]

Those findings are corroborated through our results, considering that it was observed that cluster 1 (concerning the state
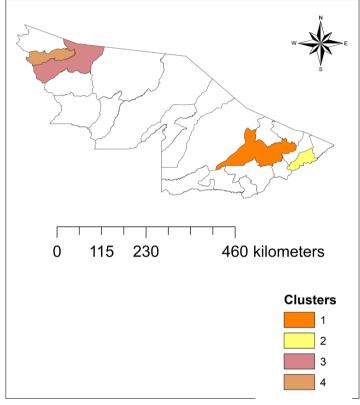
Figure 5. Spatiotemporal clusters of severe acute respiratory syndrome in municipalities in the state of Acre, Brazilian Amazon region, 2020-2021.

capital, Rio Branco) began on week 17. This was the first cluster to be formed and was also the one with the longest temporal duration (**Table 1**), which may be explained by the greater population and greater influence of this municipality in the urban hierarchy of Acre, given that this is a regional capital (**Figure 1**). Reinforcing our findings, the first three cases of COVID-19 in Acre were registered in Rio Branco: one was diagnosed in a private clinic and two in municipal emergency rooms.[20]

Given that transmission of the disease occurs via social contacts, groups with larger demographic dimensions would, over time, tend to be more affected.[21] This notion was reinforced by the findings of our study, as high incidence rates were observed in more populous cities, notably Cruzeiro do Sul (89,072 inhabitants) and Rio Branco (413,418 inhabitants).[15] This can be explained by the fact that higher population density increases the risk of transmission of contagious diseases, thus making isolation at home necessary, which may even contain the spread of the disease such that it is kept away from municipalities in which there are no case records yet.[22] Thus, cities with greater demographic density that have capillary internal transportation networks favor spatial dissemination of COVID-19,[23] which may occur through flights or even through other forms of transportation/travel such as by road or river.

From analysis of **Figures 1** and **2**, it can be seen that, in general, there is low connectivity between the cities in the state of Acre. Connections between cities is concentrated along the BR-364 highway, which links the two most populous cities in the state (Cruzeiro do Sul and Rio Branco). In addition, there was a certain level of connectivity between the municipalities close to the state capital (Rio Branco), due to its influence as a regional capital (**Figure 2**). Rio Branco is a center for logistics and communication services, which allows it to function as a meeting place, thereby adding value and flow to production and resources of all kinds. Through being endowed with information and knowledge infrastructure, a regional capital integrates into broader networks (national and even global).[24]

In the expansion process, a central agglomeration brings relationships closer and starts to share functions with neighboring municipalities and non-agglomerated centers. These can become incorporated to the same unit within a radius of approximately 200 kilometers. In general, urban-regional arrangements operate as

Table 1. Characteristics of spatiotemporal clusters of severe acute respiratory syndrome in municipalities in the state of Acre, Brazilian Amazon region, 2020-2021

Clusters	Duration (from first to last week)	Cases (observed/expected)	Relative risk	LLR	Number of municipalities
Cluster 1	17 to 48	2.39	4.10	667.75	1
Cluster 2	22 to 48	5.10	5.30	112.63	1
Cluster 3	21 to 39	2.07	2.14	37.49	1
Cluster 4	33 to 38	4.24	4.26	16.37	1

LLR = log-likelihood ratio.

receiving and diffusing spaces for decisions and capital, with integration of state, national and international scopes, such that these are marked out as focuses of concentration (and thus becoming established as the main centers of the Brazilian urban network).[25]

This scenario will have contributed to the increase in the numbers of SARS cases observed over the study period (**Figures 3** and **4**), given that cities with greater economic activity would tend to have greater movement of people, thus contributing to the circulation of the virus at home and at work. This can be further aggravated by movement of migrant workers, who are often in contact with people from different locations, thereby contributing to increased disease transmission.[26] Thus, identification of people with SARS, and consequently ensuring their isolation, can prevent transmission to other individuals.[27]

Our results showed that clusters 2, 3 and 4 started to form in week 21 (i.e. after the formation of cluster 1). This suggests that the number of cases of SARS in the municipalities of Acre spread outwards from Rio Branco. In fact, cluster 2 could possibly have been influenced by its proximity to Rio Branco, as it had a time duration of 27 weeks, in addition to having the highest RR among all the clusters (**Table 1**). Furthermore, the presence of regional airports and their importance in the regions of influence where they are located partly explains the cases of COVID-19 in more isolated regions,[19] such as Cruzeiro do Sul (a subregional center with an airport) (**Figure 2**). Reinforcing our findings, a structured compartmental model (in agreement with data observed in large countries such as Brazil) indicated that maintenance of a high number of COVID-19 cases in Brazil could be supported by the geographical spread of the disease, which would occur from the state capitals to the interior of the country.[28]

Nevertheless, there was little connection between the municipalities in the middle of the state (Jordão, Marechal Thaumaturgo, Porto Walter and Santa Rosa do Purus), which is a possible explanation for the lower rates/intensities of SARS in these cities (**Figures 3** and **4**). This can be explained by the low circulation of people between these municipalities, which would tend to give rise to low circulation of the disease. Corroborating our results, a study showed that the spread of the virus across Brazilian territory occurred from spaces with greater density of relationships, such that the country's economic organization modeled the direction, temporality and intensity of COVID-19 cases. Thus, the spread of the disease across the country took on zonal, reticular and spot geographical features.[29]

It is noteworthy that the low level of testing in this country would probably be an explanation for the reduction in rates and intensities observed in the last study period, since Brazil is one of the countries that has done least testing in the world; it even has a lower testing rate than Uruguay, Argentina and Chile.[30]

Diffusion of COVID-19 is a global public health problem that poses a challenge that needs to be faced today. It is thus necessary to take a fresh look at new problems.[31] In view of this pandemic, governments around the world have adopted a variety of measures with the objective of reducing infections and deaths, and their consequences in economic terms.[32] The spread of the disease is related to the territorial division of labor, as seen in urban networks, which present hierarchies between cities. It is necessary to combat the spatial diffusion of the disease both through reduction of infections and through treatment of patients.[19]

Although rarely considered in socioeconomic development planning, city networks transform the territory, such that cities need to be analyzed together, in order to observe their relationships with other cities. In this way, the network of cities is integrated in a territorial cross-section. As an organic system, this demands integrated attention in order to raise the quality of flows between centralities and to plan physical and virtual movements.[24]

Regarding possible limitations of this study, a secondary database with provisional and incomplete records was used, which may have led to underestimation of SARS cases in Acre or even to information bias. This type of bias may also have occurred when the municipality of residence was recorded, which was informed by the respondent. As this was an ecological study, we must also highlight possible confounding in the analyses that were carried out, which may have occurred through the characteristics of this design. Furthermore, studies using approaches at aggregated levels do not allow inferences at individual level (ecological bias).

CONCLUSION

From the analysis on the flow maps and power centers of the municipalities, it is possible to project a fairer future with regard to occupation of the territory, with more equal distribution of opportunities and more environmentally appropriate activities.[24] Based on the above, priority areas for interventions to control the transmission of COVID-19 were shown, with the aim of reducing the risks of transmission to more distant areas within the urban hierarchy of the state of Acre, through controlling human mobility.[33]

Although our results reinforce the evidence regarding the spread of the disease through airports, roads and rivers can also be highlighted as transmission routes, as they facilitate contact between people from different locations.

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Address for correspondence:
Mário Ribeiro Alves
Instituto de Saúde Coletiva (ISC), Universidade Federal de Mato Grosso (UFMT)
Av. Fernando Correa da Costa, 2.367
Boa Esperança — Cuiabá (MT) — Brasil
CEP 78060-900
Tel. (+55 65) 3615-6243
E-mail: malvesgeo@gmail.com

Risk factors for hospitalization and death due to COVID-19 among frail community-dwelling elderly people: a retrospective cohort study

Daniela Castelo Azevedo[I], Fernando César Menezes Assunção[II], Mônica Silva Monteiro de Castro[III], Estevão Alves Valle[IV]

Clínica Mais 60 Saúde, Belo Horizonte (MG), Brazil

[I]MD, PhD. Physician and Research and Data Science Head, Clínica Mais 60 Saúde, Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-8749-6541

[II]MD. Physician, Clínica Mais 60 Saúde, Belo Horizonte (MG), Brazil; and Chief Executive Officer, LifeCode™ Information System, Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0001-8527-4227

[III]MD, PhD. Postdoctoral Research Group Member, Health Policy and Social Protection Research Group, Instituto René Rachou, (FIOCRUZ Minas), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0003-2461-3699

[IV]MD, PhD. Chief Medical Officer, Clínica Mais 60 Saúde, Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0001-9138-9952

ABSTRACT

BACKGROUND: Advanced age, multiple chronic diseases and frailty have been correlated with worse prognosis among coronavirus disease 2019 (COVID-19) inpatients.

OBJECTIVE: To investigate potential risk factors for hospitalization and death due to COVID-19 among frail community-dwelling elderly people.

DESIGN AND SETTING: Retrospective cohort study of patients followed up at a geriatric outpatient clinic in Belo Horizonte, Minas Gerais, Brazil.

METHODS: The associations of demographic characteristics (age and sex) and clinical characteristics (frailty, multimorbidity, number of medications with long-term use, obesity, smoking, diabetes mellitus, pulmonary diseases, cardiovascular diseases, cerebrovascular disease, and chronic kidney disease) with the risk of hospitalization and death due to COVID-19 were explored using a multivariable logistic regression model.

RESULTS: 5,295 patients (mean age 78.6 ± 9.4 years; 72.6% females) were included. After adjustments, the number of medications with long-term use was found to increase the odds of hospitalization due to COVID-19 (odds ratio, OR: 1.13; 95% confidence interval, CI: 1.06-1.22). Frailty, multimorbidity and diabetes mellitus also increased the odds of hospitalization (OR: 1.06, 95% CI: 1.02-1.09; OR: 1.17, 95% CI: 1.09-1.26; and OR: 2.27, 95% CI: 1.45-3.54, respectively) and the odds of death due to COVID-19 (OR: 1.07, 95% CI: 1.00-1.14; OR: 1.16, 95% CI: 1.03-1.32; and OR: 2.69, 95% CI: 1.79-6.14, respectively).

CONCLUSIONS: Multimorbidity, frailty and diabetes mellitus increased the odds of hospitalization and death due to COVID-19 and the number of medications with long-term use increased the odds of hospitalization due to COVID-19 among frail community-dwelling elderly people.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic remains a major global public health problem. The World Health Organization (WHO) registered over 153 million cases and three million deaths up to the beginning of May 2021.[1] In Brazil, there have been more than 500,000 deaths due to this disease and, recently, there has been a sharp increase in the number of cases (a "second wave"), which has put a lot of pressure on the healthcare system, with occupation rates of more than 90% in intensive care units in many Brazilian states.[2]

Advanced age and several diseases, such as diabetes mellitus, chronic kidney disease, cardiovascular disease and chronic respiratory disease have been correlated with worse outcomes, such as hospitalization, need for invasive ventilation and mortality due to COVID-19.[3-6] Furthermore, in addition to older age and presence of chronic diseases, it is also important to consider frailty and multimorbidity, particularly among the elderly.[4]

Frailty is characterized by decreased strength, resistance and physiological response, which translates into faulty reestablishment of homeostasis after a stressing event, thus leading to a high risk of incapacity.[7] Studies on patients older than 60 years of age have demonstrated that frailty is associated with a higher risk of death[4] and with greater disease severity among patients hospitalized due to COVID-19.[8] Similarly, multimorbidity, which consists of co-occurrence of multiple diseases or clinical conditions in one person,[9] is a factor to be considered among older adults with COVID-19, since the presence of multiple chronic health problems may be related to unfavorable clinical outcomes, such as hospitalization and death.[10]

Associations and impacts of chronic diseases, frailty and multimorbidity in relation to the outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been studied especially among hospitalized patients.[4,8,10,11] For example, in one systematic review with meta-analysis that revealed that hypertension, diabetes mellitus, cardiovascular diseases and chronic respiratory diseases were morbidities that increased the risk of developing greater severity of infection by SARS-CoV-2, only studies on hospitalized patients were considered.[11]

OBJECTIVE

The aim of this study was to investigate which demographic and clinical characteristics, including frailty and multimorbidity, were associated with higher risk of hospitalization and death due to COVID-19 among frail elderly people who were followed up at a primary healthcare facility in Belo Horizonte, state of Minas Gerais, Brazil.

METHODS

Design and sample

A retrospective cohort study was conducted using data from an electronic medical record system (LifeCode version 2021-03-25, EFG Inteligencia e Consultoria Ltda, Belo Horizonte, Brazil) that was specially developed for primary healthcare patients (≥ 60 years old) who were being followed up at a geriatric outpatient clinic (for patients ≥ 60 years old) delivering healthcare for patients with private insurance plans in Belo Horizonte.

At this clinic, patients are followed up monthly, either in person or remotely, by members of a multidisciplinary team (doctors, nurses, physical therapists, psychologists, nutritionists, phono-audiologists and pharmacists). The data relating to the appointments are registered in these electronic medical records that were developed for following up older patients. Information on conditions and health events relevant to this population, such as diagnosis, medications with long-term use, laboratory test results, emergency department visits, hospitalizations and death is systematically registered. The multidisciplinary team contractually undertakes filling out the electronic medical records completely and assertively while working at the clinic. The data collected is stored in the Microsoft SQL server and is made available for research when requested.

All patients with valid data who were followed up from March 15, 2020, to April 15, 2021, were included in the present study.

The present study was approved by the research ethics committee of Associação Evangélica Beneficente de Minas Gerais and by the National Research Ethics Committee (CEP 3.843.183 and CAAE 28980120; date: February 17, 2020) and forms part of a cohort study that has investigated the health of community-dwelling elderly people. All participants signed a written informed consent statement after they had been informed of the nature and details of the study.

Assessment of COVID-19, hospitalization and death due to COVID-19

Since the first case of COVID-19 in Belo Horizonte, which was detected on March 16, 2020,[12] patients have been advised to call the clinic if they were exhibiting any of the symptoms that have been linked to COVID-19 (fever, coughing, fatigue, loss of smell and taste, difficulty in breathing, mental confusion or chest pain).[13] Patients are evaluated by telephone by a nurse and, if symptoms suggestive of COVID-19 are confirmed, an in-person appointment is scheduled. Whenever necessary, tests are made, and in severe cases, the patient is hospitalized.

Besides this approach, the multidisciplinary team asks about infection, emergency department visits and hospital admissions due to COVID-19, at periodic contacts with patients or with the person responsible for the patient. These events and dates are entered into the medical records. Tests performed on these occasions, as well as the hospital discharge summaries, are logged and attached to the records. Deaths among any patients followed up are informed monthly through the health insurance plan. The team assesses the families in cases of death, to record the causes and circumstances

In the present study, a diagnosis of COVID-19 registered in the medical records was considered to be an incident case of the disease. Similarly, hospitalization and death due to COVID-19 were considered from the registrations of these events in the medical records.

Assessment of demographic and clinical characteristics

Sex, age and clinical characteristics were evaluated regarding the risks of hospitalization and death due to COVID-19. Among the clinical characteristics, frailty, multimorbidity, long-term use of medications, obesity, smoking, diabetes mellitus (DM), respiratory diseases, cardiovascular diseases, cerebrovascular disease and chronic kidney disease (CKD) were considered.[5,14]

Frailty was evaluated using the Clinical-Functional Vulnerability Index - 20 (Índice de Vulnerabilidade Clínico Funcional, IVCF-20). This is a multidimensional instrument that assesses aspects of the health of older adults through 20 questions distributed into eight sections: age, self-perception of health, everyday activities, cognition, mood, mobility, communication and multiple comorbidities.[15] Each section has a specific score and these add up to a maximum of 40 points. The higher the resulting value is, the higher the clinical-functional vulnerability risk of the older adult also is. Total scores higher than 7 characterize older adults as frail.[15] This instrument has been found to be a valid and reliable measurement for assessing frailty among community-dwelling patients ≥ 60 years of age.[15]

Multimorbidity was measured through the number of medical diagnoses. The diagnosis count has been commonly used to assess multimorbidity within primary healthcare.[16] The number of medications with long-term use was evaluated as listed in the medical record. Weight and height were taken from the mobility section of IVCF-20.[15] In this section, these measurements are recorded and the body mass index (BMI, in kg/m^2) is calculated. Patients were considered to be obese if they had BMI $\geq$ 30.[17]

Smoking, DM and CKD were evaluated from their diagnoses in the medical records. Respiratory diseases were assessed through diagnoses of asthma and/or chronic obstructive lung disease. Cardiovascular disease was assessed through any of the following diagnoses: cardiomyopathy, coronary disease with or without previous acute myocardial infarction, heart failure with preserved ejection fraction and congestive heart failure. Cerebrovascular disease was assessed through a diagnosis of previous stroke.

Statistical analysis

Descriptive analyses were conducted using frequencies and percentages (%) for categorical variables and using means and standard deviations (SD) for continuous variables.

Univariate and multivariable multinomial logistic regressions were used to investigate individual associations of demographic and clinical characteristics with the risks of hospitalization and death due to COVID-19. Variables with P-values of 0.05 or less in the univariable analysis were included in the multivariable analysis and adjusted for age, sex and frailty level (IVCF-20); frailty was corrected only for sex and age.

The results were presented as odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed using STATA (version 14.1, StataCorp LP, College Station, Texas, United States).

RESULTS

A total of 5,295 patients were included, of mean age 78.6 ± 9.4 years, and most of them were women (72.6%). The mean IVCF-20 score was 16.8 ± 6.9), the mean number of diagnosis was 5.4 ± 3.0) and the mean of number of medications with long-term use was 5.2 ± 3.1).

COVID-19 affected 339 patients (6.4%) during the study period. Out of these, 82 (24.2%) needed to be hospitalized and 23 died due to complications from the infection (case-fatality rate of 6.8%). The monthly numbers of diagnoses and deaths due to COVID-19 during the 12-month period are shown in **Figure 1**.

The demographic and clinical characteristics of the sample are described in **Table 1**. The patients hospitalized due to COVID-19 and those who died from COVID-19 were older and frailer, with more morbidities and more long-term use of medications. Furthermore, DM and cardiovascular diseases also were more prevalent in this group.

Table 2 displays the results from the univariate and multivariate logistic regressions regarding associations between demographic and clinical characteristics and hospitalization due to COVID-19. Age, frailty, multimorbidity, long-term use of medications, DM and cardiovascular disease increased the odds of hospitalization due to COVID-19 in the univariate analysis (**Model 1**). Multimorbidity, number of medications with long-term use and DM also increased
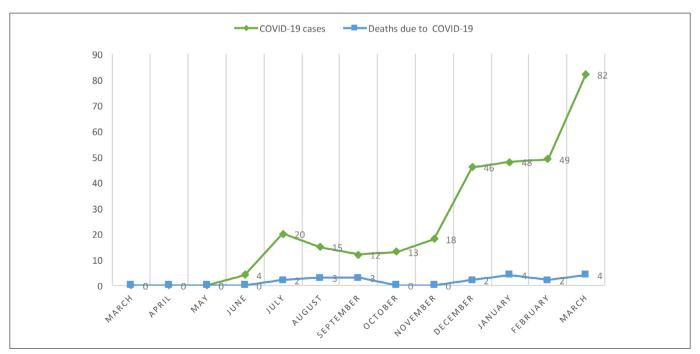
Figure 1. Monthly cases and deaths due to coronavirus disease 2019 (COVID-19): March 2020 to March 2021.

the odds of hospitalization due to COVID-19 regardless of sex, age and frailty (**Model 2**). An association of stronger magnitude was observed for DM (OR: 2.27; 95% CI: 1.45-3.56).

Table 3 displays the results from the univariate and multivariate logistic regressions on associations between demographic and clinical characteristics and death due to COVID-19. The same characteristics associated with higher odds of hospitalization also increased the odds of death due to COVID-19, except for cardiovascular disease in the univariate analysis (**Model 1**). Multimorbidity (OR: 1.16; 95% CI: 1.03-1.32) and DM increased the odds of death due to COVID-19 (OR: 2.69; 95% CI: 1.79-6.14), even after adjusting for sex, age and frailty.

DISCUSSION

In this retrospective cohort study among frail community-dwelling elderly people, older age and frailty increased the odds of hospitalization and death due to COVID-19. Our results also showed that, independently of the effects of age and frailty, multimorbidity and DM increased the odds of hospitalization and death. Furthermore, the number of medications with long-term use increased the odds of hospitalization due to COVID-19.

Advanced age has already been consolidated as a risk factor for death due to COVID-19,[18] with a case-fatality rate of 19.3% among individuals over 65 years old,[19] and a risk of death three times greater for those between 60 and 69 years old, compared

Table 1. Demographic and clinical characteristics of the sample

Demographic and clinical characteristics	Overall sample n = 5,295	With COVID-19 n = 339	Hospitalization due to COVID-19 n = 82	Death due to COVID-19 n = 23
Age (mean ± SD)	78.6 ± 9.4	77.7 ± 9.7	81.0 ± 8.1	82.6 ± 7.5
Females (%)	72.6	70.8	64.6	60.8
Frailty (mean ± SD)	16.8 ± 6.9	17.25 ± 7.01	19.6 ± 7.9	20.9 ± 8.0
Multimorbidity (mean ± SD)	5.4 ± 3.0	6.8 ± 3.2	7.3 ± 3.0	7.6 ± 2.6
Medications with long-term use (mean ± SD)	5.2 ± 3.11	5.5 ± 3.1	6.7 ± 3.0	6.6 ± 2.8
Obesity (%)	52.7	59.3	60.1	52.2
Smoking (%)	4.0	3.8	3.7	4.3
Diabetes mellitus (%)	27.5	32.2	47.6	52.2
Respiratory diseases (%)	7.9	9.7	8.5	4.3
Cardiovascular diseases (%)	9.0	10.0	15.8	17.4
Chronic kidney disease (%)	10.5	8.5	6.1	8.7
Cerebrovascular disease (%)	5.8	5.6	8.1	7.7

Frailty = values from Clinical-Functional Vulnerability Index - 20 (Índice de Vulnerabilidade Clínico Funcional – 20, IVCF-20); multimorbidity = number of diagnoses; SD = standard deviation; COVID-19 = coronavirus disease 2019.

Table 2. Demographic and clinical characteristics associated with risk of hospitalization due to coronavirus disease 2019 (COVID-19)

Demographic and clinical characteristics	Hospitalization due to COVID-19	
	Model 1 OR (95% CI)	Model 2[a] OR (95% CI)
Age	1.02 (1.00-1.05)	...
Females	1.46 (0.92-2.31)	...
Frailty	1.05 (1.02-1.09)	1.06 (1.02-1.09)
Multimorbidity	1.19 (1.12-1.27)	1.17 (1.09-1.26)
Medications with long-term use	1.16 (1.08-1.24)	1.13 (1.06-1.22)
Obesity	1.41 (0.90-2.20)	...
Smoking	0.90 (0.28-2.88)	...
Diabetes mellitus	2.42 (1.56-3.75)	2.27 (1.45-3.56)
Respiratory disease	1.08 (0.49-2.36)	...
Cardiovascular disease	1.92 (1.05-3.50)	1.60 (0.87-2.96)
Chronic kidney disease	0.54 (0.22-1.36)	....
Cerebrovascular disease	1.45 (0.66-3.18)	....

[a]Adjusted for sex, age and frailty; except frailty, adjusted for sex and age; multimorbidity = number of diagnoses; frailty = values from Clinical-Functional Vulnerability Index - 20 (Índice de Vulnerabilidade Clínico Funcional – 20, IVCF-20); OR = odds ratio; CI = confidence interval.

Table 3. Demographic and clinical characteristics associated with risk of death due to coronavirus disease 2019 (COVID-19)

Demographic and Clinical Characteristics	Deaths due to COVID-19	
	Model 1 OR (95% CI)	Model 2[a] OR (95% CI)
Age	1.05 (1.00-1.10)	...
Females	1.71 (0.73-3.96)	...
Frailty	1.04 (1.02-1.14)	1.07 (1.00-1.14)
Multimorbidity	1.22 (1.08-1.37)	1.16 (1.03-1.32)
Medications with long-term use	1.16 (1.08-1.24)	1.09 (0.96-1.25)
Obesity	0.98 (0.43-2.22)	...
Smoking	1.08 (0.14-8.08)	...
Diabetes mellitus	2.88 (1.27-6.55)	2.69 (1.79-6.14)
Respiratory disease	0.52 (0.70 -3.90)	...
Cardiovascular disease	2.13 (0.72-6.28)	...
Chronic kidney disease	0.80 (0.18-3.46)	...
Cerebrovascular disease	1.36 (0.32-5.78)	...

[a]Adjusted for sex, age and frailty; except frailty, adjusted for sex and age; multimorbidity = number of diagnoses; frailty = values from Clinical-Functional Vulnerability Index - 20 (Índice de Vulnerabilidade Clínico Funcional – 20, IVCF-20); OR = odds ratio; CI = confidence interval.

with those between 50 and 59 years old.[20] Frailty has also emerged as a factor associated with worse prognosis for older patients with COVID-19. From a cohort of 1,564 COVID-19 inpatients, with mean age of 74 years, it was shown that a more pronounced level of frailty increased the hospital stay and the risk of mortality, even after adjustments for age, sex, smoking and morbidities. The risk of death was four times higher among patients with the highest level of frailty on the Clinical Frailty Scale (hazard ratio, HR: 4.41; 95% CI: 2.90-6.71), compared with non-frail patients.[21] From another cohort of 114 COVID-19 inpatients in Wuhan, China, with mean age of 67 years, it was shown that frail and pre-frail patients presented higher risk of developing severe disease (severe pneumonia or severe acute respiratory syndrome) within 60 days.[8]

Like frailty, the presence of morbidities has also been correlated with increased risk of death due to COVID-19. In a systematic review with a metanalysis on 58 cohort studies (122,191 participants), the risk of death among COVID-19 inpatients was doubled for patients with any morbidity, compared with those without any disease.[22] In that study, DM also increased the risk of death 1.8-fold.[22]

Additionally, multimorbidity has been associated with higher mortality among COVID-19 inpatients. In a cross-sectional study with data from 1,591 patients hospitalized due to COVID-19 in Italy, it was demonstrated that patients who died from COVID-19 had higher multimorbidity, as measured using the Charlson Comorbidity Index.[23] A retrospective cohort study with 5,621 COVID-19 inpatients in South Korea provided support for the idea that multimorbidity is a predictor of worse prognosis (admission to the intensive care unit, use of mechanical ventilation or use of extracorporeal membrane oxygenation) and mortality.[24] A study in the United States using data from the Department of Veteran Affairs healthcare system, from 10,131 people infected with SARS-CoV-2, with a median age of 63.6 years, also showed that higher multimorbidity was associated with higher risk of death.[25]

While a growing number of studies has supported the notion that frailty and morbidity, including diabetes mellitus, are risk factors for adverse prognosis and death among patients hospitalized due to COVID-19, our study is one of the few to explore these risk factors among elderly people who were followed up on an outpatient basis. Therefore, our study provides an important contribution to investigation of prognostic factors relating to COVID-19. Moreover, it was possible to demonstrate that multimorbidity contributed to the COVID-19 prognosis regardless of frailty and age.

Nonetheless, the present study had some limitations relating to its observational design. Despite adjustments for potential confounding variables, the presence of residual confounders cannot be ruled out. Our use of a retrospective source of data might have compromised the quality of information, but we minimized this problem through the specificity of the electronic medical records used in our clinic. In the same way, even though the data used came from required fields in the electronic medical records, we cannot rule out the possibility that some information may have been lost due to inadequate and incomplete filling out of the electronic medical records.

CONCLUSIONS

Our results help to identify independent risk factors for hospitalization and death due to COVID-19 among frail community-dwelling elderly people. This is of fundamental importance for planning healthcare actions in this population, which remains vulnerable to complications from SARS-CoV-2 infection.

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Address for correspondence:
Daniela Castelo Azevedo
Clínica Mais 60 Saúde
R. Juiz de Fora, 1.071
Barro Preto — Belo Horizonte (MG) — Brasil
CEP: 30180-060
Tel. (+55 31) 2513-0552
E-mail: danielacastelo@mais60saude.com.br

Association between bone mineral density and content and physical growth parameters among children and adolescents diagnosed with HIV: a cross-sectional study

Suellem Zanlorenci[I], Priscila Custódio Martins[II], Carlos Alencar Souza Alves Junior[III], João Antônio Chula de Castro[IV], Luiz Rodrigo Augustemak de Lima[V], Edio Luiz Petroski[VI], Diego Augusto Santos Silva[VII]

Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil

[I]BSc. Master's Student in Physical Activity and Health, Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil
  https://orcid.org/0000-0002-7476-5511

[II]MSc. Doctoral Student, Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
  https://orcid/org/0000-0002-63885550

[III]MSc. Doctoral Student, Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
  https://orcid.org/0000-0002-5928-0567

[IV]MSc. Doctoral Student, Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
  https://orcid.org/0000-0001-6214-944X

[V]PhD. Adjunct Professor, Instituto de Educação Física e Esporte (IEFE), Universidade Federal de Alagoas (UFAL), Maceió (AL), Brazil.
  https://orcid.org/0000-0003-0280-0151

[VI]PhD. Associate Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil; and Researcher, Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil.
  https://orcid.org/0000-0001-8480-0846

[VII]PhD. Associate Professor, Department of Physical Education, Universidade Federal de Santa Catarina (UFSC), Florianópolis (SC), Brazil; and Researcher, Research Center in Kinanthropometry and Human Performance, Florianópolis (SC), Brazil.
  https://orcid.org/0000-0002-0489-7906

ABSTRACT

BACKGROUND: During childhood and adolescence, there are significant increases in bone mineral content (BMC) and bone mineral density (BMD).

OBJECTIVE: To investigate physical growth parameters associated with BMD and BMC among children and adolescents diagnosed with human immunodeficiency virus (HIV).

DESIGN AND SETTING: Cross-sectional study conducted in Florianópolis, Brazil, among 63 children and adolescents (aged 8-15 years) diagnosed with HIV.

METHOD: BMD, BMC and fat percentage z score were evaluated using dual X-ray absorptiometry. Age/height z score and body mass index (BMI)/age z score were obtained in accordance with international recommendations, and bone age was obtained through hand-wrist radiography. Sex, family income, information on HIV infection (T CD4+ lymphocyte count, viral load and type of antiretroviral therapy, moderate-vigorous physical activity and sedentary behavior) were used as adjustment variables in the analyses. Simple and multiple linear regression analyses were performed, with a significance level of $P \leq 0.05$.

RESULTS: Subtotal BMD (without the head region) was directly associated with bone age, BMI/age z score and fat percentage z score, even after adjusting for covariates. Subtotal BMC/height was directly associated with bone age, height/age z score, BMI/age z score and fat percentage z score, even after adjusting for covariates.

CONCLUSION: Subtotal BMD and subtotal BMC/height were directly associated with physical growth indicators among children and adolescents diagnosed with HIV.

INTRODUCTION

During childhood and adolescence, significant increases in bone mineral content (BMC) and bone mineral density (BMD) occur in association with the growth spurt and a high mineralization rate.[1] These factors are considered to be determinants for protection against osteopenia, and later against osteoporosis, during adult life.[2] Among children and adolescents diagnosed with human immunodeficiency virus (HIV), lower bone mass concentrations and mineralization rates may occur due to impairments of adequate physical growth and consequent pubertal delay associated with HIV infection and prolonged use of antiretroviral therapy (ART).[3,4]

In the growth process, regardless of sex, BMD and BMC concentrations do not develop linearly with chronological age. Their growth rate has been shown to be higher after the growth spurt.[5] In a study conducted among children and adolescents diagnosed with HIV (aged 8-16 years), it was found that body mass, body mass index (BMI) and body fat were directly associated with BMD.[6] The mechanisms through which HIV can lead to changes in BMD are not fully understood, but are probably multifactorial, including factors associated with HIV (ART and disease stage)[6] and modifiable risk factors (changes in physical growth, low physical activity and highly sedentary behavior).[6] Use of ART can decrease the BMC and BMD of patients diagnosed with HIV.[7] In a previous study, a direct association between moderate-vigorous physical activity (MVPA) and high gravitational or muscular load and bone mass was identified among children and adolescents without any diagnosis of HIV.[8] This highlights the importance of factors relating to disease/treatment and lifestyle, which can impact physical growth parameters.

Studies carried out among children and adolescents diagnosed with HIV showed that height/age z score was a bone mass predictor.[6,9] Cross-sectional studies have only investigated associations

between BMD and physical growth parameters, with no data regarding BMC.[6,9,10] Other studies did not consider lifestyle variables, such as MVPA and sedentary behavior, in correlating BMD and BMC with physical growth parameters.[11-13]

OBJECTIVE

Thus, the aim of this study was to investigate physical growth parameters associated with BMD and BMC among children and adolescents diagnosed with HIV.

METHODS

Research characteristics

This was a cross-sectional study that formed part of the "Saúde PositHIVa" study, carried out in the city of Florianópolis, Santa Catarina, Brazil, from August 2015 to June 2016. The study complied with all ethical procedures, and had received approval from the Research Ethics Committee of the Universidade Federal de Santa Catarina (UFSC) (protocol no. 1.410.144) (CAAE protocol: 49691815.0.0000.0121, dated June 2010) and from the Ethics Committee of the "Joana de Gusmão" Children's Hospital (HIJG) (protocol no. 850.0777, dated January 12, 2009). A free and informed consent statement was signed by the participants' parents or legal guardians and a consent statement was signed by the participating children and adolescents.

Population and sample

Children and adolescents diagnosed with HIV (vertical transmission) who were recruited at the outpatient clinic of a regional HIV reference center the HIJG, located in the city of Florianópolis, capital of the state of Santa Catarina, participated in this study. In 2015, among the children and adolescents diagnosed with HIV who were assisted at HIJG, 83 were eligible for this study. However, 14 were excluded because they refused to participate in the research, four withdrew from participation over the course of the study and two did not participate in all the data collection stages necessary for the statistical analyses of the present study. Thus, 63 participants were assessed.

The sample size was calculated *a posteriori* taking into account type I error ($\alpha = 0.05$) and type II error ($\beta = 0.95$), to identify associations between physical growth parameters and BMD and BMC, of medium effect size (0.50). All calculations were performed using the G* Power software, version 3.1.9.2 (Universität Düsseldorf, Germany), and 30% were added for losses and refusals. Thus, for multiple linear regression analysis, the sample of 63 children and adolescents made it possible to find associations with an average effect size of 0.50.

Eligibility criteria

The inclusion criteria were that the subjects needed to: 1) present HIV infection through vertical transmission in the medical record; 2) be aged 8-15 years; 3) have clinical and laboratory information available in the medical record; and 4) be able to stand and communicate.

The exclusion criteria were the following situations: 1) motor impairment or contraindication of vigorous exercise; 2) speech, hearing and/or cognitive impairment; 3) diseases that change body composition, except for those related to HIV infection; and 4) regular use of diuretic drugs or immunotherapies not related to ART.

Study variables

Dependent variables

BMD and BMC analyses were carried out by means of dual emission X-ray absorptiometry (DXA). DXA measurements were performed at the Laboratory of Anthropometry, Health Sciences Center (CCS), UFSC, using the Lunar Prodigy Advance equipment, model Discovery WiFan-Beam, serial number 81593, (GE Medical Systems, Madison, Wisconsin, United States). X-ray attenuation in body tissues was computed using the Encore 2004 software, version 8.10.027 (GE Lunar Corporation, Madison, Wisconsin, United States).

Internal quality control was obtained through a daily automatic calibration process that preceded evaluations and which was done in accordance with the manufacturer's instructions. One researcher who had previously been trained to make these measurements, was responsible for all evaluations and followed all the procedures standardized by the equipment manufacturer. During the evaluations, the participants were instructed to wear appropriate clothing (top or bikini and swimming trunks) and be barefoot, without use of earrings and/or finger rings or any metallic adornments.

The evaluations performed through DXA produced measurements of subtotal BMD (without the head region) and subtotal BMC (without the head region), with corrections for height and body fat percentage. These subtotal measurements (BMD and BMC) are considered to be parameters with good accuracy and reproducibility, compared with total BMD and BMC, which can dilute changes in bone mass.[14]

Independent variables

The physical growth variables evaluated were the age/height z score, BMI/age z score and fat percentage z score. Z scores allow specific values to be compared with the population, taking into account typical values and dispersion, and considering age and sex.[15]

To calculate the z score standardized according to age and height, height was obtained using a stadiometer (Altura Exata, Belo Horizonte, Brazil), with measurement capacity from 115 cm to 210 cm and resolution of 0.1 cm, in accordance with the recommendations proposed by the International Society for the Advancement of Kinanthropometry (ISAK).[16] Chronological age was collected through an interview.

To calculate the z score standardized according to age and BMI, body mass was obtained using a portable digital scale (Tanita; model BF-683W) with 0.1 kg accuracy and capacity for up to 150 kg. BMI was calculated from body mass and height measurements. For body mass measurements, the recommendations of the International Society for the Advancement of Kinanthropometry (ISAK)[16] were followed.

To calculate the z score standardized according to fat percentage, the fat percentage was obtained through DXA. Test-retest reproducibility for body fat was examined in an independent sample of the present study (n = 10) that was similar in age and sex distribution: 11.6 ± 5.8 and 11.5 ± 5.9 kg; intraclass correlation coefficient (ICC) = 1.00; 95% confidence interval (CI) = 0.99-1.00.[17]

Bone age was assessed by means of left-limb hand-wrist radiography, following standardized procedures,[18] in which the hand-wrist region of the left limb, in the anteroposterior direction, was positioned at a distance of 100.0 cm from the equipment. The fingers were extended, with the third finger in line with the forearm. The forearm, palm and fingers were in contact with the film plate and the x-ray beam was centered in the distal region of metacarpal III. Bone age was determined by comparing the radiography obtained with a series of standard radiographs that represent the skeletal maturation process in healthy subjects.[18] The radiographs were read by a radiology specialist and all procedures were performed at the Department of Radiology of HIJG.

Covariates

The variables of sex (male or female) and family income were collected using a questionnaire developed for this study. Family income was determined as the number of minimum monthly wages (1 minimum wage at the time of the study was R$ 724.00) and was categorized in the following ranges: ≤ 2 minimum wages; > 2 to 5 minimum wages; or > 5 minimum wages.

Information on HIV infection was obtained through analysis of the medical records, from which information was obtained regarding CD4+ lymphocyte count, viral load and type of ART. The type of ART was categorized as follows: use of ART with protease inhibitors (PI); use of ART without PI; or no use of ART.

Data on moderate to vigorous physical activity (MVPA) and sedentary behavior were collected by means of triaxial Actigraph accelerometers (3.8 x 3.7 x 1.8 cm), model GT3XE-Plus (Manufacturing Technology Inc., Fort Walton Beach, United States). These allowed measurement of acceleration produced through body movement.[19] This equipment was used continuously over a period of 7 to 14 days, including weekends.[19,20] The participants were instructed to attach the equipment to the right hemibody at the waistline early in the morning and use it until the end of the day, and only to remove it for activities in water and for sleeping.[20] The motion sensor was calibrated and the stored information was downloaded to the Actilife 6.0 software (ActiGraph, Pensacola, Florida, United States) in a process that took 15 seconds. The subject's usual physical activity was represented by at least four valid days, comprising three weekdays and one weekend day containing at least 10 hours of information (600 minutes), after removing nonuse periods of at least 60 consecutive zeros.[21] Contacts through phone calls and messages, at least once a week, were used to ensure regular use of the device. Verbal and written instructions were provided to subjects and their guardians before the device was used.[20] For subjects who did not present valid days through previous measurements, up to two further attempts to use the device were made.

The numbers of minutes at different physical activity intensities were proportionally adjusted to a 14-hour period, considering that this is the average time agreed for this population. This was done through the following formula: adjusted minutes = (registered minutes/time of use) * (14 * 60).[22] The number of minutes of MVPA was obtained considering the cutoff point proposed by Evenson et al.[23] Uninterrupted blocks (bouts) of at least five and ten minutes of MVPA were derived.[22] The test-retest reproducibility of this protocol was examined using a subsample of the present study (42.6 ± 23.2 and 34.5 ± 17.2 minutes of MVPA on the first and second visits, respectively; ICC = 0.90; 95% CI = 0.74 to 0.96; n = 17). In view of the recommendations of the World Health Organization regarding MVPA, continuous data were dichotomized into "met recommendations" (≥ 60 minutes of MVPA per day) and "did not meet recommendations" (< 60 minutes of MVPA per day).[24] Regarding sedentary behavior, the accumulation of time spent with sedentary behavior was ascertained, and this variable was continuously analyzed.

Muscle strength was assessed using a handgrip test. The Saehan hydraulic dynamometer (Model SH5001, Saehan Corporation, Masan, Korea) was used. The device was positioned between the fingers and the palm at the base of the thumb, with extended elbow joint. The opening of the dynamometer was adjusted so that the second joint of the fingers fitted into the dynamometer handle. During the test, the dynamometer or the hand did not touch any other objects. Right handgrip (D) and left handgrip (E) were alternately assessed, with two attempts per assessment. The best left and right scores obtained in each test were added together to obtain the general score (D + E, in kilograms). The standardization of the Canadian Society for Exercise Physiology[25] was adopted.

Statistical analysis

Descriptive analysis was firstly performed (mean and standard deviation; and median and interquartile range) and observations with missing data were excluded. Kurtosis and asymmetry were assessed in order to ascertain whether the data had normal distribution (range from -2 to + 2), and histograms were also analyzed to identify data distribution normality. Pearson or Spearman

linear correlation and simple and multiple linear regression were used to verify correlations and associations between dependent and independent variables, respectively. For multiple linear regression analysis, three models were built. Hierarchical adjusted analysis was performed,[26] with division into three blocks: distal (sex and income), intermediate (viral load, CD4 and use of ART) and proximal (MVPA, sedentary behavior and muscle strength). All the variables remained in the adjusted model, regardless of the P-value of the crude analysis, using the forward method.

Regression coefficients (β), 95% confidence intervals and determination coefficients were estimated for each model analyzed (R^2) and for multicollinearity diagnosis (VIF), and the Cohen's D effect size was calculated.[27] For all analyses, the SPSS software (Statistical Package for the Social Sciences - IBM: SPSS Statistics, Chicago, United States), version 23.0, was used. P-values ≤ 0.05 were taken to be statistically significant.

RESULTS

Sixty-three children and adolescents who had been diagnosed with HIV participated in the study (males = 28; females = 35). In the full sample, the mean age was 12.14 years (± 1.95), the mean height was 147.3 cm (± 13.08), the mean body mass was 39.9 kg (± 11.04) and the mean bone age was 12.02 years (± 2.68) (data not shown in tables/figures). The sample characteristics are shown in **Table 1**.

Table 2 shows the correlation matrix among all the variables. Subtotal BMC/height showed a significant positive correlation with subtotal BMD, height/age z score, BMI/age z score, fat percentage z score and bone age. Subtotal BMD showed a significant positive correlation with BMI/age z score, fat percentage z score and bone age and showed a negative correlation with CD4+ lymphocytes (**Table 2**).

Simple linear regression analysis between subtotal BMD and physical growth among these children and adolescents diagnosed with HIV demonstrated that subtotal BMD was directly associated with bone age, which explained 64% of BMD variability (P < 0.001). After adding the covariates of sex, family income, viral load, CD4+ lymphocytes, ART, MVPA, sedentary behavior and muscle strength, subtotal BMD was found to be directly associated with bone age and the model explained 79% of the subtotal BMD variability (P < 0.001) (**Table 3**).

Subtotal BMD was directly associated with BMI/age z score, which explained 14% of subtotal BMD variability (P < 0.001) in the crude model. After adding the covariates of sex, family income, viral load, CD4, use of ART, MVPA, sedentary behavior and muscle strength (model III), subtotal BMD remained directly associated with BMI/age z score and the model explained 47% of subtotal BMD variability (P < 0.001). Subtotal BMD was directly associated with fat percentage z score, which explained 4% of its variability

(p = 0.005) in the crude model. The variables of sex, income, viral load, CD4+ lymphocytes, use of ART, MVPA, sedentary behavior and muscle strength (model III) were directly associated with fat percentage z score, which explained 36% of subtotal BMD variability (P < 0.001) (**Table 3**).

Simple linear regression analysis demonstrated that subtotal BMC/height was directly associated with bone age, which explained 69% of BMC variability (P < 0.001). The variables of sex, income, viral load, CD4+ lymphocytes, ART, MVPA, sedentary behavior and muscle strength (model III) were directly associated with bone age, which explained 76% of BMC variability (P < 0.001). Subtotal BMC/height was directly associated with height/age z score, which explained 3% of BMD variability (P = 0.005) in

Table 1. Characteristics of the children and adolescents diagnosed as HIV+ (n = 63)

Total sample (n = 63)		
	Mean (± SD)	**Median (p25; p75)**
Subtotal BMC/height (kg/cm)	8.07 (3.13)	7.94 (5.54; 9.65)
Subtotal BMD (kg/cm²)	8.37 (11.49)	8.23 (7.52; 9.12)
Age/height z score	-0.53 (1.12)	-0.58 (-1.31; 0.36)
BMI/age z score	-0.19 (1.01)	-0.20 (-0.87; 0.58)
Fat % z score	-1.55 (1.87)	-1.40 (-2.65; -0.08)
Bone age (years)	12.02 (2.68)	12.50 (10.00; 14.00)
Viral load (log)	2.16 (0.97)	1.60 (1.60; 2.63)
CD4+ lymphocyte (cells/mm³)	857.63 (367.73)	819.00 (574.50; 1096.00)
Sedentary behavior (min)	388.93 (216.61)	458.54 (214.11; 555.00)
Muscle strength (kg)	21.05 (9.78)	19.00 (14.00; 26.00)
n (%)		
MVPA		
Met recommendations	20 (30.80)	
Did not meet recommendations	43 (69.20)	
ART		
No use of ART	11 (16.90)	
ART with PI	15 (23.10)	
ART without PI	39 (60.00)	
Monthly income		
≤ 2 minimum wages	26 (40.00)	
> 2 to 5 minimum wages	23 (35.40)	
> 5 minimum wages	16 (24.60)	
Sex		
Male	28 (46.20)	
Female	35 (53.80)	

HIV = human immunodeficiency virus; BMC = bone mineral content; BMD = bone mineral density; SD = standard deviation; BMI = body mass index; ART = antiretroviral drugs; PI = protease inhibitors; n = sample number; kg = kilograms; cm = centimeters; min = minutes; MVPA = moderate to vigorous physical activity.

the crude model. The variables of sex, income, viral load, CD4+ lymphocytes, use of ART, MVPA, sedentary behavior and muscle strength (model III) were directly associated with height/age z score, which explained 28% of subtotal BMC/height variability (P = 0.004). Subtotal BMC/height was directly associated with BMI/age z score, which explained 16% of subtotal BMC/height variability in the crude model (P < 0.001). The covariates of sex, family income, viral load, CD4+ lymphocytes, use of ART, MVPA, sedentary behavior and muscle strength (model III) were associated with BMI/age z score, which explained 77% of subtotal BMC/height variability (P < 0.001). Subtotal BMC/height was not associated with fat percentage z score in the simple analysis. The variables of sex, income, viral load, CD4+ lymphocytes, use of ART, MVPA, sedentary behavior and muscle strength (model III) were directly associated with fat percentage z score, which explained 52% of subtotal BMC/height variability (P < 0.001) (**Table 4**).

DISCUSSION

The main findings of this study were: 1) there were direct associations between subtotal BMD and bone age, BMI/age z score and fat percentage z score, even after adjusting for covariates; and

2) subtotal BMC/height was directly associated with bone age, height/age z score, BMI/age z score and fat percentage z score even after adjusting for covariates.

In the present study, a direct association between subtotal BMD and bone age was observed. A previous study carried out among 1,218 children aged 6-18 years of both sexes, without any HIV diagnosis, also found a direct correlation between BMD and bone age.[28] One possible explanation for the association between BMD and bone age may be the correlation between the beginning, peak and end of the puberty growth spurt and specific bone development states.[10] The period from the beginning to the end of the puberty growth spurt lasts approximately two years, and the peak growth rate occurs around one year after the start of the growth spurt.[29] Linear growth in adolescence is greatest during pubertal development, with no net gain in bone mass after peak bone mass is reached.[30] Thus, peak bone mass is considered to form the bone reservoir for future life and is the factor that determines BMD in adulthood and, consequently, the risk of osteoporotic fractures.[30] It has thus been observed that linear growth is closely linked to skeletal development. However, because HIV infection and ART can affect bone development in children and adolescents diagnosed

Table 2. Pearson and Spearman correlation matrix between the variables investigated among children and adolescents diagnosed as HIV+

	MVPA	Viral load	CD4+ lymphocyte	SB	Subtotal BMC/height	Subtotal BMD	Age/height z score	BMI/age z score	Fat % z score	Muscle strength	Bone age	Sex	ART
Total sample (n = 63)													
Pearson and Spearman correlation coefficient													
Viral load (log)	-0.038												
CD4+ lymphocyte	0.125	-0.495[*‡]											
SB	-0.168	0.219	-0.192										
Subtotal BMC/height	0.020	-0.216	-0.217	-0.159									
Subtotal BMD	0.033	-0.093	-0.274[†‡]	-0.119	0.980[*‡]								
Age/height z score	0.122	-0.158	0.201	-0.027	0.240[*‡]	0.141							
BMI/age z score	0.045	-0.294[*‡]	-0.107	0.108	0.407[*‡]	0.397[*‡]	0.283[*‡]						
Fat % z score	-0.092	0.087	-0.350[†‡]	0.415[*‡]	0.232[*‡]	0.242[†‡]	-0.007	0.555[*‡]					
Muscle strength	-0.091	0.037	0.018	0.110	0.038	-0.03	0.014	-0.062	0.03				
Bone age (years)	-0.170	-0.048	-0.235[†‡]	-0.006	0.838[*‡]	0.807[*‡]	0.139	0.226	0.197	0.022			
Income	0.125	0.030	-0.067	-0.104	-0179	-0.054	0.120	0.017	0.126	-0.156	-0.161	-0.630	0.069
Sex	0.140	0.850	-0.126	-0.080	-0.020	0.026	0.113	0.104	-0.100	0.274	-0.180		
ART	-0.003	-0.062	0.170	-0.100	0.116	0.134	-0.043	-0.062	0.083	-0.025	0.193		

[*]P-value < 0.001; [†]P-value < 0.05. [‡]Pearson correlation; [§]Spearman correlation; % = percentage.
HIV = human immunodeficiency virus; MVPA = moderate to vigorous physical activity; SB = sedentary behavior; BMC = bone mineral content; BMD = bone mineral density; ART = antiretroviral drugs; BMI = body mass index.

Table 3. Simple and multiple linear regression between subtotal BMD and physical growth among children and adolescents diagnosed as HIV+

	Total sample (n = 63)					
	β (95% CI)	β st	R²	P	VIF	Cohen's D
Bone age						
Crude model	0.03 (0.02; 0.04)	0.80	0.64	**< 0.01**	-	1.77
Model I	0.03 (0.02; 0.40)	0.80	0.66	**< 0.01**	1.01	1.94
Model II	0.03 (0.02; 0.39)	0.78	0.70	**< 0.01**	1.13	2.33
Model III	0.03 (0.02; 0.38)	0.79	0.79	**< 0.01**	1.38	3.76
Age/height z score						
Crude model	0.14 (-0.11; 0.40)	0.14	0.02	0.26	-	0.02
Model I	0.01 (-0.01; 0.45)	0.18	0.04	0.15	1.03	0.04
Model II	0.01 (0.01; 0.52)	0.26	0.04	**0.02**	1.03	0.04
Model III	0.00 (-0.32; 0.38)	0.06	0.22	0.63	1.15	0.28
BMI/age z score						
Crude model	0.04 (0.01; 0.71)	0.39	0.14	**< 0.01**	-	0.16
Model I	0.04 (0.02; 0.75)	0.42	0.18	**< 0.01**	1.01	0.21
Model II	0.03 (0.01; 0.65)	0.32	0.29	**< 0.01**	1.02	0.47
Model III	0.03 (0.01; 0.63)	0.29	0.47	**< 0.01**	1.25	0.88
Fat % z score						
Crude model	0.01 (0.00; 0.30)	0.24	0.04	**0.05**	-	0.04
Model I	0.01 (0.01; 0.30)	0.26	0.07	**0.04**	1.04	0.07
Model II	0.08 (-0.01;0.02)	0.12	0.23	0.34	1.24	0.29
Model III	0.02 (0.01; 0.40)	0.44	0.36	**< 0.01**	1.69	0.56

BMD = bone mineral density; HIV = human immunodeficiency virus; CI = confidence interval; st = standardized; VIF = multicollinearity diagnosis; BMI = body mass index.
Model I: sex and income; Model II: sex, income, viral load, lymphocyte CD4+ and use of antiretroviral; Model III: sex, income, viral load, lymphocyte CD4+, use of antiretroviral, moderate-vigorous physical activity, sedentary behavior and muscle strength.

Table 4. Simple and multiple linear regression between subtotal BMC/height and physical growth among children and adolescents diagnosed as HIV+

	Total sample (n = 63)					
	β (95% CI)	β st	R²	P	VIF	Cohen's D
Bone age						
Crude model	0.96 (0.79; 1.12)	0.83	0.69	**< 0.01**	-	2.22
Model I	0.95 (0.79; 1.12)	0.83	0.70	**< 0.01**	1.01	2.33
Model II	0.82 (0.49; 1.14)	0.71	0.71	**< 0.01**	3.42	2.44
Model III	0.86 (0.56; 1.16)	0.75	0.76	**< 0.01**	4.40	3.16
Age/height z score						
Crude model	0.94 (0.41; 1.41)	0.85	0.03	**0.05**	-	0.03
Model I	0.67 (0.13; 1.35)	0.26	0.04	**0.05**	1.00	0.04
Model II	0.74 (0.02; 1.46)	0.26	0.04	**0.04**	1.03	0.04
Model III	0.95 (0.32; 1.59)	0.34	0.28	**0.04**	1.10	0.38
BMI/age z score						
Crude model	1.26 (0.54;1.97)	0.40	0.16	**< 0.01**	-	0.19
Model I	1.26 (0.54; 1.97)	0.40	0.17	**< 0.01**	1.01	0.20
Model II	1.04 (0.60;1.49)	0.33	0.74	**< 0.01**	1.11	2.84
Model III	1.24 (0.77; 1.73)	0.40	0.77	**< 0.01**	1.04	3.34
Fat % z score						
Crude model	0.38 (-0.02; 0.79)	0.23	0.03	0.06	-	0.03
Model I	0.43 (0.01; 0.86)	0.26	0.07	**0.04**	1.04	0.07
Model II	0.21 (-0.21; 0.64)	0.12	0.18	0.32	1.24	0.21
Model III	0.67 (0.78; 19.54)	0.39	0.52	**< 0.01**	1.01	1.08

BMC = bone mineral content; HIV = human immunodeficiency virus; CI: confidence interval; st = standardized; VIF: multicollinearity diagnosis; Model I: sex and income, Model II: sex, income, viral load, lymphocyte CD4+ and use of antiretroviral; Model III: sex, income, viral load, lymphocyte CD4+, use of antiretroviral, moderate-vigorous physical activity, sedentary behavior and muscle strength.

with HIV, the relationship between BMD and bone age is not fully understood in this population.[31]

Furthermore, a study among male adolescents diagnosed with HIV infection, in comparison with a control group, showed that there were similar values for BMC and BMD in the pre-pubertal maturation stage in the two groups. In the pubertal and post-pubertal maturational stage group, BMC and BMD values were lower in children and adolescents diagnosed with HIV infection, thus demonstrating that the differences in BMC and BMD become more evident with the advancement of puberty.[32]

In the present study, direct associations between subtotal BMD and BMI/age z score and fat percentage z score were found. In other studies on pediatric populations diagnosed with HIV, results similar to those found in the present study were reported.[6,9] The possible explanation for these findings is the fact that fat cells, adipocytes and bone formation cells (osteoblasts) all originate in mesenchymal stem cells, a heterogeneous group of multipotent non-hematopoietic stromal cells that are capable of becoming differentiated into mesodermal and non-mesodermal cells (adipocytes and osteoblasts).[33] Thus, the direct association between total body fat and BMD identified in the present study can be explained by the common cellular matrix from which both adipocytes and osteoblasts originate.[34] In addition, body fat positively contributes to leptin secretion,[35] which is directly related to greater proliferation and differentiation of osteoblasts and osteoclasts, which provides balance in the remodeling process of bone structures and BMD maintenance.[35]

Subtotal BMC/height was directly associated with bone age, height/age z score, BMI/age z score and fat percentage z score in the children and adolescents diagnosed with HIV of the present study. Previous studies that investigated associations between bone development and physical growth parameters only assessed BMD, with no data regarding BMC.[6,9,10] This fact limits comparisons of the findings from the present study with previous data in the literature. A study carried out among prepubertal children diagnosed with HIV infection showed lower values for total BMC than those of their peers without a diagnosis of HIV infection, when considering age and body mass in the analyses.[36] BMC assessment among children and adolescents diagnosed with HIV is important, given that it is during childhood and adolescence that both bone deposition and bone mass formation exceed resorption, thus implying increases in BMC and BMD at phases that coincide with accelerated weight and height growth.[37] In addition, BMC assists in bone modeling regulation.[38]

In a study that compared children and adolescents diagnosed with HIV with children and adolescents without an HIV diagnosis, it was reported that exposure to HIV and use of ART since birth were associated with lower bone mass.[7] In children and adolescents diagnosed with HIV, lower bone concentrations and mineralization rates may occur due to impaired adequate physical development and subsequently delayed puberty, which can be related to HIV infection.[3,4]

The present study had limitations that need to be considered when interpreting its data: the cross-sectional design did not allow inferences regarding cause-effect relationships. The sample used, which had a wide age range that included pre and post-pubertal children and adolescents, can also be considered to have been a limitation: because of the sample size, it was not possible to perform stratifications according to maturation stage.

Some strengths of this study include its use of highly reliable methods, such as DXA to evaluate BMD and BMC, accelerometers to measure MVPA and sedentary behavior and hand-wrist radiography analyzed by a radiologist to obtain bone age.

CONCLUSIONS

Through the findings of the present study, it could be concluded that subtotal BMD and subtotal BMC/height were directly associated with physical growth indicators (BMD: bone age, BMI/age z score and fat percentage z score; and BMC: bone age, height/age z score, BMI/age z score and fat percentage z score, respectively), even after adjusting for sex, family income, viral load, CD4+ lymphocytes, use of ART, MVPA, behavior sedentary and muscle strength. Assessing and improving bone health in children and adolescents diagnosed with HIV is crucial, in order to minimize the risk of bone complications over the long term. It needs to be emphasized that with prolonged use of ART, there may be significant bone mass reductions. Thus, monitoring of physical growth indicators that are simple to assess, such as age/height z score, BMI/age z score and fat percentage z score can be useful for identifying possible bone mass deficits in children and adolescents diagnosed with HIV.

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Address for correspondence:
Diego Augusto Santos Silva
Núcleo de Pesquisa em Cineantropometria e Desempenho Humano (NUCIDH), Universidade Federal de Santa Catarina (UFSC)
Campus Universitário — Trindade — Florianópolis/SC — Brasil
CEP 88040-900
Tel. (+55 48) 3721-6342
E-mail: diegoaugustoss@yahoo.com.br

Baseline laboratory parameters for preliminary diagnosis of COVID-19 among children: a cross-sectional study

Dejan Dobrijević[I], Jasmina Katanić[II], Maša Todorović[III], Biljana Vučković[IV]

Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

[I]MD. Clinical Biochemistry Resident and Teaching Assistant, Department of Biochemistry, Medical Faculty, University of Novi Sad, Serbia; and Physician, Department of Laboratory Diagnostics, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia.
https://orcid.org/0000-0002-8726-1953

[II]MD, PhD. Medical Biochemist, Department of Laboratory Diagnostics, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia; and Assistant Professor, Department of Biochemistry, Medical Faculty, University of Novi Sad, Serbia.
https://orcid.org/0000-0002-0349-6799

[III]MD. Laboratory Medicine Resident, Department of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia; and Teaching Assistant, Department of Pathophysiology and Laboratory Medicine, Medical Faculty, University of Novi Sad, Serbia.
https://orcid.org/0000-0001-7461-4345

[IV]MD, PhD. Internal Medicine Physician, Department of Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia; and Associate Professor, Department of Pathophysiology and Laboratory Medicine, Medical Faculty, University of Novi Sad, Serbia.
https://orcid.org/0000-0001-6018-1219

ABSTRACT

BACKGROUND: Clinical judgment of initial baseline laboratory tests plays an important role in triage and preliminary diagnosis among coronavirus disease 2019 (COVID-19) patients.

OBJECTIVES: To determine the differences in laboratory parameters between COVID-19 and COVID-like patients, and between COVID-19 and healthy children. Additionally, to ascertain whether healthy children or patients with COVID-like symptoms would form a better control group.

DESIGN AND SETTING: Cross-sectional study at the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia.

METHODS: A retrospective study was conducted on 42 pediatric patients of both sexes with COVID-19. Hematological parameters (white blood cell count, absolute lymphocyte count and platelet count) and biochemical parameters (natremia, kalemia, chloremia, aspartate aminotransferase [AST], alanine amino-transferase [ALT], lactate dehydrogenase [LDH] and C-reactive protein [CRP]) were collected. The first control group was formed by 80 healthy children and the second control group was formed by 55 pediatric patients with COVID-like symptoms.

RESULTS: Leukocytosis, lymphopenia, thrombocytosis, elevated systemic inflammatory index and neutrophil-lymphocyte ratio, hyponatremia, hypochloremia and elevated levels of AST, ALT, LDH and CRP were present in COVID patients, in comparison with healthy controls, while in comparison with COVID-like controls only lymphopenia was determined.

CONCLUSIONS: The presence of leukocytosis, lymphopenia, thrombocytosis, elevated systemic inflammatory index and neutrophil-lymphocyte ratio, hyponatremia, hypochloremia and elevated levels of AST, ALT, LDH and CRP may help healthcare providers in early identification of COVID-19 patients. Healthy controls were superior to COVID-like controls since they provided better insight into the laboratory characteristics of children with novel betacoronavirus (SARS-CoV-2) infection.

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by a novel beta-coronavirus (SARS-CoV-2), is the number-one public health emergency, with more than 192 million cases worldwide.[1,2] In the Republic of Serbia, the outbreak is still ongoing with more than 941,000 registered cases so far. At the moment, the epidemiological situation is stable with a further decreasing trend in the COVID-19 incidence rate in all parts of the country.[3] Pneumonia was the initial clinical sign of COVID-19 that enabled case detection. Asymptomatic infections are common, especially among young children, and play an important role in spreading the disease.[4,5]

Making timely diagnoses is of paramount importance for appropriate management, taking into account the global epidemiology and mortality risk of COVID-19. The real-time polymerase chain reaction (RT-PCR) is considered to be the gold standard for identification of SARS-CoV-2. In addition to molecular genome sequencing, rapid antigen and serological tests are also performed in many countries.[6] However, human resource and laboratory capacities are often insufficient to ensure massive and prompt diagnostics. Since the time taken to present the results from etiological RT-PCR may be prolonged, clinical judgment of the initial baseline laboratory tests plays an important role in triage and preliminary diagnosis.

Several laboratory parameters have been recommended for distinguishing SARS-CoV-2-positive patients from patients with COVID-like symptoms.[5,6] According to the official guidelines (the WHO interim guidelines and the guidelines of the National Health Commission of China for COVID-19, 5th edition), white blood cell counts and lymphocyte counts are significant for

early diagnosis. Thrombocytosis is another common laboratory finding.[7] Hematological indices such as the systemic inflammatory index (SII), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are useful biomarkers for assessments of disease severity and prognosis among patients with pneumonia.[8] Electrolyte disturbances such as hyponatremia, hypokalemia and hypochloremia have been corelated with COVID-19 infection.[9] Even in mild cases of COVID-19, hepatic transaminase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) may be elevated due to transient liver damage.[10] Lactate dehydrogenase (LDH) is an enzyme associated with tissue damage and is a biomarker of interest in COVID-19 patients.[11,12] C-reactive protein (CRP) is an important clinical biomarker of inflammation and infection. Altered CRP levels may be linked to the degree of disease severity among COVID-19 patients.[13]

All of these data were primarily documented from adult cases. The incidence of manifest COVID-19 in the pediatric population is significantly lower than the incidence of infected adults.[8] Therefore, information about hematological and biochemical parameter alterations in children with COVID-19 is very limited worldwide. Furthermore, the interpretation of these results varies to a significant extent.[8,14]

OBJECTIVE

The objective of this study was to determine the differences in laboratory parameters between COVID-19 and COVID-like patients, and between COVID-19 patients and healthy children. Additionally, we aimed to find out whether healthy children or patients with COVID-like symptoms would form a better control group.

METHODS

A retrospective study was conducted on 42 pediatric patients of both sexes with COVID-19. All of these patients were admitted to the confirmed-infection isolation wards at the Institute for Child and Youth Health Care of Vojvodina between April 2020 and January 2021. The sample size was not calculated because we had 42 COVID cases in total within the abovementioned period and we included all of them in the study. Occurrences of SARS-CoV-2 infection were confirmed through RT-PCR, performed on nasopharyngeal and throat swab specimens from the patients.

The hematological and biochemical findings from blood samples collected on the day of admission were recorded. The patients did not receive any therapy before blood collection. The hematological values were tested using the Advia 2120 hematology analyzer (Siemens Healthcare, Germany), for complete blood counts with a differential white blood cell count. The following hematological results were collected: white blood cell count, absolute lymphocyte count and platelet count. Additionally, SII, NLR and

PLR were calculated. The biochemical values were tested using the AU 480 chemistry analyzer (Beckman Coulter, Switzerland). The following biochemical results were collected: natremia, kalemia, chloremia, AST, ALT, LDH and CRP.

For comparative analyses, two control groups of age and sex-matched SARS-CoV-2-negative patients were enrolled in the study. The first control group was formed by 80 children who were healthy at that moment and had come to our institution for their regular check-ups. A total of 55 pediatric patients with COVID-like symptoms formed the second control group. Patients with malignancy were excluded from our analysis. All the controls were tested negative for COVID-19 prior to admission by means of a rapid test for qualitative detection of SARS-CoV-2 antigen (Panbio COVID-19 Ag Rapid Test Device, Abbott) and/or an immunochromatographic IgM/IgG antibody assay (Innovita COVID-19 immunoglobulin M [IgM]/immunoglobulin G [IgG] rapid test). Informed consent was waived because of the retrospective nature of the study, and the analyses used anonymous laboratory data.

Statistical analyses (descriptive and inferential) were performed using the Statistical Package for the Social Sciences (SPSS version 26.0) software (IBM Corporation, Armonk, New York, United States). This study was approved by the ethics committee of the Institute for Child and Youth Health Care of Vojvodina (December 23, 2020; no. 4881-2).

RESULTS

Between April 2020 and January 2021, a total of 42 pediatric cases of COVID-19 infection were admitted to the Institute for Child and Youth Health Care of Vojvodina. These patients' average age was 5.24 ± 6.04 years. The female share of the group was 57.1%, with an average age of 6.12 ± 6.54 years; and 42.9% of the group were males with an average age of 4.07 ± 5.25 years. The first control group consisted of 80 healthy children with an average age of 5.84 ± 6.12 years. The female share of this group was 41.3%, with an average age of 6.63 ± 6.46 years; and 58.7% of the group were males with an average age of 5.28 ± 5.89 years. The second control group was formed by 55 children with COVID-like symptoms, with an average age of 5.39 ± 5.81 years. The female share of this group was 49.1%, with an average age of 5.38 ± 5.98 years; and 50.9% of the group were males with an average age of 5.40 ± 5.73 years. The composition of the groups according to age and sex is presented in **Table 1**.

Binary logistic regression was used to determine that age was not a risk factor for COVID-19 (P = 0.601; odds ratio, OR: 1.017; 95% confidence interval, CI: 0.955-1.083). No confounding factors were identified.

Leukocytosis, lymphopenia and thrombocytosis, elevated SII and NLR were present in COVID patients, in comparison with healthy controls; while in comparison with the COVID-like

controls, only lymphopenia was determined (**Tables 2** and **3**). No significant differences in biochemical parameters between the COVID and COVID-like groups were found. On the other hand, we determined hyponatremia, hypochloremia and elevated levels of AST, ALT, LDH and CRP in the COVID-positive patients, in comparison with the healthy controls (**Table 4**).

Furthermore, statistically significant laboratory parameters were studied through receiver operating characteristic (ROC) analyses. Only laboratory markers with an area under the curve (AUC) above 0.7 were considered acceptable for analyzing the exact cutoff value: CRP (AUC: 0.842), AST (AUC: 0.779) and LDH (AUC: 0.712) (**Figure 1**). The cutoff point for CRP values was set at 2.1

Table 1. Age-sex structure of coronavirus disease 2019 (COVID-19) group, healthy controls and COVID-like controls

Patient features		Total (n = 177)	COVID-19 group (n = 42)	Healthy controls (n = 80)	COVID-like controls (n = 55)
Gender	Female	84 (47.5%)	24 (57.1%)	33 (41.3%)	27 (49.1%)
	Male	93 (52.5%)	18 (42.9%)	47 (58.7%)	28 (50.9%)
Age (years)*	General	5.56 ± 5.98 3.0 (0.44-11.0)	5.24 ± 6.04 5.50 (0.25-10.0)	5.84 ± 6.12 3.0 (0.74-11.0)	5.39 ± 5.81 3.0 (0.44-12.0)
	Female	6.08 ± 6.29 4.0 (0.46-12.75)	6.12 ± 6.54 6.00 (1.25-10.0)	6.63 ± 6.46 4.0 (0.83-13.5)	5.38 ± 5.98 3.5 (0.54-13.0)
	Male	5.08 ± 5.68 3.0 (0.44-10.0)	4.07 ± 5.25 5.00 (0.23-10.0)	5.28 ± 5.89 3.0 (0.5-10.0)	5.40 ± 5.73 3.0 (0.43-12.0)

*Mean ± standard deviation/median (interquartile range: Q1–Q3).

Table 2. Hematological characteristics of the coronavirus disease 2019 (COVID-19) group, healthy controls and COVID-like controls*

Characteristic	COVID-19 group (group 1)	Healthy controls (group 2)	COVID-like controls (group 3)	P value†	
				1 versus 2	1 versus 3
Leukocytosis	12 (28.6%)	0	14 (26.9%)	**P < 0.001**	P = 0.541
Lymphopenia	7 (16.7%)	0	1 (1.9%)	**P < 0.001**	**P = 0.025**
Thrombocytosis	9 (21.4%)	2 (2.5%)	14 (26.9%)	**P < 0.001**	P = 0.723

*Values are n (% within group); †chi-square test and Fisher's exact test.
Values in bold are statistically significant.

Table 3. Hematological indices/ratios in the coronavirus disease 2019 (COVID-19) group, healthy controls and COVID-like controls*

Hematological indices/ratios	COVID-19 group (group 1)	Healthy controls (group 2)	COVID-like controls (group 3)	P value†	
				1 versus 2	1 versus 3
SII	1069.62	475.83	746.44	**P = 0.008**	P = 0.305
NLR	3.46	1.86	2.11	**P = 0.007**	P = 0.100
PLR	126.89	109.73	114.18	P = 0.254	P = 0.546

*Values are represented as mean values; †independent-samples t test.
Values in bold are statistically significant.
SII = systemic inflammatory index; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio.

Table 4. Biochemical characteristics of the coronavirus disease 2019 (COVID-19) group, healthy controls and COVID-like controls*

Biochemical parameter	COVID-19 group (group 1)	Healthy controls (group 2)	COVID-like controls (group 3)	P value†	
				1 versus 2	1 versus 3
Natremia (mmol/l)	136.43	141.28	135.48	**P < 0.001**	P = 0.211
Kalemia (mmol/l)	4.72	4.69	4.52	P = 0.785	P = 0.293
Chloremia (mmol/l)	102.15	103.83	100.42	**P = 0.017**	P = 0.549
AST (μkat/l)	0.94	0.47	0.88	**P < 0.001**	P = 0.832
ALT (μkat/l)	0.71	0.33	0.68	**P = 0.002**	P = 0.907
LDH (μkat/l)	5.51	3.74	4.69	**P < 0.001**	P = 0.155
CRP (mg/l)	38.63	1.15	53.82	**P < 0.001**	P = 0.280

*Values are represented as mean values; †independent-samples t test.
Values in bold are statistically significant.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein.

mg/l (P < 0.001; sensitivity: 81.8%, specificity 90%; 95% CI: 0.773–0.951). The cutoff point for AST values was set at 0.49 μkat/l (P < 0.001; sensitivity: 81.8%, specificity 60%; 95% CI: 0.681–0.877). The cutoff point for LDH values was set at 4.22 μkat/l (P < 0.001; sensitivity: 66.7%, specificity 78.7%; 95% CI: 0.591–0.832).

Additionally, we analyzed the differences between the COVID-19 group and the healthy children according to the cutoff values for CRP, AST and LDH. These differences were statistically significant for all three parameters (**Table 5**).

DISCUSSION

Considering the global epidemiology and alarming severity of COVID-19 infection, well-timed diagnostics are crucial.[15] The turnaround time for RT-PCR results is supposed to be very quick, but the lack of human and laboratory resources in many countries has led to delays in SARS-CoV-2 confirmation. During this period, baseline hematological and biochemical analyses are essential for enabling a clinical judgement when COVID-19 infection is suspected.[15,16]

ROC = receiver operating characteristic; CRP = C-reactive protein; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

Figure 1. Receiver operating characteristic curve for the most significant laboratory parameters in predicting coronavirus disease 2019 (COVID-19)-positive patients.

Table 5. Comparison of laboratory parameters according to their cutoff points[*]

Parameter	COVID-19 patients	Healthy controls	P value[†]
CRP ≥ 2.1 mg/l	32 (76.2%)	8 (10.0%)	**< 0.001**
AST ≥ 0.49 μkat/l	29 (69.0%)	31 (38.8%)	**< 0.001**
LDH ≥ 4.22 μkat/l	22 (52.4%)	17 (21.3%)	**< 0.001**

[*]Values are n (% within group); [†]chi-square test.
Values in bold are statistically significant.
CRP = C-reactive protein; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

In the initial analyses, in which patients were compared with healthy controls, we observed leukocytosis, lymphopenia, thrombocytosis, elevated SII and NLR, hyponatremia, hypochloremia and elevated levels of AST, ALT, LDH and CRP. However, comparison of patients with COVID-19 and patients with COVID-like symptoms showed that only lymphopenia might play an important role in distinguishing patients within these two groups. In a review paper published by Lippi et al., the most common laboratory findings were leukocytosis, lymphopenia, thrombocytopenia and elevated levels of AST, ALT, LDH and CRP.[17] Cai et al. reported occurrences of leukocytosis, lymphocytosis, thrombocytosis and elevated levels of AST, ALT, LDH and CRP.[18] Furthermore, the laboratory findings in a study conducted by Wang et al. were leukocytosis, lymphocytosis, thrombocytosis and elevated levels of AST, ALT and CRP, while the levels of LDH were within the reference range.[19] Thus, it can be said that the laboratory findings from different clinical and research centers vary to a significant extent.

Several factors may have influenced this discrepancy in the laboratory results. In the first place, the medical community and general public have had a constant need for new information about the COVID-19 pandemic, and this has been paramount. The methodological quality of published reports has been lower than that of similar studies published prior to the pandemic.[20] Furthermore, this need to disseminate information promptly has been forcing researchers to opt for simpler study designs. Even in some major journals, many observational studies have been published without control groups.[21]

Additionally, selecting an appropriate comparison group is crucial. Use of more than one control group has often been discussed in observational studies. When healthy controls are used, they are expected to show any laboratory distinction between COVID-19 patients and healthy children. On the other hand, when patients with COVID-like symptoms are used as controls, it is possible to determine which laboratory parameters might be specific for SARS-CoV-2 infection, regardless of the symptoms.[22]

In our study, no specific laboratory parameters were determined. Firstly, there were no COVID-specific parameters among the baseline hematological and biochemical analyses; and secondly, there are a lot of common viral infections among children, which may present with similar laboratory findings.[22,23] Therefore, healthy children formed a more convenient control group in our study, given that they showed us various alterations in laboratory parameters such as leukocytosis, lymphopenia, thrombocytosis, elevated SII and NLR, hyponatremia, hypochloremia and elevated levels of AST, ALT, LDH and CRP.

Lymphopenia is common in acute illness, when T-lymphocytes and NK-cells become exhausted and their counts start to decrease.[24] Thrombocytosis in children with viral infection of the lower respiratory tract is a reactive phenomenon and does not indicate a severe clinical course.[25]

Elevated SII and NLR are indicators of inflammation associated with a dismal outcome among adult COVID-19 patients. On the contrary, no such conclusion can be made with regard to the pediatric population according to our study since no cases of death cases were observed at our Institute, even though these parameters were significantly higher in children with SARS-CoV-2 infection.[26]

Hyponatremia and hypochloremia are not infrequent laboratory and clinical findings in infectious diseases. These may be present due to infection-induced hyperglycemia (hypertonic hyponatremia and hypochloremia), infection-induced hyperproteinemia (isotonic hyponatremia and hypochloremia) or infection-induced edema (hypotonic hyponatremia and hypochloremia).[9]

Elevated aminotransferase levels are a common biochemical abnormality in COVID-19 patients, most probably due to liver injury associated with the immune response. However, except in the sense of being another diagnostic marker, their prognostic significance still remains uncertain.[10]

The serum concentration of LDH is an important marker of tissue damage and its elevation has been correlated with worse outcomes in cases of viral infections in general.[11] Moreover, because of inflammatory reactions and tissue destruction, CRP levels in SARS-CoV-2-positive children tend to increase significantly.[27]

This study had some limitations. The first limitation was the small number of participants, given that this was a single-center study and that many children affected by the virus have no symptoms. Nonetheless, our findings could provide the basis for further research. The second limitation was that inflammation-related biomarkers, such as procalcitonin, interleukin-6 and presepsin were not included. Nor were hemostasis biomarkers such as partial thromboplastin clotting time (PTT), activated partial thromboplastin clotting time (aPTT), fibrinogen and D-dimer. Unfortunately, no such data were available for all the patients with confirmed SARS-CoV-2 infection because such analyses do not form part of the standard diagnostic protocol upon admission to our Institute, and are performed on demand only. Therefore, the baseline laboratory parameters were the main focus of interest in our study.

CONCLUSION

All the laboratory markers mentioned above may help healthcare providers in early identification of COVID-19 patients. All of these parameters may be used for developing novel diagnostic scores for pediatric COVID-19 patients. CRP, AST and LDH demonstrated the best diagnostic performances, considering their sensitivity and specificity. Based on this study, it can additionally be concluded that healthy controls are superior to COVID-like controls since they provided better insight into the laboratory characteristics of children with SARS-CoV-2 infection.

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Address for correspondence:
Dejan Dobrijević
Hajduk Veljkova 10, 21000
Novi Sad, Republic of Serbia
Tel. (+381) 65 823 32 32 — Fax. (+381) 21 48 80 444
E-mail: dejan.dobrijevic@mf.uns.ac.rs

Use of prescribed psychotropic drugs among medical students and associated factors: a cross-sectional study

Nicoli Abrão Fasanella[I], Clarissa Garcia Custódio[II], Júlia Santos do Cabo[III], Gabriel Sousa Andrade[IV], Fernando Antônio de Almeida[V], Maria Valéria Pavan[VI]

Faculdade de Ciências Médicas e da Saúde da Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba (SP), Brazil

[I]MD. Professor, Department of Public Health, Faculdade de Ciências Médicas e da Saúde (FCMS), Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba (SP), Brazil.
https://orcid.org/0000-0002-9215-073X

[II]Undergraduate Medicine Student, Faculdade de Ciências Médicas e da Saúde (FCMS), Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba (SP), Brazil.
https://orcid.org/0000-0002-6153-3850

[III]Undergraduate Medicine Student, Faculdade de Ciências Médicas e da Saúde (FCMS), Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba (SP), Brazil.
https://orcid.org/0000-0003-0506-8648

[IV]BSc, LPsy. Psychologist, Incorporee Instituto de Saúde, Guarapuava (PR), Brazil.
https://orcid.org/0000-0003-0090-6593

[V]MD, PhD. Full Professor, Department of Clinics, Faculdade de Ciências Médicas e da Saúde (FCMS), Pontifícia Universidade Católica de São Paulo (PUC-SP) Sorocaba (SP), Brazil.
https://orcid.org/0000-0002-9404-9707

[VI]MD, MSc, PhD. Professor, Department of Public Health, Pontifícia Universidade Católica de São Paulo (PUC-SP), Sorocaba (SP), Brazil.
https://orcid.org/0000-0001-8804-2499

ABSTRACT

BACKGROUND: The worldwide prevalences of anxiety and depressive disorders are 3.6% and 4.4%, respectively. Among medical students, many studies have indicated that the prevalences of these mental disorders vary between 19.7% and 47.1%, but there is a lack of information on psychotropic drug usage in this group of students.

OBJECTIVE: To evaluate the prevalence of psychotropic drug use, adherence to therapy and main clinical and diagnostic indications relating to psychotropic drug use among medical students.

DESIGN AND SETTING: Cross-sectional study at a Brazilian private university in the city of Sorocaba, state of São Paulo.

METHODS: Observational analytical cross-sectional study, conducted during the second semester of 2019, through a semi-structured online questionnaire, answered by first to sixth-year medical students.

RESULTS: Among the 263 participants (41.7% of the 630 enrolled students), the current prevalence of psychotropic drug usage was 30.4%. This prevalence increased over the course and 90.7% of the drugs were prescribed at regular medical consultations (85.5% by psychiatrists). The main indications for psychotropic drug usage were anxiety (30.0%), depression (22.8%), insomnia (7.2%), panic (5.3%) and attention deficit hyperactivity disorder (3.8%). Women were more likely to present diagnoses of depression and panic. Most of the participants used antidepressants and had good adherence to medications. Adequate sleep and regular physical activity were identified as protective factors against mental disorders.

CONCLUSION: The prevalence of mental disorders among medical students is high, which justifies the use of psychotropic drugs. This study provides valuable information and recommendations for institutional educational actions to improve students' mental health.

INTRODUCTION

An individual's mental health relates to biological, psychological, cultural and social factors, which contribute to the person's adaptability, self-management and emotional wellbeing.[1] Young adults experience rapid mental development, in which the social context is also deemed of great importance.[2] In this regard, the mental health of university students has received greater attention in recent years, especially when concerning medical students.[3-5]

Due to the very nature of medical students' education, greater requirements are placed on them regarding commitment, responsibility and academic performance.[3] They usually have long study hours, with exposure to competitive environments and often sleep deprivation, which is far from the ideal learning environment.[4] These factors may lead towards high levels of stress, which negatively influence both their physical and mental health.[3,4]

According to World Health Organization (WHO) data, the worldwide prevalence of depression in the population between 20 and 29 years old reaches 6% in women and 4% in men.[6] Anxiety is the second most common mental disorder, with prevalence in the same age group of around 5% and 3% in women and men, respectively.[6] In Brazil, 5.8% of the population are estimated to be affected by depression and 9.3% have anxiety.[6]

Among medical students worldwide, the prevalence of anxiety was estimated to be 33.8% in a meta-analysis.[3] In Brazil, symptoms of depression, anxiety and stress can be found in 30% to 47% of medical students.[7,8] Such symptoms can harm these students' lives as well as their future patients. They may be debilitating and lead to worsening of these students' academic and social performance.[5,9,10]

Use of psychotropic drugs can be a protective factor when well indicated, or may be another risk factor for mental health when misused. Studies carried out in recent years have revealed that

the global prevalence of psychotropic drug use among young adults can vary from 6.5% to 22.3%.[11-14] In Brazil, the prevalence of psychotropic drug consumption among medical students is similar and varies from 10.7% to 22.6%, depending on the class of such psychotropic drugs that is evaluated.[15,16]

OBJECTIVE

The objective of this study was to evaluate the prevalence of psychotropic drug use, the degree of therapeutic adherence and the main clinical indications relating to use of psychotropic drugs among students in the first to the sixth year of the medical course at a Brazilian private university.

METHODS

Study design

This was a cross-sectional analytical observational study, carried out during the second semester of 2019 at the Faculty of Medical and Health Sciences of the Pontifical Catholic University of São Paulo, located in the city of Sorocaba.

The students received a semi-structured, self-applicable questionnaire, built by the authors, which was sent out and answered electronically. The predefined questions of the questionnaire were organized in two parts. The first part of the questionnaire consisted of asking for personal and social data, with questions about age, gender, year of the course, whether the student had a scholarship or study funding, with whom the student was living and the student's city of origin. The second part of the questionnaire sought to identify whether the students were using (or had ever used) psychotropic drugs and asked about the determinants for use of such medication. To assess treatment adherence, the Measuring Instrument of Treatment Adherence (MITA) was used, as adapted and validated for Brazilian Portuguese by Borba et al.[17] The criterion for considering that the individual's adherence to treatment was adequate is a score of 5 or 6 (on a scale of 1 to 6).[17]

The questionnaire was built and sent through Google Forms. The link to access the informed consent statement, as well as the questionnaire, was sent by email. Access to the questionnaire necessarily depended on the acceptance of the consent statement, which was considered to represent an electronic signature.

Study participants

All medical students aged 18 and over, in any year from the first to the sixth, were invited to participate in the study. Out of the 630 medical students enrolled in 2019, 268 responses were obtained.

The sample size was calculated with tolerance of an error of 5%, a confidence level of 95% and great heterogeneity of the population (50%).[18] According to these criteria, considering the total number of students enrolled in the medical course in the second semester of 2019, it was found that a representative sample should have at least 244 participants.

Statistical analysis

The data were analyzed using the SPSS software (PASW Statistics for Windows: version 18.0; Chicago, Illinois, United States). Initially, a descriptive statistical analysis of the social characteristics of the studied population was performed. To explore the interrelation between the variables, nonparametric statistical tests were used, adopting the confidence level of 95%. These tests were performed to assess whether to reject the null hypothesis (that the variables were independent). Simple binary logistic regression models were elaborated to assess the impact of the progression within the medical course on the dependent variables of psychotropic drug use and psychiatric diagnosis, which were both binary variables. In this study, use of psychotropic drugs was the main variable of interest, while the covariables or independent variables consisted of adherence to treatment, year of progression in the medical course, sleeping hours and sociodemographic characteristics.

The statistical analysis aimed to describe the frequency of psychotropic drug use among the participants and, additionally, relate this to psychiatric diagnoses and treatment adherence. Thus, chi-square tests were conducted to identify whether there were any associations between pairs of categorical variables, and the phi (ϕ) statistic was used as a measurement of effect size. Fisher's exact test was used to investigate the significance of associations between pairs of categorical variables when the sample size was small (which would break the premises of chi-square). The Mann-Whitney U test was used to compare pairs of groups of values without assuming that these values were normally distributed, using Cliff's delta (d_{Cliff}) as a measurement of effect size. Spearman's correlation test was used to measure the strength of association between pairs of variables.

Ethical considerations

This research project and the informed consent statement that would be used were submitted to the Research Ethics Committee of the Faculty of Medical and Health Sciences of PUC-SP and the study only started after approval had been granted. Date of approval: May 14, 2019. Certificate of Presentation for Ethical Appreciation (CAAE): 11130019.8.0000.5373.

RESULTS

Participating students' profile

The final sample was composed of 263 participants out of a universe of 630 students (41.7%). The number of participants in each course year did not differ among the participants (chi-square test, χ^2; P = 0.833) The proportion of women in the sample was

significantly higher than that of men (χ^2; P < 0.001), and was also statistically higher than the proportion of female physicians aged up to 29 years in practice in Brazil (χ^2; P = 0.002).[19] The participants' profile is described in **Table 1**.

Thirty-five percent of the participants had some type of scholarship. Students originally from the city of Sorocaba were more likely to have received funding (Sorocaba 69.6%; other municipalities 31.7%; χ^2, P < 0.001).

Participants who practiced regular physical activity reported having a greater number of hours of sleep (Mann-Whitney U test; P = 0.008; with a small effect size, d_{Cliff} = 0.167).

Use of psychotropic drugs among the participants

Out of the 263 students included in the study, 109 (41.4%) reported having used psychotropic drugs at some time in their lives and 80 students (30.4%) reported that they were currently using at least one psychotropic drug. The characteristics of the psychotropic drug use among the participants are described in **Table 2**.

The great majority of the participants reported that psychotropic drugs were first prescribed by the doctors with whom they regularly had consultations (90.7%). Among these, 85.5% reported having been followed up by psychiatrists, 12.4% by doctors of other specialties and 2.1% by general practitioners. As the medical students progressed along the medical course, they were more likely to be followed up by psychiatrists than by any other specialist (Mann-Whitney U test; P = 0.01; d_{Cliff} = 0.452). Among the 9.3% of the students who had received prescriptions of psychotropic drugs from a professional other than the one who was their follow-up doctor, 30% reported receiving a prescription from their parents, 30% from a friend and 40% from "others".

Among the students using psychotropic drugs, 47.5% had already received medication prescriptions from doctors other

than those who were following them up (40.4% from family members, 21.3% from teachers, 22.3% from friends and 16% from residents). Receiving prescription drugs from other professionals is a factor associated with lack of healthcare insurance (χ^2, P = 0.003; ϕ = 0.293).

As reported by the participants, the clinical indications for psychotropic drug use are shown in **Table 3**.

Table 2. Characteristics of psychotropic drug use among participants

Participants (n = 263)	Number (%, 95% CI)
Use of psychotropic drugs at some time in life	109 (41.4%, 35.2-47.6%)
Use of psychotropic drugs currently	80 (30.4%, 25.1-35.7%)
1 psychotropic drug	65 (81.8%, 72.8-90.3%)
2 psychotropic drugs	8 (10.4%, 3.9-18.2%)
3 psychotropic drugs	6 (7.8%, 2.3-14.3%)
Classes of psychotropic drugs used:	
Antidepressants	
Selective serotonin reuptake inhibitors	50 (19.0%, 12.2-21.5%)
Serotonin and norepinephrine reuptake inhibitors	13 (4.9%, 2.3-7.3%)
Norepinephrine and dopamine reuptake inhibitors	8 (3.0%, 0.8-4.9%)
Tricyclic antidepressants	4 (1.5%, 0.0-2.7%)
Benzodiazepine anxiolytics	13 (4.9%, 1.8-6.2%)
Mood stabilizers	10 (3.8%, 1.6-6.3%)
Amphetamine-derived central nervous system stimulants	7 (2.7%, 1.1-4.6%)
Most common psychotropic drugs used:	
Escitalopram	21 (8.0%, 4.9-44.4%)
Fluoxetine	10 (3.8%, 1.9-6.4)
Bupropion	8 (3.0%, 1.1-5.3)
Desvenlafaxine	7 (2.7%, 0.8-4.6%)
Sertraline	7 (2.7%, 0.8-4.9%)
Clonazepam	7 (2.7%, 0.8-4.8%)
Medical prescription at regular follow-up	99 (90.7%, 84.4-95.4%)
Psychiatrist	93 (85.5%, 77.6-91.9%)
Other specialties	13 (11.8%, 6.4-19.4%)
General practitioner	(2.7%, 0.0-5.2%)

CI = confidence interval.

Table 1. Participants' profile

Parameter evaluated	Results observed (n = 263)
Age (mean ± SD)	22.9 ± 2.7 years
Gender	66.5% female
Sexual orientation	83.7% heterosexual
	7.6% homosexual
	7.2 % bisexual
	1.2% other
Hometown	91.3% from other municipalities
Funding/scholarship status	35% had scholarship
Healthcare insurance	75.7%
Regular physical activity[1]	65.8%
Daily sleeping hours	0.4%, less than 4 hours
	30.0%, 4 to 6 hours
	63.5%, 6 to 8 hours
	6.1%, over 8 hours

[1]At least three times/week; SD = standard deviation.

Table 3. Main clinical indications for psychotropic drug use among medical students
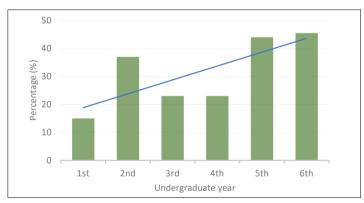
Clinical indications	Percentage (95% CI)
Anxiety	30.0% (24.7%-36.0%)
Depression	22.8% (17.8%-28.3%)
Insomnia	7.2% (4.2%-10.6%)
Panic	5.3% (2.7%-8.4%)
Attention deficit hyperactivity disorder	3.8% (1.5%-6.4%)
Bipolar affective disorder	1.5% (0.4%-3.1%)
Compulsion	1.5% (0.4%-3.1%)
Obsessive-compulsive disorder	1.1% (0.0%-2.6%)
Weight loss	1.1% (0.0%-2.7%)
Other	3.4% (1.5%-5.7%)

CI = confidence interval.

Among the participants who were currently using psychotropic drugs, 31.3% started doing this before entering the medical course, 10.0% started in the first year of medical school, 13.8% in the second, 16.3% in the third, 13.8% in the fourth, 12.5% in the fifth and 2.5% in the sixth. As shown in **Graph 1**, the prevalence of psychotropic drug use reached 45% of these medical students in the last two years of their course.

To assess the impact of the progression within the medical course on the odds of psychotropic drug use, simple binary logistic regression models were constructed. As depicted in **Table 4**, progression within the medical course predicted psychotropic drug use. According to the model, it was estimated that the chance that medical students would use psychotropic drugs increased by 27.1% (95% confidence interval, CI: 8.7-48.5%; P = 0.003) for each year of progression along the course. The same model also showed that the students' age also predicted psychotropic drug use. As seen in **Table 4**, the odds of using psychotropic drugs increased by 14.8% each year (P = 0.011).

In comparing the prevalence of psychotropic drug use among third and fourth-year students with that of fifth and sixth-year students, a statistically significant difference was observed, such

that it was higher in later years (χ^2, P = 0.003). Students in the last two years of the medical course, compared with those in the first two years, were more likely to use mood stabilizers (Fisher's exact test, P = 0,034), escitalopram (P = 0.037), clonazepam (P = 0.026), alprazolam (P = 0.016) and other psychotropic drugs (P = 0.012). It was also observed that anxiety (χ^2, P = 0.029) and panic (χ^2, P = 0.009) were reported as the main clinical indications for use of psychotropic drugs among medical students in the fifth and sixth years, with no other significant relationships.

Treatment adherence

Regarding the responses in the questionnaire relating to adherence to medication treatment, it was found that 64.5% (95% CI: 46.9-80.6%) of the participants who had used psychotropic drugs had adequate adherence to the treatment, while 35.5% (95% CI: 19.4-53.1%) were poorly adherent. The participants' mean score was 5.16 (95% CI: 4.9-5.4).

An association was observed between the symptom "discouragement" and non-adherence to treatment (Fisher's exact test, P = 0.031). A negative correlation was found between the sleep hours scale and carelessness with medication schedules, such that those who slept less tended to forget to take the medication more often (Spearman's correlation test, r = 0.353; P = 0.03). No correlations were found for the course year or participant age in relation to carelessness with psychotropic drug use or to general treatment adherence.

Psychiatric disorders as indicative for use of psychotropic drugs

Altogether, 25.5% of the participants reported having some kind of psychiatric diagnosis (95% CI: 18.4-30.4%). Among these diagnoses, the following were mentioned: anxiety disorders (11.4%), depressive disorders (11.0%), attention deficit hyperactivity disorder (1.9%), obsessive compulsive disorder or compulsion (0.8%) and personality disorders (0.4%).

Graph 1. Prevalence of psychotropic drug use among medical students.

Table 4. Simple binary logistic regression model to assess the impact of progression along the medical course on the dependent variables (psychotropic drug use and psychiatric diagnosis)

Dependent variable	Predictor	β	Seβ	Wald's χ^2	df	P-value	Exp(β)	Exp(β) (Lower 95% CI)
Psychotropic drug use	**Course year**	0.239	0.8	9.059	1	**0.003****	1.271	1.087
	Intercept	-1.67	0.321	27.022	1	< 0.001	0.188	
	Age	0.138	0.54	6.476	1	**0.011***	1.148	1.032
	Intercept	-3.896	1.268	9.433	1	0.002	0.02	
Psychiatric diagnosis	**Course year**	0.236	0.096	5.964	1	**0.015***	1.266	1.048
	Intercept	-1.958	0.387	25.612	1	< 0.001	0.141	
	Age	0.99	0.61	2.643	1	0.104	0.105	0.98
	Intercept	-3.293	1.42	5.381	1	0.02	0.037	

β coefficient; Seβ = coefficient standard error; CI = confidence interval; Wald's χ^2 = test statistics for the variables in the equation; df = degrees of freedom; Exp(β) = the average proportion at which the odds of using a psychotropic drug or having a psychiatric diagnosis increases for each unit increase in course year or age. *Significant, within 95% confidence interval; **significant, within 99% confidence interval.

Like what was observed regarding psychotropic drug use, participants who had progressed further within the medical course were more likely to report having a psychiatric diagnosis (Mann-Whitney U test, P = 0.012). As shown in **Table 4**, according to the binary logistic regression model, the chance of reporting a psychiatric diagnosis grew by approximately 26.6% (95% CI: 4.8 - 52.9%; P = 0.015) for every additional year of the students' progression along the course, such that this chance reached 42% among participants in the fifth year.

Considering the prevalence of specific disorders over the years of the course, the only significant association found was depressive disorder, which tended to increase as the course progressed (Mann-Whitney U test, P = 0.041; d_{Cliff} = 0.229;)

It was also observed that participants with psychiatric diagnoses made by a doctor reported having fewer hours of sleep than participants who did not report any psychiatric diagnosis (Mann-Whitney U test, P = 0.024; d_{Cliff} = 0.179). Among the participants who reported sleeping for less than six hours a night, 56.4% also reported having a psychiatric diagnosis, but no association was found with any specific disorder.

It was found that women were more likely to be diagnosed with depressive disorder (χ^2, P = 0.021; ϕ = 0.144) and to have symptoms like distress (χ^2, P = 0.046; ϕ = 0.123), discouragement (χ^2, P = 0.005; ϕ = 0.174) and irritability (χ^2, P = 0.001; ϕ = 0.213). Women were also more likely to report panic as a motivator for use of psychotropic drugs (χ^2, P = 0.04; ϕ = 0.131).

Students with depressive disorders were more likely to report feeling sadness (χ^2, P < 0.001; ϕ = 0.328), discouragement (χ^2, P < 0.001; ϕ = 0.238), insomnia (χ^2, P = 0.004; ϕ = 0.189), a desire to remain left alone (χ^2, P < 0.001; ϕ = 0.291), persecuted or watched (χ^2, P < 0.001; ϕ = 0.268) or irritability (χ^2, P = 0.003; ϕ = 0.188). They were also less likely to engage in regular physical activity (χ^2, P = 0.014; ϕ = -0.155).

Use of illicit drugs

Overall, 28.9% (95% CI: 24.0-34.8%) of the participants reported using some illicit drug. Marijuana use was reported by 25.5% (95% CI: 20.5-31.3%), methylenedioxymethamphetamine (MDMA) by 10.3% (95% CI: 6.6-14.6%), hallucinogens by 3.0% (95% CI: 1.1-5.3%), inhaled drugs by 3.0% (95% CI: 1.1-5.3%) and amphetamines by 1.1% (95% CI: 0.0-2.6%). Participants who reported using inhaled drugs slept less than those who did not report using them (Mann-Whitney U test, P = 0.004; d_{Cliff} = 0.512). Use of illicit drugs was not associated with use of psychotropic drugs, or with the presence of any known mental disorder among the participants.

DISCUSSION

The prevalence of mental disorders found in the sample was similar to that found in the literature.[8,10,14,20] Regarding the use of psychotropic drugs, the prevalence found was as follows: 41.4% of the medical students had used psychiatric drugs at some time in their lives and 30.4% were using it at the time of the study. This prevalence was approximately five times higher than in the general population, even when compared with young students in pre-university courses, and was usually related to a higher risk of suffering from stress.[11-13,21]

The high percentage of medical students who use or have used psychotropic drugs at some time may indicate greater psychological distress among these individuals, considering that they are exposed to stress factors that can contribute to worsening of mental disorders. Vasconcelos et al. also observed a high prevalence of anxiety and depression among medical students in the city of Recife.[9] In their study, anxiety was associated with use of psychotropic drugs, and depression with use of illicit drugs.[9]

As observed in our study sample, 69% of the participants who used some type of psychotropic drug started to do this at some point during the course. As the course progressed, the chance of receiving a psychotropic drug prescription increased by 27% annually, such that in the sixth year these prescriptions were most prevalent. It is in the last year of the course, which is also the last of the clinical years, that students experience the greatest university demands, with the greatest workload and responsibility in practical internship, and the closest contact with patients.[20]

Furthermore, in the first years of the course, there is great anxiety about the unknown: adaptation to entering university, moving to another city and adapting to new teaching methods, great changes in family dynamics, new colleagues and new teachers.[7] As reported by Vasconcelos et al.,[9] being from the region where one studies and living with one's family are mental health protective factors. Among the students evaluated, more than 90% came from other municipalities and many of them were living on their own, which could partially explain the findings.

In the third and fourth years of the course, students are experiencing the best period of the course, at a time when they have become better adapted to and familiarized with their study needs and educational activities.[7] On the other hand, in the fifth and sixth years, there is an increase in the prevalence of psychotropic drug use and psychiatric diagnoses. The last few years are characterized by intensification of practical activities, closer contact with patients and greater responsibility, as students approach the time of graduation and of assuming the life of a medical professional, and the great difficulty in accessing specializations, which are all possible stressors.[7,8,20]

Our study also identified that the profile of prescribers for these students, in 90% of the cases, was the doctor with whom the students undertook their regular healthcare. Psychiatrists were the main choice of specialist, thus indicating that these students at a private university had access to specialists for their mental healthcare

and treatment. According to Quintana et al.,[12] prescription of psychotropic drugs for the general population was done mainly by general practitioners, followed by psychiatrists. The data obtained in the present study can be interpreted as a specific characteristic of the sample presented here, which consisted of a population in which the majority had healthcare insurance. However, these data may also indicate that there is less stigmatization of the specialty of psychiatry among medical students.

Students who did not have healthcare insurance, who were a minority within the sample, were the ones who most received prescriptions from professionals other than those with whom they undertook their regular monitoring. In addition to being an ethical transgression by the prescriber, this practice may also be a risk factor, since students who are not under regular medical supervision, and receive prescriptions from someone other than their regular doctor, are not integrated into a means of broadened care in which an appropriate doctor-patient relationship is established, with therapeutic bonds and periodic reevaluations. Thus, these students are exposed to a situation of perpetuation of prescriptions that are sometimes inadequate.[22-26]

It is also necessary to consider that at least 35.5% of the study participants who were using some type of psychotropic drug did not have adequate adherence to treatment, which may have been a factor in worsening their mental health. Irregular use of these medications is associated with a greater risk of aggravation of the individual's depressive symptoms or postponement of clinical improvement, thereby worsening the prognosis.[23,24]

In the present study, no significant difference in adherence to treatment was observed between students in different years of the course. This may be an indication that there is no relationship between technical knowledge and adherence to treatment. Instead, this may indicate that medical students have a profile that leads them to neglect their own health, or even to suffer from the stigma of mental illness or the need to use psychotropic drugs, which would therefore lead them not to use medications correctly.[27]

Antidepressants are the most prescribed psychotropic drugs in the general population and are the medications of choice for treatment of anxiety and/or depressive disorders.[12,28] In the population studied, antidepressants were also the most prescribed drugs, representing about 25% of prescriptions. A significant portion (52.8%) of the students who used a psychotropic drug reported having anxious or depressive symptoms, and identified this as the main reason for using this class of medication. This was followed by insomnia, reported by 7.2%.

The students' sleep pattern seemed adequate for more than 60% of the participants, who reported having more than six hours of sleep per night, which is one of the criteria for assessing sleep quality.[29] Insomnia is a risk factor and, at the same time, a sign of mental health impairment.[30,31] Among the participants in the present study, it was observed that having less sleep was a risk factor for a diagnosis of some psychiatric disorder and for incorrect medication use. In other words, students who said that they were sleeping for fewer hours a night had higher prevalence of mental disorders and tended to forget to take their psychotropic drugs.

Also, among the participants in this study, regular physical activity was seen to be a protective factor against depression diagnosed by a doctor. Regular physical activity is a known protective factor against depression, as already reported.[32] Furthermore, in the present study, individuals who practiced regular physical activity were also sleeping for longer times.

The prevalence of use of illicit substances was close to what has been identified in the literature for this age group.[21,33,34] The most-used substance was marijuana, which is a substance for which usage has been correlated with increased risk of suicide, in addition to other cognitive impairments.[35]

Our study had some limitations, considering that it was conducted in a single private medical school. Therefore, although the sample size did represent the whole population of medical students in the institution, with a 5% tolerance error and 95% confidence level, phenomena with low prevalence cannot be evaluated in these circumstances.

CONCLUSION

This study showed the high prevalence of psychotropic drug use among medical students. The clinical indication for use of these drugs was psychological distress, and anxiety, depression, insomnia and panic were the most prevalent disorders. It also demonstrated that the prevalence of psychiatric disorders and the use of psychotropic drugs increase over the years of the course, and that there may be a reduction in the third and fourth years. The risk factors for mental disorders comprised reduced hours of sleep, lack of regular physical activity, progression along the medical course and female gender. Women were more likely to receive diagnoses of depressive disorder and panic, and to present symptoms such as distress, discouragement and irritability. Regular physical activity and a good sleep pattern were protective factor against mental disorders.

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Address for correspondence:
Nicoli Abrão Fasanella
Departamento de Saúde Coletiva da Faculdade de Ciências Médicas e da Saúde (FCMS),
Pontifícia Universidade Católica de São Paulo (PUC-SP)
R. Joubet Wey, 290
Vila Boa Vista — Sorocaba (SP) — Brasil
CEP 18030-070
Tel. (+55 15) 3212-9900 — Cel. (+55 15) 98127-6613
E-mail: nicoli.abrao@gmail.com

Perceived racism or racial discrimination and the risk of adverse obstetric outcomes: a systematic review

Glaucia Miranda Varella Pereira[I], Veronica Maria Pimentel[II], Fernanda Garanhani Surita[III], Amanda Dantas Silva[IV], Luiz Gustavo Oliveira Brito[V]

Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil

[I]PT, MSc. Doctoral Candidate, Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-4697-5295

[II]MD, MSc. Attending Physician, Department of Obstetrics and Gynecology, Saint Francis Hospital and Medical Center-Trinity Health of New England, Hartford, Connecticut, United States; Assistant Professor, Frank H. Netter M.D. School of Medicine, Quinnipiac University, North Haven, Connecticut, United States; and Assistant Professor, School of Medicine, University of Connecticut (UConn), Farmington, Connecticut, United States.
https://orcid.org/0000-0001-8365-0620

[III]MD, PhD. Associate Professor, Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-4335-0337

[IV]MD. Attending Physician, Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0001-9258-0038

[V]MD, PhD. Associate Professor, Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-7364-4718

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ABSTRACT

BACKGROUND: Racial disparities are differences among distinct subgroups of the human species; biologically, there are no scientifically proven reasons for them to exist.
OBJECTIVE: To assess the impact of racism or racial discrimination on obstetric outcomes.
DESIGN AND SETTING: Systematic review conducted at a tertiary/academic hospital.
METHODS: The Cochrane Library, SCOPUS/EMBASE, PubMed, Web of Science and ClinicalTrials.gov databases were searched from inception to June 2020. Studies presenting any type of racial discrimination, or any manifestation of racism that was perceived by women of any age in an obstetric scenario were included. Studies that only assessed racial disparities without including direct racism were excluded. The secondary outcomes evaluated included quality of antenatal care, intra and postpartum care, preterm birth and birthweight. The Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) scale was used to assess the quality of evidence from non-randomized studies.
RESULTS: A total of 508 records were retrieved and 29 were selected for qualitative synthesis. No meta-analysis could be performed due to the high heterogeneity across studies. Perceived racism was associated as a risk factor in 7/10 studies focusing on pregnancy and postpartum maternal outcomes, five studies on preterm birth, one study on small for gestational age and two studies on low birthweight. Overall, among the 29 studies, the risk of bias was classified as moderate.
CONCLUSIONS: Perceived racism presented an association with poor obstetric outcomes. Anti-racist measures are needed in order to address the problems that are causing patients to perceive or experience racism.
SYSTEMATIC REVIEW REGISTRATION: PROSPERO database, CRD42020194382

INTRODUCTION

Evidence that racial and ethnic disparities are present in healthcare matters and that structural racism is involved as a key determinant of populations' health is growing.[1] Studies within obstetrics have shown that racial disparities influence maternal morbidity and mortality, and that non-Hispanic black women are at highest risk of these outcomes in addition to being at highest risk of entering antenatal care late and being insufficient users of healthcare assistance.[2] In a recent systematic review, empirical studies provided evidence to show that race and ethnicity have a role in pregnancy-related mortality and severe maternal morbidity risk.[3] However, the number of studies on racial disparities surpasses those on racism itself.

Racial disparities are differences among distinct subgroups of the human species. However, biologically, there are no scientifically proven reasons for them to exist. Nonetheless, race has social significance because it may be used within a system of domination and oppression within which one racial group receives benefits and privileges from systematic subjugation of other racial groups.[4] Thus, racial disparities are the tip of the iceberg, as the effect is seen in relation to several disorders throughout medicine. In obstetrics, the effect of racism leads to racial disparities that involve not only the woman but also the newborn or the whole family.

Racism is defined as "an organized system, rooted in an ideology of inferiority that categorizes, classifies and allocates social resources to groups of the human population in different ways".[5] In addition to being considered to be a determinant of health, due to its dynamic nature that endures and adapts over time, thereby influencing policies and practices that affect health, racism reflects norms and practices that are perceived as common, constant and chronic.[6-8] Therefore, it

is important to study the effect of racism at every step of the way, in order to analyze outcomes that can lead to solutions.

OBJECTIVE

We aimed to assess the impact of racism or racial discrimination within obstetric outcomes, considering that in obstetrics, the effect of racism may lead to racial disparities that involve both the woman and the child.

METHODS

This systematic review was conducted in accordance with the PRISMA guidelines[9,10] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol for this review was registered in the PROSPERO database (under the number CRD42020194382).[11] The Cochrane, EMBASE/SCOPUS, PubMed, Web of Science and ClinicalTrials.gov databases were searched electronically on the same day (July 1, 2020) using Medical Subject Headings (MeSH) terms and entry terms, along with keywords and word variants, for the terms obstetrics and racism (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020194382). There were no language or time-span restrictions.

Study selection

This review included observational studies that reported any type of racial discrimination, or any racism manifestation perceived by women of any age in an obstetric scenario. We considered studies that measured manifestations of racial discrimination or racism using questionnaires, indexes or scales in association with obstetric outcomes. Studies within obstetrics or studies that considered racial disparities or racial inequalities within obstetrics that did not measure manifestations of racial discrimination or racism were excluded. We also excluded qualitative studies that did not present any quantitative data, in accordance with the inclusion criteria.

The primary outcome was the presence of perceived racism or racial discrimination, reported as a categorical answer (yes/no), or as the sum score from an instrument measuring racial discrimination or racism.

Measurements

The following scales and indexes were investigated: Experience of Discrimination Scale,[12] Daily Life Experiences of Racism and Bother Score,[13] Racism and Life Experience Scale,[14] Racial Segregation Index,[15] Major Discrimination Scale,[16] Index of Concentration at the Extremes,[17] Perception of Discrimination During Childbirth,[18] Gendered Racial Microaggressions Scale,[19] Measure of Indigenous Racism Experience,[20] Racism-Related Scale,[21] Chronic Worry,[12] Williams Scale of Everyday Discrimination[12] and Perceived Racism Scale.[22]

The Experience of Discrimination Scale is a validated and reliable nine-item questionnaire that has been used in eleven studies. It is based on a previous seven-item instrument developed by Krieger et al. in 1990.[23,24] This multi-item self-report instrument measuring experiences of racial discrimination presents nine-item questions about discrimination in several domains, including at school and work, and investigates the frequency of discrimination.[12] The Experience of Discrimination questionnaire was validated in the American population through confirmatory factor analysis and the results showed adequate model-fit indices.[12]

We used a spreadsheet for data extraction that had previously been pilot-tested. It exhibited the following variables: author/year, subject, variables, the time when the interview took place, sample size and main results (with descriptive data or crude/adjusted analysis if the variables were estimating the effect of an association between racism/racial discrimination and a dependent variable).

Data extraction

Two researchers (GMVP and LGOB) independently evaluated the titles and abstracts of screened articles. A full-text evaluation was performed when the abstracts did not provide sufficient methodological information. The two researchers also independently analyzed full-text articles to determine study eligibility and to extract data. A third reviewer (FGS) helped in cases of any inconsistencies in the data.

Assessment of risk of bias

Study quality was assessed by two investigators independently using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. The studies were judged in terms of bias as "low risk", "moderate risk", "serious risk", "critical risk" and "no information", for the following domains: confounding, selection of participants, classification, deviations from intended interventions, missing data, measurement of outcomes, reported result and overall bias.[25]

Data synthesis

Interventions and outcomes were presented differently among the studies selected, which precluded meta-analysis (due to heterogeneity). The present analysis was therefore restricted to a systematic review. We divided the results according to maternal outcomes (maternal smoking, antenatal entry, antenatal stress, delayed antenatal care, maternal blood pressure, antenatal sleep quality, trust in providers, etc.) and neonatal outcomes (preterm birth, small for gestational age and low birthweight).

RESULTS

The search strategy identified 508 articles; of these, two studies were excluded because they did not meet the inclusion criteria

and 29 studies were included for final qualitative synthesis and are displayed in **Figure 1**. These comprised 16 cross-sectional studies, 11 cohort studies and two case-control studies. No randomized clinical trials were found regarding this subject. The number of participants per study ranged among the studies from 39 to 8,962 women.

The maternal outcomes (**Table 1**) included racial discrimination in pregnancy and childbirth. Four studies included antenatal care that involved racial discrimination with regard to smoking,[26] perceived discrimination through delayed antenatal care,[27] experience of racial discrimination in antenatal entry[28] and racial discrimination regarding perceived antenatal stress/depression.[29] Eleven studies on pregnancy assessed general perceived racism,[30-34] racial discrimination in relation to Epstein-Barr virus reactivation,[35] racism

in relation to blood pressure changes,[36] racism in relation to trust in providers,[37] racial segregation with regard to smoking,[38] perceived discrimination in maternity care[39] and racial discrimination in relation to biological measurements.[40] One study included racial discrimination with regard to perinatal sleep quality.[41] Lastly, perceived discrimination during childbirth was reported in one study.[18]

Fourteen studies assessed racial discrimination in relation to neonatal outcomes (**Table 2**) involving preterm birth (gestational age below 37 weeks) and low birthweight (less than 2500 grams).[32,36,42-53]

The risk of bias of the studies included is described in **Figure 2**.[18,28-53] The overall classification of bias in these studies was moderate. Overall bias was classified as a moderate risk of bias in all 29 studies.
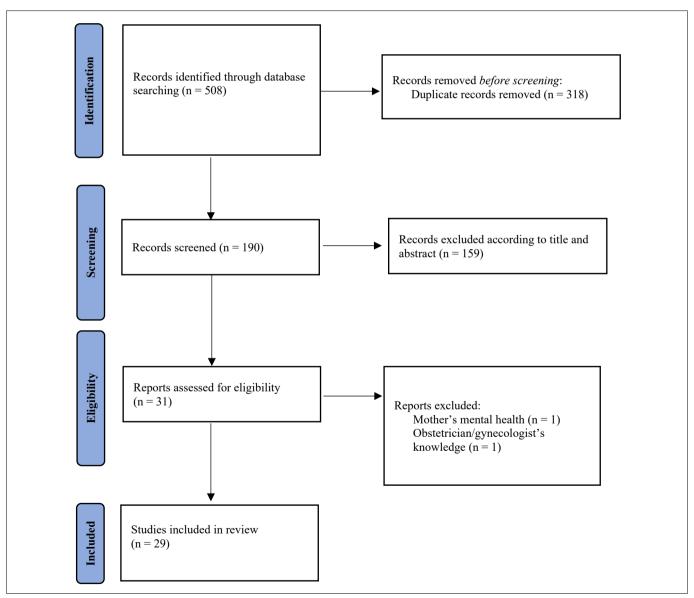
Figure 1. Flowchart of different steps of the systematic review.

Table 1. Racism or racial discrimination within studies comprising antenatal care, childbirth and postpartum period

Author, year/ study design	Subject	Measurement	Time of interview	Sample size	Main results (descriptive or after crude/adjusted analysis)
Nguyen et al.,[26] 2012/ CS	Racial discrimination in relation to PN smoking	EODQ	Baseline interview at mean of 26.9 weeks of gestation	n = 677 -n = 265 black -n = 412 Hispanic	EODQ (whole sample) - moderate: (adjusted OR 1.00) - none: (adjusted OR 1.67; CI 0.86-3.21) - high: (adjusted OR 2.64; CI 1.25-5.60) EODQ (stratified) Hispanic women - moderate: (adjusted OR 1.00) - none: (adjusted OR 2.45; CI 0.90-6.70) - high: (adjusted OR 2.08; CI 0.60-7.14) Black women - moderate: (adjusted OR 1.00) - none: (adjusted OR 1.05; CI 0.42-2.62) – high: (adjusted OR 3.36; CI 1.23-9.19)
Slaughter-Acey et al.,[28] 2013/CH	Racism in relation to PN care	DRI: RaLES	At 22 to 28 weeks of gestation and then during postpartum hospitalization	n = 762 African-American	Prenatal care entry 4-6 months - Overall DRI: (crude OR 1.08; CI 0.95-1.23) and (adjusted OR 1.00; CI 0.87-1.14) - Denial of personal racism: (crude OR 1.05; CI 0.88-1.26) and (adjusted OR 0.95; CI 0.78-1.14) - Denial of group racism: (crude OR 1.24; CI 0.96-1.61) and (adjusted OR 1.12; CI 0.85-1.47) Prenatal care entry ≥ 7 months or no care - Overall DRI: (crude OR 1.20; CI 1.02-1.42) and (adjusted OR 1.19; CI 1.00-1.41) - Denial of personal racism: (crude OR 1.12; CI 0.89-1.42) and (adjusted OR 1.08; CI 0.84-1.38) - Denial of group racism: (crude OR 1.64; CI 1.20-2.25) and (adjusted OR 1.64; CI 1.18-2.28)
Bécares et al.,[29] 2016/ CS	Racial discrimination in relation to PN perceived stress	EODQ	Last trimester of pregnancy	n = 3,355 women	Personal attack: Physical attack ever: (coeff. 1.27; CI -0.18-2.72); physical attack past: (coeff. 1.14; CI -1.20-3.49) Verbal attack ever: (coeff. 1.68; CI 1.06-2.29); verbal attack past: (coeff. 1.62; CI 0.74-2.49) Any personal attack ever: (coeff. 1.68; CI 1.08-2.28); any personal attack past: (coeff. 1.50; CI 0.65-2.35) Unfair treatment: Healthcare professional ever: (coeff. 1.42; CI 0.44-2.39); healthcare professional past: (coeff. 1.79; CI 0.51-3.07) Work ever: (coeff. 2.08; CI 1.20-2.97); work past: (coeff. 1.23; CI -0.23-2.69) Housing ever: (coeff. 1.51; CI 0.58-2.44); housing past: (coeff. 2.27, CI 0.81-3.74) Criminal justice system ever: (coeff. 1.22; CI 0.05-2.38); criminal justice system past: (coeff. 1.25; CI -0.56-3.07) Banking system ever: (coeff. 2.55; CI 1.05-4.04); banking system past: (coeff. 1.21; CI -1.06-3.48) Educational system ever: (coeff. 0.98; CI 0.15-1.82); educational system past: (coeff. 1.75; CI -0.50-3.99) One experience ever: (coeff. 1.08, CI 0.43-1.73); one experience past: (coeff. 1.64; CI 0.84-2.44) Two or more experiences ever: (coeff. 2.65; CI 1.95-3.35); two or more experiences past: (coeff. 2.02; CI 0.91-3.12)
Slaughter-Acey et al.,[27] 2019/CH	Racial macro-aggressions in relation to delayed PN care	20-item DLE-B	Interviewed 24-48 hours after delivery	-n = 909 first PN care -n = 300 no or late PN care	- African-American women with DLE-B score > 71 for no or late PNC: (unadjusted OR = 1.24; 95% CI = 0.95-1.61) and (adjusted OR = 1.31; 95% CI = 1.00-1.72) - Stratified according to maternal skin tone with DLE-B score > 71 for no or late PNC: light brown African-American women (adjusted OR = 1.67; 95% CI = 1.02- 2.71) and dark brown African-American women (adjusted OR = 2.29; 95% CI = 1.18-4.43)

Continue...

Table 1. Continuation

Author, year/ study design	Subject	Measurement	Time of interview	Sample size	Main results (descriptive or after crude/adjusted analysis)
Stancil et al.,[30] 2000/ CS	Racial discrimination in relation to pregnancy outcomes	EODQ	In first half and second half of pregnancy	n = 94 African-American	Racial discrimination - ever: 54.3% (51); applying for housing: 23.4% (22); applying for a job: 28.7% (27); at school: 26.6% (25); getting medical care: 7.4% (7); dealing with police or in court: 11.7% (11); at work: 28.7% (27); other: 7.4% (7)
Christian et al.,[35] 2012/ CS	Racial discrimination in relation to Epstein-Barr virus (EBV) reactivation in pregnancy and postpartum	EODQ	1st, 2nd and 3rd trimesters and at 4-9 weeks postpartum	n = 56 -n = 38 African-American -n = 18 white	- High versus low discrimination: higher EBV virus capsid antigen immunoglobulin G (VCA IgG) antibody titers during the first (P = 0.03) and second trimesters of pregnancy (P = 0.04); 3rd trimester (P = 0.12) and at postpartum (P = 0.06) - White vs African American women Higher EBV VCA IgG antibody titers at all three trimesters and at postpartum [high discrimination: P values < 0.001; low discrimination: P = 0.01 (1st), 0.001 (2nd), 0.002 (3rd) and 0.001 (postpartum)
Hilmert et al.,[36] 2014/ CS	Racism in relation to blood pressure changes during pregnancy	EODQ	22 to 24 weeks of gestation	-n = 39 African-American women	Diastolic blood pressure (DBP) change analyses: Racism in relation to changes in DBP interactions was significant in the analyses involving childhood: indirect racism (β = - 0.36; ΔR^2 = 0.12; P < 0.01); and childhood personal racism (β = -0.30; ΔR^2 = 0.07; P < 0.05), both showing the same pattern of associations depicted. Systolic blood pressure (SBP) change analyses. Parallel analyses on changes in SBP did not reveal any statistically significant results (all P values > 0.05).
Peters et al.,[37] 2014/ CS	African-American women's trust in provider during pregnancy	Trust in Physician Scale RaLES-Brief	Once a month during weeks 4-28; every 2 weeks during weeks 28-36 and every week from week 36 until birth	n = 189 African American women	Trust was inversely associated with previous experience of racism, specifically in healthcare (r = -0.16; P = 0.03), as women who reported experiencing racism in healthcare had significantly lower trust scores than women who did not report such an experience (t (187) = 2.17; P = 0.03)
Yang et al.,[38] 2014/CS	Racial segregation in relation to maternal smoking during pregnancy	Racial Segregation Index	Pregnancy	County-level n = 2556 (NHW) (59%) (NHB) (16%) (NHA) (4%) (H) (21%).	Racial segregation index: NHB: living in a county where blacks are more segregated from whites was associated with higher probability of maternal smoking during pregnancy NHA: Asian women seemed to benefit more from living in a county where Asians were segregated from whites than in a county where these two racial groups were integrated H: Living in a Hispanic-white segregated community could be beneficial for Hispanic mothers
Attanasio et al.,[39] 2015/ CS	Perceived discrimination in maternity care	- 7 questions: during prenatal care (communication) - 3 questions: during birth hospitalization (Perceived discrimination domain)	Before, during and after recent birth	n = 2,231 -n = 1,308 NHW -n = 368 NHB -n = 555 H	Race: - NHB: (adjusted OR 2.99; CI 1.56-5.74) - H: (adjusted OR 2.25; CI 1.32-3.81) Maternal health: - Pregnancy hypertension: (adjusted OR 2.41; CI 1.38-4.22) - Diabetes (adjusted OR 3.25; CI 2.09-5.04) - Obese pre-pregnancy (adjusted OR 0.63; CI 0.35-1.13)

Table 1. Continuation

Author, year/ study design	Subject	Measurement	Time of interview	Sample size	Main results (descriptive or after crude/adjusted analysis)
Borders et al.,[40] 2015/ CH	Hormonal and inflammatory measurements of chronic stress during pregnancy according to racial discrimination scale	EODQ	14 and 22 weeks of gestation	Total: n = 112 - 55 NHB - 57 NHW	Krieger Discrimination Scale P < 0.001 - blacks: 11.3 ± 1.7 – whites: 13.3 ± 0.9 Association of mean stress biomarkers with race NHB women had significantly higher mean C-reactive protein levels in the second trimester (12.7 ± 11.9 versus 7.4 ± 8.3; P < 0.01) and third trimester (12.2 ± 14.9 versus 6.9 ± 7.4; P = 0.04) relative to NHW women. NHB women also had significantly higher adrenocorticotropic hormone levels in the second trimester (21.6 ± 11.9 versus 16.5 ± 8.5; P = 0.01) and third trimester (6.4 ± 15.1 versus 3.9 ± 4.0; P = 0.03) relative to NHW women. No differences in Epstein-Barr virus or corticotropin-releasing hormone levels were detected between the two racial/ethnic groups
Grobman et al.,[31] 2016/ CH	Psychosocial states and traits during pregnancy	EODQ	21 weeks of gestation.	n = 7,690	Krieger Racism ≥ 3: (%) - NHW: 2.0% - NHB: 21.0% - H: 13.2% - A: 15.8% - other: 15.8%; P < 0.0001
Grobman et al.,[32] 2018/ CH	Associations of preterm birth, hypertensive disease of pregnancy and SGA birth with self-reported measurements of psychosocial stress	EODQ	16 and 21 weeks of gestation	n = 8,962	Hypertensive disease of pregnancy - NHB (OR 0.98; CI 0.81-1.20) - H (OR 0.71; CI 0.58-0.86) - Asian (OR 0.82; CI 0.56-1.20) - Other (OR 0.85; CI 0.63-1.14) - Krieger > 3 (OR 0.81; CI 0.62-1.06)
Mendez et al.,[33] 2020/ CH	Racism in relation to pregnancy and postpartum	- TMDS - GRMS	18-32 weeks of gestation and at delivery	n = 230 -n = 146 white -n = 57 black	Only descriptive: black participants indicated more racism than white participants, and white participants indicated more sexism than black participants
Chambers et al.,[34] 2020/ CS	Racial discrimination among pregnant and postpartum black women	ICE (concentrations at the extremes) race + income measurement (formula)	Currently pregnant or early postpartum (6 weeks) with a singleton birth	n = 42 -n = 20 least deprived -n = 22 most deprived	Racial Discrimination - 93% of the women: at least one situational domain - 59.5% of the women: in three or more situational domains - The three most common situational domains were at school (59.5%), on the street or in a public setting (59.5%) and getting service in a store or restaurant (54.8%)
Francis et al.,[41] 2017/ CS	Racial discrimination in relation to perinatal sleep quality	EODQ	Each trimester and postpartum	n = 640 - PN n = 247 - Postnatal n = 393	Cross-sectional unadjusted analysis associations between discrimination and overall sleep quality: - Overall (overall sleep quality 0.058) - prenatal (overall sleep quality 0.042) - postpartum (overall sleep quality 0.076) - Black (overall sleep quality 0.048) - White (overall sleep quality 0.072)
Attanasio et al.,[18] 2017/ CS	Perceived discrimination during hospitalization for childbirth	Survey	8 weeks after birth	n = 2,400	Perceived discrimination during hospitalization for childbirth and non-attendance of postpartum visit (multivariate models) - Treated poorly due to race: (unadjusted OR 2.11; CI 1.25-3.57) and (adjusted OR 2.11; CI 1.15-3.87)

CS = cross-sectional study; CH = cohort study; PN = prenatal; EODQ = Experience of Discrimination Questionnaire; DRI = Denial of Racism Index; RaLES = Racism and Life Experiences Scale; DLE-B = Daily Life Experiences of Racism and Bother score; TMDS = The Major Discrimination Scale; GRMS = Gendered Racial Microaggressions Scale; NHB = non-Hispanic black; NHW = non-Hispanic white; H = Hispanic; OR = odds ratio; CI = confidence interval; coeff = coefficient; PNC = prenatal care; EBV = Epstein-Barr virus.

Table 2. Racism or racial discrimination assessed within studies on low birthweight and preterm infants

Author, year /study design	Subject	Measurement	Time of Interview	Sample size	Control group	Main results (descriptive or after crude/adjusted analysis)
Rosenberg et al.,[42] 2002/CS	Racial discrimination in relation to premature birth	EODQ	Singleton births that had occurred in the previous two years.	n = 4,966 -n = 422 mothers of preterm babies -n = 4,544 mothers of full term babies	N/A	Preterm versus full term: - Job: (unadjusted OR 1.3; CI 1.1-1.7; adjusted OR 1.3; CI 1.1-1.6) - Housing: (unadjusted OR 1.0; CI 0.8-1.3; adjusted OR 1.0, CI 0.8-1.3) - Police: (unadjusted OR 1.2; CI 0.9-1.5; adjusted OR 1.1; CI 0.9-1.4) - Poorer service: (unadjusted OR 1.1; CI 0.7-1.5; adjusted OR 1.1; CI 0.7-1.5) - Not intelligent: (unadjusted OR 1.1; CI 0.9-1.5; adjusted OR 1.1; CI 0.8-1.4) - Causing fear: (unadjusted OR 1.4; CI 1.1-2.0; adjusted OR 1.4; CI 1.0-1.9) - Dishonest: (unadjusted OR 1.2; CI 0.8-1.7; adjusted OR 1.2; CI 0.8-1.7) - Worse than others: (unadjusted OR 1.2; CI 0.9-1.5; adjusted OR 1.1; CI 0.9-1.4) - Thinking about their race: (unadjusted OR 1.0; CI 0.7-1.4; adjusted OR 1.0; CI 0.7-1.4)
Mustillo et al.,[43] 2004/CS	Self-reported racial discrimination in relation to differences in black and white preterm and low-birthweight deliveries	EODQ	Year 7 examination (1992–1993)	n = 352 - Black women n = 152 - White women n = 200	N/A	Preterm deliveries (n = 328) - Race/ethnicity: black versus white (OR 2.54; CI 1.33- 4.85) - Self-reported racial discrimination in 1 or 2: (OR 1.97; CI 0.89-4.38) - Self-reported racial discrimination in ≥ 3: (OR 2.42; CI 1.03-5.69). Low birthweight deliveries (LR) (n = 320) - Race/ethnicity: black versus white (OR 4.24; CI 1.31-13.67) - Self-reported racial discrimination in 1 or 2: (OR 2.04; CI 0.50-8.31) - Self-reported racial discrimination in ≥ 3: (OR 4.81; CI 1.50-15.40)
Misra et al.,[44] 2010/CH	Racism in relation to risk of preterm birth	RALES and RRS	22-28 weeks of gestation and postpartum	n = 843 African-American women	N/A	Racism and stress Lower stress: (unadjusted HR 0.88; CI 0.59-1.32) and (adjusted HR 0.92; CI 0.61-1.38). Higher stress: (unadjusted HR 1.29; CI 0.83-2.01) and (adjusted HR 1.30; CI 0.83-2.04).
Braveman et al.,[45] 2017/CS	Racial discrimination in relation to preterm birth	Racial discrimination Chronic worry	4 months postpartum	Black women: n = 2,201 White women: n = 8,122	N/A	Chronic worry and racial discrimination unadjusted: - Black women: (PR 1.73; CI 1.12-2.67); - white women: (PR 1.77; CI 0.83-3.77) Chronic worry, racial discrimination and social/demographic covariates: - Black women: (PR 1.95; CI 1.27-2.97); - white women: (PR 1.67; CI 0.73-3.79) Chronic worry, racial discrimination and social/demographic, behavioral and medical covariates: - Black women: (PR 2.00; CI 1.33-3.01); - white women: (PR 1.84; CI 0.91-3.71)
Bower et al.,[46] 2018/CS	Racism in relation to preterm birth	ERQ	2-6 months postpartum	-n = 426 primiparous -n = 912 multiparous term birth -n = 268 multiparous preterm birth	N/A	Weighted population (crude) - Racism (OR 1.27; CI 1.04-1.54) Adjusted for maternal age and BMI - Racism (OR 1.29; CI 1.04-1.59)

Table 2. Continuation

Author, year /study design	Subject	Measurement	Time of Interview	Sample size	Control group	Main results (descriptive or after crude/adjusted analysis)
Fryer et al.,[47] 2020/CS	Everyday discrimination in relation to preterm birth among African-American and Latina women	WSED	One month postpartum	n = 1,732 - 1,154 African-American - 578 Latina	N/A	Spontaneous preterm delivery - African-American (high discrimination): (unadjusted HR 1.4; CI 0.7-2.7) and (adjusted HR 1.5; CI 0.7-3.1) - Latina (high discrimination): (unadjusted HR 3.8; CI 0.9-15.1) and (adjusted HR 3.6; CI 0.9-14.4)
Wheeler et al.,[48] 2018/CH	Racism in relation to preterm birth	PSS	Current pregnancy	n = 1,606 -n = 1,256 NHB -n = 350 NHW	N/A	Perceived racism score in relation to spontaneous preterm birth - Primiparous (adjusted OR 1.29; CI 0.91-1.83) - Multiparous term birth (adjusted OR 1.01; CI 0.79-1.30) - Multiparous preterm birth (adjusted OR 1.05; CI 0.78-1.40) Perceived racism score in relation to spontaneous preterm birth among black women - Primiparous (adjusted OR 1.36; CI 0.93-1.96) - Multiparous term birth (adjusted OR 1.03; CI 0.80-1.31) - Multiparous preterm birth (adjusted OR 0.98; CI 0.72-1.35)
Grobman et al.,[32] 2018/CH	Associations of preterm birth and SGA birth with self-reported measurements of psychosocial stress	ERQ	16-21 weeks of gestation	n = 8,962 women	N/A	Any preterm birth - NHB (OR 1.31; CI 1.04-1.64); - H (OR 0.95; CI 0.76-1.20); - Asian (OR 0.87; CI 0.56-1.36); - other (OR 1.14; CI 0.82-1.59); - Krieger > 3 (OR 0.91; CI 0.67-1.23) Small for gestational age - NHB (OR 2.07; CI 1.69-2.53); -H (OR 1.45; CI 1.19-1.77); - Asian (OR 2.08; CI 1.54-2.81); - other (OR 1.42; CI 1.05-1.93); - Krieger > 3 (OR 1.01; CI 0.78-1.31)
Slaughter-Acey et al.,[49] 2016/CH	Racism in relation to risk of preterm birth	DLE-B	24 and 48 hours after delivery	n = 1,232 African-American women	N/A	Mild to moderate depressive symptoms: perceived racism was significantly associated with preterm birth Severe depressive symptoms: perceived racism was not associated with preterm birth
Brown et al.,[50] 2019/CH	Perceived discrimination in birth outcomes among women giving birth to an Aboriginal baby	4-item questions adapted from MIRE	When women's infant was 4-12 months old.	n = 344 women	N/A	Discrimination report - < 37 weeks: (unadjusted OR 1.0; CI 0.5-1.9) and (adjusted OR 1.1; CI 0.5-2.1) - SGA: (unadjusted OR 2.0; CI 1.1-3.6) and (adjusted OR 1.7; CI 0.9-3.2) Discrimination report - < 2500 grams: (unadjusted OR 2.1; CI 1.1-4.1) and (adjusted OR 2.0; CI 1.0-3.9)
Lespinasse et al.,[51] 2004/CC	Racial discrimination in relation to birthweight of infants of African-American women	ERQ	3 days after delivery.	-n = 104 mothers (low birthweight)	- n = 208 mothers (normal birthweight)	Exposure to racial discrimination (%OR): - 1 or more domain: (OR 1.9; CI 1.2-3.0) - 3 or more domains: (OR 2.7; CI 1.3-5.4)
Collins et al.,[52] 2004/CC	Maternal exposure to interpersonal racial discrimination in relation to infants with very low birthweight	ERQ	72 hours after infants' admission to the neonatal intensive care unit or nursery	-n = 104 African American infants (< 1500 g), born preterm (< 37 weeks)	-n = 208 African American women with term infants	Reported racial discrimination incidents Lifetime: - Job: (OR 3.0; CI 1.6-5.4); - at work: (OR 2.0; CI 1.1-3.5); - at school: (OR 1.9; CI 1.0-3.7); - public settings: (OR 1.4; CI 0.8-2.3); - medical care: (OR 0.9; CI 0.3-2.7) - ≥ 1: (OR 1.9; CI 1.2-3.1); - ≥ 2: (OR 2.1; CI 1.2-3.8); - ≥3: (OR 3.2; CI 1.5-6.6) - Adjusted ≥ 1 domain: OR 1.7; CI 1.0-9.2 - Adjusted ≥ 3 domains: OR 2.6; CI 1.2- 5.3

Table 2. Continuation

Author, year /study design	Subject	Measurement	Time of Interview	Sample size	Control group	Main results (descriptive or after crude/adjusted analysis)
Dominguez et al.,[53] 2008/CH	Racism as predictor of birthweight	ERQ	24-26 weeks of gestation	-n = 51 African American women -n = 73 NHW	N/A	Race step 1 (β = -0.25; P < 0.05), with African American infants weighing an average of 280.84 g less than white infants. Perceived racism lifetime score step 2: each unit increase in lifetime perceived racism was associated with a 39.59-g decrease in birth weight. Interaction term (step 3) - Childhood-direct racism (β = 0.17; P < 0.10). Each unit increase was associated with a 137.10-g increase in birth weight -Childhood-vicarious racism (β = - 0.25; P < 0.01). Each unit increase was associated with a 167.85-g decrease in birth weight.
Hilmert et al.,[36] 2014/CS	Association between birthweight and racism	ERQ	22 to 24 weeks of gestation	n = 39 African American pregnant women	N/A	Childhood indirect, adulthood personal and total racism exposure: significant amount of variance in birth weight (all P values < 0.05). Association between adjusted birthweight and childhood indirect racism (β = -0.24) was not significant (P > 0.10). Association between birthweight and total racism (β = -0.27) was slightly significant (P < 0.10).

CS = cross-sectional study; CH = cohort study; CC = case-control study; EODQ = Experience of Discrimination Questionnaire; SGA = Small for Gestational Age; MIRE = Measure of Indigenous Racism Experience; RRS = Racism-Related Scale; WSED = Williams Scale of Everyday Discrimination; RaLES = Racism and Life Experiences Scale; DLE-B = Daily Life Experiences of Racism and Bother score; PSS = Perceived Stress Scale; ERQ = Experiences of Racism Questionnaire; NHB = non-Hispanic black; NHW = non-Hispanic white; H = Hispanic; OR = odds ratio; CI = confidence interval; HR = hazard ratio; PR = prevalence ratio; N/A = not applied.

Pregnancy

Two studies assessed the association between racial discrimination and maternal smoking. Nguyen et al.[26] described experiences of discrimination as a predictor for smoking during pregnancy. They found that women who experienced high levels of discrimination ($\geq$ 3 domains) were 2.6 times (odds ratio, OR 2.64; confidence interval, CI 1.25 to 5.60) more likely to smoke during pregnancy. When stratified according to race, black women reporting high levels of discrimination were 3.4 times (OR 3.36; CI 1.23 to 9.19) more likely to smoke during pregnancy than Hispanic women. Yang et al.[38] reported a higher probability of maternal smoking during pregnancy when black women were less integrated into society at large than non-Hispanic whites were.
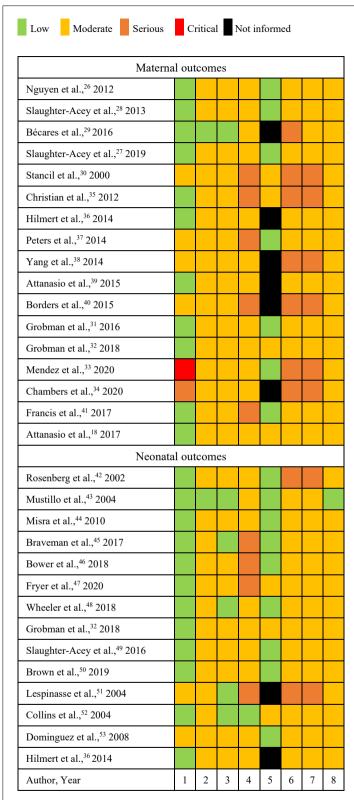
Slaughter-Acey et al.[28] investigated the indices of denial of racism in antenatal care for African-American women; they found that the overall denial of racism index was 19% higher (adjusted odds ratio, AOR 1.19; CI 1.00–1.41) for African-American women with no prenatal care or late to antenatal care (attendance at $\geq$ seven months of gestation), compared with early prenatal care attendance (attendance at $\leq$ three months of gestation).

Becares et al.[29] reported on lifetime and past-year experiences of racial discrimination covering personal attacks and unfair treatment in a group of multiple-ethnicity women categorized as Māori, Pacific, Asian and European. Lifetime and past-year experiences of racial discrimination with any unfair treatment were more common among Māori women; however, they were highly prevalent among all non-European mothers.

Slaughter-Acey et al.[27] revealed that African-American women with Daily Life Experience of Racism and Bother score > 71 were 31% more likely to present delayed antenatal care than non-African-American women. Fifty-one (54.3%) out of 94 African-American women reported experiences of racial discrimination in a study by Stancil et al.[30] Of these, 28.7% reported these experiences while applying for a job and 28.7% reported that these were occurrences at work.

Christian et al.[35] investigated the association between racial discrimination and Epstein-Barr virus capsid antigen immunoglobulin G during pregnancy and postpartum. Epstein-Barr virus capsid antigen immunoglobulin G antibody titers were significantly higher during the first (P = 0.03) and second trimesters of pregnancy (P = 0.04) in women reporting high levels of racial discrimination, compared with those reporting low racial discrimination.

Two studies by Grobman et al.[31,32] were selected. One study showed that non-Hispanic black women were more likely to perceive

Figure legend: Low (green), Moderate (yellow), Serious (orange), Critical (red), Not informed (black)

Maternal outcomes

Author, Year	1	2	3	4	5	6	7	8
Nguyen et al.,[26] 2012	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Slaughter-Acey et al.,[28] 2013	Low	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Moderate
Bécares et al.,[29] 2016	Low	Low	Low	Moderate	Not informed	Serious	Moderate	Moderate
Slaughter-Acey et al.,[27] 2019	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Stancil et al.,[30] 2000	Moderate	Moderate	Moderate	Serious	Low	Serious	Moderate	Moderate
Christian et al.,[35] 2012	Low	Moderate	Moderate	Moderate	Serious	Serious	Moderate	Moderate
Hilmert et al.,[36] 2014	Low	Moderate	Moderate	Moderate	Not informed	Moderate	Moderate	Moderate
Peters et al.,[37] 2014	Moderate	Moderate	Moderate	Serious	Low	Moderate	Moderate	Moderate
Yang et al.,[38] 2014	Moderate	Moderate	Moderate	Moderate	Not informed	Serious	Serious	Moderate
Attanasio et al.,[39] 2015	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Borders et al.,[40] 2015	Moderate	Moderate	Moderate	Serious	Not informed	Serious	Serious	Moderate
Grobman et al.,[31] 2016	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Grobman et al.,[32] 2018	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Mendez et al.,[33] 2020	Critical	Moderate	Moderate	Moderate	Moderate	Serious	Serious	Moderate
Chambers et al.,[34] 2020	Serious	Moderate	Moderate	Moderate	Not informed	Serious	Serious	Moderate
Francis et al.,[41] 2017	Low	Moderate	Moderate	Serious	Low	Moderate	Moderate	Moderate
Attanasio et al.,[18] 2017	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Neonatal outcomes

Author, Year	1	2	3	4	5	6	7	8
Rosenberg et al.,[42] 2002	Low	Moderate	Moderate	Low	Moderate	Serious	Serious	Moderate
Mustillo et al.,[43] 2004	Low	Low	Low	Moderate	Moderate	Moderate	Moderate	Low
Misra et al.,[44] 2010	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Braveman et al.,[45] 2017	Low	Moderate	Low	Serious	Moderate	Moderate	Moderate	Moderate
Bower et al.,[46] 2018	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Fryer et al.,[47] 2020	Low	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Moderate
Wheeler et al.,[48] 2018	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Grobman et al.,[32] 2018	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Slaughter-Acey et al.,[49] 2016	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Brown et al.,[50] 2019	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Lespinasse et al.,[51] 2004	Moderate	Moderate	Low	Serious	Not informed	Serious	Serious	Moderate
Collins et al.,[52] 2004	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Dominguez et al.,[53] 2008	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Hilmert et al.,[36] 2014	Low	Moderate	Moderate	Moderate	Not informed	Moderate	Moderate	Moderate

1 - Confounding; 2 - Selection of participants; 3 - Classification;
4 - Deviations from intended interventions; 5 - Missing data;
6 - Measurement of outcomes; 7 - Reported result; 8 - Overall bias.

Figure 2. ROBINS-I tool (Risk Of Bias In Non-randomized Studies – of Interventions) applied to the studies included.

racism and with the least social support. In the other, no association was observed between race-ethnicity and hypertensive disease of pregnancy.[36] Mendez et al.[33] used smartphone technology to assess exposure to racism and found that black women experienced more racism than white women. Peters et al.[37] investigated African-American women's trust in providers during pregnancy. Trust was negatively correlated with previous experience of racism (r = -0.16; P = 0.03).

In the study by Attanasio et al.,[39] black and Hispanic race/ethnicity were found to be associated, respectively, with threefold and twofold increases in perceived racial discrimination. Borders et al.[40] found an association between stress biomarkers and race. Non-Hispanic black women presented significantly higher adrenocorticotropic hormone and C-reactive protein levels in the second and third trimesters, in comparison with non-Hispanic whites.

Chambers et al.[34] described racial discrimination in nine situations. 93% of the women reported racial discrimination in at least one situational domain and the three most frequent ones were at school (59.5%), on the street or in a public setting (59.5%) and getting service in a store or restaurant (54.8%). Lastly, perinatal sleep quality was studied and correlated with racial discrimination in the study by Francis et al.[41] This positive association showed that greater reported everyday racial discrimination was associated with poorer overall sleep quality.

Childbirth and postpartum period

Attanasio et al.[18] investigated perceived discrimination in relation to hospitalization for childbirth and non-attendance of postpartum visit. Women who reported racial discrimination were more than twice as likely to miss their postpartum visit, compared with women who did not report this type of discrimination (AOR 2.11; CI 1.15–3.87).

Preterm birth

Rosenberg et al.[42] showed that preterm birth occurred 30% more often among women who reported unfair treatment on the job and 40% more often among women who reported that people acted fearfully in relation to them at least once a week.

Mustillo et al.[43] showed that black women were 2.5 times more likely to have a preterm birth than white women. Women who reported having three or more experiences of racial discrimination were 2.4 times more likely to have a preterm birth than those who did not report racial discrimination. Similarly, Braveman et al.[45] reported that racial discrimination was significantly associated with preterm birth among black women before (prevalence ratio, PR 1.73; CI 1.12–2.67) and after (PR 2.00; CI 1.33–3.01) adjustment for social/demographic, behavioral and medical covariates. Preterm birth was also associated with experiences of racism, with a 29% increased risk.[46]

Grobman et al.[32] found that non-Hispanic black women experiencing racism were at higher risk of any preterm birth and of small-for-gestational-age birth, compared with non-Hispanic white women. Similarly, Hispanic and Asian women experiencing racism were also at risk of small-for-gestational-age birth.

In four studies, exposure to racial discrimination did not interfere in the frequency of preterm birth among black women.[44,47-49] On the other hand, Fryer et al.[47] showed that Latina women presented a significant association between racial discrimination and preterm birth. Moreover, in the study by Brown et al.,[50] Aboriginal women who experienced racial discrimination in perinatal care showed a 90% higher risk of having an infant who was small for gestational age. They did not find any association with preterm birth in their sample.

Birthweight

Two case-control studies found an association between very low birthweight and maternal exposure to racial discrimination. Very low birthweight was associated with incidents of lifetime exposure to interpersonal racism in three or more domains of the racial discrimination questionnaire (AOR 2.6; CI 1.2–5.3).[52] Exposure to racial discrimination perceived in three or more domains of the racial discrimination questionnaire and being alone in the delivery room were associated with a twofold greater chance of having an infant with very low birthweight (OR 2.7; CI 1.3–5.4).[51]

Mustillo et al.[43] found a strong association between racial discrimination and birthweight. Black women were over four times more likely to deliver low birthweight infants than white women. Moreover, women reporting elevated levels of racial discrimination were almost five times more likely to deliver a low birthweight infant than women who did not report racial discrimination.

Dominguez et al.[53] reported that each unit increase in the perception of racial discrimination over women's lifetimes was associated with a 39.59-gram decrease in infant birthweight. Furthermore, childhood-vicarious racism (i.e. indirect exposure to prejudice and discrimination) was a significant predictor of decreased birthweight.

Hilmert et al.[36] also analyzed the involvement of racism in birthweight. In their interview method, adapted from Krieger et al.,[12] they included subscales for direct and indirect exposure during childhood ($\leq$ 16 years) and in adulthood (> 16 years). Correlation analyses showed that childhood indirect, adulthood personal and total racism exposure demonstrated significant amounts of variance in birth weight (all P-values < 0.05). After including control variables, the association between adjusted birthweight and indirect racism during childhood (β = -0.24) ceased to be significant (P > 0.10).

Lastly, Brown et al.[50] revealed that women who experienced racial discrimination in perinatal care were 90% more likely to have a baby with low birthweight than were women who did not experience such discrimination.

DISCUSSION

This review found that perceived racism or racial discrimination was negatively associated with maternal and neonatal outcomes. It supports the reality that racism is a public health problem that warrants significant discussion with the goal of finding practical solutions through implementation of anti-racist measures.

This review also demonstrated that women experiencing racial discrimination were more likely to present poorer maternal health outcomes during pregnancy and childbirth and in the postpartum period. Trust in providers was compromised during pregnancy; it was inversely associated with previous experiences of racism. Racial discrimination during antenatal care was associated with later onset of antenatal visits or lack of attendance of postpartum visits. It was also associated with smoking, which is a well-known risk factor for poor health outcomes.[54] Stress biomarkers also presented elevated during the second and third trimester among African-American women. Epstein-Barr virus immunoglobulin G (IgG) antibody titers were significantly elevated in women reporting high levels of racial discrimination. African-American women were found to have elevated antibody titers throughout pregnancy and the postpartum period. There is research supporting the notion that maternal stress before and during pregnancy is associated with poor pregnancy outcomes, including low birthweight, preterm birth and infant mortality.[55]

Racial discrimination also plays a negative role in pregnancy blood pressure. Pre-pregnancy hypertension and diabetes were associated with higher odds of perceived racial discrimination. Childhood exposure to racism presented a significant association with change in diastolic blood pressure in African-American women. High blood pressure during pregnancy is associated with pregnancy complications, such as preeclampsia, cesarean delivery, preterm delivery, low birth weight, neonatal intensive care admission and perinatal death.[56]

Racism appears to be a risk factor for worse neonatal outcomes, with greater occurrence of low birthweight and preterm birth. Racial discrimination was also significantly associated with premature birth in most, but not all the studies on this subject.

One major strength of our study was that it used a defined search strategy and predetermined eligibility criteria. We included studies that measured racial discrimination using an instrument that showed some association with obstetric outcomes, unlike previous studies, in which disparities or inequities between groups of women were reported but no mention of the racism or racial discrimination suffered by these women was made. We highlighted the social determinants of maternal and neonatal health: specifically, exposure to stress or stressors and social relationships and

interactions that influence health outcomes, such as racism or racial discrimination.[57-60]

On the other hand, this review presented several limitations. In addition to methodological problems, the interventions and outcomes differentiated substantially among the studies included. Comparison among those studies would induce bias and the results would need to be interpreted with caution. The use of thirteen different questionnaires limited the possibility of performing a meta-analysis. The existence of thirteen different questionnaires also points to the need for further study on this topic and defini-tion of the best instruments for its evaluation. The limitations on the use of scales for questions that assess personal experience are widely known. However, even with these limitations, use of scales provides the means to take the first step towards knowledge of issues that are more personal and cultural.

CONCLUSION

Perceived racism presented an association with poor obstet-ric outcomes. In summary, even with the stated limitations to these studies, a prompt response from society is urged, in order to be attentive to prevention of racism in all healthcare spaces. Our institution, peers, trainees and patients need to engage in anti-racist training. Anti-racist measures are needed so as to address the problems that are causing patients to perceive or experience racism. These measures should ultimately contribute to reduction of racial disparities in obstetric outcomes.

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Address for correspondence:

Luiz Gustavo Oliveira Brito

CAISM – Hospital da Mulher Prof. Dr. José Aristodemo Pinotte,

Universidade Estadual de Campinas (UNICAMP)

Rua Alexander Fleming, 101

Cidade Universitária — Campinas (SP) — Brasil

CEP 13083-881

Tel. (+55 19) 3521-9595

E-mail: lgobrito@gmail.com

Prevalence of Helicobacter pylori infection among asymptomatic children in southeastern Brazil: a cross-sectional study

Ana Beatriz Marques Carlos[I], Vladimir Eliodoro Costa[II], Renata Kobayasi[III], Maria Aparecida Marchesan Rodrigues[IV]

Faculdade de Medicina de Botucatu (FMB), Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil

[I]MSc. Postgraduate Student, Department of Pathology, Faculdade de Medicina de Botucatu (FMB), Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil.
ⓘD https://orcid.org/0000-0001-5248-2150

[II]PhD. Coordinator, Stable Isotope Center, Instituto de Biociências de Botucatu (IBB), Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil.
ⓘD https://orcid.org/0000-0003-3889-7514

[III]MD, PhD. Assistant Physician, Sírio Libanês Hospital, Department of Internal Medicine, Faculdade de Medicina da Universidade de São Paulo (FMUSP), Brazil.
ⓘD https://orcid.org/0000-0003-2993-255X

[IV]MD, PhD. Full Professor, Department of Pathology, Faculdade de Medicina de Botucatu (FMB), Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil.
ⓘD https://orcid.org/0000-0002-8355-1929

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ABSTRACT

BACKGROUND: The prevalence of *Helico bacter pylori* (*H. pylori*) infection is decreasing worldwide, but is still high in developing countries. We previously observed an *H. pylori* infection rate of 52% among children and adolescents with chronic non-ulcer dyspepsia.

OBJECTIVE: To investigate the prevalence of *H. pylori* infection among asymptomatic children living in a single region and to evaluate the risk factors for this infection.

DESIGN AND SETTING: Cross-sectional study in which 161 children aged 5-13 years (mean age 7.8 years), at a public school in Botucatu, state of São Paulo, southeastern Brazil, were assessed.

METHOD: The children's *H. pylori* infection status was determined through the urea breath test and the risk factors for acquisition of the infection were determined based on a sociodemographic questionnaire.

RESULTS: The overall prevalence of *H. pylori* infection was 20.5%: 18.7% among females and 22.2% among males. The results from the sociodemographic survey did not differ between children with and without *H. pylori* infection. 30.9% of the children had previous records of upper gastrointestinal symptoms, which consisted of *H. pylori* infection in only 26.5% of these cases. Family histories of gastritis and peptic ulcer disease were found in relation to 50% and 32.3% of the children with *H. pylori* infection respectively.

CONCLUSION: The prevalence of *H. pylori* infection among asymptomatic children in southeastern Brazil is lower than that recorded among symptomatic children in the same region and similar to the prevalence of *H. pylori* infection observed in developed countries.

INTRODUCTION

The prevalence of *Helicobacter pylori* (*H. pylori*) infection is decreasing worldwide, but is still high in developing countries.[1-3] In Brazil, epidemiological studies have shown that the rates of *H. pylori* infection vary widely across different regions; for example, the highest rates have been reported in northern and northeastern regions (up to 90%), in contrast to lower prevalence in the southeastern region (less than 36%).[4,5]

We previously observed an *H. pylori* infection rate of 52% among children and adolescents with chronic non-ulcer dyspepsia in southeastern Brazil.[6,7] This prompted us to investigate the prevalence of *H. pylori* infection among asymptomatic children living in a single community.

OBJECTIVE

To investigate the prevalence of *H. pylori* infection among asymptomatic children using the urea breath test. Sociodemographic data and previous records of gastrointestinal symptoms were assessed to investigate risk factors for this infection.

METHODS

This cross-sectional prospective study was conducted among children at a public school in the city of Botucatu city, São Paulo, southeastern Brazil, from October 2019 to February 2020. They were aged between 5 and 13 years and were living in the same geographical area as those of a previous study on symptomatic children[6,7] The exclusion criteria were occurrences of therapy with antibiotics or antisecretory drugs within the preceding four weeks. A sociodemographic questionnaire was administered to the parents. Questions asking about previous records of upper

gastrointestinal symptoms in the last year, like nausea, vomiting, epigastric pain, post-prandial fullness and nocturnal pain, were included in the questionnaire.

H. pylori infection was evaluated through the urea breath test. This was applied to the children in the school, in the morning, before the recess, when the children had had a fasting time of approximately two hours. A baseline breath sample was collected, and then the children received a solution containing ^{13}C-labeled urea (^{13}C-urea): 50 mg for children ≤ 30 kg and 75 mg for children > 30 kg, dissolved in 80 ml of water. After 15 minutes, the final breath sample was collected. The samples were analyzed using an Automated Breath [13]C Analyzer Isotope Ratio Mass Spectrometer (ABCA-IRMS) (SerCon-Cheshire, United Kingdom) at the Stable Isotope Center, at the Universidade Estadual de São Paulo (UNESP). The cutoff value for *H. pylori* infection to be considered present was 4‰ for the difference between the values obtained from the final and baseline breath samples

The data were analyzed using the R statistical software, version 4.0.3 (public domain). The significance level was taken to be P < 0.05.

This study was approved by the local Research Ethics Committee (CAAE 25856119.7.0000.5411) on December 4, 2019.

RESULTS

The study sample consisted of 161 asymptomatic children (80 males and 81 females). The age range was 5-13 years, and the mean age was 7.8 ± 1.7 years. *H. pylori* infection was identified in 33/161 children (20.5%), i.e. 15/80 females (18.7%) and 18/81 males (22.2%). Half of the children were male and 45.3% were between 5 and 7 years of age **(Table 1)**. The results regarding sociodemographic, economic and sanitary condition data did not differ between children with and without *H. pylori* infection **(Table 1)**.

30.4% of the children had previous records of upper gastrointestinal symptoms, which consisted of *H. pylori* infection in only 26.5% of these cases. The frequency of prior gastrointestinal symptoms was 39.4% among children with *H. pylori* infection and 28.1% in the non-infected group (P > 0.05).

A family history of gastritis was reported in relation to 50% of the children with *H. pylori* infection and 48.2% of the non-infected children (P > 0.05). Presence of a peptic ulcer was reported in relation to 32.3% of the children with *H. pylori* infection and 20.2% in the non-infected group (P > 0.05).

DISCUSSION

In this study, we found that the *H. pylori* infection rate was 20.5% among 161 asymptomatic school children living in a single community. This was significantly lower than the *H. pylori* infection rate of 52% previously recorded among symptomatic children living in the same region, despite the differences in age and diagnostic methods between the groups of symptomatic and asymptomatic children.[6,7]

A recent systematic review and meta-analysis on the prevalence of *H. pylori* infection in Latin America and the Caribbean reported an *H. pylori* infection rate of 48.3% among children and adolescents.[8] Similar rates have been registered in this age group in Brazilian studies conducted in São Paulo.[9,10] Prevalence rates higher than 40% have been reported among asymptomatic children up to six years of age in the northeastern region.[11,12] In these studies, low socioeconomic status and poor hygiene conditions were the main risk factors for *H. pylori* infection.

The 20.5% rate of *H. pylori* infection identified in the present study is similar to the values recorded in developed countries, such as 22.1% in Denmark, 24.6% in Australia and 25.4% in the United States.[1,2,13] Our result is lower than the 32.6% worldwide prevalence of *H. pylori* infection among children, reported by Zamani et al. According to these authors, the rate of *H. pylori* infection can be considered to be an additional benchmark for the socioeconomic and health status of a region or a country.[2]

In the present study, only 14.3% of all the children and 12.1% of the children with *H. pylori* infection had parents whose educational level was low. Thus, the educational background of most of our study population was good. Moreover, we did not find differences in family income, number of people in the household, number of children or occurrence of bed-sharing, between children with and without *H. pylori* infection. The similarity between the two groups of children may be explained by particular conditions of the city of Botucatu, which is located in the most developed region of Brazil and has one of the highest human development indexes (HDIs) of the country (0.8), similar to the HDI reference values of developed countries.[14,15] These findings document the adequate socioeconomic and hygiene conditions of the study population and highlight the relevance of socioeconomic status and family education in relation to protection against *H. pylori* infection.[2,16]

In this study, previous reports of gastrointestinal symptoms were observed in relation to 30.4% of the children, which consisted of *H. pylori* infection in only 26.5% of these cases. Thus, the majority of the children with previous records of gastrointestinal symptoms did not have *H. pylori* infection. These findings are in agreement with previous studies, which did not find any relationship between gastrointestinal symptoms and *H. pylori* infection.[7,17]

A family history of gastritis was reported in half of the children with *H. pylori* infection, and peptic ulcer disease in 32.3% of the children with *H. pylori*. These findings highlight the importance of transmission from one human to another, as the main route for acquisition and transmission of *H. pylori* infection.[18]

Table 1. Sociodemographic characteristics of the study sample in relation to presence or absence of *H. pylori* (Hp) infection

Characteristic	Hp-positive n = 33 (%)	Hp-negative n = 128 (%)	Total n = 161 (%)	P value
Gender				
Male	18 (54.5)	63 (49.2)	81 (50.3)	0.697[a]
Female	15 (45.5)	65 (50.8)	80 (49.7)	
Age (years)				
5 to 7	17 (51.5)	56 (43.8)	73 (45.3)	
8 and 9	8 (24.2)	48 (37.5)	56 (34.8)	0.355[b]
10 to 13	8 (24.2)	24 (18.7)	32 (19.9)	
First born				
Yes	11 (33.3)	42 (33.6)	53 (33.5)	0.977[b]
No	22 (66.7)	83 (66.4)	105 (66.5)	
Siblings				
≤ 2	22 (68.8)	89 (71.2)	111 (70.7)	0.829[a]
> 2	10 (31.3)	36 (28.8)	46 (29.3)	
Bed-sharing				
Yes	7 (21.2)	29 (22.8)	36 (22.5)	0.842[b]
No	26 (78.8)	98 (77.2)	124 (77.5)	
Nº of rooms				
≤ 2	22 (71.0)	91 (72.2)	113 (72.0)	0.889[b]
> 2	9 (29.0)	35 (27.8)	44 (28.0)	
Nº of people in household				
≤ 4	22 (66.7)	79 (62.2)	101 (63.1)	0.690[a]
> 4	11 (33.3)	48 (37.8)	59 (36.9)	
Nº of children				
≤ 2	21 (67.7)	86 (71.7)	107 (70.9)	0.663[a]
> 2	10 (32.3)	34 (28.3)	44 (29.1)	
Water supply				
Treated piped water	33 (100)	123 (96.9)	156 (97.5)	0.302[b]
Underground well	0 (0)	4 (3.1)	4 (2.5)	
Family education				
None	1 (3.0)	0 (0)	1 (0.6)	
Elementary	3 (9.1)	19 (15.0)	22 (13.8)	0.585[b]
High school	22 (66.7)	86 (67.7)	108 (67.5)	
College/university	7 (21.2)	22 (17.3)	29 (18.1)	
Family income (minimum monthly wages)*				
≤ 1	7 (23.3)	24 (19.8)	31 (20.5)	
1-2	11 (36.7)	58 (47.9)	69 (45.7)	0.497[b]
2-3	9 (30.0)	23 (19.0)	32 (21.2)	
> 3	3 (10.0)	16 (13.2)	19 (12.6)	

*1 minimum monthly wage = R$ 1,048.00 (approximate U$ 260.00) in February 2020; [a]from Fisher's exact test; [b]from Pearson's chi-square test.

CONCLUSION

The prevalence of *H. pylori* infection among asymptomatic children in southeastern Brazil is lower than the prevalence recorded among symptomatic children living in the same region and similar to the rates of *H. pylori* infection observed in developed countries.

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Address for correspondence:
Maria Aparecida Marchesan Rodrigues
Departamento de Patologia, Faculdade de Medicina de Botucatu (FMB),
Universidade Estadual Paulista (UNESP)
Av. Professor Mário Rubens Guimarães Montenegro, s/nº
Jardim São José — Botucatu (SP) — Brasil
CEP 18603-970
Tel. (+55 14) 3811-6238 — Fax. (+55 14) 3811-2348
E-mail: maria.marchesan@unesp.br

Dermatological manifestations relating to nutritional deficiencies after bariatric surgery: case report and integrative literature review

Andressa Christine Ferreira Silva[I], Laura Moya Kazmarek[II], Elemir Macedo de Souza[III], Maria Letícia Cintra[IV], Fernanda Teixeira[V]

Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil

[I]MD. Physician, Department of Pathology, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0001-6950-7756

[II]MD. Physician, Department of Pathology, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-1973-9510

[III]MD, PhD. Associate Professor with Tenure (Phased Retirement), Department of Dermatology, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-3944-0711

[IV]MD, PhD. Professor and Head, Department of Pathology, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0001-7125-2238

[V]MD, PhD. Consultant Professor, Department of Pathology, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (FCM-UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0002-7833-1948

KEY WORDS (MeSH terms):
Bariatric surgery.
Skin manifestations.
Malnutrition.
Skin diseases.
Deficiency diseases.

AUTHORS' KEY WORDS:
Xerophthalmias.
Phrynoderma.
Acrodermatitis enteropathica.
Bariatric surgical procedures.
Nutritional deficiencies.
Dermatopathies.

ABSTRACT

BACKGROUND: The number of bariatric surgeries performed worldwide is growing. Among the main short, medium or long-term complications after surgery are nutritional deficiencies. Many of these, such as those of Zn, Cu and vitamins A, B1, B3, B6 and B12, are manifested by dermatological lesions before potentially fatal systemic disorders occur.

OBJECTIVE: To identify the main dermatological manifestations associated with nutritional deficiencies after bariatric surgery, and the associated variables.

DESIGN AND SETTING: Integrative literature review carried out at a public university in Brazil.

METHODS: This was a case report and a review of health research portals and databases of national and international biomedical journals, without publication date limitation. The descriptors used for searches followed the ideal methodology for each database/search portal: "bariatric surgery", "skin", "skin disease", "skin manifestation", "deficiency disease" and "malnutrition".

RESULTS: A total of 59 articles were selected, among which 23 were review articles or articles that addressed specific dermatological manifestations. The other 36 articles described 41 cases, which were organized into a table with the clinical variables.

CONCLUSIONS: Although nutritional deficiencies are expected as complications after bariatric surgery, few articles relating them to their dermatological manifestations were found. It is important to recognize skin changes caused by nutritional deficiencies in patients treated via bariatric surgery, as these may occur before systemic complications appear and are easier to diagnose when the patient does not have any systemic symptoms yet. However, there is generally a delay between the appearance of skin lesions and making the diagnosis of nutritional deficiency.

INTRODUCTION

Obesity is associated with decreased quality of life,[1] comorbidities and increased mortality.[2] Cancer is also associated with obesity, particularly in the breast, endometrium, colon and prostate.[3] Obesity is probably an independent risk factor for greater severity of COVID-19[4] and decreases protection in immunization against influenza.[5]

The growing incidence of obesity and overweight is among the biggest public health problems worldwide.[6]

As a result, the number of bariatric surgeries, which are considered to be an effective treatment for obesity (and diseases resulting from it),[7] is growing.

Nonsurgical treatment modalities may promote some weight loss, but it is usually not maintained over the long term because patient compliance is generally not adequate. Surgical treatment is attractive for patients because it enables a more pronounced weight loss that can be sustained over the long term, in addition to having a positive impact on comorbidities associated with obesity, thereby reducing mortality and improving quality of life. However, like any treatment, bariatric surgery is not without complications, whether perioperative (such as bleeding, infection or thrombotic events) or malabsorptive (which would lead to or worsen vitamin and mineral deficiencies). The indications for surgery need to be individualized for each patient's condition; rigid criteria do not apply, and risk/benefit ratios should always be considered.[8]

There are three main categories of bariatric surgery:[9] 1 – restrictive: gastric banding, sleeve gastrectomy, banded sleeve gastrectomy and intragastric balloon; 2 – predominantly restrictive: Roux-en-Y

gastric bypass, with or without retention ring; and 3 – predominantly malabsorptive: biliopancreatic shunt with sleeve gastrectomy, with or without distal gastric preservation, and biliopancreatic shunt with sleeve gastrectomy and pyloric preservation. Roux-en-Y is the type of surgery most performed, followed by sleeve gastrectomy and gastric banding (these three procedures make up 92.2% of those performed worldwide).[10] Among the main complications reported are nutritional deficiencies, which can be due to great weight loss, malabsorption of nutrients and/or changes to the patient's dietary habits.

The skin is one of the most effective health indicators. Changes in color and texture can be a sign of systemic dysfunctions.[11] Knowing the dermatological changes relating to vitamin and mineral deficiencies that appear after bariatric surgery can help in their identification, thus preventing evolution of the patient to systemic disorders.
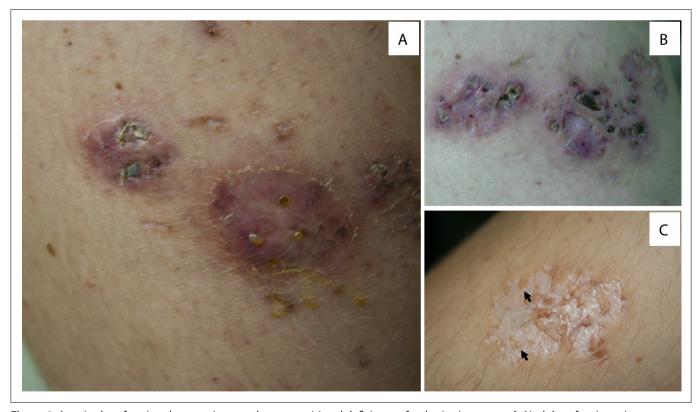
CASE REPORT

What prompted us to start this study was witnessing the evolution of a teenager, a 17-year-old Caucasian female, who had undergone Roux-en-Y gastric bypass surgery at age 15 years. Before the surgery, she was a normal, albeit obese girl. After surgery, she received vitamin B12 and folic acid supplementation regularly.

At age 16 years, she complained of painful areas on her thighs and buttocks, 5 mm to 20 mm in diameter, which progressively became larger, more numerous, deeper and more painful, suggestive of erythema nodosum. Soon afterwards, the areas showed numerous sinuses that expelled a viscous yellow fluid (**Figure 1A**). She also complained of chronic diarrhea and decreased visual acuity.

On examination, she looked tired, pale and distressed. Her body mass index was 31 kg/m². Her skin lesions were now quite numerous and measured up to 30 mm in diameter. A punch biopsy was obtained with the following differential diagnoses: acquired perforating dermatosis due to vitamin deficiencies, deep mycosis, atypical mycobacterial infection, pyoderma gangrenosum and subcutaneous Sweet's syndrome. Ophthalmological examination showed keratinization of the bulbar conjunctiva, suggestive of hypovitaminosis A.

Blood tests results showed the following: vitamin A: 0.1 mcm/l (normal range 1.2–4.2); vitamin E: 3.7 µg/ml (normal range 15–40); Hb: 9.5 g/dl (normal range 12–15.5); iron: 43 mcg/dl (normal range 60–170); and ferritin: 7.2 ng/ml (normal range 10–120) The lipid profile was normal, except for the triglyceride levels, which were very low (27.2 mg/dl). Histological examination of the skin showed horn cysts, perforating folliculitis with transepithelial elimination of elastic fibers and fibrosis (**Figure 2**).

Figure 1. Acquired perforating dermatosis secondary to nutritional deficiency after bariatric surgery. **A**: Nodules of various sizes, erythematous and pigmented, with multiple sinuses exuding a viscous, yellow fluid. Some of the sinuses are closed by scabs. **B**: With treatment, the lesions became flat and the sinuses closed. Redness and swelling progressively resolved. **C**: Lesions resolved with white atrophy and sinus sites were replaced by anetodermal scars and residual pseudothesaurismotic papules (arrows).

She was treated with supplementation of oral fat-soluble vitamins and B vitamins, iron and calcium. After thirteen months of this, all the skin lesions had resolved, albeit with considerable scarring (**Figures 1B and 1C**). Lifetime monitoring was instituted to prevent recurrent nutrient deficiency conditions.

This impressive case raised the issues of postoperative vitamin and mineral deficiencies and of patient compliance, which will be discussed in this paper. However, it was also a sad reminder of patients' and their parents' expectations and the ethics regarding bariatric surgery in the pediatric population; issues that will not be tackled here.[12]

METHODS

A literature search was performed, without publication time restriction, up to 2020, through the following biomedical databases: PubMed/MEDLINE (www.ncbi.nlm.nih.gov/pubmed), Virtual Health Library (https://bvsalud.org/), SCOPUS (www.scopus.com), EMBASE (www.embase.com), Web of Science (www.webofknowledge.com) and SciELO (https://scielo.org/en/). The following descriptors were used: "bariatric surgery", "skin", "skin disease", "skin manifestation", "deficiency disease", "malnutrition" and "undernutrition"; and, for EMBASE, equivalent descriptors.

The eligibility criteria were the following: (a) systematic reviews, meta-analyses, case reports and case series among post-bariatric patients of any sex and age who presented dermatological manifestations resulting from nutritional deficiencies; (b) the languages English, French, Italian, Portuguese and Spanish. The information contained in each text was synthetized and recorded on protocol sheets, so that the team members could verify their validity and applicability and, possibly, find elements to support the discussion that would lead to interpretation of the data. These data were manually collected and stored in spreadsheet format, using the Microsoft Excel 2013 software (Microsoft Windows, Redmond, WA, United States).

The studies that were retrieved through searches in the databases were compared individually. None of the participants in this review were blinded to the titles of journals, studies, authors or even the institutions to which the authors were affiliated. Duplicate or split studies were computed and analyzed as single studies, thereby avoiding repetition and data overlap. In the case of partially published studies or studies still under development, only the most recently published information was considered. Doubts about the suitability and eligibility of each study were discussed by the team. The main dermatological manifestations associated with nutritional deficiencies in patients treated by some type of bariatric surgery and the proposed etiopathogenesis of such processes were discussed.

Exploratory data analysis was performed using summary measurements (mean, standard deviation, minimum, median,
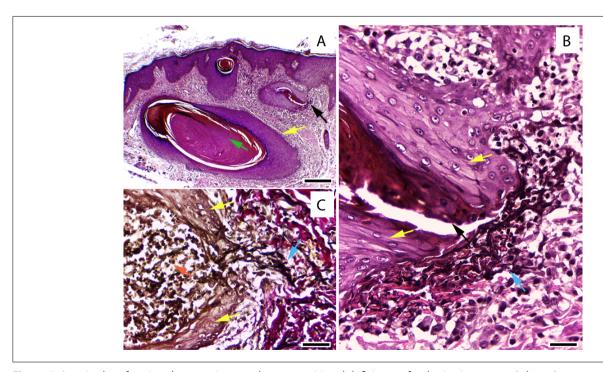
Figure 2. Acquired perforating dermatosis secondary to nutritional deficiency after bariatric surgery. **A**: horn (green arrow) cyst (yellow arrow) and open distorted follicle (black arrow); **B**: follicle with hyperplastic epithelium (yellow arrows), with perforation (black arrow), close to the degenerated elastic fibers (blue arrow); **C**: the same follicle (yellow arrows) stained using Verhoeff-van Gieson method, containing polymorphonuclear cells (red arrow), showing transepithelial elimination of black elastic fibers (blue arrow). Hematoxylin and eosin (H&E) x 100 (A) and x 400 (B). Verhoeff-van Gieson x 400 (C). Scale bar: 0.25 mm (A); 0.05 mm (B, C).

maximum, frequency and percentage). To assess associations between the variables, a meta-analysis was performed on individual participant data (IPD meta-analysis) using logistic regression models with mixed effects, through the Laplace method. The significance level adopted was 5%.

The patient's mother was shown the pictures included in this article and consented, in writing, to their publication. This document is in our custody and can be produced for perusal. The institutional Ethics Committee deemed further approval unnecessary, considering that that the main content of the manuscript is a review of the literature.

RESULTS

Fifty-nine of the 138 articles retrieved were selected, after applying the inclusion and exclusion criteria described above. Among these 59 articles, 23[13-34] consisted of literature reviews, topic discussions or research focusing on specific dermatological manifestations, which were used to support the introduction and discussion of the present article (**Figure 3**). The remaining 36 articles[35-68] referred to 41 case reports on patients with cutaneous manifestations secondary to nutritional deficiencies after bariatric surgery, whose data are compiled in **Table 1**. Five of them were papers presented at two congresses and were referenced together.[25,47] The mean age was 44 years (range 29–66). The mean time between the day of surgery and the dermatological manifestation was 6.4 years (range 3–16).

The most frequent type of bariatric surgery among the patients who developed dermatological manifestations was Roux-en-Y gastric bypass (70%), followed by biliopancreatic bypass (14%). Among the articles that reported whether the patient adhered to post-surgical nutritional supplementation (18/41 patients; 44%), we found that only 61% of them adhered to this. Most of the patients (75%) had multiple-need malnutrition and the deficiencies identified were the following: zinc (68%); vitamin A (36%); vitamin D (34%); albumin (29%); copper (27%); vitamins B3 and B6 (12% each); and iron, ferritin, folic acid, vitamins B1, B12, C and E and selenium (1% or less each). The most common manifestation, found in 39%, was acquired acrodermatitis enteropathica, which
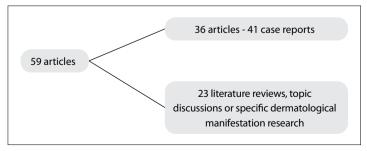

Figure 3. Article selection flowchart.

was significantly associated with bariatric surgery consisting of Roux-en-Y gastric bypass (P value < 0.001), and which bore no relationship with the post-surgical time interval. This manifestation was followed, in frequency, by xerosis (31%), hair loss (22%) and pellagra-like lesions (12%).

DISCUSSION

After bariatric surgery, regular multidisciplinary follow-up of the patients must be maintained for many years. It includes adoption of a balanced diet, supplementation with minerals and vitamins and periodic laboratory evaluations. However, despite the recommendations, studies[69] have shown that these patients are often monitored irregularly and that their adherence to vitamin and mineral supplementation is low.

Our search in the literature showed that only 61% of the patients who developed dermatological signs of nutritional deficiencies adhered to supplementation. Sunil et al.[70] found that being female, not having a full-time job and having symptoms of attachment anxiety were factors that related to lower adherence to post-surgical recommendations. Mahawar et al.[71] reported that the main reasons given by patients for non-adherence to supplementation were: 1 – difficulty remembering to take the pills; 2 – high number of pills; 3 – the advent of side effects; and 4 – financial cost. In addition, it needs to be considered that patients can present nutritional deficiencies even before being treated through bariatric surgery and that these conditions are worsened in the postoperative period, over both the short and the long term.[72]

This review showed that most nutritional deficiencies present with dermatological manifestations at a relatively early stage (53% within five years or less after the date of surgery). The most common manifestation was acquired acrodermatitis enteropathica.[73] This is associated with zinc (Zn) deficiency and presents with eczematous plaques over the extremities and around natural orifices. Zn and Zn transporters have many physiological functions in the skin: Zn is a cofactor of hundreds of enzymatic reactions, is an important structural component of gene regulatory proteins, regulates apoptosis and is fundamental for protein synthesis and RNA packaging. Zn binds to approximately 10% of human proteins. Therefore, this metal is associated with many organic activities, such as cell development, differentiation and growth, and Zn deficiency manifests itself in several ways, in all organs.[74] It should be noted that zinc supplementation may impair copper absorption, and in bariatric surgery patients with low zinc levels it is recommended that oral copper should be administered separately.[75]

The second most-common manifestation was pellagra-like lesions, which manifest as symmetrical erythematous plaques that can be accompanied by edema and sometimes blisters, located on sun-exposed areas of the skin.[76] Pellagra is caused by a deficiency of niacin also known as nicotinic acid, a form of vitamin B3. Niacin

Table 1. Summary of findings from the literature search, detailing the deficient mineral or vitamin, the associated dermatosis, type of procedure, age, gender, evolution and associated systemic involvement

Article (Ref.)	Nutritional deficiency after surgery	Dermatological manifestation	Type of surgery	Age	Sex	Adhered	Time to signs	Rx	Evolution	Systemic manifestations
Lopez et al.[52]	Zn	Pellagra-like erythema	VBG	51	F	DNA	5	O + A	Resolved in a few days	U
Bae-Harboe et al.[39]	Zn	Acrodermatitis enteropathica acquisita	RYGP	62	M	U	3	O	Resolved in a week	U
Mankaney et al.[53]	Zn	Acrodermatitis enteropathica acquisita	RYGP	54	F	A	8	U	Significant improvement	U
Rana et al.[59]	Zn, Vit. B6, Se, Alb	Acrodermatitis enteropathica acquisita, xerosis, diffuse non-scarring alopecia.	RYGP	39	F	A	13	P	Significant improvement	U
Jacob et al.[47]	Zn, Cu	Erythematous rash on the back and limbs	RYGP	54	M	U	10	P+O	U	Neurological, hematological.
Cunha et al.[41]	Zn, Cu, Fe, Alb	Acrodermatitis enteropathica acquisita, xerosis, pruritus	VBG/JIB	30	F	A	0.6	O	Significant improvement	Neurological, hematological
Stephens et al.[61]	Fe, Vit A + D	Photosensitivity, hair loss, discolored hair.	BPD	30	F	DNA	5	O	U	Endocrinological, neurological, ophthalmological
Boutin et al.[40]	Vit A+B6+B9+D, Alb	Generalized skin pigmentation	RYGP	44	F	DNA	4	O	Resolved	General, hematological
Messenger et al.[54]	Zn, Vit B3, Alb	Kwashiorkor, cracked eczema-like lesions	RYGP	35	F	U	10	P	Resolved	Hepatic steatosis
Panetta et al.[57]	Vit A	Acrodermatitis enteropathica acquisita, eczematous plaques on the limbs	BPD	51	M	U	.	P	Improved, but hyperpigmentation persisted	Ophthalmological
Vallabhaneni et al.[64]	Vit A + D	Phrynoderma	VBG/DS	50	F	U	NI	U	U	Polyarthralgia, fever
Wilson et al.[67]	Zn, Vit A + D	BADAS (bowel-associated dermatitis-arthritis syndrome). Ulcers and pustules on the limbs.	BPD	40	F	A	6	P+O	Died	Osteoporosis, ophthalmological
Zouridaki et al.[68] Case 1	Vit B12 + D	Acrodermatitis enteropathica acquisita, pallor, hair loss, pruritic papular rash on back and limbs.	RYGP	45	F	U	2	P+O	Improved in 3 months	U
Zouridaki et al.[68] Case 2	Vit B12	Leg ulcers, round scars on forearms, impetigo-like lesions on the scalp, localized alopecia, angular cheilitis	RYGP	62	F	DNA	8	P	Resolved in 6 months	Hematological
Gillette et al.[47]	Vit B1, B3, Alb, Fe	Large abscesses and ulcers on lower limbs	RYGP	47	F	U	10	BR+O	Improved in a year.	Neurological
Ashourian et al.[38]	Zn, Vit B3, B6	Kwashiorkor, thinning hair, xerosis on the trunk, hyperpigmented, macular rash	RYGP	32	F	U	0.3	O	Significant improvement in 4 weeks	None
Katugampola et al.[49]	Vit A, D, E, K	Acrodermatitis enteropathica acquisita, pellagra	JIB/GJ	66	F	DNA	12	BR	Resolved, but died after 7 months.	CKD, arthropathy, anemia
Vick et al.[66]	Zn, Cu	Erythema nodosum	RYGP	38	F	A	10	P	Significant improvement	U
Jaffe et al.[48]	Zn, Alb	Acrodermatitis enteropathica acquisita	GJ/SS	48	F	U	16	U	U	Gastrointestinal, malnutrition, coma
Garg et al.[46] Case A	Zn, Vit A, Cu, Alb	Kwashiorkor, cheilitis, "cracked enamel" appearance on buttocks, thighs, and arms	RYGP	60	F	U	9	P	Died	Weakness, gastrointestinal.
Garg et al.[46] Case B	Zn, Cu	Acrodermatitis enteropathica acquisita	RYGP	46	F	U	10	P	Significant improvement	Weakness, neurological, gastrointestinal.
Shackelton et al.[60] Case 1	Zn, Cu, Vit A	Kwashiorkor, hair loss	RYGP	36	F	U	10	U	Resolved	U
Shackelton et al.[60] Case 2	Zn	Acrodermatitis enteropathica acquisita	RYGP	45	F	U	0.7	U	Resolved, but intertrigo persisted.	U

Table 1. Continuation

Article (Ref.)	Nutritional deficiency after surgery	Dermatological manifestation	Type of surgery	Age	Sex	Adhered	Time to signs	Rx	Evolution	Systemic manifestations
Shackelton et al.[60] Case 3	Zn, Cu, Vit A, B3	Acrodermatitis enteropathica acquisita	RYGP	32	F	U	3	U	Resolved	U
Garcovich et al.[45]	Zn, Fe, Vit D	Acrodermatitis enteropathica acquisita	BPD/DS	47	M	A	2	U	U	Endocrinological
Levenbergh et al.[51]	Vit B3, C, Alb	Hidradenitis suppurativa; phrynoderma	RYGP	58	F	U	1	O	Resolved in a few days	Gastrointestinal
Abad et al.[35]	Zn, Vit A, D3, E	Pellagra	BPB	46	M	A	13	O+P	Resolved in 10 months	Hematological
Ocon et al.[56]	Vit A, D, Fe	Phrynoderma	BPD	54	M	DNA	1	O+P	Resolved in 2 months but hyperpigmentation persisted	Osteoarticular, gastrointestinal, ophthalmological
Monshi et al.[55] Case 1	Zn, Vit A, D, E, Alb	Phrynoderma	RYG	31	F	U	4	P	Improvement in 5 months	U
Monshi et al.[55] Case 2	Zn, Vit A, B9, D	Phrynoderma; sharply demarcated perianal scaly plaques.	RYGP	29	F	U	7	P	Resolved in 7 days	U
Khanal et al.[50]	Zn	Acrodermatitis enteropathica acquisita	RYGP	45	F	A	0.1	P	U	Coma
Al Alawi et al.[36]	U	Facial and extremity macular rash	LOLGB	40	F	U	2	BR	U	U
Ramos-Levi et al.[58]	Zn, Vit A, D, E, Se, Cu, Alb	Hair loss, dry, pale skin.	RYGP/DS	48	F	A	2	BR	Improvement in 6 months	Ophthalmological, gastrointestinal
Velazquez et al.[65]	Fe	Xerosis; eczema and pruritus on back and limbs.	RYGP	34	F	A	0.3	O	Improvement in 3 months	Neurological
Vales-Montero et al.[63]	Vit A, B12, D	Hair loss	RYGP	40	M	DNA	5	P	Improvement in 3 months	Ophthalmological
Al-Douri et al.[37]	Zn, Cu	Papulosquamous lesions on limbs	RYGP	41	F	U	5	O	U	Gastrointestinal, osteoarticular, neurological
Evans et al.[42]	Zn, Cu	Hyperpigmentation of forehead, upper back, and upper arms	RYGP	40	F	U	NI	U	U	Steatohepatitis
Freitas et al.[43]	Zn, Vit A, B1, B6, C	Acrodermatitis enteropathica acquisita, pili torti, hair loss with short, brittle, lusterless hair.	RYGP	39	F	A	6	P	Significant improvement in 14 days	Neurological
Garcia et al.[44]	Zn, Vit B1, B6, C, Alb	Acrodermatitis enteropathica acquisita	RYGP	39	F	U	4	U	U	U
Sung et al.[62]	Zn	Acrodermatitis enteropathica acquisita. Eczema craquelé-like plaques.	RYGP	35	F	U	4	O	U	Hepatic
Wang et al.[25]	Zn	Palpable, painful purpuric rash on lower trunk and limbs. Desquamation of the dorsa of feet.	RYGP	37	F	U	5	P	Resolved	Gastrointestinal

Title lines: article (ref.): author's name and year of publication; Nutritional deficiency after surgery: nutritional deficiency status after bariatric surgery; Dermatological manifestation: describes skin manifestations; Type of surgery: type of bariatric surgery; Age: patient's age at the time of the report; Adhered: adherence to nutritional complementation; Time to signs: time (in years) between the date of the surgery and the dermatological manifestation; Rx: treatment offered; Evolution: Skin lesions follow-up and evolution; Systemic manifestations: systemic manifestation associated.

Zn = zinc; Se = selenium; Cu = copper; Alb = albumin; Fe = iron; U = data unknown; VBG = vertical banded gastroplasty; RYGP = Roux-en-Y gastric bypass; VBG/JB = vertical band gastroplasty and jejunoileal bypass; VBG/DS = vertical band gastroplasty with duodenal switch; JIB/CJ = jejunoileal bypass and cholecysto-jejunostomy; GJ/SS = gastrojejunostomy and stomach stapling; BPD/DS = biliopancreatic diversion with duodenal switch; BPB = biliopancreatic bypass; LOLGB = gastric bypass with laparoscopic omega loop; RYGP/DS = RYGP and duodenal switch; Adhered: to the supplementation protocol. DNA: did not adhere; O+A: oral supplementation of nutrients and antibiotics; O: oral nutrient supplementation; P: parenteral nutrient supplementation; P+O = parenteral and oral nutrient supplementation; BR = bariatric reversal; BR+O = bariatric reversal and oral nutrient supplementation; BR+P = bariatric reversal and parenteral nutrient supplementation.

is absorbed from the diet, or synthesized from the amino acid tryptophan, and is important for synthesis of NAD and NADP: coenzymes that generate high-energy phosphate bonds that are essential for the metabolism of glucose, amino acids and proteins. Niacin deficiency will be felt first in tissues with a high cell turnover, such as the intestines (manifesting as diarrhea) and the skin, and in organs with high energy demands, such as the brain (causing insomnia, fatigue, nervousness, irritability and depression).[77]

The next most-common complaints were xerosis and hair thinning, which have been correlated with deficiencies of various nutrients, particularly fat-soluble vitamins, given that malabsorptive surgery impairs the absorption of lipids.[78] Retinoic acid (vitamin A) is a biologically active retinoid with life-sustaining functions, and severe deficiency of this can result in illness and death. Retinoids fulfill many essential physiological processes and are critical for normal growth, development of normal skin and eyesight, an effective immune system and fertility. Normal levels of this vitamin depend on consumption, and its metabolism is complex, mediated by triglycerides and cholesterol.[79] Vitamin A deficiency can affect the eyes, causing night blindness and xerophthalmia,[80] and can also cause skin changes, such as phrynoderma and perforating folliculitis with elimination of elastic fibers. This can lead to considerable scarring, as occurred in the example above.[81,82]

Regarding vitamin D3, epidermal keratinocytes are a primary source of vitamin D for the body, as they have the enzymatic machinery to metabolize it into its active metabolite $1\alpha,25$-dihydroxyvitamin D. They also express the vitamin D receptor and can thus respond to the vitamin D3 that they produce. This vitamin has essential functions in the skin, including control of cell proliferation and differentiation and stimulation of innate immunity and the hair cycle. The actions of vitamin D on the skin are controlled by two classes of coactivators: vitamin D receptor interacting proteins (DRIPs) and the p160 steroid receptor (SRC) family of coactivators.[83]

Another important element for skin health is vitamin E, which is not synthesized by humans and must be consumed in the diet. There are eight types of vitamin E, and γ-tocopherol is the most abundant type found in foods, while α-tocopherol is the most abundant type found in human tissues and serum. In human skin, vitamin E inhibits production of prostaglandin E2 and nitric oxide and prevents oxidative stress from ultraviolet (UV) radiation, manifested through formation of sunburn cells, lipid peroxidation and edema. Vitamin E has a protective role against cancer because it reduces formation of UV-induced photo adducts and immunosuppression.[84]

Vitamin B12 deficiency was also commonly detected (**Table 1**) and presented in the forms of angular cheilitis, glossitis, hair depigmentation and mucocutaneous hyperpigmentation. Methylcobalamin and adenosylcobalamin are two biologically active forms of vitamin B12. Methylcobalamin is a coenzyme with methionine synthase that is essential for synthesis of pyrimidines and purines,

while adenosylcobalamin degrades fatty acids. Excess or deficiency of cobalamin can lead to dermatological manifestations, due to changes in the complex biochemistry and metabolism of this vitamin.[85] Excess B12 can produce acneiform reactions, as it modulates the transcriptional activities of *Propionibacterium acnes*. This is an indication that development of the disease depends on the interaction mediated by metabolites between the host and the skin flora.[86] If untreated, patients with this deficiency may present with megaloblastic anemia and even neurological manifestations such as paresthesia, loss of positional awareness and cognitive impairment.[77,87]

As demonstrated in **Table 1**, among the 41 patients selected, 27 had systemic manifestations and these were potentially fatal or fatal in 11 patients.[37,41,43,46-47,49,50,61,65,67]

Although not the purpose of this review, it is also necessary to consider that there are cutaneous manifestations that occur after bariatric surgery, which are not due to nutritional deficiency. On the contrary, these are due to excessive replacement of micronutrients, a situation seen with relative frequency in patients in the late postoperative period of bariatric surgery.[86]

Discussion of the clinical guidelines for nutrition and metabolic support for patients under follow-up after bariatric surgery was beyond the scope of the present study.[88]

Ha et al.[89] published a systematic review and meta-analysis of longitudinal studies on bariatric surgery patients who received postoperative supplementation in accordance with the guidelines. They found that despite adequate monitoring and treatment, there were significant reductions in micronutrient levels at 11 postoperative time points, with a moderate level of evidence (vitamin A at 12–23 months, vitamin E at $\geq$ 24 months after Roux-en-Y gastric bypass and ferritin at $\geq$ 24 months after sleeve gastrectomy). Their results help in understanding the optimal micronutrient monitoring times for these patients. They stated limitations to their study, which were identical to ours: few studies included detailed information on patients' adherence to the recommended treatment, and most articles did not describe the dietary modifications after surgery. The latter is an important point to be considered, as micronutrient absorption is affected by food intake.

In our series, none of the articles described the prescribed supplementation regimens and there was no information on the preoperative nutritional status of the patients. Further studies that are prospective and well-controlled should be conducted to generate more accurate data, so that the consequences of bariatric surgery on the skin can be properly evaluated.

CONCLUSION

Patients who underwent bariatric surgery must be monitored frequently for mineral and vitamin deficiencies. Skin diseases can be a manifestation of such conditions and should prompt immediate investigation of the patient's nutritional status.

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Address for correspondence:

Maria Letícia Cintra

Departamento de Patologia, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (UNICAMP)

R. Tessália Vieira de Camargo, 126

Cidade Universitária "Zeferino Vaz" — Campinas (SP) — Brasil

CEP 13083-887

Tel./Fax. (+55 19) 3289-3897

E-mail: marialet@fcm.unicamp.br

Exome sequencing of 500 Brazilian patients with rare diseases: what we have learned

Caio Robledo D'Angioli Costa Quaio[I], Caroline Monaco Moreira[II], Christine Hsiaoyun Chung[III], Sandro Felix Perazzio[IV], Aurelio Pimenta Dutra[V], Chong Ae Kim[VI]

Instituto da Criança (ICr), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[I]MD. Researcher and PhD Candidate, Instituto da Criança (ICr), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, SP, BR; Medical Geneticist, Fleury Medicina e Saúde, São Paulo (SP), Brazil; Medical Geneticist, Laboratório Clínico, Hospital Israelita Albert Einstein (HIAE), São Paulo (SP), Brazil.
 https://orcid.org/0000-0003-2873-2820

[II]MSc. Molecular Biology Leader, Fleury Medicina e Saúde, São Paulo (SP), Brazil.
 https://orcid.org/0000-0001-9074-2259

[III]MD. Medical Geneticist, Fleury Medicina e Saúde, São Paulo (SP), Brazil.
 https://orcid.org/0000-0003-0411-2299

[IV]MD, PhD. Immunology Division, Fleury Medicina e Saúde, São Paulo (SP), Brazil; Division of Rheumatology, Universidade Federal de Sao Paulo, Sao Paulo, Brazil; Central Laboratory, Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, SP, Brazil.
 https://orcid.org/0000-0003-1203-8287

[V]MD, PhD. Neurology Division, Fleury Medicina e Saúde, São Paulo (SP), Brazil.
 https://orcid.org/0000-0001-6342-9654

[VI]MD, PhD. Head of Genetics Unit and Associate Professor, Instituto da Criança (ICr), Hospital das Clinicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, SP, BR.
 https://orcid.org/0000-0002-1754-1300

Dear Editor,

Rare diseases comprise a large and diverse group of an estimated 7,000 different conditions that collectively affect millions of people worldwide. We recently studied the genomic findings of 500 Brazilian patients with suspected rare diseases of genetic etiology who have undergone exome sequencing (ES) for diagnostic purposes.[1]

We observed an overall diagnostic yield of 31.6% in our cohort. Figure 1–A shows the inheritance patterns of the genetic diseases. These diagnoses were associated with 195 sequence variants, among which 38% were rare variants that have not been previously published in the literature (Figure 1–B). The diagnostic rate varied widely depending on age, and we observed higher diagnostic rates in prenatal samples (67%) and children younger than one year (44%) and lower rates for adults older than 50 years (13%). Undiagnosed patients still comprise the majority of patients in our cohort (68.4%) and remain a challenge in genomics. Even with the advances in genomic technology, for many patients with rare diseases, the diagnostic odyssey has not come to an end. Valuable techniques such as trio exome analysis (testing of samples from a proband and both parents) or genome sequencing may increase the genetic diagnosis of rare diseases.

We also found additional genetic alterations that may directly affect the morbidity and mortality of individuals. In 37 patients (7.4%), we found deleterious genetic variants associated with clinically actionable conditions, such as hereditary cancer, arrhythmia, metabolic diseases, and cardiomyopathies. These secondary findings were previously referred to as "incidental findings". (Figure 2).

Determining reportable secondary findings remains controversial and challenging.[2-4] Discussions on this subject are prevalent in North American, European, and some Asian countries but have yet to take place in Brazil and other Latin American countries. Indeed, there are no regulatory documents, legislation, or policies from scientific societies in Brazil regarding the protocols for reporting secondary findings in genomic studies. We urge our medical societies to adopt specific policies for reporting these conditions, and more importantly, consider the Brazilian frequencies of rare diseases. We believe that our study has made an important contribution to the knowledge of rare diseases of genetic etiology in Brazil, a country very underrepresented on this subject.

We also studied the carrier status for recessive diseases in 320 symptomatic patients in this cohort.[5,6] We found at least one pathogenic or likely pathogenic heterozygous variant associated with recessive diseases in the majority of individuals (71.9%). We believe that population studies of recessive diseases are important because recessive diseases are relatively frequent in aggregate, have a high clinical impact, early management can impact clinical outcomes, and some of them can be detected by neonatal screening (e.g., phenylketonuria).

In one of the largest cohorts of rare diseases in Latin America, we observed that ES was a powerful method for identifying the molecular basis of monogenic disorders, redirecting clinical care, and guiding health policies for rare diseases. We hope that our study will encourage others to better understand the clinical and social burden of rare genetic diseases in developing countries.
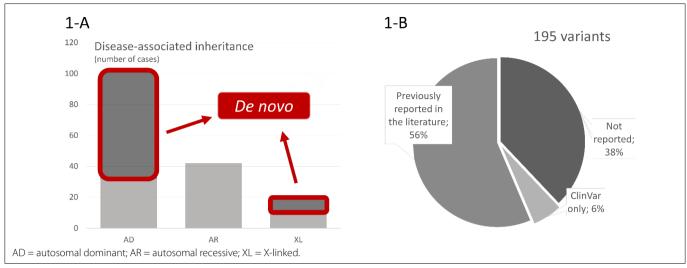
Figure 1. Inheritance pattern and variant characteristics. **A** shows the distribution of inheritance patterns of the 164 diagnoses and highlights the proportion of *de novo* events; exome sequencing was able to unravel the diagnosis in 158 patients (six patients presented dual molecular diagnoses), which represents an overall diagnostic yield of 31.6%. The 164 diagnoses comprised 101 autosomal dominant, 42 autosomal recessive, and 21 X-linked conditions. **B** shows the distribution of variants according to the literature (HGMD Professional Database) and ClinVar database.
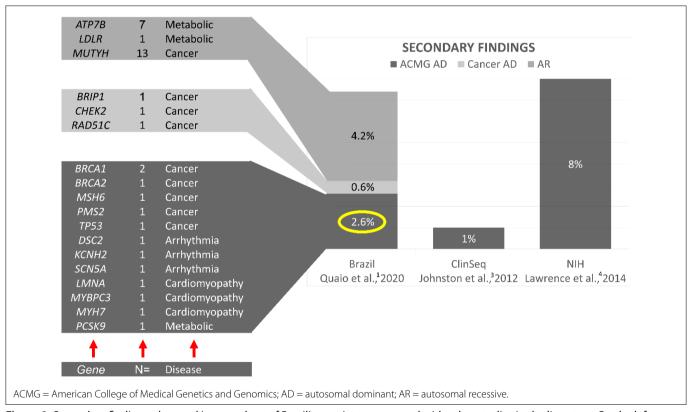

Figure 2. Secondary findings observed in our cohort of Brazilian patients compared with other studies in the literature. On the left, we observe the distribution of secondary findings: 37 patients (7.4%) presented a reportable secondary finding, among which 2.6% are those who harbored pathogenic or likely pathogenic variants associated with autosomal dominant diseases of obligatory report according to the American College of Medical Genetics and Genomics recommendations, 0.6% presented other autosomal dominant forms of hereditary cancer and 4.2% were carriers for variants associated with autosomal recessive diseases in American College of Medical Genetics and Genomics list of reportable secondary findings.

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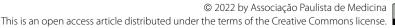
Address for correspondence:
Caio Robledo D'Angioli Costa Quaio
Instituto da Criança do Hospital das Clínicas da FMUSP – Unidade de Genética
Av. Dr. Enéas Carvalho de Aguiar, 647
Cerqueira César — São Paulo (SP) — Brasil
CEP 05403-900
Tel. (+55 11) 2661-8671 — Fax. (+55 11) 2661-8503
E-mail: cquaio@gmail.com

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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.

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Articles will be rejected without peer review if:
- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

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

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

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

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

Submission

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

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

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

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

Covering letter

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

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

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

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

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search

strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);

2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;

3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;

4. Place or institution where the work was developed, city and country;

5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;

6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);

8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);

9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.

10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.

11. Description of any conflicts of interest held by the authors (see above).

12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.

- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh. These terms will help librarians to quickly index the article.

- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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