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COVID-19: long-term respiratory consequences

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Coronavirus disease-19 (COVID-19) was first documented in China in late 2019 and was declared a pandemic in March 2020. It has produced death and dysfunction around the world. In Brazil, as of May 20, 2021, there had been more than 15 million confirmed cases of COVID-19 and more than 400,000 deaths. Although COVID-19 was initially identified as a pneumonia-like illness, its pathophysiology in severe cases can include destruction of lung epithelial cells, thrombosis, hypercoagulation and vascular leakage. These events lead to acute respiratory distress syndrome (ARDS).

After one year of the pandemic, researchers are looking beyond the acute illness. Increased attention is being given, with considerable debate, to persistent symptoms and complications that have the potential to impose an appreciable burden of chronic respiratory symptoms or fibrotic disease on recovered individuals. No consensus has yet been reached regarding the terminology and clinical definition of the long-term consequences of COVID-19, but understanding of the issues is increasing rapidly.

The terms post-COVID syndrome or long COVID have been used in the literature, with the suggestion that this condition can be classified as subacute or ongoing symptomatic COVID-19 (symptoms and abnormalities present 4-12 weeks beyond acute COVID-19) and chronic or post-COVID-19 syndrome (symptoms and abnormalities persisting or present beyond 12 weeks after the onset of acute COVID-19 and not attributable to alternative diagnoses).[1] In initiatives implemented to quantify and evaluate sequels, it has been estimated that around one in five people who tested positive for COVID-19 had symptoms that lasted for five weeks or longer, and one in ten people had symptoms that lasted for 12 weeks or longer.[1] The World Health Organization (WHO) has recommended that patients who have COVID-19 (both confirmed and suspected) should have access to follow-up care if they have persistent, new or changing symptoms.[2]

Respiratory dysfunction has been described as one of the most prevalent symptoms in long COVID. In one study, dyspnea and chest pain were found at high proportions after two months among previously hospitalized patients.[3] One third of the patients who required noninvasive ventilation or mechanical ventilation still presented dyspnea after six months. Even individuals who were not hospitalized were at greater risk of dyspnea during the first six months after acquiring COVID-19 than were controls who had not had COVID-19. Dyspnea was also found to be more frequent among patients hospitalized for COVID-19 than among those hospitalized due to influenza.[4]

Further respiratory symptoms have been seen to occur frequently in long COVID. Chest pain was present in a quarter of the patients discharged from hospital two months after COVID-19. At six months, the risk of chest pain, compared with patients without COVID-19, was higher. Dry cough, one of the most common symptoms of COVID-19, along with fever, anosmia and ageusia, can persist for weeks or months after COVID-19. Long COVID-19 patients have also presented evidence of high burden of incident use of bronchodilators, antitussives, expectorants, anti-asthmatics and glucocorticoids.[4]

Hypoxemia and exertional desaturation are associated with dyspnea and might represent pulmonary impairment in long COVID. The National Institute for Health and Care Excellence (NICE) guidelines suggest that all patients should be evaluated using an exercise tolerance test to record their levels of breathlessness, heart rate and O_2 saturation.[1] A one-minute sit-to-stand test (1STST) is currently used to evaluate long COVID-19 patients.

At six months, it was found that survivors presented greater risk of hypoxemia than did controls with other diagnoses. COVID-19 survivors after hospitalization were at threefold greater risk of hypoxemia than non-hospitalized COVID-19 survivors, and survivors from intensive care unit (ICU) admission presented sevenfold greater risk of this than did other COVID survivors. Comparison of patients who were hospitalized with COVID and those who were hospitalized due to seasonal influenza also showed that the risk of hypoxemia was higher among COVID patients.[4]

Functionally, reduced forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity (DLCO) have been found in patients with long COVID, but no airway obstruction. Lung function assessment at six months after COVID-19 showed that a considerable proportion of the participants had pulmonary diffusion abnormalities.[5] At 12 months, residual abnormalities of pulmonary function were observed in a third of the patients, and the most common finding was a reduction in DLCO. DLCO was also independently correlated with greater severity of the initial disease.[6]

The higher forced expiration volume in first second (FEV1)/FVC ratio in the severe/critical subgroup suggested that it presented restrictive physiology. There was no difference between critical and non-critical patients in terms of respiratory muscle dysfunction strength, which suggested that a lung parenchymal rather than a respiratory muscle dysfunction was present.[7]

A negative correlation between the duration of mechanical ventilation and pulmonary function at a four-month follow-up has been demonstrated.[7] This may have been due to prolonged or more severe disease after very severe COVID-19 or may have been related to ventilator-induced lung injury, which is a well-described challenge post-ARDS and can reduce pulmonary function after recovery.[8]

Respiratory viral infection might potentially induce distinct fibroblast activation in the convalescence phase.[5] Lung dysfunction has been correlated with pulmonary interstitial change seen on computed tomography (ground-glass opacifications and reticulations/parenchymal bands). A mosaic attenuation pattern (abnormally hypodense areas alternating with normal or abnormally hyperdense areas) and air trapping have also been observed and may indicate small-airway disease. The association of mosaic attenuation pattern and impaired DLCO can cause ventilation-perfusion mismatch, thus contributing to reduced physical performance and hypoxemia. Potential development of progressive interstitial lung disease might be triggered by COVID-19, drug-induced lung injury or progression from pre-existing interstitial lung abnormalities.

Long COVID patients also present higher risk of thromboembolic diseases, and pulmonary emboli have been highlighted as a differential for dyspnea. At six months, survivors of COVID-19 were found to present greater risk of thromboembolism than controls with other diagnosis. After six months, COVID-19 survivors who had been hospitalized were at sevenfold greater risk of thromboembolism than were non-hospitalized COVID-19 survivors; and survivors of COVID-19 intensive care unit admission were at 18-fold greater risk than all other survivors of COVID. Comparison of patients who were hospitalized due to COVID with those hospitalized due to seasonal influenza showed that the risk of venous thromboembolism (VTE) was about twice as high after six months.[4]

Since the impact of COVID-19 varies from full recovery to severe and persistent debilitating symptoms, patients who remain symptomatic after four weeks should be considered for an initial evaluation to identify and treat disorders, with medication reconciliation and doctor referral if needed. The objectives in managing long-COVID are to support patients in the ambulatory setting, avoid the additional burden of predicted readmissions, understand the trajectory of each patient and identify therapeutic opportunities. Persistent respiratory symptoms should be evaluated to exclude diagnoses such as organized pneumonia, pulmonary embolism, heart disease, lung fibrosis and neuromuscular weakness.

No conclusive evidence for routine use of corticosteroids and anticoagulation in cases of long-COVID has been found. Therefore, currently, such use should be individualized based on functional and radiological findings¸ degree of symptoms and risk/benefit analysis. Cough and chest pain could be managed through administration of opioid derivatives. Gabapentin and pregabalin, which are neuromodulators, could be considered for treating post-COVID syndrome, although they have the potential to worsen any cognitive dysfunction. Antimuscarinic drugs, such as tiotropium, could be used to control COVID-19 cough, because these can decrease cough sensitivity in cases of acute viral upper respiratory tract infection.[9]

The importance of multidisciplinary rehabilitation has been acknowledged for patient management post-COVID. Rehabilitation programs should be adjusted to the needs of the patient and details are still required regarding who would benefit from rehabilitation, and what kind of rehabilitation this should be. It is also necessary to verify that sufficient capacity is available within community rehabilitation services to assist in cases of long COVID.[10]

Studies involving long COVID-19 are dynamic and are being published quickly, thereby updating comprehension of the biological basis of symptoms and the therapeutic opportunities for recovery and rehabilitation. It will be crucial to offer individualized, evidence-based care for these patients.

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Intra and intersession repeatability and reliability of dynamic parameters in pressure platform assessments on subjects with simulated leg length discrepancy. A cross-sectional research

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ABSTRACT

BACKGROUND: Leg length discrepancy (LLD) may play a key role in exercise biomechanics. Although the Podoprint platform has been used in dynamic pressure studies, there are no data regarding the reliability and repeatability of dynamic measurements under simulated LLD conditions.

OBJECTIVES: To determine the intra and intersession repeatability and reliability of dynamic parameters of the Podoprint pressure platform under simulated LLD conditions.

DESIGN AND SETTING: Observational cross-sectional study at a public university.

METHODS: Thirty-seven healthy volunteers participated in this study. LLD was simulated using ethyl vinyl acetate plantar lifts with heights of 5 mm, 10 mm, 15 mm and 20 mm located under the right shoe of each volunteer. The procedure was performed to capture the dynamic parameters of each participant under five different simulated LLD conditions. Stance time, mean pressure and peak pressure measurements were registered in three trials for each foot and each LLD level. Data were collected during two separate testing sessions, in order to establish intrasession and intersession reliability.

RESULTS: The intraclass correlation coefficients (ICCs) for intrasession reliability ranged from 0.775 to 0.983 in the first session and from 0.860 to 0.985 in the second session. The ICCs for intersession reliability ranged from 0.909 to 0.990. Bland-Altman plots showed absence of systematic measurement errors.

CONCLUSIONS: The results from this study indicate that the Podoprint platform is a reliable system for assessing dynamic parameters under simulated LLD conditions. Future studies should evaluate plantar pressures under LLD conditions, in association with exercise, biomechanics and musculoskeletal disorders.

INTRODUCTION

Leg length discrepancy (LLD) is a situation in which the lower limbs have different lengths.[1] LLD has been discussed in the clinical and research communities for decades. However, there is no consensus regarding many aspects of LLD, including its prevalence, the scope of its clinical significance, assessment of measurement methods and its impact on several neuromusculoskeletal alterations.[2] LLD is estimated to affect 40-70% of the population and approximately 0.1% present inequality greater than 2 cm.[1] Knutson conducted a meta-analysis on 573 subjects and concluded that only 10% of the population had equal lower-limb lengths.[3]

LLD can be classified as anatomical when the difference in length between the limbs can be measured directly in the tibias, femurs, or both; or it can be classified as functional when the discrepancy is caused by postural inaccuracies.[4] LLD has been correlated with several pathological conditions, such as hip or knee osteoarthritis, due to inappropriate distribution of mechanical loads.[5,6] Asymmetry in the kinetics of LLD-induced gait has also been linked to the etiology of plantar fasciitis,[7] lower back pain[8] and knee pain.[9] Concretely, LLD may play a key role in skeletal malalignment disorders such as patellofemoral conditions.[10] Asymmetries in the kinematics of human gait have been correlated with different degrees of anatomical LLD,[5] such as pelvic drop and hip adduction in the stance phase.[11,12] Additional studies have found flexion abnormalities in the sagittal plane of the hip, knee, ankle and first metatarsophalangeal joint.[11,13-15] LLD also appears to be related to decreased load times in the shorter limb, reduced gait velocity, decreased stride length on the shorter leg and increased cadence.[16] In addition, several studies have found that LLD produces asymmetrical pressure patterns.[17,18]

As described in the literature, there are two methods for studying LLD: evaluation of real LLD cases or simulation of LLD in healthy subjects, to assess the role of LLD regarding gait alterations. The first method has limitations because subjects with LLD commonly develop physical anomalies as a result of compensations and therefore cannot be considered to be pure LLD subjects. Moreover, LLD may frequently be associated with several disease processes that can also alter gait.[2] To address these limitations, Betsch et al. designed a noninvasive method for simulating and studying LLD and its consequences on the musculoskeletal apparatus, using plantar lifts.[19,20]

Pedobarography is the study of foot-ground pressures. It has been used to study foot interactions with the ground and with posture,[21] and to screen for plantar footprint alterations in healthy subjects that could lead to pathological conditions.[22] Foot pressure measurement devices, essentially consisting of platforms and instrumented insoles, are used to quantify the static and dynamic parameters between the foot and floor; foot and shoe; and shoe and floor.[23,24] These devices are generally intended for both clinical and research use.

Consequently, assessments on the reliability, validity and effectiveness of pressure systems are extremely relevant.[22,25] A variety of plantar pressure devices are available, but one of the most commonly used devices in clinical podiatry is the Podoprint platform (Namrol Group, Barcelona, Spain). While this platform has been used in dynamic pressure and postural analysis studies,[24,26,27] there are no data regarding the reliability and repeatability of dynamic measurements made using the platform. As previously mentioned, although a few studies have reported that LLD causes alterations to gait time and pressure patterns, the reliability and validity of the platform measurements have not, to the best of our knowledge, been addressed.[28,29]

OBJECTIVE

Our aim was to assess the reliability and repeatability of the Podoprint platform for measuring dynamic plantar parameters obtained from healthy subjects under simulated LLD conditions. We hypothesized that the pressure platform could be accurately used to assess gait dynamic parameters, in order to study simulated LLD effects.

METHODS

Design and sample

Thirty-seven healthy volunteers (24 women and 13 men) aged 19 to 76 years participated in this study (**Table 1**). We used an observational cross-sectional research design in accordance with the criteria of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[30] and a nonrandom consecutive sampling technique. The inclusion criteria were that the subjects needed to be over 18 years of age; have a normal gait pattern;[31] and have normal leg and foot joint ranges. Subjects were excluded if they reported having pain, anatomical or functional LLD,[32] previous lower limb surgery, congenital or acquired deformities of the lower extremities upon clinical examination, or any other condition that might affect their gait.

The sample size was calculated using the GRANMO software, version 7.12, which was previously developed through a research program on inflammatory and cardiovascular disorders, at IMIM-Hospital del Mar, Barcelona, Spain.[33] A study on the correlation between the dynamic parameters of gait and different degrees of simulated LLD was used as a reference.[28] With a standard deviation (SD) of 4.34-3.48, 80% statistical power ($\beta = 20\%$), a 95% confidence interval ($\alpha = 0.05$) and two-tailed tests, it was calculated that 37 participants were required to detect a difference greater than or equal to 0.4 units. A SD of 0.86 and a loss to follow-up rate of 0% was assumed.

Dynamic data collection

LLD was simulated using ethyl vinyl acetate plantar lifts of 70A Shore hardness and heights of 5 mm, 10 mm, 15 mm or 20 mm, which were attached with adhesive double-sided tape to the bottom of the volunteer´s own right shoe. This method mimics LLD by producing pelvic obliquity. In order to record the dynamic parameters, a Podoprint platform was integrated into the center of a flat 4.8 m walkway at ground level. The platform measured 610 mm x 580 mm with a thickness of 10 mm and a weight of 6.6 kg. It was composed of a self-calibrating system with 1600 10 mm x 10 mm resistive sensors.

Table 1. Descriptive data on the study participants showing demographics and anthropometric characteristics for the total sample and according to sex

Variable	Male n = 13	Female n = 24	Total (n = 37)
	mean ± SD (95% CI)	mean ± SD (95% CI)	mean ± SD (95% CI)
Age (years)	48.08 ± 17.38 (37.57-58.58)	42.17 ± 14.76 (35.93-48.40)	44.24 ± 15.75 (38.99-49.50)
Weight (kg)	73.38 ± 8.31 (68.36-78.40)	64.50 ± 12.95 (59.02-69.97)	67.62 ± 12.19 (63.55-71.68)
Height (cm)	174.46 ± 9.27 (168.85-180.06)	163.62 ± 8.54 (160.01-167.23)	167.43 ± 10.14 (164.05-170.81)
BMI (kg/m^2)	24.18 ± 2.82 (22.47-25.89)	24.74 ± 5.32 (22.49-26.99)	24.54 ± 4.56 (23.02-26.07)
Foot size (EC)	42.23 ± 2.37 (40.79-43.66)	38 ± 1.37 (37.41-38.58)	39.48 ± 2.69 (38.58-40.38)

BMI = body mass index; SD = standard deviation; 95% CI = 95 percent confidence interval; EC = Europe countries.

Each subject was instructed to walk naturally while looking forward. The starting position was determined so that the footstep would coincide on the platform. Participants walked at a self-selected speed for all trials; however, speeds were within the limits considered to be normal cadence under laboratory conditions, which range from 81-138 steps per minute.[34]

The procedure was performed with the aim of capturing the dynamic parameters of each participant under five simulated LLD conditions with increasing amounts of plantar lift (0 mm, 5 mm, 10 mm, 15 mm and 20 mm). Stance time (ms), mean pressure (g/cm^2), and peak pressure (g/cm^2) measurements were recorded. These parameters were regarded as the ones most frequently used in functional foot appraisals under pathological conditions.[25]

Two testing sessions were conducted on seven separated days. Three trials for each foot and LLD level were collected per session. Before recording the dynamic data, all subjects completed three minutes of walking on the walkway to familiarize themselves with the platform and the plantar lifts. Four steps of each foot were registered per trial using the "multiple dynamic" mode of the platform, which automatically provides averaged parameters. The sampling rate was 100 Hz. The same researcher measured all subjects.

The data obtained from the platform were processed and stored using the manufacturer-specific software Podoprint for Windows, version 8.6.5 (Namrol Group, Barcelona, Spain), on a computer.

Statistical analysis

All data were checked for normal distribution by means of the one-sample Kolmogorov-Smirnov test. Normally distributed data were presented as the mean and standard deviation.

Intrasession reliability was measured from three repeated trials for each simulated LLD condition and for each foot during the first and second testing sessions. The intraclass correlation coefficient (ICC) obtained using the (2,1) model (two-way random, single-measurement, absolute agreement ICC model) was calculated first, in order to analyze the reliability between trials.[35] The coefficient of variation (CoV)[36] was used to refer to the relationship between the size of the mean and the variability of each of the variables studied. The standard error of measurement (SEM) was expressed as a percentage of the mean (SEM%).[37]

In addition, the minimum detectable change (MDC) was calculated. This was defined as the magnitude of the value variation of each scale, below which change can be interpreted as inherent to the variability of the measurement method, without any real change to the clinical situation of the subject. MDC was calculated as a standardized mean (95% MDC).[38,39]

Intersession reliability was ascertained by retesting all subjects seven days after the first session. The average of the measurements for each session, for each subject and LLD condition, was used to calculate the ICC (2,1). For absolute comparison of the results obtained in the two sessions, CoV, SEM and MDC were expressed as percentages of the mean. The repeatability coefficient (RC) was also calculated as a percentage of the average values from the two measurement sessions, while the limits of agreement (LoA)[37] were calculated to define the amount of variation that might be influencing the measurements. In addition, we used Bland-Altman plots to evaluate systematic measurement errors.

Paired Student's t tests were used to determine systematic differences between the first and second sessions. From this, P-values were obtained, such that if $P < 0.05$, then there was a difference between the two variables. The IBM SPSS for Windows statistical package, version 22.0, was used for data analysis (SPSS, Inc., Chicago, Illinois, United States).

Ethical considerations

The Research Ethics Committee of Universidad Rey Juan Carlos, Spain, issued the authorization certificate number 0904201907519, approved on May 22, 2019, for this study, which followed the ethical principles of the Helsinki declaration.[40] All subjects signed an informed consent statement before participating in this study.

RESULTS

Intrasession reliability

Normative data (represented by mean ± SD) and reliability data (represented by ICC, CoV, SEM% and MDC%) for the first session are presented in **Table 2**. The ICC for intrasession reliability ranged from 0.775 to 0.983 and the SEM ranged from 0.059% to 1.095%. The CoV ranged from 0.322% to 2.474% and the MDC ranged from 0.051% to 3.037%.

Normative data and reliability data for the second session are shown in **Table 3**. The ICC for intrasession reliability ranged from 0.860 to 0.985 and the SEM ranged from 0.014% to 0.635%. The CoV ranged from 0.077% to 1.848% and the MDC ranged from 0.038% to 1.759%.

Intersession reliability

The average for measurements from each test session and the ICC, CoV, SEM%, MDC%, RC% and Student's t test for intersession reliability are presented in **Table 4**. The ICC for intersession reliability ranged from 0.909 to 0.990 and the SEM ranged from 0.05% to 0.49%. The CoV ranged from 0.5% to 1.70%, the MDC ranged from 0.14% to 1.36% and the RC ranged from 0.84% to 19.22%. All variables were compared using Student's t test and had P-values > 0.05.

Intersession limits of agreement and Bland-Altman plots are shown in **Figures 1-5**. The mean differences between sessions for the variables studied ranged from -2.15% to 1.69%.

DISCUSSION

Plantar pressure platforms are clinical devices that are used to assess foot interactions with the ground,[21] and to screen gait patterns that could lead to pathological conditions.[22] The Podoprint platform system is commonly used by clinicians and researchers as a tool to develop their work. One of the applications of this technology could be to study LLD and its consequences on the patient's health.[28] Hence, the aim of this study was to determine the intra and intersession repeatability and reliability of dynamic parameters of this pressure platform among subjects with simulated leg length discrepancy.

The ICC is an extensively used descriptive statistic for quantifying the repeatability of a measurement. Using the classification proposed by Landis and Koch, ICC values between 0.40 and 0.60 have moderate reliability, whereas scores in the highest category, ranging from 0.80 to 1.00, are considered nearly perfect.[35] Other authors have indicated that an ICC value of at least 0.75[36] needs to be available to obtain reliability. According to Portney and Watkins' recommendations, clinical measurements with an ICC greater than 0.90 improve the probability of valid measurements.[37] In our study, the results showed consistent intra and intersession reliability and repeatability of the Podoprint platform under all LLD conditions. Intrasession variability was very low. All ICCs were higher than 0.775 and most were higher than 0.9.

SEM is considered to represent the amount of measurement error of a test and MDC shows the value for the smallest change needed in order to recognize that the observed change is real and not a result from instrument measurement error.[41,42] In this study, the SEMs were in most of the cases lower than 1% and the MDC

Table 2. Repeatability of dynamic variables for each foot under simulated LLD conditions. First session

Variable	Mean ± SD	CoV (%)	ICC (2.1) (95% CI)	SEM%	95% MDC%
0 mm of LLD					
Stance time left (ms)	780.360 ± 7.131	0.913	0.898 (0.825-0.944)	0.291	0.808
Stance time right (ms)	772.613 ± 6.698	0.866	0.917 (0.857-0.954)	0.249	0.692
Mean pressure left (g/cm²)	763.027 ±11.271	1.447	0.915 (0.854-0.953)	0.43	0.156
Mean pressure right (g/cm²)	769.324 ± 7.263	0.944	0.892 (0.813-0.941)	0.31	0.111
Peak pressure left (g/cm²)	1449.297 ± 13.402	0.924	0.914 (0.852-0.953)	0.271	0.051
Peak pressure right (g/cm²)	1445.532 ± 17.208	1.19	0.931 (0.881-0.962)	0.312	0.866
5 mm of LLD					
Stance time left (ms)	778.396 ±13.756	1.767	0.873 (0.783-0.930)	0.628	1.743
Stance time right (ms)	770.351 ± 14.163	1.839	0.775 (0.613-0.876)	0.872	2.417
Mean pressure left (g/cm²)	776.240 ± 7.500	0.966	0.940 (0.896-0.967)	0.237	0.656
Mean pressure right (g/cm²)	761.991 ± 10.201	1.339	0.912 (0.849-0.952)	0.397	1.101
Peak pressure left (g/cm²)	1495.225 ± 12.651	0.846	0.906 (0.837-0.948)	0.259	0.719
Peak pressure right (g/cm²)	1365.090 ± 16.766	1.228	0.928 (0.877-0.961)	0.33	0.913
10 mm of LLD					
Stance time left (ms)	787.207 ± 6.588	0.837	0.973 (0.954-0.985)	0.138	0.381
Stance time right (ms)	793.063 ± 5.697	0.718	0.976 (0.959-0.987)	0.111	0.308
Mean pressure left (g/cm²)	780.432 ± 5.791	0.742	0.965 (0.940-0.981)	0.139	0.385
Mean pressure right (g/cm²)	741.081 ± 12.886	1.739	0.919 (0.861-0.956)	0.495	1.372
Peak pressure left (g/cm²)	1456.297 ± 9.645	0.662	0.909 (0.843-0.950)	0.2	0.554
Peak pressure right (g/cm²)	1274.694 ± 26.494	2.078	0.869 (0.774-0.928)	0.752	2.085
15 mm of LLD					
Stance time left (ms)	786.486 ± 7.819	0.994	0.983 (0.970-0.991)	0.13	0.359
Stance time right (ms)	798.378 ±7.206	0.903	0.980 (0.965-0.989)	0.128	0.354
Mean pressure left (g/cm²)	779.225 ± 2.512	0.322	0.966 (0.942-0.982)	0.059	0.165
Mean pressure right (g/cm²)	721.721 ± 5.353	0.742	0.922 (0.866-0.957)	0.207	0.574
Peak pressure left (g/cm²)	1451.928 ± 7.477	0.515	0.889 (0.807-0.939)	0.172	0.476
Peak pressure right (g/cm²)	1247.279 ± 22.891	1.835	0.778 (0.617-0.878)	0.865	2.397
20 mm of LLD					
Stance time left (ms)	788.288 ± 3.357	0.426	0.975 (0.956-0.986)	0.067	0.187
Stance time right (ms)	807.928 ± 4.092	0.506	0.976 (0.959-0.987)	0.078	0.217
Mean pressure left (g/cm²)	782.468 ± 3.751	0.479	0.964 (0.938-0.980)	0.091	0.252
Mean pressure right (g/cm²)	723.595 ± 2.566	0.355	0.894 (0.817-0.942)	0.115	0.32
Peak pressure left (g/cm²)	1446.685 ± 23.562	1.629	0.917 (0.857-0.954)	0.469	1.301
Peak pressure right (g/cm²)	1232.351 ± 30.494	2.474	0.804 (0.663-0.892)	1.095	3.037

SD = standard deviation; CoV = coefficient of variation; ICC = intraclass correlation coefficient; 95% CI = 95 percent confidence interval; SEM% = standard error of measurement percentage; MDC% = minimum detectable change percentage; LLD = leg length discrepancy.

ranged from 0.038% and 3.037%. Low MDC values strengthened the ICCs. These results indicated that the reliability measurements were higher than those in other similar studies.[22,43] One explanation for this may be that the measurements were obtained using the multiple dynamic mode of the platform. In this mode, the platform software automatically provides the average results from four measurements for each foot.

According to Becerro de Bengoa et al., the expected physiological changes in muscle activity, posture and gait velocity can affect variables during the measurements. Therefore, using a single trial to obtain foot dynamic parameters from a sample is not sufficient. By averaging multiple trials, the variability of gait patterns is decreased.[22] Other authors have suggested that three trials are sufficient to obtain a consistent outcome.[44] In our three-trial protocol, each trial needed four measurements from each foot. In fact, this is equivalent to 12 trials per session.

Gurney et al. conducted a study on the between-day reliability of repeated plantar pressure distribution measurements in a healthy population by analyzing 10-foot areas. Their intersession ICCs for total area averages were higher than 0.8 and the highest CoV was 13%.[44] Izquierdo-Renau et al. also found ICC values greater than 0.89.[44] In the present study, intersession repeatability was extremely high. All ICCs were greater than 0.9 for all measured dynamic variables and the highest CoV was 1.7%, which was concordant with the outcomes from previous studies.[22,25,43] We did not find any significant

Table 3. Repeatability of dynamic variables for each foot under simulated LLD conditions. Second session

Variables	Mean ± SD	CoV (%)	ICC (2.1) (95% CI)	SEM%	MDC%
0 mm of LLD					
Stance time left (ms)	775.099 ± 0.595	0.077	0.968 (0.945-0.983)	0.014	0.038
Stance time right (ms)	771.712 ± 5.022	0.651	0.974 (0.955-0.986)	0.105	0.291
Mean pressure left (g/cm²)	776.775 ± 6.734	0.867	0.958 (0.929-0.977)	0.178	0.492
Mean pressure right (g/cm²)	786.541 ± 7.346	0.934	0.923 (0.867-0.958)	0.259	0.718
Peak pressure left (g/cm²)	1473.108 ± 9.370	0.636	0.923 (0.868-0.958)	0.177	0.489
Peak pressure right (g/cm²)	1476.541 ± 14.250	0.965	0.958 (0.927-0.977)	0.198	0.548
5 mm of LLD					
Stance time left (ms)	781.739 ± 11.497	1.471	0.860 (0.758-0.923)	0.55	1.525
Stance time right (ms)	781.532 ± 5.250	0.672	0.982 (0.968-0.990)	0.09	0.25
Mean pressure left (g/cm²)	772.883 ± 3.435	0.444	0.957 (0.925-0.976)	0.092	0.255
Mean pressure right (g/cm²)	774.243 ± 11.728	1.515	0.922 (0.865-0.957)	0.423	1.173
Peak pressure left (g/cm²)	1467.964 ± 14.614	0.996	0.927 (0.874-0.960)	0.269	0.746
Peak pressure right (g/cm²)	1361.396 ± 10.761	0.79	0.948 (0.910-0.971)	0.18	0.5
10 mm of LLD					
Stance time left (ms)	789.550 ± 3.527	0.447	0.982 (0.969-0.990)	0.06	0.166
Stance time right (ms)	785.045 ± 6.698	0.853	0.976 (0.958-0.987)	0.132	0.366
Mean pressure left (g/cm²)	777.108 ± 2.357	0.303	0.966 (0.942-0.981)	0.056	0.155
Mean pressure right (g/cm²)	733.541 ± 5.050	0.688	0.913 (0.851-0.952)	0.203	0.563
Peak pressure left (g/cm²)	1468.613 ± 24.001	1.634	0.930 (0.880-0.962)	0.432	1.199
Peak pressure right (g/cm²)	1277.036 ± 13.052	1.022	0.930 (0.879-0.961)	0.27	0.75
15 mm of LLD					
Stance time left (ms)	792.162 ± 2.742	0.346	0.985 (0.975-0.992)	0.042	0.118
Stance time right (ms)	806.757 ± 3.375	0.418	0.981 (0.967-0.990)	0.058	0.16
Mean pressure left (g/cm²)	785.369 ± 6.983	0.889	0.968 (0.944-0.982)	0.159	0.441
Mean pressure right (g/cm²)	728.414 ± 8.107	1.113	0.944 (0.903-0.969)	0.263	0.73
Peak pressure left (g/cm²)	1470.207 ± 10.147	0.69	0.945 (0.906-0.970)	0.162	0.449
Peak pressure right (g/cm²)	1262.550 ± 12.141	0.962	0.899 (0.826-0.945)	0.306	0.847
20 mm of LLD					
Stance time left (ms)	793.784 ± 3.783	0.477	0.976 (0.959-0.987)	0.074	0.205
Stance time right (ms)	807.658 ± 4.904	0.607	0.986 (0.975-0.992)	0.072	0.199
Mean pressure left (g/cm²)	785.207 ± 4.703	0.599	0.964 (0.937-0.980)	0.114	0.315
Mean pressure right (g/cm²)	724.856 ± 8.859	1.222	0.889 (0.810-0.939)	0.407	1.129
Peak pressure left (g/cm²)	1457.306 ± 26.924	1.848	0.882 (0.798-0.935)	0.635	1.759
Peak pressure right (g/cm²)	1247.450 ± 3.442	0.276	0.878 (0.790-0.933)	0.096	0.265

SD = standard deviation; CoV = coefficient of variation; ICC = intraclass correlation coefficient; 95% CI = 95 percent confidence interval; SEM% = standard error of measurement percentage; MDC% = minimum detectable change percentage; LLD = leg length discrepancy.

Table 4. Intersession reliability of dynamic variables for each foot under simulated LLD conditions

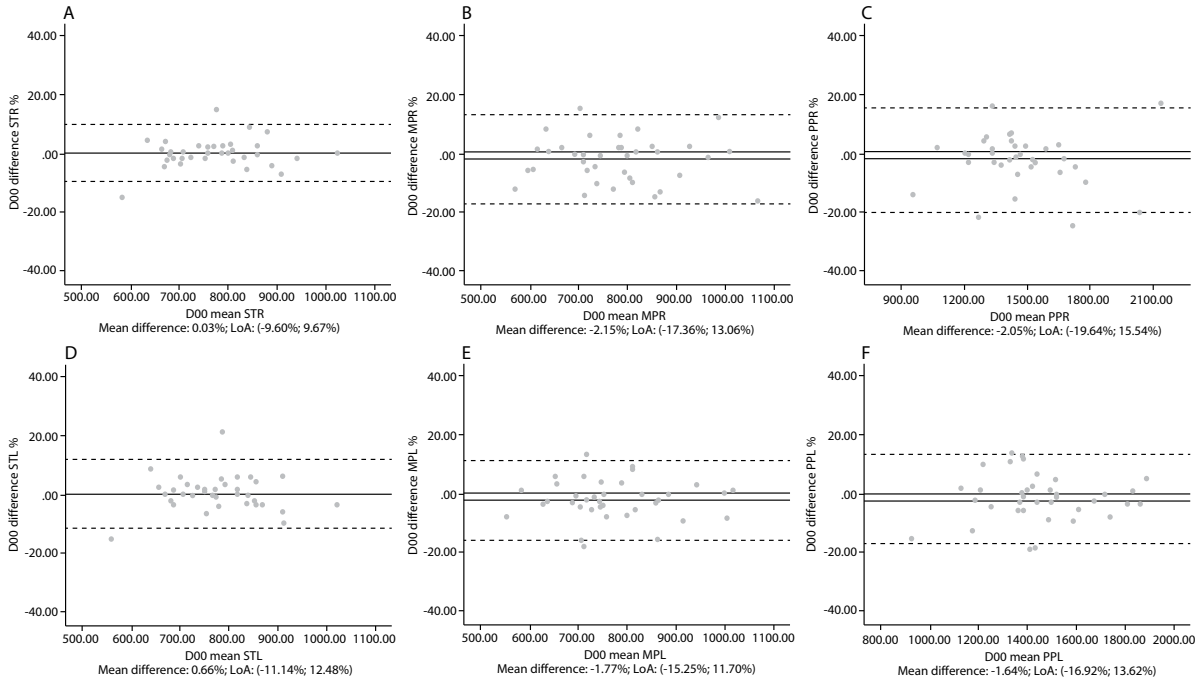
Variables	Mean ± SD	CoV (%)	ICC (2.1) (95% CI)	SEM%	MDC%	RC%	STS
0 mm of LLD							
Stance time left (ms)	777.730 ± 5.365	0.69	0.960 (0.936-0.977)	0.14	0.38	11.37	0.483
Stance time right (ms)	772.162 ± 5.318	0.69	0.969 (0.951-0.982)	0.12	0.34	9.18	0.88
Mean pressure left (g/cm²)	769.901 ± 11.210	1.46	0.962 (0.940-0.978)	0.28	0.79	13.17	0.115
Mean pressure right (g/cm²)	777.932 ± 11.472	1.47	0.946 (0.914-0.969)	0.34	0.95	15.67	0.101
Peak pressure left (g/cm²)	1461.203 ± 16.645	1.14	0.954 (0.926-0.973)	0.24	0.68	14.12	0.177
Peak pressure right (g/cm²)	1461.036 ± 22.094	1.51	0.956 (0.930-0.975)	0.32	0.88	19.22	0.196
5 mm of LLD							
Stance time left (ms)	780.068 ± 11.486	1.47	0.923 (0.878-0.956)	0.41	1.13	16.46	0.758
Stance time right (ms)	775.941 ± 11.347	1.46	0.936 (0.898-0.963)	0.37	1.03	13.36	0.207
Mean pressure left (g/cm²)	774.577 ± 5.537	0.71	0.974 (0.959-0.985)	0.12	0.32	9.00	0.566
Mean pressure right (g/cm²)	768.117 ± 11.903	1.55	0.953 (0.925-0.973)	0.34	0.93	13.66	0.172
Peak pressure left (g/cm²)	1481.595 ± 19.287	1.30	0.955 (0.928-0.974)	0.28	0.77	12.88	0.097
Peak pressure right (g/cm²)	1363.243 ± 12.762	0.94	0.967 (0.947-0.981)	0.17	0.47	10.11	0.751
10 mm of LLD							
Stance time left (ms)	788.378 ± 4.897	0.62	0.990 (0.984-0.994)	0.06	0.17	3.80	0.357
Stance time right (ms)	789.054 ± 7.086	0.90	0.986 (0.978-0.992)	0.11	0.29	6.90	0.088
Mean pressure left (g/cm²)	778.770 ± 4.353	0.56	0.984 (0.974-0.991)	0.07	0.20	0.84	0.427
Mean pressure right (g/cm²)	737.311 ± 9.678	1.31	0.961 (0.938-0.978)	0.26	0.72	8.78	0.173
Peak pressure left (g/cm²)	1462.455 ± 17.696	1.21	0.957 (0.932-0.975)	0.25	0.70	12.48	0.426
Peak pressure right (g/cm²)	1275.865 ± 18.723	1.47	0.943 (0.909-0.967)	0.35	0.97	13.69	0.874
15 mm of LLD							
Stance time left (ms)	789.324 ± 6.093	0.77	0.990 (0.985-0.994)	0.08	0.21	6.63	0.204
Stance time right (ms)	802.568 ± 6.811	0.85	0.987 (0.979-0.992)	0.10	0.27	8.66	0.159
Mean pressure left (g/cm²)	782.297 ± 5.775	0.74	0.984 (0.974-0.991)	0.09	0.26	6.91	0.184
Mean pressure right (g/cm²)	725.068 ± 7.155	0.99	0.964 (0.943-0.980)	0.19	0.52	11.48	0.344
Peak pressure left (g/cm²)	1461.068 ± 12.798	0.88	0.957 (0.932-0.976)	0.18	0.50	12.42	0.238
Peak pressure right (g/cm²)	1225.914 ± 18.399	1.50	0.909 (0.855-0.948)	0.45	1.25	16.40	0.382
20 mm of LLD							
Stance time left (ms)	791.036 ± 4.392	0.56	0.986 (0.978-0.992)	0.07	0.18	6.84	0.234
Stance time right (ms)	807.793 ± 4.042	0.50	0.990 (0.984-0.994)	0.05	0.14	5.86	0.946
Mean pressure left (g/cm²)	783.838 ± 4.090	0.52	0.980 (0.969-0.989)	0.07	0.20	8.96	0.645
Mean pressure right (g/cm²)	724.225 ± 5.874	0.81	0.948 (0.917-0.970)	0.18	0.51	10.24	0.84
Peak pressure left (g/cm²)	1451.995 ± 23.364	1.61	0.951 (0.922-0.972)	0.36	0.99	12.00	0.472
Peak pressure right (g/cm²)	1239.901 ± 21.097	1.70	0.917 (0.868-0.952)	0.49	1.36	12.67	0.259

SD = standard deviation; CoV = coefficient of variation; ICC = intraclass correlation coefficient; 95% CI = 95 percent confidence interval; SEM% = standard error of measurement percentage; MDC% = minimum detectable change percentage; RC% = repeatability coefficient percentage; STS = Student's t test significance; LLD = leg length discrepancy.

differences between the first and second sessions when comparing means, with P-values > 0.05. All of the variables evaluated were highly homogeneous across all LLD conditions and for both feet.

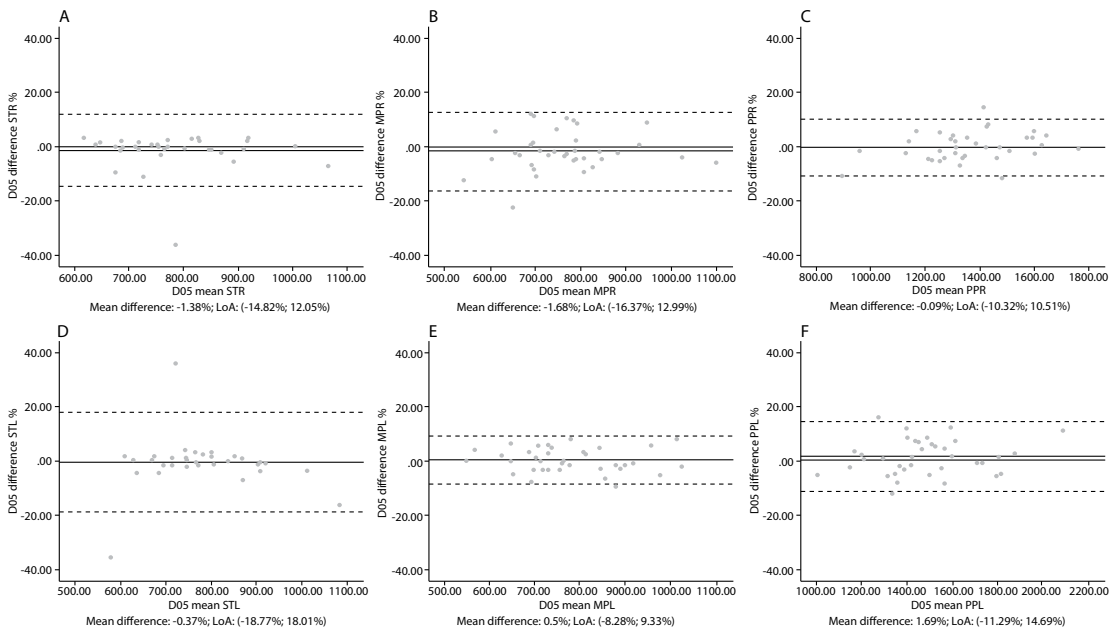
In addition, the limits of agreement and Bland-Altman plots were also calculated and showed differences between sessions plotted against the mean.[38] This complementary analysis revealed that the distribution of such graphs did not show any systematic measurement errors or heteroscedasticity. All of the values for the variables were similar, independent of the LLD condition, and also presented very high repeatability and reliability in all cases.

One limitation of the present study was that pressures were evaluated for total foot plantar surface. Previous investigations have found greater intrasession variability when using a regional analysis.[25,45] Furthermore, the lifts were used in non-randomized order and, thus, the potential learning effects may have influenced the outcomes. Future studies should consider the relationship between several dynamic parameters measured on pressure platforms, such as total stance time, mean pressure, peak pressure and degree of simulated LLD. In addition, patients who have skeletal malalignment disorders such as patellofemoral or hip disorders should be dynamically evaluated using this plantar pressures device under conditions of leg length discrepancy.[10]



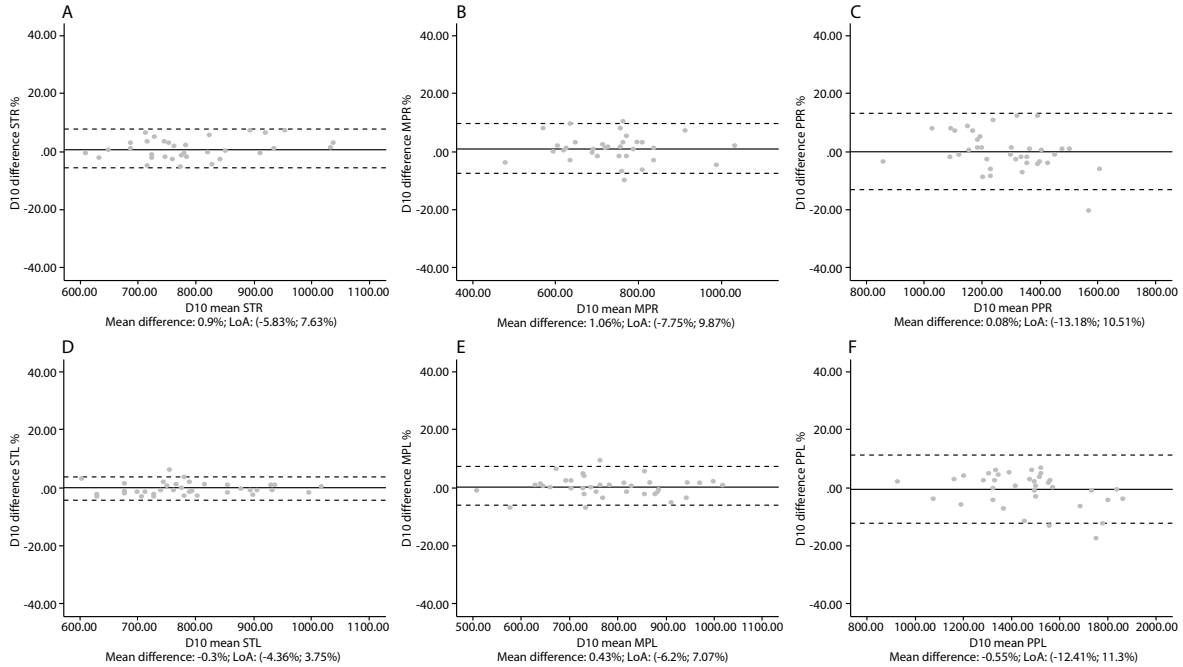
D00 = 0 mm of discrepancy; STR = stance time right; MPR = mean pressure right; PPR = peak pressure right; STL = stance time left; MPL = mean pressure left; PPL = peak pressure left; LoA = limits of agreement.

Figure 1. Bland-Altman plots for dynamic variables for each foot without leg length discrepancy (LLD). Differences between sessions plotted against the mean. Stance time right (A); Mean pressure right (B); Peak pressure right (C); Stance time left (D); Mean pressure left (E); Peak pressure left (F). Abbreviations: D00, 0 mm of discrepancy; STR, stance time right; MPR, mean pressure right; PPR, peak pressure right; STL, stance time left; MTL, mean pressure left; PPL, peak pressure left; LoA, limits of agreement.



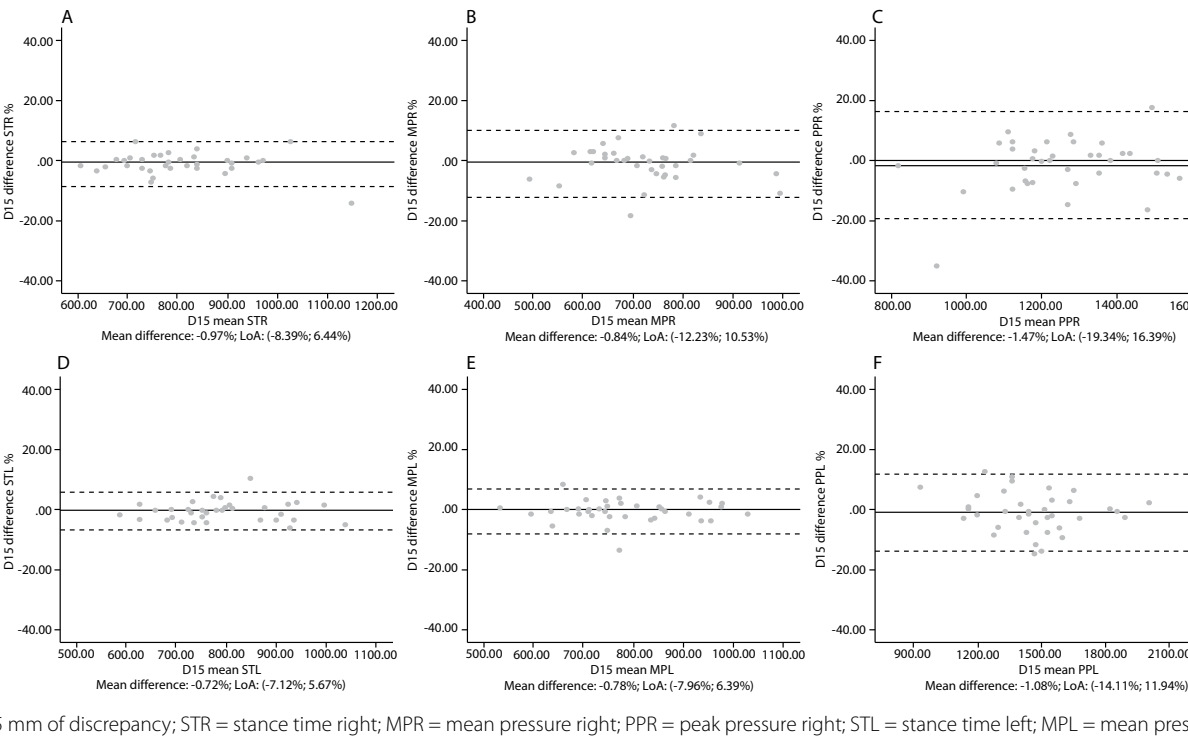
D05 = 5 mm of discrepancy; STR = stance time right; MPR = mean pressure right; PPR = peak pressure right; STL = stance time left; MPL = mean pressure left; PPL = peak pressure left; LoA = limits of agreement.

Figure 2. Bland-Altman plots for dynamic variables for each foot with 5 mm of leg length discrepancy (LLD). Differences between sessions plotted against the mean. Stance time right (A); Mean pressure right (B); Peak pressure right (C); Stance time left (D); Mean pressure left (E); Peak pressure left (F).



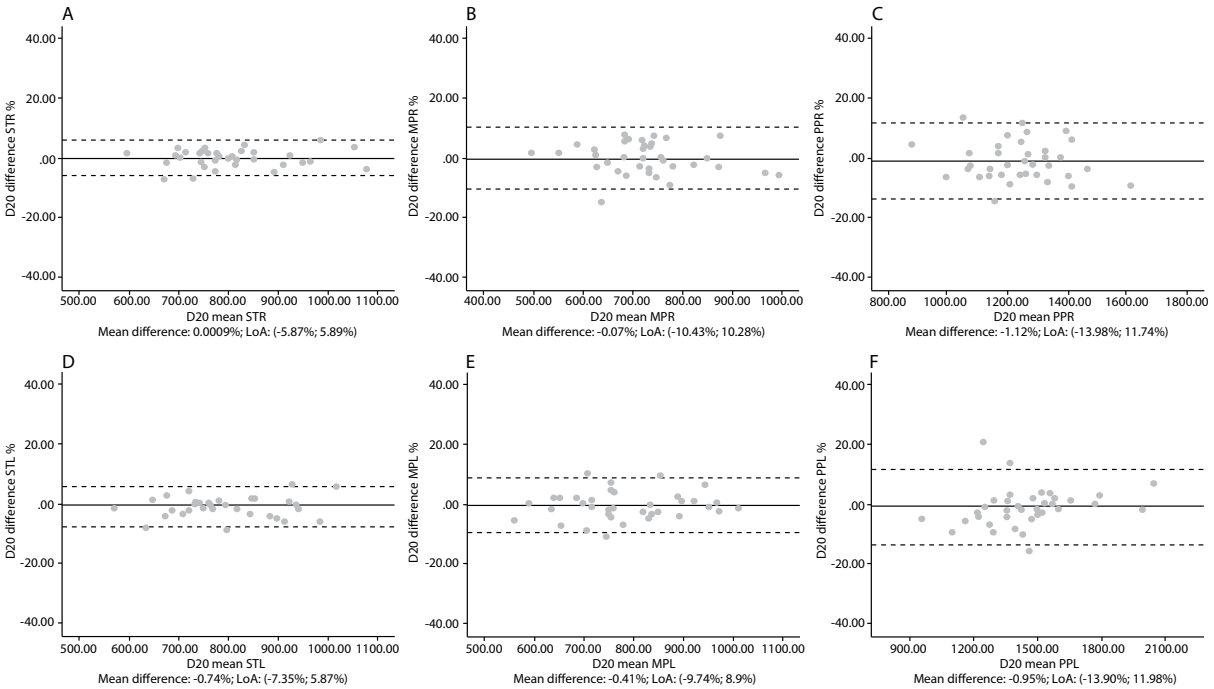
D10 = 10 mm of discrepancy; STR = stance time right; MPR = mean pressure right; PPR = peak pressure right; STL = stance time left; MPL = mean pressure left; PPL = peak pressure left; LoA, limits of agreement.

Figure 3. Bland-Altman plots for dynamic variables for each foot with 10 mm of leg length discrepancy (LLD). Differences between sessions plotted against the mean. Stance time right (A); Mean pressure right (B); Peak pressure right (C); Stance time left (D); Mean pressure left (E); Peak pressure left (F).



D15 = 15 mm of discrepancy; STR = stance time right; MPR = mean pressure right; PPR = peak pressure right; STL = stance time left; MPL = mean pressure left; PPL = peak pressure left; LoA = limits of agreement.

Figure 4. Bland-Altman plots for dynamic variables for each foot with 15 mm of leg length discrepancy (LLD). Differences between sessions plotted against the mean. Stance time right (A); Mean pressure right (B); Peak pressure right (C); Stance time left (D); Mean pressure left (E); Peak pressure left (F).



D20 = 20 mm of discrepancy; STR = stance time right; MPR = mean pressure right; PPR = peak pressure right; STL = stance time left; MPL = mean pressure left; PPL = peak pressure left; LoA = limits of agreement.

Figure 5. Bland-Altman plots for dynamic variables for each foot with 20 mm of leg length discrepancy (LLD). Differences between sessions plotted against the mean. Stance time right (A); Mean pressure right (B); Peak pressure right (C); Stance time left (D); Mean pressure left (E); Peak pressure left (F).

CONCLUSIONS

The results from this study indicate that the Podoprint platform is a reliable system for assessing dynamic parameters for both normal and simulated LLD subjects, due to its high reliability, independent of the LLD condition. This testing device can be confidently used by researchers and clinicians to assess dynamic parameters during research or clinical screenings. Given the reliability results from this study, future studies should evaluate plantar pressures under conditions of length leg discrepancy that are associated with skeletal malalignment disorders such as patellofemoral disorders.

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Clinical and cytogenetic characteristics of patients diagnosed with Turner syndrome in a clinical genetics service: cross-sectional retrospective study

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ABSTRACT

BACKGROUND: Turner syndrome (TS) is a rare genetic disease. Understanding its clinical findings contributes to better management of clinical conditions.

OBJECTIVE: To investigate the clinical and karyotypic characteristics of patients diagnosed with TS at two reference services for clinical genetics in southern Brazil.

DESIGN AND SETTING: Retrospective cross-sectional study conducted in two clinical genetics services in Porto Alegre (RS), Brazil.

METHODS: The sample consisted of 59 patients with TS diagnosed from 1993 to 2019. A review of their medical records was performed and a standard protocol was filled out.

RESULTS: The average age of the patients at diagnosis was 15.9 years, and 40.7% were over 13 years old. The largest proportion of them (42.4%) had been referred from an endocrinology department and their constitution was 45,X (40.7%). The most common clinical findings were short stature (85.7%), hypoplastic/hyperconvex nails (61.2%), low posterior hairline (52.1%) and cubitus valgus (45.8%). There was no difference regarding the presence of short stature (P = 0.5943), number of dysmorphia (P = 0.143), anatomical regions affected and malformations identified through imaging examinations (P = 1.0000), regarding the presence or absence of 45,X constitution. Only 6% of the patients had used growth hormone and 43%, estrogen.

CONCLUSION: We found that, in general, patients with TS were being diagnosed late. This has important implications for their treatment. In addition, only a small proportion of the patients were undergoing further examination or evaluation, which appeared to be leading to underdiagnosis of many abnormalities.

INTRODUCTION

Turner syndrome (TS), or Ullrich-Turner syndrome, is a genetic condition clinically characterized by findings such as short stature, hypogonadism, webbed neck, broad thorax and dysplastic nails.[1] It has an incidence of 1/2500 female births. Among the TS-associated chromosomal constitutions, the most common is X chromosome monosomy, which is present in about 45% of the cases. Another frequent abnormality is a long-arm isochromosome of the X chromosome (10-20% of the cases), which occurs due to loss of the short arm and duplication of the X chromosome long arm. Other constitutions consist of cases of mosaicism involving a 45,X lineage associated with one or more additional cell lines, a ring X chromosome and short-arm partial deletions of the X chromosome.[2,3]

Some clinical features are associated with *SHOX* gene haploinsufficiency, such as short stature and skeletal anomalies, which can be treated with growth hormone. Patients with TS usually also present hypergonadotropic hypogonadism due to ovarian failure and require hormone replacement therapy with sex steroids.[3]

It is noteworthy that in TS there may be great variability of clinical findings. While some girls may present the classic form with the main dysmorphia that has already been described, there may be others with few findings. Thus, girls and women with the syndrome may often go unnoticed and may present late diagnosis, which has important implications for case management and treatment. Growth deficit without a known cause is considered to be one of the most important TS findings. Thus, attention can be drawn to this diagnosis through performing karyotype evaluation.[4]

OBJECTIVE

The aim of this study was to investigate the clinical and karyotypic characteristics of patients diagnosed with TS at two reference services for clinical genetics in southern Brazil, in order to identify findings that might especially assist in making early diagnoses among these patients.

METHODS

This was a retrospective cross-sectional study. The sample consisted of 59 patients diagnosed with TS at two clinical genetics services, one at a university and the other at a mother-and-child hospital, both in Porto Alegre (RS), Brazil, from 1993 to 2019. Patients with records presenting incomplete clinical descriptions were excluded. The study was approved by the ethics committees of the university (protocol number 2.230.086, date: August 21, 2017) and hospital (protocol number 2.326.171, date: October 10, 2017). This paper was written in accordance with the guidelines for reporting observational epidemiological studies (STROBE).

For data collection, a review of the patients' records was performed and a standard protocol was filled out. The data collected consisted of age at diagnosis, reason for referral and specialty from which the referral was made, evaluation period, GTG-banding karyotype result obtained from a peripheral blood sample, dysmorphological physical examination with anthropometric measurements and description of the dysmorphia and secondary sexual characteristics, use of growth hormone and estrogen therapy, and presence of associated diseases and abnormalities that were identified through complementary imaging examinations and expert assessments.

The patients were classified according to their age at diagnosis, as follows: 0 to < 2 years; 2 to 13 years; and > 13 years.[5] For this, we considered the starting ages recommended by the Brazilian Ministry of Health for hormone treatments.[6]

The evaluation period was divided into two: patients attended between 1993 and the end of 2005; and those attended between the beginning of 2006 and 2019. The division into these two periods was done because public policies for supporting the diagnosis of these patients were created and medical records became computerized at the beginning of the second period.

Regarding karyotype results, the patients were divided into groups with and without the chromosomal constitution 45,X. The patients' heights and weights were evaluated using standard growth curves for females.[7] Microcephaly was reported in relation to age (absolute microcephaly) and height (relative or true microcephaly). To evaluate the body mass index (BMI), we used the virtual calculator of the Ministry of Health's Virtual Health Library (VHL) for primary healthcare and took the patient's age into consideration (child or adult). The patients were classified according to their BMI into groups with low weight, adequate (normal) weight, overweight or obesity (https://aps.bvs.br/apps/calculadoras/?page=7 and https://aps.bvs.br/apps/calculadoras/?page=6). Dysmorphia was divided according to the anatomical region affected.[8] Secondary sexual characteristics were described in accordance with Tanner's stages.[9] Malformations identified through complementary imaging examinations and expert assessments were classified according to the body system involved.

Data processing and analysis were performed using the Microsoft Excel 2013 software and the Statistical Package for the Social Sciences (SPSS) software for Windows, version 2.0 (IBM Corp, Armonk, New York, United States). In the analysis, we used the two-tailed Fisher exact test and the t test for mean comparisons. $P < 0.05$ was considered significant.

RESULTS

The sample consisted of 59 patients, ranging in age from 1 month to 34 years (mean of 15.9 years and median of 10.6 years). Regarding age, 16 patients (27.1%) were between 0 and < 2 years of age, 19 (32.2%) between 2 and 13 years and 24 (40.7%) > 13 years. It is noteworthy that a significant number of patients were already > 13 years old, i.e. they were beyond the age indicated for treatment with growth hormone.

Regarding referrals, the largest proportion of the patients had been referred from an endocrinology department (n = 25; 42.4%). Among the remainder, 11 (18.7%) came from pediatrics, 10 (16.9%) from gynecology, 5 (8.5%) from neonatology, 4 (6.8%) from genetics, 1 (1.7%) from gastroenterology and 1 (1.7%) from cardiology. Only a small proportion of the patients aged 0 to 13 years (n = 35) had been referred by pediatricians (25.7%). Thirty-two patients (54.2%) had already been referred with a suspicion of TS. The others had secondary amenorrhea (n = 7; 11.9%), multiple malformations (n = 4; 6.8%), primary amenorrhea (n = 3; 5.1%) and growth retardation (n = 3; 5.1%). It was noteworthy that one patient (1.7%) was referred due to suspicion of an inborn metabolism error.

The evaluation period ranged from 1993 to 2019: 45 patients (76.3%) were attended between 1993 and the end of 2005; and 14 (23.7%) between 2006 and 2019. Among the chromosomal constitutions observed, the most common was 45,X (n = 24; 40.7%). Others included 45,X/46,X,i(X)(q10) (n = 4; 6.8%); 45,X/46,X,r(X) (n = 4; 6.8%); 45,X/46,XX (n = 3; 5.1%); 46,X,del(Xq) (n = 3; 5.1%); and 46,X,del(Xp) (n = 2; 3.4%). The total number of cells analyzed ranged from 18 to 116 (average of 29.7). Structural changes to the X chromosome were observed in 27 cases (45.8%) and mosaicism in 26 (44.1%).

Short stature was presented by 85.7% of the patients. In 5.4% of them, short stature was the only clinical finding observed, while in 8.1% up to two types of dysmorphia were seen in association with this finding. Among the patients with absolute microcephaly

(27.7%), none of them had true microcephaly (**Figure 1**). Regarding weight, the BMI showed that 18.5% were overweight and 33.3% were obese. The anatomical regions most affected were the skin, hair and nails (83.4%), limbs (70.8%) and neck (53.1%). The types of dysmorphia most frequently described in the physical examination were hypoplastic/hyperconvex nails (61.2%), low posterior hairline (52.1%) and cubitus valgus (45.8%). It was possible for the patients to present more than one phenotypic characteristic. In comparing the presence of short stature between patients with and without the constitution 45,X, we did not find any significant difference (P = 0.5943). Patients with or without constitution 45,X also did not show any significant difference regarding the number of types of dysmorphia per patient (P = 0.143). We did not find any significant association between the presence of short stature and occurrence of overweight/obesity (P = 1.0000).

In comparing the anatomical regions affected in patients with and without the constitution 45,X, we did not observe any significant association in relation to any of them. However, there appeared to be a tendency towards involvement of the eyes (P = 0.0595) and neck dysmorphia (P = 0.0753) in occurrences of the constitution 45,X. In analyzing dysmorphia alone, we also did not find any association.

Regarding treatment, out of the 33 patients with an indication for use of growth hormone, only 6% were using this, and for estrogen, only 43%. Fifteen patients out of the total sample (25.9%) were

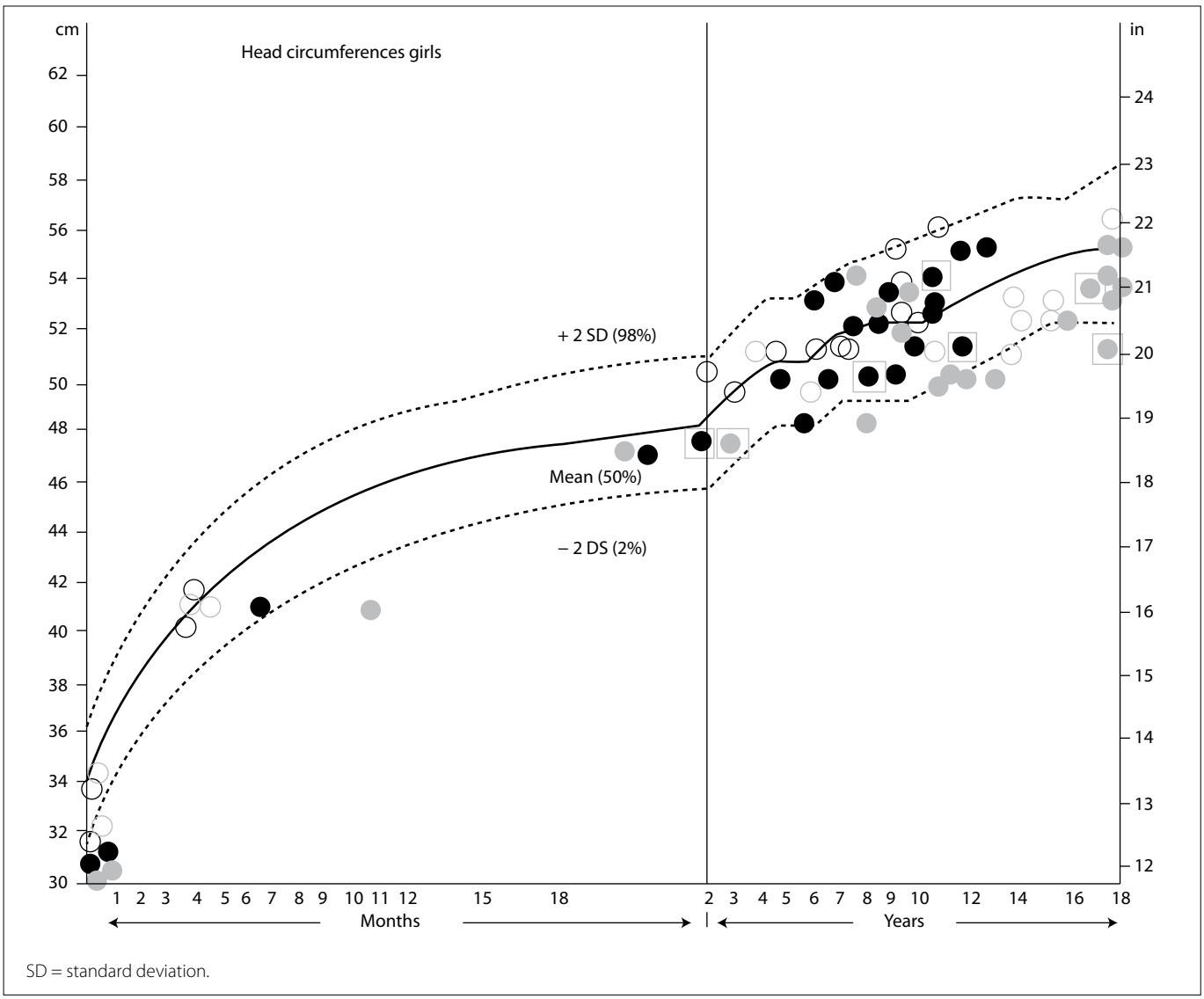

Figure 1. Head circumference according to age (gray circles) and height (black circles). The cases in which the circle is empty correspond to those with the constitution 45,X (the filled circles, which are the remaining cases, presented other chromosomal constitutions relating to Turner´s syndrome). The cases in which the circles are inside squares are of patients who used growth hormone.

prepubescent. Among the patients aged ≥ 12 years, most had pubic hair at Tanner P1 stage (55%). The others presented P2 (15%), P3 (5%), P4 (10%) and P5 (15%). Regarding breast development, a large number of patients (70%) were in stage M1. Among the others, 6% were in M2, 12% in M3, 3% in M4 and 6% in M5.

Malformations were identified through imaging examinations in 25% of the patients. These included neural tube defects (n = 1) and cardiac (n = 9), musculoskeletal (n = 2) and urinary tract abnormalities (n = 3). It should be noted that although examinations at the clinic showed that all the patients presented gonadal abnormalities, not all of them underwent confirmatory imaging tests. We did not find any relationship between the presence of these malformations and the chromosomal constitution 45,X (P = 1.0000).

It was noteworthy that only a small proportion of the patients from the sample underwent additional examinations or evaluations, including those who made part of the follow-up protocol for patients with TS: 6.8% underwent a head computed tomography scan, 3.4% electroencephalogram, 8.5% skull radiography, 6.8% spine radiography, 33.9% hand and wrist radiography, 22% echocardiography, 30.5% abdominal ultrasound, 1.6% abdominal and pelvic computed tomography scans and 25.4% pelvic and renal ultrasound. Among additional evaluations, a cardiac assessment was performed on only 13.6% of the patients, endocrinological on 10.2%, otorhinolaryngological on 10.2%, ophthalmic on 6.8%, nephrological on 5% and gynecological on 5%.

DISCUSSION

Rare diseases are characterized by a wide diversity of signs and symptoms and can be chronic, progressive, degenerative and even disabling, thus affecting the quality of life of families and individuals. They are defined in terms of their frequency: for example, affecting up to 1.3 people per 2,000 individuals, or 65 people per 100,000 individuals. It is noteworthy that more than 80% of them derive from genetic causes, and TS is one of these. In Brazil, there are guidelines for comprehensive care for rare-disease patients, which enables organization of access to diagnostic and therapeutic resources. Therefore, these patients with TS have a clinical protocol and therapeutic guidelines that establish the diagnostic criteria and the management and treatment algorithm.[10]

Regarding the age at diagnosis, we found in our study that the average was higher than that of a Brazilian study carried out in São Paulo, in which the average was 12 years, and also higher than in studies conducted in Europe.[11-13] We can highlight that 40.7% of our sample was diagnosed at more than 13 years of age, which is in agreement with another study conducted in southeastern Brazil, which found that this proportion was up to 70%.[14]

Thus, we found that the diagnosis of TS is being made late. This makes it impossible to perform important treatments, such as growth hormone treatment, which is recommended by the Brazilian Ministry of Health. Moreover, late diagnosis directly influences the evaluation and even the prognosis of the patients. In this situation, patients may not be properly investigated and the protocol and therapeutic guidelines may not be followed. Consequently, patients may present complications due to lack of investigation, resulting from abnormalities that, for example, involve internal organs. Other comorbidities may also be detected.

We therefore emphasize that it is important for pediatricians and other healthcare professionals who treat children to pay attention to the possibility that girls who have short stature of undefined cause, regardless of any presence of other associated types of dysmorphia, might have TS. Among the referrals, we noticed that only a small proportion of the patients were referred by pediatricians.[15]

Among the referred patients, more than half of them were suspected of having TS, and secondary amenorrhea was the main reason for referral. However, in other studies, short stature is described as the main reason.[16] This finding in our study corroborates to the late referral age and diagnosis of these patients. It perhaps suggests that findings such as short stature among girls may be undervalued, since non-physiological amenorrhea is a finding present only in late adolescence and most of adulthood (excluding the time after the menopause).

In the literature, karyotype 45,X is the main chromosomal constitution described among patients with TS (40-50%),[17] a finding similar to what was observed among our patients. Mosaicisms are found at variable frequencies, which are usually in the range of 9-56%.[18] This is concordant with the finding from our study (44.1%). We believe that this may be related to the average number of cells analyzed, which in our case was 29.7. The American College of Medical Genetics recommends that for all individuals with suspected TS, a 20-cell karyotype should be evaluated.[19]

Structural alterations can be found in up to 31% of the patients, such as the presence of a ring X chromosome and deletion of the long arm of the X chromosome.[20] In our study, this result was found in 45.8% of the patients, and 6% had chromosomal constitutions with mosaicism and presence of structural alterations. We highlight the presence of patients with deletion of the short and long arm of the X chromosome, in our sample. It has been established in the literature that it is mainly the patients with short-arm deletions of the X chromosome who present short stature and musculoskeletal alterations.[21]

In addition, it is important to highlight the existence of patients with TS presenting mosaicism involving a chromosomal lineage with a Y chromosome. Although we did not have patients with this chromosomal constitution in our sample, it has been described in up to 10% of patients with TS in studies with large samples. These patients have peculiarities regarding their management, since the presence of the lineage with a Y chromosome leads to a

risk of gonadal malignancy. Therefore, it is very important to identify these patients, because this risk gives rise to an indication for performing prophylactic gonadectomy.[22]

Short stature was present in 85.7% of our sample, but we found that there were no differences between patients with and without chromosomal constitution 45,X, in relation to this. Furthermore, occurrence of overweight/obesity was found to be unrelated to presence or absence of this chromosomal constitution, thus corroborating the results from a study conducted in Egypt.[23] In our study, 13.5% of the patients had up to two types of dysmorphia, including short stature, and so it is important to highlight that this is the most characteristic finding among TS patients. In our study, only 6% of the patients had made correct use of growth hormone, which was a much lower proportion than in a study conducted in Albania,[24] in which correct use was found among 54.3% of the patients. This shows the impact that late diagnosis has on treatment for patients with TS. Growth hormone treatment for TS patients has been shown to be effective and is preferably indicated between the ages of 4-6 years, and treatment needs to be started before the ages of 12-13 years.[25]

We also did not find patients with true microcephaly. However, it is important to note that almost one third of our patients had smaller-than-expected head circumference. Thus, if age is the only factor taken into consideration (absolute microcephaly), a wrong diagnosis may often be made. Microcephaly is uncommon in TS, and only a few cases with this finding have been reported in the literature.[26]

Regarding body weight, our patients' BMI was higher than that found in a national study in Ukraine,[27] in which 13.8% of the patients were found to be overweight and 6.9%, obese. In our study, 18.5% and 33.3% of the patients were overweight and obese, respectively. This points out the importance of having endocrinological and nutritional follow-up for these patients, since the frequency of overweight and obesity is higher in TS patients than in the general population.[28] In addition, it is noteworthy that specific growth charts, including charts for height and for weight, already exist for individuals with TS. These growth charts can be used to monitor patients after diagnosis.[29]

Among the phenotypic manifestations, low posterior hairline, cubitus valgus and hyperconvex nails were the ones most frequently observed in our sample. These observations were in line with what had previously been described in studies in both Mexico and Brazil.[30,31] The tendency in our study for there to be higher frequency of dysmorphia involving the eye and neck regions was noteworthy. However, we did not find any association in comparing patients with or without the chromosomal constitution 45,X, in relation to the anatomical region affected and dysmorphia. In a study by Bispo et al.[31] in Brazil, a tendency that patients with X-chromosome monosomy would have more severe phenotypes was found. However, the genotype-phenotype correlation of the dysmorphia described, between patients with and without chromosomal constitution 45,X, remains at an initial stage, which corroborates our findings.

In our study, it was also noteworthy that among the patients aged 12 years and over, 55% were in Tanner P1 stage in relation to pubic hair and 70% in M1 in relation to breast development. This matches another finding from our sample: only 43% of the patients underwent estrogen therapy. This result is of concern, as non-treatment has other important implications, including development of osteoporosis.[32] Thus, these patients are either not being properly managed or are not adhering to the proposed treatment.

TS is associated with several abnormalities that affect the organ systems. Cardiovascular abnormalities are reported in 50% of adult and 30% of pediatric patients. In our study, they were most frequently found through imaging examinations that the patients underwent, which was consistent with previous reports.[33,34] However, only 22% of the patients underwent an echocardiographic evaluation, which contrasts sharply with the established recommendation that all patients with TS should undergo this evaluation at the time of diagnosis, given that cardiovascular abnormalities are considered to be one of the main causes of death among them.[35]

Complementary examinations such as hand and wrist radiography and renal ultrasound were also only infrequently done among our sample (33.9% and 25.4%, respectively). It should be noted that these tests are also recommended for patients with TS, and, for example, hand and wrist radiography is indicated by the Ministry of Health to be done within the follow-up of patients with TS, i.e. there is a recommendation that the examination should be performed periodically.

In addition, renal anomalies may be silent or asymptomatic. These may have the potential to lead to renal failure and even a need for transplantation.[36]

Moreover, we found that only 25.4% of the patients in our sample underwent pelvic ultrasound examinations. For this reason, in a large number of cases, internal genitalia and gonads could not be adequately assessed. This is important, because some patients with TS may have significant gonadal abnormalities. These may even be cancerous, as previously mentioned in relation to patients who have an associated Y chromosome lineage.[22] Therefore, this is one more reason to emphasize the importance of carrying out complementary assessments among patients with TS.

CONCLUSION

We conclude from the data on our sample that the largest proportion of our TS patients had a chromosomal constitution 45,X, which is in agreement with the literature, and that they are being diagnosed late, often in adulthood. As discussed, this has important implications regarding absence of growth hormone therapy

and estrogen use, which can lead to severe complications, such as osteoporosis. In addition, there was poor use of screening and control examinations such as echocardiography and abdominal ultrasound among these patients. This can lead to underdiagnosing of abnormalities involving internal organs, such as congenital heart diseases or renal malformations. There may be important consequences from this, especially with regard to these patients' quality of life and even their survival. Therefore, awareness of the diagnosis and findings commonly observed in TS may provide early identification and better management of the clinical conditions associated with this syndrome.

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Impact of lifestyle on health-related quality of life among young university students: a cross-sectional study

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ABSTRACT

BACKGROUND: Lifestyle is strongly involved in the pathogenesis and progression of noncommunicable diseases, and has a great impact on quality of life. The goal of the present study was to analyze the lifestyle and body composition (BC) of young university students during the pandemic, and their relationship with health-related quality of life (HrQoL).

DESIGN AND SETTING: Observational cross-sectional study conducted in the Universidad Europea de Madrid, Spain.

METHODS: A total sample of 56 healthy university students was recruited. Activity, sitting time, adherence to Mediterranean diet and BC were measured.

RESULTS: Regarding BC, only 5% and 10.7% of the subjects had health risk values for waist circumference and waist-to-height ratio, respectively. The mean daily sitting-time was 8.26 hours, while 19.64% of the subjects spent ≥ 10 hours per day sitting. 92.86% of the subjects complied with the World Health Organization 2020 physical activity recommendations. The mean PREDIMED score was 7.41, while 51.8% of the subjects had low adherence to the Mediterranean diet. Regarding HrQoL, 22 subjects (39.2%) and 26 subjects (46.4%) were in the lowest quintile of physical component summary and mental component summary, respectively, according to the reference values for their age range. There was a negative correlation between physical function and sitting time (r = -0.38).

CONCLUSIONS: There were high levels of sedentary behavior and low HrQoL values, with a negative moderate correlation between these variables. The findings from the present study especially highlight the importance of implementing public health programs targeting reduction of sitting time among university students.

INTRODUCTION

Lifestyle, through epigenetic mechanisms, is strongly involved in the pathogenesis and progression of noncommunicable diseases (NCDs),[1] and has a great impact on quality of life.[2] In this order, physical inactivity and obesity are, respectively, the two lifestyle risk factors most associated with the development of NCDs.[3] Physical inactivity is the fourth largest risk factor for mortality worldwide,[3] and it is associated with the comorbidities of overweight and obesity. People with these two conditions account for 27% of type 2 diabetes mellitus (T2DM) cases worldwide and 30% of ischemic heart disease cases.[4] Consequently, the World Health Organization (WHO) has instituted the target of reducing the prevalence of physical inactivity by 15% worldwide by 2030.[5]

Every extra hour of daily sedentary behavior has a negative impact on health.[6] Compared with subjects who sit for 6 hours a day, those who sit for 8 hours have a 14% higher cardiovascular risk and those who sit for 10 hours a day, 29%.[7] There is strong evidence that individuals who maintain sedentary behavior over time have greater all-cause mortality, as well as several negative health-related outcomes. This is more pronounced among physically inactive people, given that physical activity attenuates mortality risk. Higher physical activity levels among highly sedentary individuals are thus required.[8]

The possible pathways to negative health-related outcomes facilitated by a sedentary lifestyle include promotion of increased oxidative stress. This is a strong precursor of endothelial dysfunction and gives rise to greater release of free fatty acids in the bloodstream, thus favoring

development of cardiovascular diseases (CVDs).[9] In addition, a sedentary lifestyle causes insulin resistance[10] and promotes accumulation of visceral fat.[11,12]

Previous studies have reported that each additional hour of sedentary time is associated with greater gain in body mass index (BMI) and waist circumference (WC).[8] A sedentary lifestyle can lead to development of obesity, which is the second highest risk factor for lifestyle-related premature death, after physical inactivity.[13] Moreover, overweight and obesity cause insulin resistance[14,15,16] and promoting deposition of ectopic lipids or visceral fat in different organs.[17] This interferes with the normal function of organs, which thus increases the risk of many NCDs, especially CVD and T2DM.[18] Physical activity is essential for achieving energy balance and weight control, thereby enabling maintenance of healthier body composition (BC) with an acceptable ratio of fat and muscle.[19] It also protects against numerous NCDs,[20,21] because it has a systemic dose-dependent anti-inflammatory effect.[6,22,23]

Regarding nutritional habits, adherence to the Mediterranean diet has been shown to have significant inverse associations with all-cause mortality[24] and with the prevalence of CVD and T2DM, which are related to the anti-inflammatory properties of this diet.[25,26] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered in Wuhan, Hubei province, China, in a pneumonia epidemic in January 2020.[27] On January 30, 2020, it was declared by WHO to be a global health emergency[28] and, since then, the virus has spread throughout the world, causing more than a million deaths.

The coronavirus disease 2019 (COVID-19) pandemic has affected and overwhelmed healthcare systems in unprecedented ways. Consequently, pending mass and effective vaccination, social distancing is the main preventive measure against SARS-CoV-2. Social distancing implies massive reorganization of society and lifestyles.[29] During the period of confinement experienced between March and May 2020 in many countries, the number of people who practiced physical activity decreased by approximately 30%[30] and the number of hours spent sitting increased by 28.6%.[31] However, adherence to the Mediterranean diet was not significantly affected.[32]

NCDs generally develop in the elderly population, but lifestyle behaviors become established during young adulthood, when individuals do not perceive that an unhealthy lifestyle implies a higher health risk.

There is great variability in the dietary patterns of university students, in part because there are many different questionnaires assessing the adherence to the Mediterranean diet.[33] Generally, university students have a low adherence to the Mediterranean diet.[34,35] Regarding physical activity levels, university students normally are highly active, but also report high amounts of sedentary behavior.[36,37] Students with higher levels of physical activity usually report greater levels of health-related quality of life (HrQoL), especially regarding the mental component summary (MCS).[38-40]

Further research on young adulthood is needed in order to ascertain the impact of lifestyle on HrQoL in young populations.

OBJECTIVE

We aimed to analyze the lifestyle and BC of young university students during the pandemic, and their relationship with HrQoL. We hypothesized that physical activity levels, sedentary behavior, unhealthy BC and poor adherence to the Mediterranean diet would have moderate negative associations with HrQoL.

METHODS

Design

An observational cross-sectional study was developed, following the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines, between October and November 2020 at Universidad Europea de Madrid, in Spain.

Settings and participants

A total sample of 56 healthy young students was recruited at Universidad Europea de Madrid: age 23.5 ± 3.4 years; height 175 ± 8.1 cm; and body mass 68.3 ± 10.2 kg. The participants were recruited via e-mail between October and November 2020. The potential participants were reassured that nonparticipation would not have any consequences. A code was assigned to participants, prior to statistical analysis, thus guaranteeing the confidentiality of their data.

The inclusion criteria were that the participant needed to be a student at the Universidad Europea de Madrid[34] and be between 18 and 34 years of age.[41] The exclusion criteria were situations of: 1) having a chronic disease;[42] 2) undergoing pharmacological therapy;[42] or 3) having any condition that led to development of pain or any disturbances during physical exercise.[42]

Ethical considerations

The current study was approved by the Research Ethics Committee of Universidad Europea de Madrid, under the protocol number CIPI/20/16, on September 30, 2020, and also respected the Helsinki guidelines at all times. All the participants read and signed an informed consent statement before becoming part of this investigation.

Measurements

- *Physical activity level and sitting time* were measured using the Global Physical Activity Questionnaire (WHO, Geneva, Switzerland) (GPAQ), a validated tool that was developed by WHO for estimating physical activity levels (MET-minutes/week) in diverse countries around the world. This questionnaire makes it possible to see whether the subjects are complying with the 2020

WHO physical exercise recommendations, and whether they are spending large amounts of time seated. The amount of sitting time associated with greater all-cause mortality among adults varies from 6 to 8 hours per day, so we established > 420 minutes/day as the health risk threshold for this study.[4,8,43-45]

- *Adherence to the Mediterranean diet* was measured using the PREDIMED questionnaire (Schröder et al., Barcelona, Spain).[43] High adherence is considered to be shown by scores ≥ 10 points; medium adherence, 8-9 points; and low adherence ≤ 7 points. Having high adherence to the Mediterranean diet brings strong protection against CVD.[44]
- *HrQoL* was measured using the short-form-36 (SF-36) health survey, version 2 (Alonso et al., Barcelona, Spain),[45] which gives scores from 0 (worst health status) to 100 (best health status) in eight sections: physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning(SF), role emotional (RE) and mental health (MH). The eight sections are regrouped into two main components: physical component summary (PCS) and mental component summary.[41] The mean values for PCS and MCS are: 55.02 and 51.47 for men aged 18-24 years; 54.96 and 51.53 for men aged 25-34 years; 54.58 and 48.92 for women aged 18-24 years; and 53.87 and 49.62 for women aged 25-34 years.[41]
- *Body composition*: height, weight and WC were measured using a stadiometer (in cm; Ano Sayol SL height rod, Barcelona, Spain), a scale (in kg; Asimed T2 scale, Barcelona, Spain) and a tape (in cm), respectively. BMI and the waist-to-height ratio (WtHr) were then calculated. The values associated with an exponential risk of developing CVD and T2DM are WC ≥ 102 cm in men and ≥ 88 cm in women,[46] and WtHr ≥ 0.5 in men and women.[47] WC and WtHr are highly correlated with visceral adipose tissue, which is the most clinically relevant adiposity variable, because of its association with the increased risk of NCDs. In contrast, BMI has a poor correlation with visceral adipose tissue.[47,48] However, individuals with high BMI are at greater risk of developing high visceral adipose tissue levels, compared with individuals with healthy BMI.[49]

Statistical analysis

Frequencies (sample size and proportion of samples) were assessed for categorical variables (adherence to Mediterranean diet and sitting time). The Kolmogorov-Smirnov test was used to assess the normality of distribution.[50] A descriptive analysis was developed for all the subjects using the mean ± standard deviation (SD) to describe the parametric data and the median ± interquartile range (IQR) for nonparametric data. The coefficient of variation (CV%) was calculated for all continuous variables. In addition, an independent-sample t test (in situations of normal distribution) or the Mann-Whitney U test (in situations of non-normal distribution) was applied to determine differences between high/low adherence to the Mediterranean diet and the remainder of the continuous variables (HrQoL, physical activity and BC).

The Spearman correlation test with 95% coefficient intervals was carried out to analyze the relationships between continuous variables. The magnitudes of correlations between continuous variables were qualitatively interpreted using the following criteria: trivial (r ≤ 0.1), small (r = 0.1-0.3), moderate (r = 0.3-0.5), large (r = 0.5-0.7), very large (r = 0.7-0.9) and almost perfect (r ≥ 0.9).[51] Otherwise, correlation was interpreted as the observed magnitude. The statistical significance was set at an alpha level of < 0.05. All analyses were conducted using IBM SPSS for Windows, version 23 (IBM Corporation, Armonk, New York, United States).

RESULTS

Sociodemographic data of the sample

A total of 56 subjects aged 23.5 ± 3.4 years were analyzed. Their mean BMI was 22.15 ± 2.28 kg/m^2. Regarding WC and WtHr, only three (5%) and six subjects (10.7%), respectively, had health-risk values.

The adherence to Mediterranean diet showed equality of distribution. Twenty-seven subjects (48.2%) showed medium-high adherence while the remaining 29 subjects (51.8%) showed low adherence. Analysis on sitting time revealed that 25 subjects were at risk (44.6%) while the remainder of the subjects were at low risk (n = 31; 55.4%). Regarding HrQoL, 22 subjects (39.2%) and 26 subjects (46.4%) were in the lowest quintiles of PCS and MCS, respectively, according to the reference values for their age range.

The descriptive analysis, Kolmogorov-Smirnov normality test and CV% for all the continuous variables is presented in **Table 1**.

Correlations between body composition, lifestyle and HrQoL

The Spearman correlation test with 95% coefficient intervals was used to analyze possible correlations between continuous variables (Table 2). Three HrQoL variables, namely VT (P = 0.013), RE (P = 0.018) and MCS (P = 0.015), showed moderate correlations (range for r = 0.31-0.33) with WC. In turn, SF was moderately correlated (r = 0.27) with sitting time and there was a negative correlation between PF and sitting time (r = -0.38; moderate magnitude). In addition, trivial-small correlations (range for r = -0.15 to 0.23) were found between HrQoL variables and the remainder of the physical activity and BC variables.

Between physical activity variables and the remainder of the continuous variables (BC and HrQoL), trivial-small correlations (range for r = -0.17 to 0.24) were found. On the other hand, large-very large correlations (range for r = 0.56-0.82) were found between BC variables (**Table 2**).

Table 1. Descriptive analysis on all continuous variables

	Variable (n = 56)	Value	CV%	P-value of Kolmogorov-Smirnov test
Body composition	Waist circumference	76.00 ± 9.50 (65.0-102.0)†	10	0.003
	Body mass index	22.15 ± 2.28 (18.6-26.9)*	10	0.200
	Waist-to-height ratio	0.43 ± 0.04 (0.35-0.59)†	9	0.001
Physical activity	Physical activity level	1880.37 ± 738.90 (240.0-3440.0)*	39	0.200
	Sedentary time	420.00 ± 127.50 (360.0-920.0)†	26	0.000
Health-related quality of life	Physical functioning	100.00 ± 5.00 (50.0-100.0)†	8	0.000
	Role physical	100.00 ± 43.80 (0.0-100.0)†	44	0.000
	Bodily pain	84.00 ± 22.00 (20.0-100.0)†	25	0.000
	General health	72.58 ± 16.56 (30.0-97.0)*	23	0.028
	Vitality	66.07 ± 17.12 (20.0-100.0)*	26	0.070
	Social functioning	87.50 ± 25.00 (37.5-100.0)†	17	0.000
	Role emotional	83.50 ± 91.80 (0.0-100.0)†	71	0.000
	Mental health	80.00 ± 20.00 (20.0-100.0)†	19	0.003
	Physical component summary	53.16 ± 7.15 (35.4-67.4)*	13	0.200
	Mental component summary	48.75 ± 18.60 (16.8-62.5)†	25	0.004

Values shown are *mean ± standard deviation (SD) (minimum-maximum) or †median ± interquartile range (IQR) (minimum-maximum). CV% = coefficient of variation.

Table 2. Relationship (Spearman correlation test) between continuous variables with 95% coefficient intervals

Variables			Body composition			Physical activity	
			Waist circumference	Body mass index	Waist-to-height ratio	Physical activity level	Sitting time
Body composition	Waist circumference	r	-	**0.62****	**0.82****	0.19	-0.07
		P [95% CI]	-	0.000 [0.427, 0.759]	0.001 [0.723, 0.896]	0.146 [-0.070, 0.437]	0.968 [-0.328, 0.196]
	Body mass index	r	**0.62****	-	**0.56****	0.22	-0.12
		P [95% CI]	0.000 [0.427, 0.759]	-	0.000 [0.429, 0.761]	0.093 [-0.039, 0.462]	0.368 [-0.373, 0.145]
	Waist-to-height ratio	r	**0.82****	**0.56****	-	0.10	-0.10
		P [95% CI]	0.000 [0.723, 0.896]	0.000 [0.429, 0.761]	-	0.441 [-0.162, 0.358]	0.449 [-0.356, 0.164]
Physical activity	Physical activity level	r	0.19	0.22	0.10	-	-0.23
		P [95% CI]	0.146 [-0.070, 0.437]	0.093 [-0.039, 0.462]	0.441 [-0.162, 0.358]	-	0.078 [-0.471, 0.027]
	Sitting time	r	-0.07	-0.12	-0.10	-0.23	-
		P [95% CI]	0.968 [-0.328, 0.196]	0.368 [-0.373, 0.145]	0.449 [-0.356, 0.164]	0.078 [-0.471, 0.027]	-
Health-related quality of life	Physical functioning	r	0.16	0.18	0.18	0.06	**-0.38***
		P [95% CI]	0.217 [-0.100, 0.412]	0.165 [-0.079, 0.430]	0.164 [-0.078, 0.430]	0.651 [-0.205, 0.319]	0.003 [-0.588, 0.136]
	Role physical	r	-0.07	-0.11	-0.10	-0.05	0.12
		P [95% CI]	0.594 [-0.229, 0.194]	0.398 [-0.367, 0.152]	0.453 [-0.356, 0.165]	0.684 [-0.314, 0.210]	0.353 [-0.141, 0.377]
	Bodily pain	r	0.06	-0.01	0.04	-0.15	0.18
		P [95% CI]	0.623 [-0.199, 0.324]	0.891 [-0.280, 0.245]	0.725 [-0.218, 0.307]	0.266 [-0.398, 0.116]	0.185 [-0.087, 0.423]
	General health	r	-0.05	-0.07	0.04	0.21	-0.07
		P [95% CI]	0.715 [-0.309, 0.216]	0.600 [-0.328, 0.195]	0.752 [-0.222, 0.303]	0.116 [-0.054, 0.450]	0.573 [-0.333, 0.190]
	Vitality	r	**0.33***	0.16	0.22	0.16	0.04
		P [95% CI]	0.013 [0.073, 0.545]	0.224 [-0.102, 0.410]	0.101 [-0.044, 0.458]	0.218 [-0.100, 0.412]	0.755 [-0.302, 0.223]
	Social functioning	r	0.22	**0.27***	0.17	0.15	0.04
		P [95% CI]	0.096 [-0.041, 0.460]	0.038 [-0.016, 0.504]	0.205 [-0.095, 0.416	0.245 [-0.110, 0.404]	0.733 [-0.219, 0.306]
	Role emotional	r	**0.31***	0.11	0.21	-0.03	0.14
		P [95% CI]	0.018 [0.073, 0.545]	0.752 [-0.156, 0.364]	0.105 [-0.046, 0.456]	0.781 [-0.298, 0.227]	0.273 [-0.119, 0.396]
	Mental health	r	0.12	0.04	0.13	-0.09	0.06
		P [95% CI]	0.375 [-0.147, 0.372]	0.752 [-0.222, 0.303]	0.314 [-0.130, 0.386]	0.500 [-0.346, 0.175]	0.622 [-0.199, 0.324]
	Physical component summary	r	-0.12	-0.09	-0.07	0.06	-0.00
		P [95% CI]	0.368 [-0.374, 0.145]	0.469 [-0.352, 0.169]	0.601 [-0.328, 0.195]	0.625 [-0.200, 0.324]	0.979 [-0.266, 0.259]
	Mental component summary	r	0.32*	0.15	0.21	0.04	0.10
		P [95% CI]	0.015 [0.068, 0.541]	0.257 [-0.113, 0.401]	0.110 [-0.050, 0.453]	0.747 [-0.221, 0.303]	0.443 [-0.163, 0.358]

Statistical significance difference was set at an alpha level of < 0.05 (P < 0.05*, P < 0.001**). CI = confidence interval.

Nonsignificant differences in BC, physical activity and HrQoL were found between medium-high and low adherence to the Mediterranean diet (**Table 3**). The comparisons of BC, physical activity and HrQoL between risk and non-risk sitting times are displayed in **Table 4**.

DISCUSSION

The subjects analyzed in this study had healthy BC values, as only 5% and 10.7% of the subjects had health-risk values for WC and WtHr, respectively. Regarding lifestyle, 44.6% of the subjects spent more than seven hours a day sitting down, which is a predisposing factor for development of cardiometabolic diseases over the long term.[24,52] Individuals who maintain sedentary behavior over time have the highest all-cause mortality.[8] Levels of physical activity were high (1880.37 ± 738.90 MET-min/week), such that 92.86% of the subjects were complying with the WHO 2020 physical activity recommendations.[53] This was similar to the results reported in other studies with a student population.[36,37]

Physical activity attenuates mortality risk, and higher physical activity levels are required among highly sedentary individuals.[8]

Table 3. Differences in body composition, physical activity and health-related quality of life between medium-high and low adherence to the Mediterranean diet

	Variable	Medium-high adherence group (n = 27)	Low adherence group (n = 29)	P value
Body composition	Waist circumference (cm)	76.00 ± 8.00 (67.0-92.0)†	76.00 ± 12.50 (65.0-102.0)†	0.967‡
	Body mass index (%)	22.07 ± 2.17 (18.6-26.8)*	22.22 ± 2.41 (19.0-26.9)*	0.820
	Waist-to-height ratio	0.44 ± 0.04 (0.3-0.5)†	0.43 ± 0.05 (0.3-0.5)†	0.373‡
Physical activity	Physical activity level (MET-min/week)	2011.85 ± 707.89 (800.0-3360.0)*	1757.93 ± 756.33 (240.0-3440.0)*	0.201
	Sitting time (minutes/week)	420.00 ± 60.00 (360.0-920.0)†	480.00 ± 180.00 (420.0-900.0)†	0.195‡
Health-related quality of life	Physical functioning	100.00 ± 0.00 (85.0-100.0)†	100.00 ± 5.00 (50.0-100.0)†	0.106‡
	Role physical	100.00 ± 25.00 (25.0-100.0)†	100.00 ± 5.00 (50.0-100.0)†	0.312‡
	Bodily pain	84.00 ± 22.00 (20.0-100.0)†	84.00 ± 22.00 (32.0-100.0)†	0.839‡
	General health	73.88 ± 17.42 (30.0-97.0)*	71.37 ± 15.94 (42.0-97.0)*	0.576
	Vitality	66.48 ± 21.29 (20.0-100.0)*	65.69 ± 12.44 (45.0-85.0)*	0.865
	Social functioning	87.50 ± 25.80 (37.5-100.0)†	87.50 ± 18.80 (62.5-100.0)†	0.473‡
	Role emotional	100.00 ± 100.00 (00.0-100.0)†	66.70 ± 83.50 (00.0-100.0)†	0.677‡
	Mental health	80.00 ± 24.00 (20.0-96.0)†	80.00 ± 16.00 (56.0-100.0)†	0.615‡
	Physical component summary	54.09 ± 5.69 (40.9-65.4)*	52.29 ± 8.30 (35.4-67.4)*	0.352
	Mental component summary	44.60 ± 20.80 (16.8-60.9)†	45.37 ± 16.10 (24.3-62.5)†	0.883‡

Comparisons are between high (n = 27) and low (n = 29) adherence to the Mediterranean diet. *Mean ± standard deviation (SD) (minimum–maximum) or †Median ± interquartile range (IR) (minimum-maximum). Statistical significance was set at an alpha level of < 0.05 (*). ‡Mann-Whitney U test was used.

Table 4. Differences in body composition, physical activity and health-related quality of life between risk and non-risk sitting time

	Variable	Risk (n = 25)	Non-risk (n = 31)	P-value
Body composition	Waist circumference	75.00 ± 10.00 (66.0-92.0)†	77.00 ± 10.00 (65.0-102.0)†	0.967‡
	Body mass index	22.82 ± 2.10 (19.0-26.9)*	22.41 ± 2.41 (18.6-26.8)*	0.337
	Waist-to-height ratio	0.43 ± 0.05 (0.3-0.5)†	0.44 ± 0.05 (0.3-0.5)†	0.373‡
Physical activity	Physical activity level	1689.60 ± 807.75 (240.0-3440.0)*	2034.19 ± 649.22 (960.0-3360.0)*	0.082
	Sitting time	560.00 ± 135.00 (480.0-920.0)†	420.00 ± 0.00 (360.0-420.0)†	0.195‡
Health-related quality of life	Physical functioning	95.00 ± 5.00 (85.0-100.0)†	100.00 ± 0.00 (50.0-100.0)†	0.106‡
	Role physical	100.00 ± 25.00 (00.0-100.0)†	100.00 ± 75.00 (00.0-100.0)†	0.312‡
	Bodily pain	84.00 ± 17.00 (51.0-100.0)†	74.00 ± 23.00 (20.0-100.0)†	0.839‡
	General health	71.16 ± 17.48 (37.0-97.0)*	73.74 ± 15.98 (30.0-97.0)*	0.567
	Vitality	66.00 ± 15.87 (40.0-100.0)*	66.12 ± 18.33 (20.0-90.0)*	0.978
	Social functioning	87.50 ± 25.00 (62.5-100.0)†	87.50 ± 25.80 (37.5-100.0)†	0.473‡
	Role emotional	100.00 ± 83.40 (00.0-100.0)†	66.70 ± 100.00 (00.0-100.0)†	0.677‡
	Mental health	80.00 ± 20.00 (60.0-96.0)†	80.00 ± 24.00 (20.0-100.0)†	0.615‡
	Physical component summary	53.35 ± 6.84 (37.6-67.4)*	53.00 ± 7.51 (35.4-66.1)*	0.856
	Mental component summary	49.00 ± 16.70 (25.4-58.4)†	43.40 ± 19.80 (16.8-62.5)†	0.883‡

Comparisons are between risk (n = 25) and non-risk (n = 31) sitting time. *Mean ± standard deviation (SD) (minimum-maximum) or †median ± interquartile range (IQR) (minimum-maximum). Statistical significance was set at an alpha level of < 0.05 (*). ‡Mann-Whitney U test was used.

Each additional hour of sedentary time is associated with greater gain in BMI and WC.[8] However, in this study, we found only trivial-small correlations for physical activity and sitting time in relation to BC. The mean daily sitting time was 8.26 hours, while 19.64% of the subjects spent ≥ 10 hours per day sitting.[8] This is of great importance because if these habits are maintained over time, the risk of developing NCDs increases,[3] given that sedentary behavior is associated with loss of metabolic flexibility,[3] higher oxidative stress, insulin resistance, inflammation and DNA damage.[54,55] Self-reported estimates from other studies have indicated that university students spend an average of 7.29 hours per day sitting, which is similar to our results. In contrast, data from accelerometer-based studies have suggested that university students engage in 9.82 hours of sedentary behavior per day. Chastin et al. suggested that self-reports underestimate sedentary behavior, compared with accelerometer-based methods,[37] so the subjects of our study may have been spending more time sitting that we thought.

Concerning nutritional habits, half of the subjects analyzed (51.8%) had low adherence to the Mediterranean diet. The mean PREDIMED score was 7.41, which denotes acceptable adherence to the Mediterranean diet, in line with data from the Spanish population that was previously reported.[26] However, other studies on student populations reported lower adherence to the Mediterranean diet.[34,35] Considering these data, it is necessary to seek strategies to reduce sitting time in the young population, in addition to promoting the Mediterranean diet, since the lifestyle habits developed in youth can affect health in old age. It was striking that 39.2% and 46.4% of the subjects were in the lowest quintiles of PCS and MCS, respectively, according to the reference values for their age range.[41]

We did not find any study reporting on HrQoL using the SF-36 questionnaire among students that we could compare with our results. However, several authors have argued that the negative impact on QoL among sedentary individuals and university students was related to foot health disorders.[56,57] The low levels of HrQoL reported in the present study are probably related to the massive reorganization of our society and our lifestyle due to the COVID-19 pandemic.[29]

Regarding the relationship between BC and lifestyle variables and HrQoL, WC showed moderate correlations with VT, RE and MCS. This is not of great clinical relevance because most of the subjects had healthy values for WC. In turn, sitting time was negatively correlated with PF, which highlights the negative impact of sedentary behavior on health.[7] However, taking > 7 hours of sitting time per day as a reference value for health risk, no significant correlations were found between sitting time and the other variables. Adherence to the Mediterranean diet did not show any significant correlation with HrQoL or BC, which is relevant because this young population may not see any motivation to engage in changes in this regard. Moreover, large correlations exist between WC and BMI, and very large correlations exist between WC and WtHr. It is known that WC is more associated with cardiometabolic diseases risk factors, as well as WtHr,[58] compared with BMI. In fact, in other populations, WC is a better indicator of poor physical HrQoL than BMI.[59]

The aim of this study was to characterize the lifestyle of young students in a pandemic period. We mainly found that these subjects were complying with the 2020 WHO physical exercise recommendations[53] and had healthy BC. However, half of them had a poor dietary pattern and spent too many hours sitting. According to several studies, during the current COVID-19 pandemic period, physical activity levels have decreased by 30%[30] and daily sitting time has increased (28.6%),[31] while adherence to the Mediterranean diet has not been affected.[32] This indicates that there needs to be a focus on improving these two aspects of the lifestyle of the young population. We also wanted to analyze HrQoL and its correlations with lifestyle. Sitting time was the variable that most negatively affected HrQoL, and it was striking that 39.2% and 46.4% of the subjects were in the lowest quintiles of PCS and MCS, respectively, according to the reference values for their age range. These results might be related to the difficult times of uncertainty and restriction of mobility that we have been going through, in the context of the COVID-19 pandemic.

Study limitations and future lines

Our sample was obtained from just one particular university in one particular city. It would be very useful to obtain information from more universities in different locations. In addition, studying the implementation of a strengthening program or physical activity in relation to the Mediterranean diet, both among healthy individuals and among individuals presenting any pathological condition (e.g. COVID-19, musculoskeletal disorders or metabolic diseases) would be very interesting. Lastly, no comparative data from before the pandemic were obtained and, thus, the PCS and MCS cannot be attributed to the COVID-19 pandemic.

CONCLUSION

In this young student population, the results showed that the subjects generally had healthy BC, high physical activity levels, acceptable adherence to the Mediterranean diet, high levels of sedentary behavior and very low levels of HrQoL. Regarding the relationship between lifestyle and HrQoL, only trivial-small correlations were found. Regarding lifestyle, the findings of the present study especially highlight the importance of implementation of public health programs targeting reductions in sitting time among university students.

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Performance of the CKD-EPI and MDRD equations for estimating glomerular filtration rate: a systematic review of Latin American studies

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ABSTRACT

BACKGROUND: The most-used equations for estimating the glomerular filtration rate (GFR) are the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations. However, it is unclear which of these shows better performance in Latin America.

OBJECTIVE: To assess the performance of two equations for estimated GFR (eGFR) in Latin American countries.

DESIGN AND SETTING: Systematic review and meta-analysis in Latin American countries.

METHODS: We searched in three databases to identify studies that reported eGFR using both equations and compared them with measured GFR (mGFR) using exogenous filtration markers, among adults in Latin American countries. We performed meta-analyses on P30, bias (using mean difference [MD] and 95% confidence intervals [95% CI]), sensitivity and specificity; and evaluated the certainty of evidence using the GRADE methodology.

RESULTS: We included 12 papers, and meta-analyzed six (five from Brazil and one from Mexico). Meta-analyses that compared CKD-EPI using creatinine measured with calibration traceable to isotope dilution mass spectrometry (CKD-EPI-Cr IDMS) and using MDRD-4 IDMS did not show differences in bias (MD: 0.55 ml/min/1.73m^2; 95% CI: -3.34 to 4.43), P30 (MD: 4%; 95% CI: -2% to 11%), sensitivity (76% and 75%) and specificity (91% and 89%), with very low certainty of evidence for bias and P30, and low certainty of evidence for sensitivity and specificity.

CONCLUSION: We found that the performances of CKD-EPI-Cr IDMS and MDRD-4 IDMS did not differ significantly. However, since most of the meta-analyzed studies were from Brazil, the results cannot be extrapolated to other Latin American countries.

REGISTRATION: PROSPERO (CRD42019123434) - https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019123434.

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem: in 2014, 10.6% of adults aged over 30 years had stage 3-5 CKD.[1] In 2017, CKD caused 35,800,000 disability-adjusted life-years (1.4% of all disability-adjusted life-years) worldwide,[2] and 1,230,200 deaths (2.2% of all deaths).[3]

Assessing the glomerular filtration rate (GFR) is the cornerstone for performing adequate screening, diagnosis and classification of CKD.[4] However, the methods used for directly measuring GFR (measured GFR, mGFR) require use of exogenous filtration markers and are laborious and costly. Thus, some equations are routinely used to obtain estimated GFR (eGFR) from endogenous markers such as creatinine[5] or serum cystatin C.[6] The most commonly used equations are the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) equations.[7]

The MDRD equation originally used six variables (MDRD-6): serum creatinine, urea, albumin, age, sex and ethnicity.[8] A later version used only four variables (MDRD-4), excluding serum urea and albumin.[9] Most recently, the MDRD-4 was re-edited to use creatinine measured with calibration traceable to isotope dilution mass spectrometry (IDMS).[10,11]

The CKD-EPI originally used the same four variables of the MDRD-4.[12] Later, other CKD-EPI equations were developed, which used serum cystatin C instead of creatinine,[13] or used both serum creatinine and cystatin C.[14]

Differences in the performance of these equations across certain ethnic groups have been reported,[15-18] and attributed to differences in the production and excretion of creatinine.[19] This, in turn, is related to diet (protein intake) and muscle mass (endogenous production of creatinine), which vary according to ethnicity.[19-21] Thus, it is possible that results from regions with different ethnic compositions such as Europe or North America, which are mostly Caucasian and secondly, Blacks and Hispanics, cannot be extrapolated to Latin American populations that are composed of a mixture of Amerindians, Mestizos, Blacks, Asians and Caucasians.[22]

OBJECTIVE

Latin American stakeholders and practitioners need to know which equation has the best diagnostic performance in their specific context, in order to better inform their decisions. Therefore, we conducted a systematic review with the aim of comparing the performance of the CKD-EPI and MDRD equations for estimating the GFR in Latin American countries, and we evaluated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

METHODS

The study protocol was registered in PROSPERO (CRD42019123434). We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[23]

Literature search and study selection

In this systematic review, we included original observational studies that were performed in Latin American countries and compared both the CKD-EPI and the MDRD equation with mGFR (the gold standard, measured using any exogenous filtration markers such as inulin, iohexol, iothalamate, 51Cr-EDTA or DTPA, among others) in adult populations (≥ 18 years). We did not exclude any study on the basis of language or any other criteria.

We performed a two-step sensitive search. First, we carried out a literature search in PubMed and Scopus in January 2019, and in "Biblioteca Regional de Medicina" (BIREME) in February 2019. The search strategy for each database or virtual library is shown in **Supplementary Material 1** (for all supplementary material, see https://doi.org/10.6084/m9.figshare.14614788.v1).

Duplicated records were removed using the EndNote software. Later, two researchers (ABC and NBC) independently selected abstracts for full-text review and final inclusion. Any differences were resolved by a third researcher (JHZT).

Secondly, we searched the lists of references of all studies included, and the lists of articles that cited each of the studies included (through Google Scholar), in order to identify other studies that fulfilled the inclusion criteria.

Data extraction

Two researchers (ABC and NBC) independently extracted data from each article that met the inclusion criteria, using a standardized Microsoft Excel sheet. Any differences were resolved by a third researcher (JHZT).

The following variables were extracted from each study: first author, year of publication, country, design (prospective or retrospective), population characteristics (inclusion and exclusion criteria, number of participants, sex, age, ethnic group, CKD diagnosis and CKD etiology), intervention (type of MDRD and CKD-EPI equations), gold standard (exogenous filtration marker), mGFR, eGFR and numerical results from diagnostic measurements.

The main diagnostic measurement comprised bias (defined as the mean of the difference between eGFR and mGFR), P30 (percentage of results of eGFR that did not deviate more than 30% from mGFR) and accuracy measurements (sensitivity, specificity and area under the curve).

Other measurements made included the following: precision (defined as one standard deviation of bias, or as the interquartile range), bias% (mean of the difference between eGFR and mGFR, as a function of mGFR), P15, P10, combined root mean square error (CRMSE), Pearson coefficient, intraclass correlation coefficient, kappa coefficient and limits of agreement (defined as bias ± 2 standard deviations).

When there were doubts about some information reported in the studies, we sent an email to the authors in order to clarify the information.

Risk of bias and certainty of evidence

Two researchers (NBC and VEFR) assessed the four risk-of-bias domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool:[24] patient selection, index test, reference standard and flow and timing. In any cases of disagreement, a consensus was achieved together with a third researcher (JHZT).

We used the GRADE methodology[25] to report our certainty regarding the evidence of accuracy of the diagnostic test results. To show this certainty, we created tables of summary of findings (SoF), in accordance with the GRADE specifications.[26,27]

Statistical analyses

When possible, we performed meta-analyses on P30, bias, sensitivity and specificity. This was done when studies compared similar equations, showed their confidence intervals or standard deviations, or enabled calculation of these values.

For P30 and bias, we calculated mean differences (MD) and their 95% confidence intervals (95% CI). For sensitivity and specificity, we built a 2 x 2 table when possible. As there were fewer than four studies to meta-analyze, we could not perform a meta-analytical hierarchical regression for diagnostic accuracy. Instead, we performed a meta-analysis of proportions using the exact binomial distribution. We assessed heterogeneity using an I^2 statistic and used random-effects models when I^2 was higher than 40%.

For bias and P30, we performed a subgroup analysis according to the presence of CKD (using the cutoff of 60 ml/min/1.73 m^2), since a previous systematic review showed that the eGFR equation performance varies across these subgroups[28]. We could not perform a subgroup analysis for comorbidities since no more than one study assessed the same version of the equation in any of the comorbidity groups. The data were processed using the Review Manager (RevMan) [Computer program], version 5.4.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

Ethics committee approval

This was not applicable since this review did not directly involve human participants.

RESULTS

Studies characteristics

In total, we identified 379 records after removing duplicates. Among these, 31 were considered potentially eligible and we did full-text reviews on them. Nineteen were excluded through this process (reasons are detailed in **Supplementary Material 2**, https://doi.org/10.6084/m9.figshare.14614788.v1) and 12 were included for analysis.[29-40] In addition, we did not identify any new studies after searching the lists of references of all the studies included and the lists of articles that cited each of the included studies (done through Google Scholar) (**Figure 1**).

The characteristics of the 12 studies included are summarized in **Table 1** and detailed in **Supplementary Material 3** (https://doi.org/10.6084/m9.figshare.14614788.v1). The numbers of participants ranged from 14 to 354 in these studies. Two studies reported results from the same cohort.[30,40] One study[38] added data from two cohorts, one of which[36] was also included in our review and the other had not been published as a separate original paper.

Regarding the country, six studies were conducted in Brazil,[31-33,36,38,39] two in Mexico,[29,35] two in Argentina[34,37] and two reported results from the same cohort conducted in Jamaica.[30,40] Regarding the population, six studies were performed among healthy people,[29,31,34,37-39] one among candidates for living kidney donation,[34] three among type 2 diabetics,[31,36,38] two among the elderly,[32,33] one among people with systemic lupus erythematosus (SLE),[35] two from the same cohort on homozygous SS sickle cell disease[30,40] and three among people diagnosed with CKD.[37-39]

Nine studies compared MDRD-4 using IDMS (MDRD-4 IDMS) and CKD-EPI-Cr using IDMS (CKD-EPI-Cr IDMS),[29,31-36,38,39] one compared MDRD-4 IDMS and CKD-EPI cystatin C,[33] one compared MDRD-4 IDMS and CKD-EPI-Cr-cystatin C,[33] three compared MDRD-4 without IDMS and CKD-EPI-Cr without IDMS,[30,37,40] one compared MDRD-4 without IDMS and CKD-EPI cystatin C[40] and one compared MDRD-4 without IDMS and CKD-EPI-Cr-cystatin C.[40] Out of the nine studies that compared MDRD-4 IDMS and CKD-EPI-Cr IDMS, six could be included in the meta-analyses (five from Brazil and one from Mexico), since the others did not have enough information to estimate standard errors (**Table 1**).

Regarding use of a correction factor for black race, these six studies included this in the MDRD-4 IDMS equation. Five studies (four from Brazil and one from Mexico) used a CKD-EPI-Cr equation that included the correction factor. One study from Brazil[32] did not included the correction factor in the CKD-EPI-Cr equation: the population of this study (n = 70) was mostly Caucasian (only 12 people aged ≥ 60 years were of other races and the study did not detail which races these were).

Risk of bias

Using the QUADAS-2 tool, we found that the risk of bias was uncertain for most studies, regarding patient enrolling, interpretation of index test results without knowledge of the reference standard, interpretation of the reference standard without knowledge of the index test results and the interval between the index and reference standard tests (**Figure 2**).[29-40]

Diagnostic outcomes

The results from each study are detailed in **Supplementary Material 4** (https://doi.org/10.6084/m9.figshare.14614788.v1). Meta-analyses could only be performed for the comparison between CKD-EPI-Cr IDMS and MDRD-4 IDMS, since other versions of the equations were not evaluated or were evaluated only in one study for the outcomes of interest.

Meta-analyses on bias and P30 are shown in **Figure 3**. Meta-analyses on sensitivity/specificity (for the cutoff of GFR 60 ml/min/1.73 m^2) are shown in **Figure 4**.

Regarding bias: meta-analyses on five studies (four performed in Brazil and one in Mexico)[29,31-33,38] showed no differences between these equations, although point estimates tended to slightly favor the CKD-EPI-Cr IDMS equation (MD: 0.55 ml/min/1.73 m^2; 95% CI: -3.34 to 4.43). For the record, the CKD-EPI-Cr IDMS advantage is higher (although still not significant) in populations with GFR ≥ 60 ml/min/1.73 m^2. In addition, these meta-analyses showed

that both equations tended to overestimate mGFR in people with CKD and to underestimate it in people without CKD.

Regarding P30: meta-analyses on two studies (both performed in Brazil)[29,31-33,38] showed a P30 of 74% (95% CI: 57% to 90%) for CKD-EPI-Cr IDMS, and of 69% (95% CI: 59% to 78%) for MDRD-4 IDMS. However, the final mean difference was not compatible with a significant difference, although point estimates tended to slightly favor the CKD-EPI-Cr IDMS equation (MD: 4%; 95% CI: -2% to 11%). It should be noted that the CKD-EPI-Cr IDMS advantage is higher (although still not significant) in populations with GFR ≥ 60 ml/min/1.73 m^2.

Regarding sensitivity and specificity, two studies (both performed in Brazil)[33,38] showed similar sensitivity (76% for CKD-EPI-Cr IDMS and 75% for MDRD-4 IDMS) and specificity (91% for CKD-EPI-Cr IDMS and 89% for MDRD-4 IDMS).

Certainty of evidence

We used GRADE SoF tables to report the certainty of evidence. Regarding bias and P30, the certainty of evidence was very low for both CKD-EPI-Cr IDMS and MDRD-4 IDMS (**Table 2**). Regarding differences in true positives, true negatives, false positives and false negatives between equations (obtained through

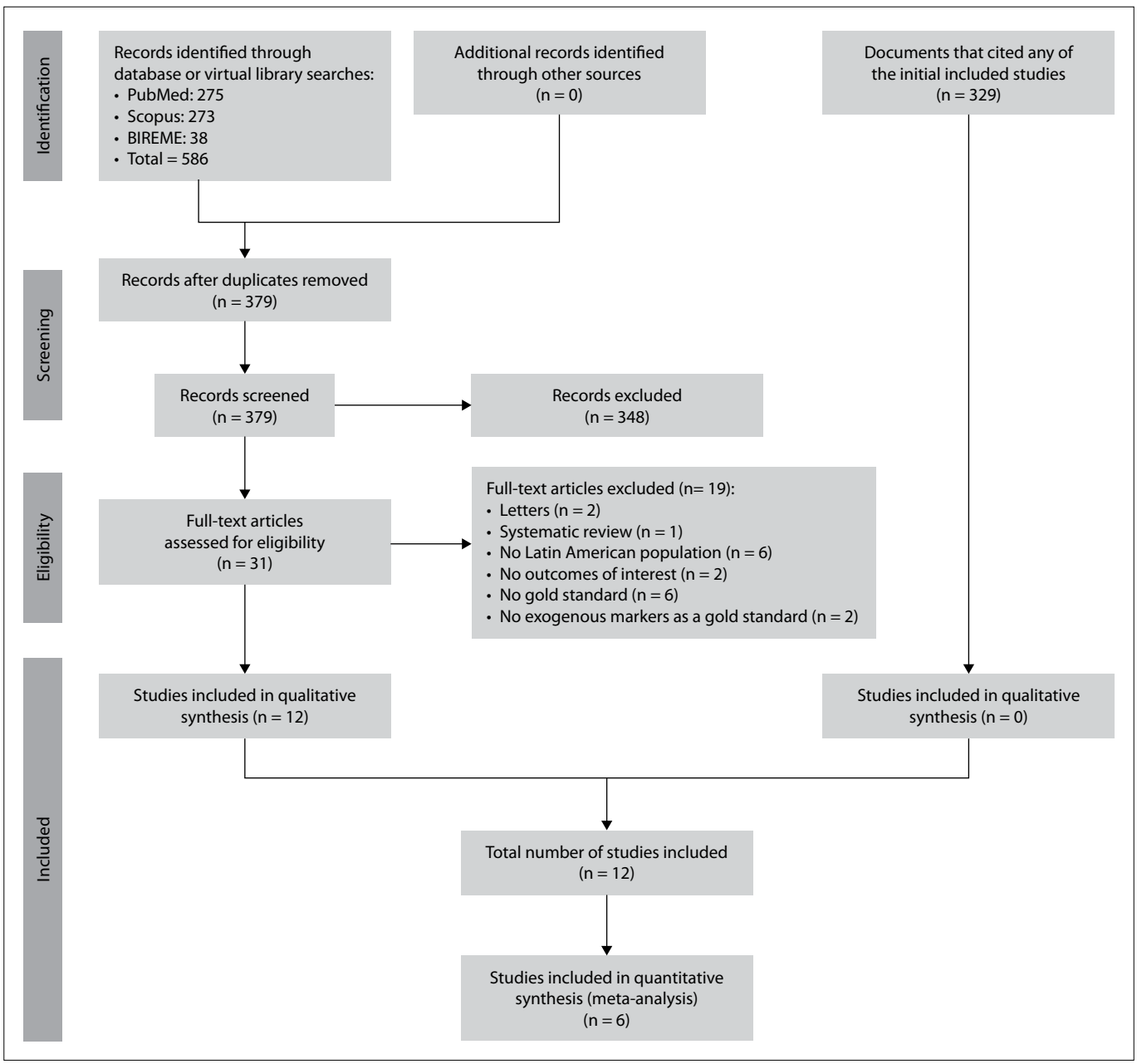


Figure 1. Flow diagram summarizing the process of searching the literature and selecting studies.

Table 1. Characteristics of the studies included

Authors	Country	Population/setting	n	% of females	Age (mean in years)	CKD-EPI	MDRD	Diagnostic measurements (P30, bias, sensitivity, or specificity)*	Gold standard	mGFR (mean in ml/min/1.73 m²)
Studies that were included in the meta-analyses										
Arreola-Guerra et al.[29]	Mexico	Healthy/ hospital	97	41.2	35.8	CKD-EPI-Cr IDMS	MDRD-4 IDMS	**Bias**, P30	^{99m}Tc DTPA	102.7
Camargo et al.[31]	Brazil	Healthy/ hospital	55	47	56	CKD-EPI-Cr IDMS	MDRD-4 IDMS	**Bias**, P30	^{51}Cr-EDTA	98
		Type 2 diabetics/ hospital	56	56	59	CKD-EPI-Cr IDMS	MDRD-4 IDMS	**Bias**, P30		106
David-Neto et al.[32]	Brazil	Elderly/ renal-transplanted	70	40	65	CKD-EPI-Cr IDMS	MDRD-4 IDMS	**Bias**, P30	^{51}Cr-EDTA	47
Lopes et al.[33]	Brazil	Elderly/ community	95	70	85.3	CKD-EPI-Cr IDMS, CKD-EPI cystatin C	MDRD-4 IDMS	**Bias, P30, SE, SP**	Iohexol	55
Silveiro et al.[36]	Brazil	Type 2 diabetics/ hospital	105	50	57	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, **P30**	^{51}Cr-EDTA	103
Veronese et al.[38]	Brazil	Healthy, type 2 diabetics, CKD/ community, hospital	354	55	53	CKD-EPI-Cr IDMS	MDRD-4 IDMS	**Bias, P30, SE, SP**	^{51}Cr-EDTA	87
Studies that were not included in the meta-analyses										
Asnani et al.[30]	Jamaica	Homozygous sickle cell disease/ hospital	98	56	34	CKD-EPI-Cr	MDRD-4	Bias, P30	^{99m}Tc DTPA	94.91
Asnani et al.[40]	Jamaica	Homozygous sickle cell disease/ hospital	98	56	34	CKD-EPI-Cr, CKD-EPI-cystatin C	MDRD-4	Bias, P30	^{99m}Tc DTPA	94.9
Lujan et al.[34]	Argentina	Healthy/ potential donor	85	54	41	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, SE, SP	Non-radiolabeled iothalamate	116
Martinez-Martinez et al.[35]	Mexico	SLE/ hospital	14	100	32.5	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	Non-radiolabeled iothalamate	Not mentioned
Trimarchi et al.[37]	Argentina	CKD, healthy/ hospital	300	42	Median: 48.6	CKD-EPI-Cr	MDRD-4		^{99m}Tc DTPA	For different stages of CKD: Control: 81.53 1: 95.26 2: 70.05 3: 45.59 4: 22.60 5: 11.18
Zanocco et al.[39]	Brazil	CKD, healthy/ hospital	244	57	Males: 40.6; females: 42.6	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Sensitivity and specificity	Iohexol	61.31

CKD = chronic kidney disease; SLE = systemic lupus erythematosus, SE = sensitivity, SP = specificity; mGFR: measured glomerular filtration rate.
Asnani et al.[30] and Asnani et al.[40] evaluated the same cohort; Veronese et al.[38] added data from two cohorts, one of which was Silveiro et al.[36]
*In bold: diagnostic measurements included in the meta-analyses.

Study	Risk of bias									
	Patient selection			Index test		Reference standard		Flow and timing		
	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the reference standard?	If a threshold was used, was it pre-specified*?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the index test results?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Arreola-Guerra et al.[29]	?	☺	☺	?	N.A.	☺	?	?	☺	☹
Asnani et al.[30]	?	☺	☺	?	N.A.	☺	?	?	☺	?
Asnani et al.[40]	?	☺	☺	?	N.A.	☺	?	☺	☺	☺
Camargo et al.[31]	?	☺	☺	?	N.A.	☺	?	?	☺	☺
David-Neto et al.[32]	?	☺	☺	?	N.A.	☺	?	☺	☺	☺
Lopes et al.[33]	?	☺	☺	?	☺	☺	?	☺	☺	☺
Lujan et al.[34]	☺	☺	?	?	☺	☺	?	?	☺	☺
Martinez-Martinez et al.[35]	☺	☺	☺	?	N.A.	☺	?	?	☺	☺
Silveiro et al.[36]	?	☺	?	?	N.A.	☺	?	?	☺	☺
Veronese et al.[38]	?	☺	☺	?	☺	☺	?	?	☺	☺
Trimarchi et al.[37]	?	☺	☺	?	N.A.	☺	?	?	☺	☺
Zanocco et al.[39]	?	☺	?	?	☺	☺	?	?	☺	☺

☺ = Yes; ? = Unclear; ☹ = No; N.A. = not applicable.
*Only applicable for studies that showed sensitivity/specificity.

Figure 2. Risk of bias.

sensitivity and specificity), the certainty of evidence was low (**Table 3**).

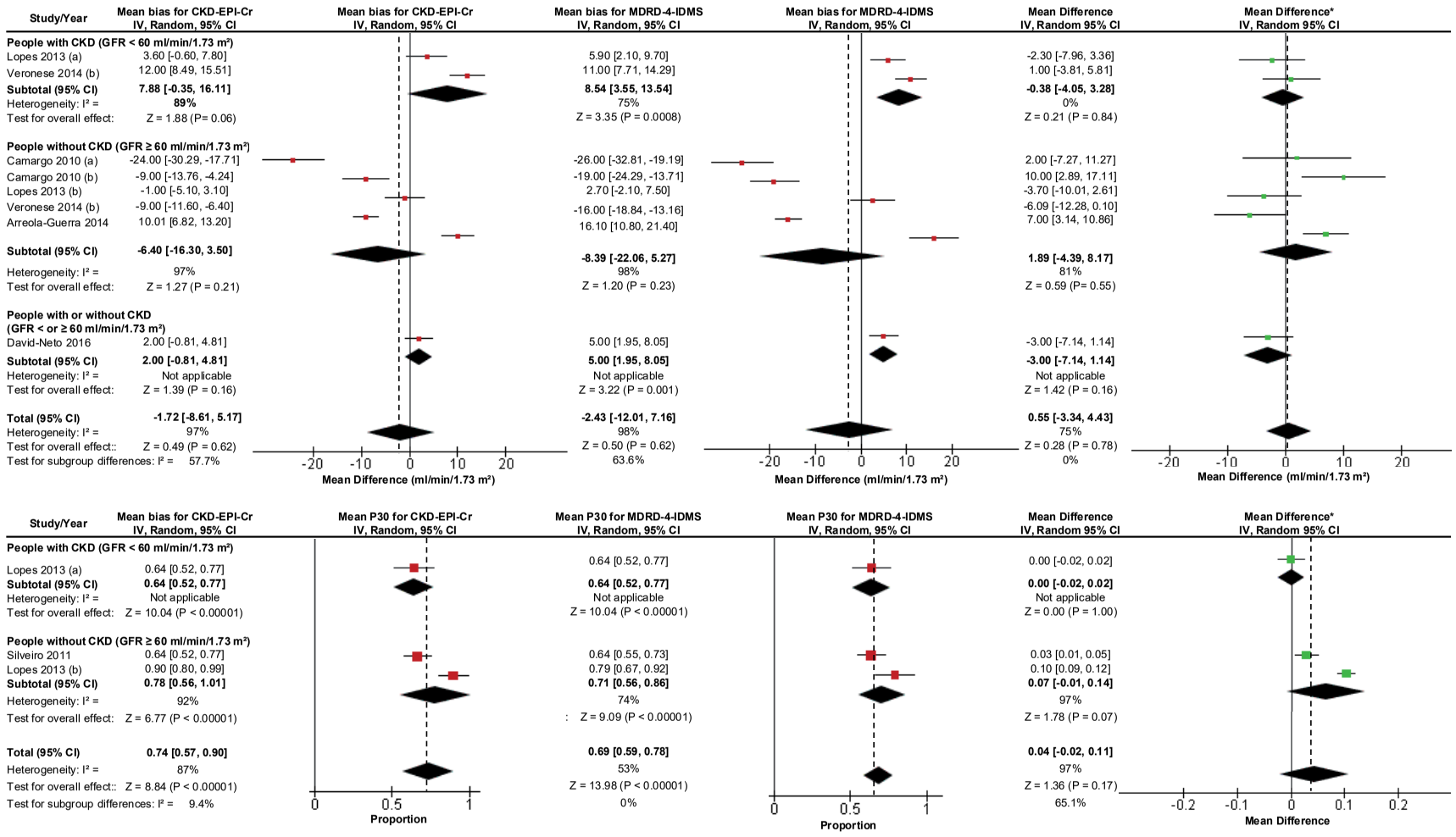
DISCUSSION

Comparison with other studies

We performed meta-analyses on six studies conducted in Latin American countries (five from Brazil, one from Mexico) that compared CKD-EPI-Cr IDMS and MDRD-4 IDMS. No clear differences between these equations were found with regard to bias, P30, sensitivity or specificity. However, point estimates showed a lower bias and a higher P30 (both non-statistically significant) using CKD-EPI-Cr IDMS, in comparison with using MDRD-4.

A previous systematic review among patients in primary care settings searched for studies up to 2017 and included six studies conducted in Latin American countries (all of which were included in our review).[28] That review found that in studies using IDMS, CKD-EPI-Cr IDMS had lower bias (MD: 2.2 ml/minute/1.73 m^2; 95% CI: 1.1 to 3.2) and higher P30 (MD: 2.7%; 95% CI: 1.6 to 3.8) than MDRD-4 IDMS. Considering this, it is possible that in our population, as well as in the population reported in the previous review, the CKD-EPI-Cr IDMS equation could really have slightly better performance, which cannot be observed due to the lack of power (given the small sample size and high heterogeneity) and the absence of sufficient data to be considered for inclusion in the meta-analysis on the other studies that evaluated bias and P30.

This presumed advantage of CKD-EPI-Cr IDMS over MDRD-4 IDMS was more evident in studies in which the population did not have CKD (GFR ≥ 60 ml/minute/1.73 m^2). A similar trend was found in the previous systematic review.[28] This could be due



*The difference was calculated as CKD-EPI-Cr IDMS minus MDRD-4 IDMS values.

The groups were separated according to the measured GFR that was reported in the studies.

Camargo et al.[31] from Brazil (a: type 2 diabetics; b: healthy); Lopes et al.[33] from Brazil (elderly); Veronese et al.[38] from Brazil (a: type 2 diabetics, CKD; b: healthy, type 2 diabetics); Arreola-Guerra et al.[29] from Mexico (healthy), and David-Neto et al.[32] from Brazil (elderly renal-transplanted).

Figure 3. Forest plot for bias and P30.

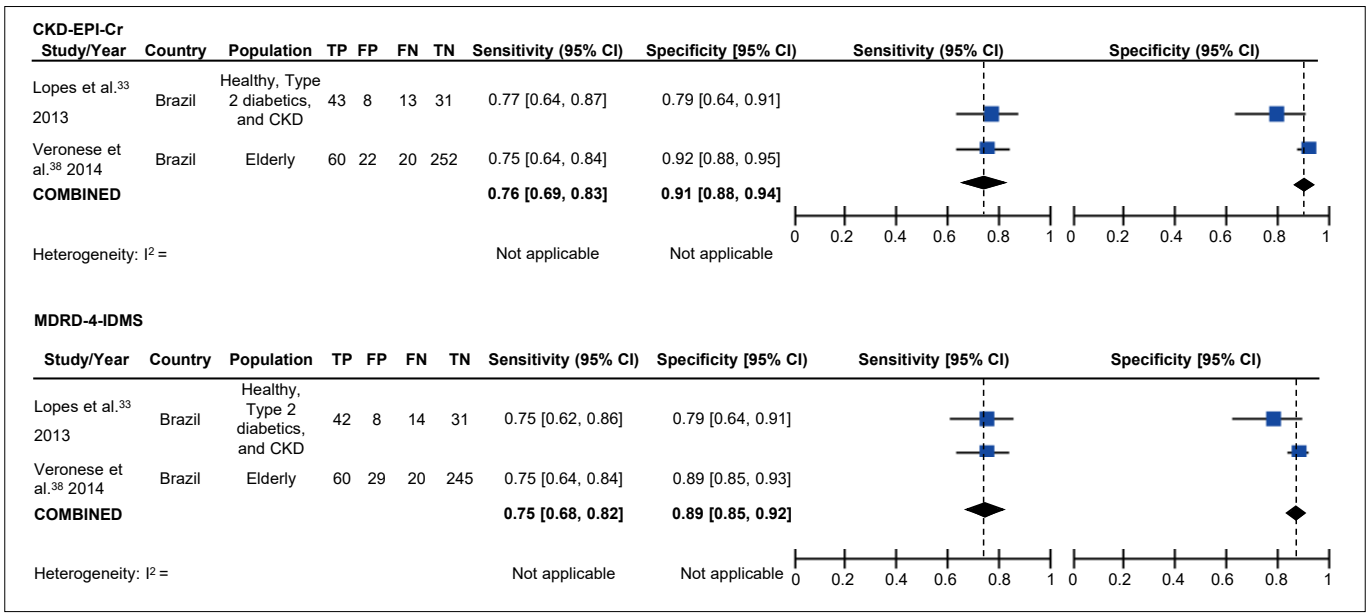


Figure 4. Forest plot for sensitivity and specificity (cutoff of GFR 60 ml/minute/1.73 m²).

Table 2. Summary of findings of bias and P30

Question: How good are the performances of the CKD-EPI-Cr IDMS and MDRD-4 IDMS equations for diagnosing CKD in adult populations (≥ 18 years) in Latin America?			
Patient or population: Adults in Latin American countries			
Settings: The studies included involved community-dwelling adults and hospital-based patients (mean prevalence of CKD across studies included: 41%)			
New test: CKD-EPI-Cr IDMS			
Comparison test: MDRD-4 IDMS			
Reference test: The measured glomerular filtration rate (mGFR) was taken to be the gold standard and was obtained using the Cr-EDTA single-injection method in four studies, Iohexol clearance in one study, and ^{99m}Tc DTPA in one study.			
Outcome	**Number of studies (number of participants)**	**Test result (95% CI)**	**Quality of the evidence (GRADE)**
Bias			
CKD-EPI-Cr IDMS	5 (727)	**-1.72** (-8.61 to 5.17)	⊕◯◯◯ **VERY LOW**[1,2,3,4]
MDRD4 IDMS		**- 2.43** (-12.01 to 7.16)	⊕◯◯◯ **VERY LOW**[1,2,3,4]
P30			
CKD-EPI-Cr IDMS	2 (200)	**73.78%** (58.03 to 89.52)	⊕◯◯◯ **VERY LOW**[3,5]
MDRD-4 IDMS		**68.83%** (59.21 to 78.44)	⊕◯◯◯ **VERY LOW**[3,5]

GRADE Working Group grade of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates; Low quality: Further research is very likely to have an important impact on our confidence in the estimates of effect and is likely to change the estimates; Very low quality: We are very uncertain about the estimates.
Bias: Defined as the mean of the difference between eGFR (from equations) and mGFR; P30: Defined as the percentage of results for eGFR that did not deviate more than 30% from mGFR.
eGFR = estimated glomerular filtration rate; mGFR = measured glomerular filtration rate; CI = confidence interval; CKD = chronic kidney disease; CKD-EPI-Cr IDMS = CKD epidemiology collaboration equation using creatinine with isotope dilution mass spectrometry method to determine creatinine levels; MDRD-4 IDMS = modification of diet in renal disease (with four variables) equation with isotope dilution mass spectrometry method to determine creatinine levels.
[1]It was decided to downgrade the level of evidence due to risk of bias because, in more than 50% of the studies, it was uncertain whether the gold standard and reference results were collected at the same time; [2]It was decided to downgrade the level of evidence due to high heterogeneity between the studies (I^2 higher than 90%); [3]It was decided to downgrade the level of evidence due to risk of bias (the gold standard was not the same in all the studies); [4]It was decided to downgrade the level of evidence due to imprecision (both equations could overestimate or underestimate the real value of the GFR); [5]It was decided to downgrade by one level due to risk of bias (it was uncertain whether the results for the gold standard and the reference were collected at the same time, and in one of the studies, no analysis was done on the results from some of the participants).

Table 3. Summary of sensitivity and specificity findings for the 60 ml/min/1.73 m^2 cutoff point

Question: How accurate are the CKD-EPI-Cr IDMS and MDRD-4 IDMS equations for diagnosing CKD in adult populations (≥ 18 years) in Latin America?					
Number of participants (Studies)	449 (2)	**Pooled sensitivity CKD-EPI-Cr IDMS**	**0.76** (95% CI: 0.69 to 0.83)	**Pooled sensitivity MDRD4-IDMS**	**0.75** (95% CI: 0.68 to 0.82)
		Pooled specificity CKD-EPI-Cr IDMS	**0.91** (95% CI: 0.88 to 0.94)	**Pooled specificity MDRD4-IDMS**	**0.89** (95% CI: 0.85 to 0.92)
Test result		**Number of results per 1,000 patients tested (95% CI)** Baseline risk across studies included: **41%**		**Quality of the evidence (GRADE)**	
		CKD-EPI-Cr IDMS	**MDRD4-IDMS**		
True positives (TP)		**312** (283 to 340)	**308** (279 to 336)		
TP absolute difference		**4 more TP in CKD-EPI-Cr IDMS**		⊕⊕◯◯	
False negatives (FN)		**98** (70 to 127)	**102** (74 to 131)	**LOW** [1,2]	
FN absolute difference		**4 less FN in CKD-EPI-Cr IDMS**			
True negatives (TN)		**537** (519 to 555)	**525** (502 to 543)		
TN absolute difference		**12 more TN in CKD-EPI-Cr IDMS**		⊕⊕◯◯	
False positives (FP)		**53** (35 to 71)	**65** (47 to 88)	**LOW** [1,2]	
FP absolute difference		**12 less FP in CKD-EPI-Cr IDMS**			

CI = confidence interval; CKD = chronic kidney disease; CKD-EPI-Cr IDMS = CKD Epidemiology Collaboration equation using creatinine with isotope dilution mass spectrometry method to determine creatinine levels; MDRD4 IDMS = Modification of Diet in Renal Disease (with four variables) equation with isotope dilution mass spectrometry method to determine creatinine levels.

[1]It was decided to downgrade the level of evidence due to risk of bias (in both studies, it was uncertain whether a consecutive or random sample of patients was enrolled and whether the results from the index test were interpreted without knowledge of the results of the gold standard); [2]It was decided to downgrade the level of evidence due to risk of bias (the gold standard was not the same in all the studies).

to the fact that the CKD-EPI-Cr equation was developed in a study in which the mean GFR was higher than the GFR of the study in which the MDRD-4 equation was created (94.5 ml/minute versus 39.8 ml/minute respectively).[12]

How to better evaluate eGFR in Latin American populations

These equations may not be accurate for all racial groups due to differences in muscle mass and, consequently, differences in creatinine excretion.[21] Thus, attempts to correct the estimates according to race have been made in these equations using different coefficients for white or black people, but other races have not been taken into account.

Given this limitation, modifications of the formulas have been proposed for several ethnic groups, including Asians,[41] Japanese,[18] Chinese,[42] Pakistanis[43] and Africans.[15] However, previous attempts to modify the CKD-EPI-Cr formula for Latin American populations[44] and a Brazilian population[39] did not find any significant improvements in the modified formula, compared with the original formula. This may be due to the fact that Latin American populations do not include a single ethnic group, but a confluence of multiple ethnicities from diverse origins, and the profile of each population (in terms of percentage of European-descendant, Afrodescendent or indigenous) may vary between and within countries and regions.[45-47]

Given this ethnic heterogeneity, it is possible that equation performance may differ from one country to another. However, among the six studies that could be meta-analyzed in our study, five were performed in Brazil, where the ethnic composition differs from that of other countries in the region. As an example, while around 60% of the Brazilian population is Caucasian and less than 0.5% is Amerindian,[48] in Peru around 60% of the population identifies themselves as Mestizo, 25% as Quechua or Aymara (Amerindians) and only around 6% as Caucasians.[49] This prevents conclusions being drawn in relation to other Latin American countries where Amerindians represent an important proportion of the population. In this way, further studies comparing equations or trying to validate coefficients for other Latin American countries are needed.

Implications

Our results suggest that in Latin American populations (mostly from Brazil), as in other populations, these equations do not vary greatly. However, CKD-EPI-Cr IDMS tends to have a non-significant better performance than MDRD-4 IDMS, in term of P30 and among people with GFR < 60 ml/minute/1.73 m^2.

Nevertheless, it is necessary to highlight that the certainty of evidence was very low or low, which suggests that further well-designed studies are needed. In addition, extrapolation to other Latin American countries is difficult because almost all the meta-analyzed studies were performed in Brazil. Lastly, all the meta-analyzed studies used IDMS for creatinine calculation, which has to be taken into account in contexts that do not have IDMS.

Limitations and strengths

Some limitations of this review should be considered: 1) not all studies had enough information to perform a meta-analysis on the outcomes of interest, even after the authors were consulted; and 2) we found differences in the characteristics of the populations included, but we were not able to perform any subgroup analysis to understand how these differences affected the accuracy of the formulas.[21] The influence of other factors, such as the different causes of CKD or the medicines taken, was not studied either.[50]

In spite of these limitations, we believe that our study is important because this is the first systematic review that has compared the GFR equations in Latin American countries (mostly from Brazil), through a two-step sensitive search (the first in two international databases and one local database, and the second in the references and articles that cited each of the articles included in the first step). In addition, we performed a comprehensive search that including papers in Spanish and Portuguese, and the selection and extraction of data were performed in duplicate.

CONCLUSION

We performed a systematic review to assess the performance of the CKD-EPI and the MDRD equations for estimating the GFR in Latin American countries. We found 12 studies and were able to meta-analyze six of them (five were conducted in Brazil). We found that the performances of CKD-EPI-Cr IDMS and MDRD-4 IDMS did not differ significantly, although CKD-EPI-Cr IDMS tended to have a non-significantly better performance in terms of P30 and among people with GFR ≥ 60 ml/min/1.73m^2. However, since most of the meta-analyzed studies were from Brazil, the results cannot be extrapolated to other Latin American countries.

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Knowledge of healthcare professionals about poliomyelitis and postpoliomyelitis: a cross-sectional study

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ABSTRACT

BACKGROUND: Postpoliomyelitis syndrome is a clinical condition that can affect poliomyelitis survivors.

OBJECTIVE: Our aim was to evaluate knowledge of poliomyelitis and postpoliomyelitis syndrome among Brazilian healthcare professionals.

DESIGN AND SETTING: Cross-sectional study conducted at a Brazilian public higher education institution located in the state of Goiás.

METHODS: The participants (n = 578) were Brazilian physicians, physical therapists, nurses, nutritionists and psychologists. A self-administered questionnaire (30 questions) was designed to probe knowledge about poliomyelitis and postpoliomyelitis syndrome. From the questionnaire, we created a structured test to objectively evaluate the knowledge of these professionals. The test was composed of 20 questions and was scored over a range from 0 (totally ill-informed) to 20 (totally well-informed).

RESULTS: In general, the physicians, physical therapists and nurses demonstrated better understanding of poliomyelitis and postpoliomyelitis syndrome. The healthcare professionals who had received previous information about poliomyelitis and postpoliomyelitis syndrome had significantly higher scores than those who had never received information ($P < 0.001$). On average, this difference was approximately 28.6%.

CONCLUSIONS: The findings from the present study indicate that there is a critical need for improvement of knowledge about postpoliomyelitis syndrome among Brazilian healthcare professionals. The services provided by these professionals may therefore become compromised. Furthermore, public healthcare initiatives should be implemented to improve knowledge among healthcare professionals.

INTRODUCTION

Poliomyelitis is an infectious viral disease that may attack people at any age. It affects the nervous system, resulting in paralysis and muscle spasms, and in some cases encephalitis.[1,2] There are several regions in the world that are certified as free from poliomyelitis.[3] However, there are some endemic countries, such as Afghanistan, Nigeria and Pakistan, and there are records of imported cases in some African countries.[3] In Brazil, even though poliomyelitis has been eradicated, according to the Brazilian Health Ministry, 312 Brazilian municipalities have polio vaccine coverage of below 50%. This creates a state of alert and threatens the eradication of the disease. Therefore, there is a need to maintain permanent and effective actions of disease surveillance and adequate levels of immunological protection for the population.[4]

Postpoliomyelitis syndrome (PPS) is the term used to describe a collection of signs and symptoms that may be experienced by individuals afflicted by paralytic poliomyelitis after years of clinical and functional stability.[5] The signs and symptoms that characterize PPS are new muscle weakness, muscle fatigue, muscle atrophy, muscle and joint pain, sleep disturbances, intolerance to cold, respiratory and swallowing difficulties and a recent increase in body mass.[6-8] It is a slowly progressive disease, usually insidious, with subacute onset, sometimes resulting in significant restrictions of activities associated with everyday life.[7,9-16]

Although the pathophysiology of PPS is unclear, different mechanisms have been proposed. The most accepted mechanism postulates that degeneration or dysfunction of giant motor units, manifested by peripheral deterioration (axon and/or neuromuscular junction), probably as a result of metabolic requirements of giant motor units (muscle overuse), has a central role in the etiology of the disease.[9,17] However, there are different hypotheses associated with the pathophysiology of

the disease, which include: muscle disuse, the normal loss of motor units with age, predisposition to motor neuron degeneration due to glial vascular and lymphatic damage, reactivation of the virus or persistent infection, immunological factors related to poliomyelitis,[9,15,18-20] the effect of growth hormone and the combined effect of overuse, disuse, pain, body mass gain or other diseases.[9,18,20]

Regarding the diagnostic criteria for PPS, a clinical approach aimed at ruling out other neurological diseases, orthopedic conditions, psychiatric disorders or even consequences linked to the aging process is required, since these conditions could develop the same signs and symptoms as seen in PPS.[9,21] Therefore, it is extremely important that patients should be managed by a multidisciplinary healthcare professional team that includes neurologists, rheumatologists, orthopedists, pulmonologists, physical education professionals, physical therapists, nutritionists, nurses and psychologists.[9,22,23]

Despite the significant decline in the incidence of paralytic poliomyelitis,[3] PPS will remain a major health problem for many years. In western countries, where the last large epidemics date back to the 1940s and 1950s, many survivors of paralytic poliomyelitis are now aged between 70 and 80 years.[24] In Brazil, the last major outbreak was in 1984.[24] Therefore, the future outlook is for continued or even increased need for rehabilitation programs and management of people with PPS.[9,25] In addition, according to the World Health Organization, it is estimated that there are about 18 million people alive who were affected by paralytic poliomyelitis.[3]

As it is reasonable to assume that success in the treatment of any disease depends on the knowledge that the healthcare professional has about the disease, assessment of knowledge about poliomyelitis and PPS among healthcare professionals is of great value. Previously, it was demonstrated that physical education professionals have misconceptions about poliomyelitis and PPS.[8] Therefore, it is reasonable to assume that other healthcare professionals present similar misconceptions regarding poliomyelitis and PPS. Furthermore, other studies have shown that healthcare professionals can present misconceptions about epilepsy,[26,27] acquired immune deficiency syndrome (AIDS),[28] cancer,[29] hypertension and diabetes.[30]

OBJECTIVE

The aim of this study was to verify the knowledge of health professionals about poliomyelitis and PPS regarding the pathophysiology, etiology, symptomatology and forms of treatment of PPS.

METHODS

Participants

This was a cross-sectional study in which a total of 578 participants (454 women and 124 men) were recruited. This was done using different sources of advertisement (i.e. internet, local newspapers, magazines and billboards in universities, clinics, hospitals and gyms). The inclusion criterion for the study was that the participants should be professionals with at least an undergraduate degree in medicine, physical therapy, nursing, nutrition or psychology. Healthcare professionals with specialization in neurology and/or neuromuscular disorders were excluded from the study.

All the participants were informed of the aim of the study and experimental procedures, and written informed consent was obtained from each participant before any data were collected. All procedures involved in this study were approved by the Universidade Federal de Goiás (UFG) Ethics Committee (protocol number: 198/2009; approved on August 1, 2010) and followed the principles outlined in the Declaration of Helsinki.

Questionnaire

To evaluate knowledge about poliomyelitis and PPS, we used the same questionnaire as described by de Lira et al.[8] This was a self-administered questionnaire divided into three parts: (i) personal data; (ii) knowledge about poliomyelitis; and (iii) knowledge about PPS. The questionnaire consisted of 14 questions about poliomyelitis and 16 questions about PPS and the aspects of these conditions that were addressed related to pathophysiology, diagnosis, forms of treatment, prognosis and previous work experience, with simple scales for closed-type responses. This questionnaire had been prepared in accordance with previous recommendations.[31,32] The questions are shown in **Tables 2** and **3**.

In addition, a knowledge assessment test was created. This aimed to objectively show the knowledge of the professionals interviewed. The test comprised 20 questions within the questionnaire, which were analyzed as a score for correct responses, ranging from 0 to 20 points. These questions are marked with an asterisk in **Tables 2** and **3**.

Statistical analysis

Descriptive statistics were used to analyze the findings (mean, standard deviation and absolute and relative frequencies). The Gaussian distribution of the sample was tested by means of the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was used to compare age and professional experience among categories of healthcare professionals. The chi-square test was used to determine the association between healthcare professionals and knowledge about poliomyelitis and PPS. The Kruskal-Wallis test was used to compare scores from the questionnaire, obtained by the different healthcare professional categories, followed by Dunn post-hoc comparison. The Mann-Whitney test was used to compare scores obtained in the questionnaire between the exposure ('yes' and 'no') groups. For all statistical procedures, the significance level assumed was 5%.

RESULTS

Participants

A total of 578 participants (454 women and 124 men, comprising a convenience sample) were evaluated. Of these, 69 were physicians (19 women and 50 men), 151 were physical therapists (116 women and 35 men), 224 were nurses (203 women and 21 men), 78 were nutritionists (74 women and 4 men) and 56 were psychologists (42 women and 14 men). Out of the 578 participants approached, 305 (52.8%) had a specialization degree, 126 (21.8%) had a PhD, 86 (14.9%) had a master's qualification, 59 (10.2%) only had an undergraduate degree and two (0.2%) did not report their highest graduation level. The other characteristics of the participants are presented in **Table 1**.

Knowledge about poliomyelitis

The first part of the questionnaire was designed to assess knowledge about poliomyelitis. Out of the 578 participants approached, 576 (99.7%) had heard about poliomyelitis. Surprisingly, two nurses (0.35% of the participants) had never heard of poliomyelitis (**Table 2**). The chi-square test did not reveal any significant association between healthcare professional category and having heard about poliomyelitis (P = 0.530).

Out of the 578 participants approached, 461 (79.8%) answered that they had received information about the disease through books, pamphlets and lectures. While approximately 90% of the physicians, physical therapists and nurses had had access to information on how to deal with poliomyelitis in their undergraduate courses, this proportion fell to approximately half among the nutritionists (43.6%) and psychologists (50.0%) (**Table 2**). The chi-square test revealed that there was a significant association between healthcare professional category and receiving information about poliomyelitis (P < 0.001).

With regard to the biological agent that causes poliomyelitis, some healthcare professionals reported that they did not know that the disease is caused by a virus (7.6%); and 4.0% of the participants stated that poliomyelitis is not caused by a virus. More than 90% of the physicians, physical therapists and nurses and approximately 70% of the nutritionists and psychologists correctly answered that poliomyelitis is caused by a virus. The chi-square test revealed that there was a significant association between healthcare professional category and knowledge of the biological agent that causes poliomyelitis (P < 0.001).

Out of the 578 participants approached, 78.3% of the physicians, 39.7% of the physical therapists, 54.5% of the nurses, 21.8% of the nutritionists and 25% of the psychologists knew that poliomyelitis can be spread through water and/or food contaminated with feces from a sick person. The chi-square test revealed that there was a significant association between healthcare professional category and knowing that poliomyelitis can be spread through water and/or food contaminated with feces from a sick person (P < 0.001).

Regarding the symptoms of poliomyelitis, 72.5% of the physicians, 41.1% of the physical therapists, 48.7% of the nurses, 26.9% of the nutritionists and 26.8% of the psychologists knew that poliomyelitis can cause gastrointestinal symptoms. The chi-square test revealed that there was a significant association between healthcare professional category and knowing that poliomyelitis can cause gastrointestinal symptoms (P < 0.001).

Regarding neuromuscular symptoms, more than 90% of the healthcare professionals knew that poliomyelitis can cause neuromuscular symptoms such as paralysis, paresis, muscle atrophy and weakness. The chi-square test did not reveal any significant association between healthcare professional category and knowing that poliomyelitis can cause neuromuscular symptoms (P = 0.262).

In relation to recovery of functional capacity after the acute poliomyelitis stage, 82.6% of the physicians, 70.2% of the physical therapists, 54% of the nurses, 33.3% of the nutritionists and 48.2% of the psychologists knew that after the acute poliomyelitis stage, patients can recover the functional capacity of affected structures. The chi-square test revealed that there was a significant association between healthcare professional category and knowing that patients can recover the functional capacity of affected structures (P < 0.001).

Regarding epidemiology, between 60 and 80% of the healthcare professionals knew that poliomyelitis is a disease that has not been eradicated worldwide. The chi-square test did not reveal any significant association between healthcare professional categories and knowing that poliomyelitis is a disease that has not been eradicated around the world (P = 0.406). Also, there was no significant association between health professional category with regard to knowing that a poliomyelitis vaccine is available (P = 0.133). Indeed, more than 90% of the healthcare professionals knew that a vaccine is available to prevent poliomyelitis.

With regard to treatment, 94.2% of the physicians, 78.8% of the physical therapists, 73.7% of the nurses, 33.3% of the nutritionists

Table 1. Characteristics of participants (n = 578)

Variable (years)	Physicians n = 69	Physical therapists n = 151	Nurses n = 224	Nutritionists n = 78	Psychologists n = 56
Age	42.0 ± 13.4	32.1 ± 8.3*	33.7 ± 14.0*	30.3 ± 8.0*†	36.1 ± 11.5*
Professional experience	17.8 ± 12.6	8.2 ± 8.0*	7.9 ± 8.8*	7.3 ± 9.1*	11.2 ± 9.3*

Data are presented as mean ± standard deviation; *Statistically different from physicians (one-way analysis of variance (ANOVA) and Tukey post-test; P < 0.05); †Statistically different from psychologists (one-way ANOVA and Tukey post-test; P < 0.05).

Table 2. Answers among healthcare professionals relating to poliomyelitis

Questions	Physicians n = 69 (%)	Physical therapists n = 151 (%)	Nurses n = 224 (%)	Nutritionists n = 78 (%)	Psychologists n = 56 (%)	P-value of χ^2 test
Have you heard about poliomyelitis?						
Yes	69 (100)	151 (100)	222 (99.1)	78 (100)	56 (100)	0.004
No	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	
	a/b/c/d	a/e/f/g	b/e/h/i	c/f/h/j	d/g/i/j	
Have you had information about poliomyelitis (books, pamphlets and lectures)?						
Yes	64 (92.8)	137 (90.7)	198 (88.4)	34 (43.6)	28 (50)	< 0.001
No	5 (7.2)	14 (9.3)	26 (11.6)	44 (56.4)	28 (50)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	a/c	b/c	d	d	
Is poliomyelitis caused by a virus?*						
Yes	68 (98.6)	137 (90.7)	209 (93.3)	56 (71.8)	39 (69.6)	< 0.001
No	0 (0.0)	5 (3.3)	8 (3.6)	4 (5.1)	6 (10.7)	
Did not know	1 (1.4)	7 (4.6)	7 (3.10	18 (23.1)	11 (19.6)	
Did not answer	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b/c	a/d/e	b/d/f	g	c/e/f/g	
Can poliomyelitis be spread through water and/or food contaminated with feces from a sick person?*						
Yes	54 (78.3)	60 (39.7)	122 (54.5)	17 (21.8)	14 (25)	< 0.001
No	10 (14.5)	57 (37.7)	72 (32.1)	42 (53.8)	14 (25)	
Did not know	5 (7.2)	34 (22.5)	30 (13.4)	19 (24.40	28 (50)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	a/c/d	b/c/e	d/e		
Can poliomyelitis cause gastrointestinal symptoms?*						
Yes	50 (72.5)	62 (41.1)	109 (48.7)	21 (26.9)	15 (26.8)	
No	8 (11.6)	25 (16.6)	61 (27.2)	25 (32.1)	8 (14.3)	
Did not know	11 (15.9)	63 (41.7)	54 (24.1)	32 (41)	33 (58.9)	
Did not answer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	c/d	a/e	b/c/e	d/e	
Can poliomyelitis cause neuromuscular symptoms such as paralysis, paresis, muscle atrophy and weakness?*						
Yes	68 (98.6)	146 (96.7)	222 (99.1)	76 (97.4)	52 (92.9)	< 0.001
No	0 (0.0)	2 (1.3)	1 (0.4)	0 (0.0)	1 (1.8)	
Did not know	1 (1.4)	3 (2)	1 (0.4)	2 (2.6)	3 (5.4)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b/c/d	a/e/f/g	b/e/h/i	c/f/h/j	d/g/i/j	
After the acute poliomyelitis stage, can patients recover functional capacity of affected structures fully or partially?*						
Yes	57 (82.6)	106 (70.2)	121 (54)	26 (33.3)	27 (48.2)	< 0.001
No	9 (13)	41 (27.2)	63 (28.1)	17 (21.8)	11 (19.6)	
Did not know	1 (1.4)	4 (2.6)	40 (17.9)	34 (43.6)	18 (32.1)	
Did not answer	2 (2.9)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	
	a/b/c/d	a	b/e	c/f	d/e/f	
Has poliomyelitis been eradicated around the world?*						
Yes	9 (13)	36 (23.8)	53 (23.7)	17 (21.8)	11 (19.6)	< 0.001
No	55 (79.7)	96 (63.9)	148 (66.1)	50 (64.1)	36 (64.3)	
Did not know	5 (7.2)	19 (12.6)	23 (10.3)	11 (14.1)	9 (16.1)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	c/d/e	a/c/f/g	d/f/h	b/e/g/h	
Is there a vaccine available to prevent poliomyelitis?*						
Yes	69 (100)	148 (98)	220 (98.2)	74 (94.9)	53 (94.6)	0.002
No	0 (0.0)	1 (0.7)	2 (0.9)	0 (0.0)	0 (0.0)	
Did not know	0 (0.0)	2 (1.3)	2 (0.9)	4 (5.1)	3 (5.4)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b/c	a/d/e/f	b/d/g/h	e/g/i	c/f/h/i	

Continue...

Table 2. Continuation.

Questions	Physicians n = 69 (%)	Physical therapists n = 151 (%)	Nurses n = 224 (%)	Nutritionists n = 78 (%)	Psychologists n = 56 (%)	P-value of χ^2 test
Can poliomyelitis treatment involve admission to an intensive care unit, due to respiratory impairment?*						
Yes	65 (94.2)	119 (78.8)	165 (73.7)	26 (33.3)	17 (30.4)	< 0.001
No	2 (2.9)	6 (4)	20 (8.9)	2 (2.6)	4 (7.1)	
Did not know	2 (2.9)	26 (17.2)	39 (17.4)	50 (64.1)	35 (62.5)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	b	a/b	c	c	
Are you afraid to live with a person who had poliomyelitis?						
Yes	0 (0.0)	0 (0.0)	13 (5.8)	0 (0.0)	2 (3.6)	0.007
No	69 (100)	146 (96.7)	207 (92.4)	77 (98.7)	53 (94.6)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	5 (3.3)	4 (1.8)	1 (1.3)	1 (1.8)	
	a/b	c/d/e	c/f/g	a/d/f/h	b/e/g/h	
During your undergraduate course, did you have access to information on how to handle patients with poliomyelitis in your future profession?						
Yes	41 (59.4)	90 (59.6)	91 (40.6)	3 (3.8)	5 (8.9)	< 0.001
No	28 (40.6)	60 (39.7)	128 (57.1)	75 (96.2)	51 (91.1)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	1 (0.7)	5 (2.2)	0 (0.0)	0 (0.0)	
	a/b/c	a	b	c/d	d	
In your practice, have you ever provided a service for people with sequelae of poliomyelitis?						
Yes	48 (69.6)	78 (51.7)	82 (36.6)	10 (12.8)	12 (21.4)	< 0.001
No	21 (30.4)	69 (45.7)	137 (61.2)	68 (87.2)	43 (76.8)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	4 (2.6)	5 (2.2)	0 (0.0)	1 (1.8)	
	a	a	b	c	b/c	
Can people with sequelae of poliomyelitis perform any type of physical activity?*						
Yes	64 (92.8)	137 (90.7)	177 (79)	50 (64.1)	37 (66.1)	< 0.001
No	1 (1.4)	3 (2)	18 (8)	2 (2.6)	4 (7.1)	
Did not know	4 (5.8)	11 (7.3)	29 (12.9)	26 (33.3)	15 (26.8)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b/c	a/d/e	b/d/f	g	c/e/f/g	

*Question that composed the knowledge assessment test on paralytic poliomyelitis and PPS. Frequencies followed by the same letters, in the rows, did not differ.

and 30.4% of the psychologists knew that poliomyelitis treatment can involve admission to an intensive care unit, due to respiratory impairment. The chi-square test revealed that there was a significant association between healthcare professional categories and knowing that poliomyelitis treatment can involve admission to an intensive care unit, due to respiratory impairment ($P < 0.001$).

Surprisingly, 15 healthcare professionals (2.6%) said that they were afraid to live with people with poliomyelitis (**Table 2**). The chi-square test revealed that there was a significant association between healthcare professional category and being afraid to live with people with poliomyelitis ($P = 0.001$).

Only 39.8% had received information about how to deal with patients with poliomyelitis during their undergraduate courses. Specifically, 59.5% of the physicians, 59.6% of the physical therapists, 40.6% of the nurses, 3.8% of the nutritionists and 8.9% of the psychologists had received information about poliomyelitis during their undergraduate courses. The chi-square test revealed that there was a significant association between healthcare professional category and provision of information about poliomyelitis during undergraduate courses ($P < 0.001$).

Regarding physical exercise, 92.8% of the physicians, 90.7% of the physical therapists, 79.0% of the nurses, 64.1% of the nutritionists and 66.1% of the psychologists responded that people with poliomyelitis sequelae can perform some kind of physical activity. The chi-square test revealed that there was a significant association between healthcare professional category and knowing about physical exercise ($P < 0.001$).

Knowledge about postpoliomyelitis syndrome

The second part of the questionnaire was designed to assess knowledge about PPS. Out of the 578 participants approached, 243 (42%) had heard about PPS (**Table 3**). Specifically, 60.9% of the physicians, 67.5% of the physical therapists, 34.8% of the nurses, 12.8% of the nutritionists and 19.6% of the psychologists

Table 3. Answers among healthcare professionals relating to post-poliomyelitis syndrome (PPS)

Questions	Physicians n = 69 (%)	Physical therapists n = 151 (%)	Nurses n = 224 (%)	Nutritionists n = 78 (%)	Psychologists n = 56 (%)	P-value of χ^2 test
Have you heard about PPS?						
Yes	42 (60.9)	102 (67.5)	78 (34.8)	10 (12.8)	11 (19.6)	< 0.001
No	26 (37.7)	29 (32.5)	145 (64.7)	68 (87.2)	45 (80.4)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	1 (1.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	
	a	a		b	b	
Have you received information about PPS?						
Yes	37 (53.6)	82 (54.3)	59 (26.3)	5 (6.4)	8 (14.3)	< 0.001
No	32 (46.4)	69 (45.7)	159 (71)	72 (92.3)	47 (83.9)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	0 (0.0)	6 (2.7)	1 (1.3)	1 (1.8)	
	a	a	b	c	b/c	
Is PPS a disease that only affects patients who have had paralytic poliomyelitis?*						
Yes	23 (33.3)	64 (42.4)	65 (29)	15 (19.2)	9 (16.1)	< 0.001
No	19 (27.5)	27 (17.9)	41 (18.3)	4 (5.1)	9 (16.1)	
Did not know	27 (39.1)	60 (39.7)	118 (52.7)	59 (75.6)	38 (67.9)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a/b	b/c	d	c/d	
Is there any restriction on intense physical activity for poliomyelitis patients?*						
Yes	30 (43.5)	72 (47.7)	83 (37.1)	16 (20.5)	15 (26.8)	< 0.001
No	17 (24.6)	22 (14.6)	39 (17.4)	4 (5.1)	4 (7.1)	
Did not know	22 (31.9)	57 (37.7)	102 (45.5)	58 (74.4)	37 (66.1)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a/b	b	c	c	
Can people with PPS perform any type of physical activity?*						
Yes	48 (69.6)	104 (68.9)	95 (42.4)	23 (29.5)	19 (33.9)	< 0.001
No	1 (1.4)	2 (1.3)	12 (5.4)	1 (1.3)	1 (1.8)	
Did not know	20 (29)	45 (29.8)	117 (52.2)	54 (69.2)	36 (64.3)	
Did not answer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a	b/d	c	b/c	
Is there a need for clinical follow-up of patients, years after having been affected by poliomyelitis?*						
Yes	48 (69.6)	115 (76.2)	156 (69.6)	40 (51.3)	27 (48.2)	< 0.001
No	8 (11.6)	4 (2.6)	17 (7.6)	4 (5.1)	2 (3.6)	
Did not know	13 (18.8)	31 (20.5)	51 (22.8)	34 (43.6)	27 (48.2)	
Did not answer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	a/c	b/c	d	d	
Is the most appropriate way to diagnose PPS based on symptomatology?*						
Yes	39 (56.5)	86 (57)	106 (47.3)	16 (20.5)	12 (21.4)	< 0.001
No	6 (8.7)	6 (4)	11 (4.9)	6 (7.7)	2 (3.6)	
Did not know	24 (34.8)	58 (38.4)	107 (47.8)	56 (71.8)	42 (75)	
Did not answer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a/b	b	c	c	
Because PPS is a poorly understood syndrome, there is still no effective form of treatment*						
Yes, agree	30 (43.5)	34 (22.5)	52 (23.2)	8 (10.3)	8 (14.3)	< 0.001
No, disagree	10 (14.5)	39 (25.8)	29 (12.9)	4 (5.1)	8 (14.3)	
Did not know	29 (42)	76 (50.3)	143 (63.8)	66 (84.6)	40 (71.4)	
Did not answer	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a	b	c	b/c	
Is the poliovirus responsible for the onset of PPS?*						
Yes	13 (18.8)	42 (27.8)	76 (33.9)	11 (14.1)	8 (14.3)	< 0.001
No	31 (44.9)	35 (23.2)	32 (14.3)	2 (2.6)	4 (7.1)	
Did not know	25 (36.2)	73 (48.3)	115 (51.3)	65 (83.3)	44 (78.6)	
Did not answer	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	
		a	a	b	b	

Continue...

Table 3. Continuation.

Questions	Physicians n = 69 (%)	Physical therapists n = 151 (%)	Nurses n = 224 (%)	Nutritionists n = 78 (%)	Psychologists n = 56 (%)	P-value of χ^2 test
Is PPS considered a neuromuscular disease?*						
Yes	44 (63.8)	104 (68.9)	138 (61.6)	28 (35.9)	19 (33.9)	< 0.001
No	1 (1.4)	6 (4)	4 (1.8)	1 (1.3)	0 (0.0)	
Did not know	24 (34.8)	40 (26.5)	82 (36.6)	49 (62.8)	37 (66.1)	
Did not answer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
	a/b	a	b	c	c	
Are the following main clinical manifestations presented by PPS patients: new weakness, fatigue and muscle and/or joint pain?*						
Yes	40 (58)	107 (70.9)	104 (46.4)	20 (25.6)	15 (26.8)	< 0.001
No	3 (4.3)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	
Did not know	26 (37.7)	42 (27.8)	118 (52.7)	58 (74.4)	41 (73.2)	
Did not answer	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a		b	b	
Can neuromuscular symptoms of PPS occur in limbs previously affected by poliomyelitis?*						
Yes	42 (60.9)	98 (64.9)	104 (46.4)	20 (25.6)	12 (21.4)	< 0.001
No	3 (4.3)	1 (0.7)	6 (2.7)	0 (0.0)	1 (1.8)	
Did not know	24 (34.8)	50 (33.1)	114 (50.9)	58 (74.4)	43 (76.8)	
Did not answer	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
	a	a		b	b	
Can PPS be considered to be a progressive neuromuscular disease, presenting slow worsening of signs and symptoms?*						
Yes	35 (50.7)	62 (41.1)	98 (43.8)	20 (25.6)	15 (26.8)	< 0.001
No	7 (10.1)	26 (17.2)	14 (6.2)	1 (1.3)	2 (3.6)	
Did not know	27 (39.1)	60 (39.7)	112 (50)	56 (71.8)	39 (69.6)	
Did not answer	0 (0.0)	3 (2)	0 (0.0)	1 (1.3)	0 (0.0)	
	a/b	a	b	C	c	
Are you afraid to live with a person who has PPS?						
Yes	1 (1.4)	3 (2)	7 (3.1)	2 (2.6)	2 (3.6)	0.57
No	68 (98.6)	146 (96.7)	214 (95.5)	76 (97.4)	54 (96.4)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	2 (1.3)	3 (1.3)	0 (0.0)	0 (0.0)	
	a/b/c/d	a/e/f/g	b/e/h/i	c/f/h/j	d/g/i/j	
During your undergraduate course, did you have access to information on how to handle PPS?						
Yes	10 (14.5)	40 (26.5)	12 (5.4)	0 (0.0)	0 (0.0)	< 0.001
No	59 (85.5)	109 (72.2)	208 (92.9)	78 (100)	56 (100)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	0 (0.0)	2 (1.3)	4 (1.8)	0 (0.0)	0 (0.0)	
	a/b		b	c	c	
In your practice, have you ever provided a service for people with PPS?						
Yes	18 (26.1)	46 (30.5)	16 (7.1)	2 (2.6)	1 (1.8)	< 0.001
No	50 (72.5)	103 (68.2)	204 (91.1)	75 (96.2)	55 (98.2)	
Did not know	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Did not answer	1 (1.4)	2 (1.3)	4 (1.8)	1 (1.3)	0 (0.0)	
	a	a	b/d	b/c	c	

*Question that composed the knowledge assessment test on paralytic poliomyelitis and PPS. Frequencies followed by the same letters, in the rows, did not differ.

had heard about PPS. The chi-square test revealed that there was a significant association between healthcare professional category and having heard about PPS (P < 0.001).

Out of the 578 participants approached, 373 (65.6%) answered that they had received no information about PPS. While 53.6% of the physicians and 54.3% of the physical therapists had received information about PPS, only 26.3% of the nurses, 6.4% of the nutritionists and 14.3% of the psychologists had received information about PPS (**Table 3**). The chi-square test revealed that there was a significant association between healthcare professional category and having received information about PPS (P < 0.001).

Regarding pathophysiology, 302 (52.2%) did not know that the PPS affects only people who have had paralytic poliomyelitis in the past. While 33.3% of physicians and 42.4% of physical

therapists knew that PPS is a disease that only affects patients who have had paralytic poliomyelitis, only 29% of the nurses, 19.2% of the nutritionists and 16.1% of the psychologists understood this. The chi-square test revealed that there was a significant association between healthcare professional category and knowing that PPS is a disease that only affects patients who have had paralytic poliomyelitis ($P < 0.001$).

In relation to restrictions that the patient must obey, 276 (47.8%) did not know whether there is any restriction on physical activity for people with poliomyelitis sequelae and only 216 (37.4%) knew that exercise should be limited among people with paralytic poliomyelitis sequelae (especially intense exercise). Specifically, 31.9% of the physicians, 37.7% of the physical therapists, 45.5% of the nurses, 74.4% of the nutritionists and 66.1% of the psychologists did not know about any restriction on intense physical activity for PPS patients. The chi-square test revealed that there was a significant association between healthcare professional category and knowing about any restriction on intense physical activity for PPS patients ($P < 0.001$).

Furthermore, 50% of the healthcare professionals answered that PPS patients can perform any type of physical activity and only 2.9% of them correctly answered that PPS patients cannot perform any type of physical activity (**Table 3**). The chi-square test revealed that there was a significant association between healthcare professional category and knowing that PPS patients cannot perform any type of physical activity ($P < 0.001$).

Regarding treatment, 386 (66.9%) believed that clinical follow-up is necessary, even years after acute poliomyelitis, while 156 (27.0%) did not know whether there is a need for clinical follow-up years after an individual has had polio. The chi-square test revealed that there was a significant association between healthcare professional category and knowing about the need for clinical follow-up of patients, years after having been affected by poliomyelitis ($P < 0.001$).

Also regarding treatment, approximately 61.1% of the healthcare professionals did not know whether there is an effective treatment for PPS. Specifically, 42.0% of the physicians, 50.3% of the physical therapists, 63.8% of the nurses, 84.6% of the nutritionists and 71.4% of the psychologists did not know about this issue. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$).

With regard to diagnosis, 287 (49.7%) did not know that the most appropriate way to diagnose PPS is based on symptomatology. Specifically, 34.8% of the physicians, 38.4% of the physical therapists, 47.8% of the nurses, 71.8% of the nutritionists and 75% of the psychologists did not know about this issue. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$).

Regarding PPS etiology, only 104 (18.0%) knew that poliovirus is not responsible for PPS. Specifically, 44.9% of the physicians, 23.2% of the physical therapists, 14.3% of the nurses, 2.6% of the nutritionists and 7.1% of the psychologists did not know about this issue. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$).

Regarding PPS classification, 232 healthcare professionals (40.1%) did not know that PPS is a neuromuscular disease. Specifically, 34.8% of the physicians, 26.5% of the physical therapists, 36.6% of the nurses, 62.8% of the nutritionists and 66.1% of the psychologists did not know about this issue. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$).

Regarding the main clinical manifestations presented by PPS patients, 285 of the healthcare professionals (49.3%) did not know that the main clinical manifestations of PPS are new weakness, fatigue and muscle and/or joint pain. Specifically, while 58% of the physicians, 70.9% of the physical therapists and 46.4% of the nurses knew about this topic, only 25.6% of the nutritionists and 26.8% of the psychologists knew that PPS patients can present with new weakness, fatigue and muscle and/or joint pain. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$).

Furthermore, while 60.9% of the physicians, 64.9% of the physical therapists and 46.4% of the nurses knew that neuromuscular symptoms of PPS occur in limbs previously affected by poliomyelitis, only 25.6% of the nutritionists and 21.4% of the psychologists knew about this topic. The chi-square test revealed that there was a significant association between healthcare professional category and this matter ($P < 0.001$). A similar pattern was found for answers to question 27.

Surprisingly, 15 participants (2.6%) said that they were afraid to live with people with PPS. The chi-square test did not reveal any association between healthcare professional category and being afraid to live with a person who has PPS ($P = 0.877$).

Regarding the provision of information about this disease during the undergraduate course, only 62 participants (10.7%) reported that during their undergraduate courses they had had access to information about management of PPS, and only 83 healthcare professionals (14.4%) reported that they had already provided services to people with PPS (**Table 3**). The chi-square test did not reveal any association between healthcare professional category and these topics ($P < 0.001$).

Knowledge of the professionals about paralytic poliomyelitis and PPS

With regard to the questionnaire that was created, the professionals scored on average 11.0 ± 4.4 (which corresponded to

approximately 55% of the total score), out of a maximum score of 20. Specifically, the Kruskal-Wallis test [$X^2(4) = 107.500$; $P < 0.001$] demonstrated that the knowledge of the physicians, physical therapists and nurses was significantly higher than that of the nutritionists and psychologists ($P < 0.05$, **Figure 1**); and that the knowledge of the physicians and physical therapists was significantly higher than that of the nurses, nutritionists and psychologists ($P < 0.05$).

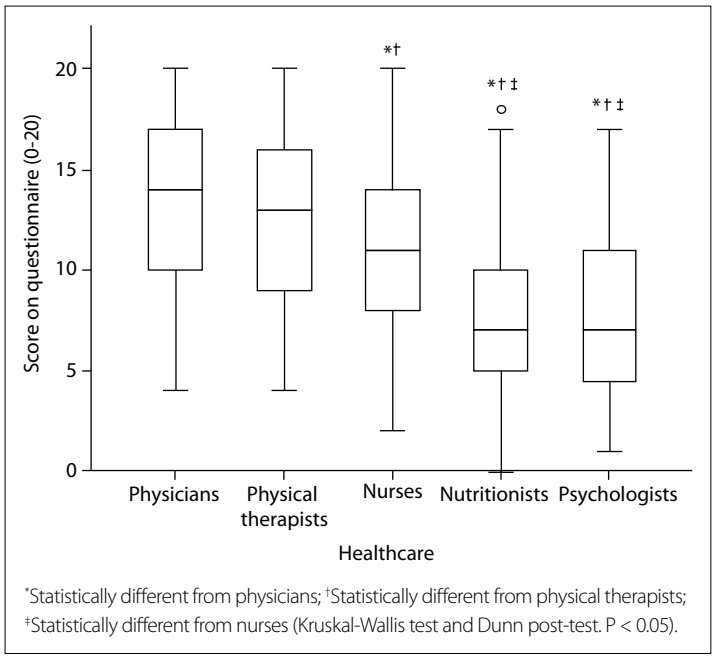

Figure 1. Questionnaire result (0-20) separated according to healthcare professional categories.

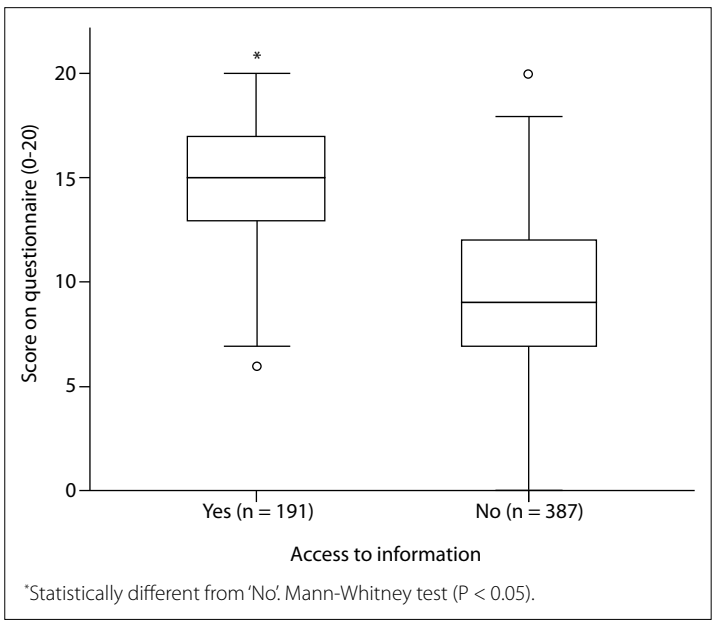

Figure 2. Questionnaire result (0-20) separated according to healthcare professionals with (Yes; n = 191) or without (No; n = 387) access to information about poliomyelitis and post-poliomyelitis syndrome.

We also found that healthcare professionals who had received previous information about poliomyelitis and PPS had significantly higher scores than those who had never received information ($P < 0.001$). On average, this difference was approximately 28.6% (**Figure 2**). Five volunteers did not respond to this question.

DISCUSSION

This study evaluated knowledge about paralytic poliomyelitis and PPS among healthcare professionals (physicians, physical therapists, nurses, nutritionists and psychologists). Considering that success in treating a disease depends on the knowledge level that healthcare professionals have, with regard to etiology, signs and symptoms and management of the disease, studies with the aim of investigating the knowledge of these professionals about a particular disease are important. Despite finding misconceptions about poliomyelitis and PPS in all the healthcare professional categories assessed, our results revealed that physicians, physical therapists and nurses present higher knowledge about poliomyelitis and PPS than nutritionists and psychologists. Furthermore, we found that those who had received previous information about poliomyelitis and PPS had significantly higher scores than those who had never received information.

Previous studies have investigated healthcare professionals' knowledge about certain diseases. Morin et al.[33] investigated physicians' knowledge about cryptosporidiosis and reported that these professionals did not have adequate knowledge about this disease. Vancini et al.[26] investigated the knowledge of physical education professionals about epilepsy and also found low knowledge among these professionals. Regarding paralytic poliomyelitis and PPS, de Lira et al.[8] found that physical education professionals had low knowledge about these diseases. Therefore, our results are in line with the literature.

The low level of knowledge about paralytic poliomyelitis and PPS can be explained because poliomyelitis is a disease that has been eradicated in various countries (including Brazil).[34] In addition, PPS is a relatively unknown disease and physicians commonly confound the signs and symptoms of this disease with the aging process. Only recently, as a result of an initiative led by professionals at the Federal University of São Paulo, PPS was included in the International Classification of Diseases.[35] Therefore, our findings were expected.

It is necessary to highlight that the low levels of knowledge demonstrated by these healthcare professionals (especially by the nutritionists and psychologists) are worrying, because it is reasonable to assume that patient care procedures can be influenced by the professional knowledge level. In this context, we found that healthcare professionals who had received previous information about poliomyelitis and PPS had significantly higher scores than those who had never received information. This result suggests

that universities should include information about poliomyelitis and PPS in their undergraduate curricula, in order to improve the students' knowledge about poliomyelitis and, consequently, as future professionals. Not least, this result suggests that continuing education programs should be implemented as a government initiative. Furthermore, the low knowledge about paralytic poliomyelitis and PPS is worrying, because it is reasonable to assume that low knowledge could decrease professionals' ability to provide counseling about the importance of vaccines.

We also found that physicians, physical therapists and nurses presented higher knowledge than psychologists and nutritionists, as demonstrated by the scores in the knowledge assessment test. Considering that approximately 90% of the physicians, physical therapists and nurses had access to information on how to deal with poliomyelitis in their undergraduate studies and that this proportion fell to approximately 50% among the nutritionists and psychologists, this result was expected. Indeed, the fact that psychologists and nutritionists demonstrate less knowledge about the disease can be explained by the lack of material dedicated to infectious diseases in the undergraduate curricula of such courses. In particular, it is extremely important that physicians have high knowledge about the criteria for diagnosing PPS, because it is a syndrome for which the symptoms include new muscle weakness and muscle fatigue, among patients who have a history of paralytic poliomyelitis.[22,25] However only 33% of the physicians knew that PPS affects individuals who have had polio in the past, and this is important because it is the main diagnostic criterion.

With regard to knowing that PPS is considered to be a progressive neuromuscular disease, with slow worsening of signs and symptoms, approximately 51% of the physicians had correct knowledge, while 42% of the physical therapists, 43% of the nurses, 26% of the nutritionists and 27% of the psychologists had correct knowledge. This shows that there are wide differences in knowledge among healthcare professionals. This result can probably be explained by the fact that physicians, physical therapists and nurses are directly involved in diagnosis and treatment in hospitals and clinics[25] and, as mentioned above, by the presence of material dedicated to infectious diseases in the undergraduate curricula. On the other hand, the participation of nutritionists and psychologists is associated with ameliorating secondary symptoms, such as recent body mass gain[36] and mood disorders.[34]

Although paralytic poliomyelitis has been eradicated in most countries (including Brazil), there are still some countries with new cases of paralytic poliomyelitis.[37] In 2018, the World Health Organization (WHO) recorded 32 cases of poliomyelitis derived from wild poliovirus and 105 cases of poliomyelitis derived from circulating vaccine-derived poliovirus.[37] Furthermore, in the recent humanitarian crisis due to the civil war in Syria, the WHO officially acknowledged an outbreak on October 29, 2013. In May 2014, the WHO declared polio to be a global health emergency for the first time in the organization's history. This was a substantial challenge to the 25-year-old efforts of the Global Polio Eradication Initiative, which had been successful in eliminating polio from Syria in 1995.[38] Specifically in Brazil, the authorities reported difficulties in attaining vaccine coverage in the 2018 campaign against paralytic poliomyelitis.[39] For this reason, the Brazilian authorities have launched another vaccine campaign in order to reach the vaccine coverage recommended by the WHO.[39] Altogether, this information highlights the need to improve knowledge about poliomyelitis and PPS among healthcare professionals.

Our study had some limitations. Firstly, like all studies in which questionnaires are used, the present results rely on the honesty and level of recall of the respondents. Secondly, the reliability and validity of the instrument used to gather the data for this study has not been determined, although the questionnaire was previously evaluated by two experienced researchers. Nevertheless, we believe that these limitations do not prevent us from drawing conclusions from this study.

CONCLUSION

Our study showed that, overall, there is a lack of knowledge about PPS and poliomyelitis, especially among psychologists and nutritionists. Therefore, the services provided by these professionals may become compromised. Furthermore, government initiatives should be implemented to increase knowledge among healthcare professionals.

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Prevalence of psoriatic arthritis among patients with plaque psoriasis: a Brazilian retrospective study

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CASPAR.
PASI.

ABSTRACT

BACKGROUND: Psoriatic arthritis is the most frequent and impactful comorbidity among psoriatic patients and appears in most cases after skin disease. Dermatologists play a key role in its early diagnosis and treatment.

OBJECTIVES: To determine the prevalence of psoriatic arthritis and associated variables among patients with plaque psoriasis seen at a reference center for treating psoriasis.

DESIGN AND SETTING: Retrospective cross-sectional study conducted among 300 patients at an outpatient clinic in a university center in Juiz de Fora, MG, Brazil.

METHODS: Standardized records of 300 patients with plaque psoriasis were examined. Demographic data and medical variables relating to psoriasis (Psoriasis Area and Severity Index (PASI), family history, age at onset and disease progression) and psoriasis arthritis (CASPAR criteria) were evaluated. Laboratory and radiographic tests in the medical records were reviewed.

RESULTS: Seventy-three (24.3%) of these 300 patients with plaque psoriasis had psoriatic arthritis. Asymmetric oligoarthritis (58.9%) was the most common clinical form, followed by polyarthritis (20.5%), distal interphalangeal arthritis (15.2%) and spondyloarthritis (5.4%). Dactylitis was present in 21.9% and enthesitis in 35.6% of patients. Compared with patients without arthritis, patients with arthritis had higher average age, higher frequency of positive family history of psoriasis, longer duration of evolution and higher PASI rates.

CONCLUSION: Psoriatic arthritis is often underdiagnosed. Since dermatologists perform the initial approach, these professionals need to be trained to diagnose this comorbidity and treat it, together with rheumatologists.

INTRODUCTION

Psoriasis is a chronic inflammatory pathological condition of recurrent nature and multifactorial etiology that affects about 2% to 5% of people worldwide.[1,2] Currently, psoriasis is considered to be a systemic disease and it may be associated with several comorbidities, including psoriatic arthritis.[3-6] Psoriatic arthritis is a progressive disease, and some patients can progress to severe forms with joint damage and permanent functional changes.[5-8] Although it was previously recognized as a rare condition, its prevalence among psoriatic patients was found to be high in a recent systematic review, ranging from 4.2% to 33.6%.[9] In addition, it is considered to be the comorbidity that has the greatest impact on the quality of life of these patients, thus requiring early diagnosis and treatment.[10]

In Brazil, the prevalence of psoriatic arthritis exclusively in patients with plaque psoriasis has not yet been defined. Given this context, and combined with the fact that skin lesions precede joint injuries in more than 80% of cases,[7-9] dermatologists have the opportunity to identify patients at risk and diagnose and treat them early.

OBJECTIVE

The aim of this study was to determine the prevalence of psoriatic arthritis and associated variables among patients who had been diagnosed with plaque psoriasis at a teaching center in Juiz de Fora, MG, Brazil.

METHODS

Sample selection and ethics compliance

We conducted a cross-sectional, comparative, retrospective study that included 300 patients with plaque psoriasis who were treated in the psoriasis outpatient clinics of the Dermatology Service at the University Hospital of the Faculty of Medicine, Universidade Federal de Juiz de Fora (UFJF), between January and December 2016. The inclusion criteria were that the patients could be of either sexes, aged between 18 and 60 years, and needed to have a clinical and/or histopathological diagnosis of plaque psoriasis. This diagnosis was made in accordance with the Classification criteria for Psoriatic Arthritis (CASPAR).[11] Patients with other clinical forms of psoriasis, and those for whom data were missing from the standardized medical records for psoriasis, were excluded. Data collection only started after approval of the investigation by our institution's ethics committee (protocol 3.142.153; approved on November 2, 2019, by the Research Ethics Committee of the University Hospital, UFJF). All procedures involved in this study were in conformity with the Declaration of Helsinki of 1975, as updated in 2013.

Clinical, laboratory and radiographic evaluation

The standardized medical records for each patient were reviewed and the following variables were evaluated: sex, age, family history of psoriasis, age at disease onset, duration of the disease, presence of psoriatic arthritis (according to the CASPAR criteria)[11] and disease severity according to the Psoriasis Area and Severity Index (PASI).[12] Using PASI, the severity of psoriasis was stratified as mild (PASI < 10) or moderate-to-severe (PASI > 10). Rheumatoid factor and radiographic reports were also reviewed.

Statistical analyses

Descriptive data analysis was performed, and we assessed normality of distribution by applying the Shapiro-Wilk test. The homogeneity of the variance was assessed by applying the Levene test. When the assumptions of normal distribution and homogeneity of variance were met, the t test was used to ascertain the differences in quantitative variables between the two groups. The chi-square test (χ^2), or Fisher's exact test for less than five data points, was used to test for possible differences in the proportions of qualitative variables. In all statistical analyses, the significance level adopted was 5% ($P < 0.05$). The analyses were performed using the R software package for Windows [R Core Team (2019); version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria); URL https://www.R-project.org/].

RESULTS

The characteristics of the patients with plaque psoriasis with and without arthritis are shown in **Table 1**. Three hundred patients with plaque psoriasis were assessed, among whom 227 (75.7%) only presented skin lesions, while 73 (24.3%) patients had concomitant arthritis. The arthritis patients had a higher average age (49.98 ± 11.12 versus 46.34 ± 13.21 years; P = 0.021).

Table 1. General characteristics of psoriatic patients with and without arthritis

Variables	Psoriasis without arthritis n (%) 227 (75.67)	Psoriasis with arthritis n (%) 73 (24.33)	P-value
Age in years (mean ± SD)	46.34 ± 13.21	49.98 ± 11.12	0.021
Male/female (n)	121/106	40/33	-
Prevalence of men (%)	53.3	54.8	0.824
Positive family history [n (%)]	69 (30.4)	42 (57.5)	0.001**
Age at diagnosis in years (mean ± SD)	34.46 ± 15.58	34.60 ± 16.10	0.949
Duration of psoriasis in years (mean ± SD)	11.85 ± 11.12	15.63 ± 12.43	0.002*
PASI (mean ± SD)	12.79 ± 6.75	17.08 ± 4.68	0.001**
Severity [n (%)]			0.001**
Mild	58 (25.5)	1 (1.4)	-
Moderate-to-severe	169 (74.5)	72 (98.6)	-

PASI = Psoriasis Area and Severity Index; SD = standard deviation. *P < 0.01; *P < 0.001.

The distribution according to sex was similar in the two groups, as also was the age at diagnosis of the disease, which started on average at 34 years of age (patients with arthritis: 34.60 ± 16.10 years, versus patients without arthritis: 34.46 ± 15.58 years, P = 0.949). A positive family history was statistically more frequent among patients with arthritis (57.5% versus 30.4%, P < 0.001), and the disease duration was longer in the arthritis group (15.63 ± 12.43 versus 11.85 ± 11.12 years; P < 0.01) (**Figure 1**).

More than 80% of the patients in the study had moderate-to-severe psoriasis, and PASI values were significantly higher in the arthritis group (17.08 ± 4.68 versus 12.79 ± 6.75; P < 0.001) (**Figure 2**).

Regarding joint patterns, the most common clinical form was asymmetric oligoarthritis (58.9%), followed by polyarthritis (20.5%), distal interphalangeal arthritis (15.2%) and spondyloarthritis (5.4%). Dactylitis was present in 21.9% of patients and enthesitis in 35.6% (**Table 2**).

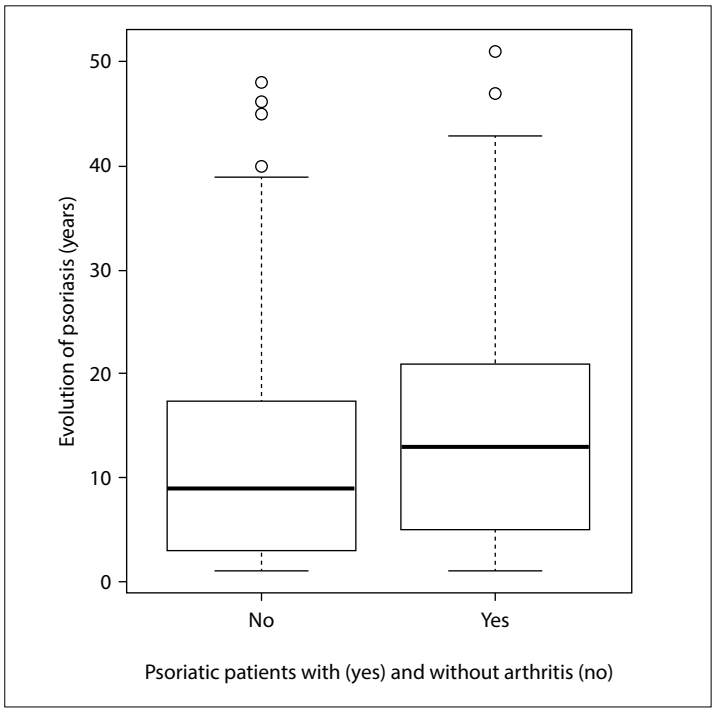

Figure 1. Comparison of duration of psoriasis between patients with and without psoriatic arthritis. The disease duration was longer in the arthritis group (15.63 ± 12.43 versus 11.85 ± 11.12 years; P < 0.01).

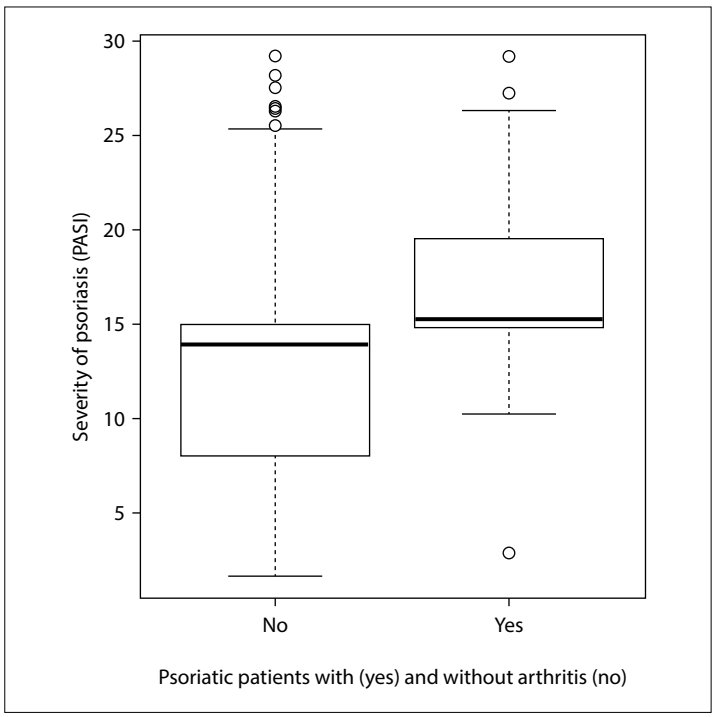

Figure 2. Comparison of Psoriasis Area and Severity Index (PASI) between patients with and without psoriatic arthritis. PASI values were significantly higher in the arthritis group (17.08 ± 4.68 versus 12.79 ± 6.75; P < 0.001).

Table 2. Clinical patterns of psoriatic arthritis (n = 73)

Clinical manifestations	n (%)
Asymmetric oligoarthritis	43 (58.9)
Polyarthritis	15 (20.5)
Distal interphalangeal arthritis	11 (15.2)
Spondyloarthritis	4 (5.4)
Dactylitis	16 (21.9)
Enthesitis	26 (35.6)

DISCUSSION

This study investigated the prevalence of psoriatic arthritis among 300 patients with plaque psoriasis who were treated by a dermatologist at a teaching center that is a reference center for treating psoriasis, in Juiz de Fora, Brazil. The medical care included use of a standardized questionnaire for psoriasis, and joint involvement was analyzed through the CASPAR criteria, which has high specificity (98.7%) and sensitivity (91.4%) for early diagnosis of psoriatic arthritis.[11,13] These criteria are also used for dispensation of high-cost drugs by the Brazilian government.

The prevalence rate found in the present study was 24.33%. In Brazil, previous studies using the CASPAR criteria have shown prevalences of 35%[14] and 33%.[15] However, one of the reasons for these differences is probably the fact that the authors of the previous studies included patients with other clinical forms of psoriasis in the assessment, accounting for 17.59%[14] and 20.41%[15] of their total samples.

Similar results were observed by Christophers et al.,[16] who evaluated 1,560 patients in Europe using the CASPAR criteria and estimated the prevalence at 20.5%. Reich et al.[17] evaluated the prevalence and clinical pattern of psoriatic arthritis among 1,511 patients with plaque psoriasis: 312 (20.6%) had psoriatic arthritis, and 85% of these cases were diagnosed for the first time through that study. In contrast, an American study[18] conducted by means of telephone interview found an 11% prevalence. These differences between studies are explainable in terms of geography, ethnicity, genetic background, clinical forms and different diagnostic criteria used to define psoriatic arthritis.[9] In approximately 80% of the cases, the skin disease precedes the joint disease by at least 10 years. However, in a minority of cases (10%-15%), arthritis may precede cutaneous involvement.[7,11]

In Brazil, access to a rheumatologist is limited, even in university centers. However, a well-trained and qualified dermatologist can assess skin and joints. Early detection of arthritis is a key issue and gives dermatologists an important role in detection and management of these patients. Among the characteristics of patients with concomitant arthritis, the following were relevant: older age, greater frequency of a positive family history, longer evolution time and higher PASI.

The onset of psoriasis had no relationship with sex or age, in agreement with previously reported data.[19] However, the age at onset of psoriasis has been reported by other authors[17] to be a predictor of psoriasis arthritis. Other factors associated with arthritis risk include the following: several markers of psoriasis severity, such as higher PASI,[5,20] body surface area (BSA)[17,19] and Dermatology Life Quality Index (DLQI);[17,21] greater lengths of hospitalization due to psoriasis in the last five years; more workdays lost in the last 12 months;[17] and having more than three body sites affected by psoriasis.[5]

In our study, patients with psoriatic arthritis had higher PASI values than those without arthritis, in agreement with a previous study,[17] thus showing that a severe skin condition is associated with a risk of psoriatic arthritis. Although we did not evaluate the association between skin severity and the number of joints involved, a previous study showed that the correlation between the skin and the joints may be low: a patient may have mild psoriasis and severe arthritis, and the opposite is also true.[22] Regarding the clinical forms presented by our patients, oligoarthritis was the most common, and axial involvement was the least, in agreement with previous reports.[23] The data relating to the presence of enthesitis (35.6%) and dactylitis (21.9%) were in accordance with previous studies,[24,25] which stated that these rates can reach up to 50% among patients, and that presence of dactylitis is related to earlier joint damage, such as bone neoformation and erosion. To our knowledge, our study was the first in Brazil to assess the prevalence of psoriatic arthritis among patients with plaque psoriasis, in which dermatologists made the diagnosis by using the CASPAR criteria. Therefore, the data in this study can be considered representative of a considerable proportion of patients with psoriasis in Brazil.

According to our findings, dermatologists can expect that out of every 10 patients with plaque psoriasis, about 2.5 of them will have psoriatic arthritis. In addition, the severity of the disease verified through PASI among patients with concomitant arthritis emphasizes that there is a need for dermatologists to become familiar with the diagnostic criteria and clinical findings, which are already well documented for arthritis. Increased PASI and involvement of the scalp, nail and intergluteal or perianal groove form clinical markers that facilitate early diagnosis and treatment.

CONCLUSIONS

Psoriatic arthritis is often underdiagnosed. Since dermatologists perform the initial approach, these professionals need to be trained to diagnose this comorbidity and treat it, together with rheumatologists.

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Daily physical activity, human development index and insomnia in a representative sample of Brazilian adolescents: a cross-sectional analysis

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ABSTRACT

BACKGROUND: Although there is a growing body of research pointing towards the need to investigate how different movement behaviors, such as physical activity and sleep, influence each other, the joint relationship between these factors and insomnia has been little explored among adolescents in developing countries.

OBJECTIVES: To investigate the association between daily physical activity and insomnia in a national sample of Brazilian adolescents, according to the Human Development Index (HDI) of each Brazilian region.

DESIGN AND SETTINGS: Cross-sectional study on 102,072 Brazilian students aged 11 to 19 years, selected from all regions of the country.

METHODS: Information on insomnia and physical activity was self-reported by adolescents.

RESULTS: Our analyses revealed that girls who accumulated at least 60 minutes/day of physical activity on up to three days/week were less prone to present insomnia. This pattern of association was maintained only for those who lived in high HDI regions (odds ratio, 0.87; 95% confidence interval, 0.75-0.99). For boys, there was a positive association between the number of active days and protection against insomnia, especially for those who lived in high HDI regions.

CONCLUSION: Even amounts of physical activity that were lower than the weekly guidelines, were associated with better sleep quality for Brazilian adolescents, especially girls, and even for those who lived in regions with greater social and economic vulnerability.

INTRODUCTION

Insomnia is defined as persistent difficulty in falling asleep and staying asleep, despite adequate sleep opportunities,[1] and is considered to be the most common sleep disorder during adolescence, with an estimated prevalence ranging from 6% to 30% in this age group.[1] Previous research has shown that insomnia is associated with symptoms of depression, substance abuse, poor school performance, mood disorders,[2,3] social withdrawal and loneliness,[4] lower emotional regulation,[5,6] anxiety and suicidal thoughts.[7] Despite the recommendations that adolescents should sleep for 8 to 10 hours per day,[8] few young people achieve sufficient amounts of sleep,[9] which converges on a secular trend of reduced sleep duration among children and adolescents.[10] This scenario highlights insomnia as an important public health issue, as well as demonstrating the need to establish effective and suitable ways to address this problem during adolescence.

In this regard, the scientific literature provides arguments for different strategies for treating insomnia, such as cognitive-behavioral therapy and pharmacotherapy.[11,12] However, although similar efficacy has been demonstrated between these therapies for treating insomnia,[13] both of them are difficult to apply on a large scale, especially in the context of developing countries.[14] Thus, studies have pointed towards physical activity (PA) as a possible low-cost strategy for reducing the effects of insomnia among adolescents.[15] In a meta-analysis on 12 studies that investigated the relationship between PA and sleep among adolescents, it was concluded that individuals with higher PA levels, assessed subjectively and objectively, were more likely to present better sleep quality.[16] Furthermore, the results from a clinical review demonstrated that moderate aerobic exercise training could be prescribed as pertinent non-pharmacological treatment for sleep

disorders.[17] Likewise, cross-sectional data from a survey of 14,782 American adolescents showed that only those who were active for at least 60 minutes/day, every day, presented an association with sufficient amounts of sleep (≥ 8 hours of sleep per night on an average school night).[18] However, that analysis was not stratified by sex, which may have limited the interpretation of the results, since boys and girls differ in their PA levels and sleep quality.[19]

In addition, although research has shown that higher total PA levels are associated with better sleep quality,[16,18,20] this relationship remains unclear. Studies carried out among adolescents in 33 European countries[21] and in Canada[22] did not find any association between higher PA levels and sleep disorders. Complementing these findings, the results from a longitudinal study on adolescents indicated that changes to accumulation of physical activity were unrelated to changes in mental health outcomes, such as mental distress,[23] although the latter can be a confounder between physical activity and sleep disorders. However, considering the social and economic differences between developed and developing countries, there is a lack of information on how this association occurs among Brazilian adolescents, considering that the prevalence of PA varies according to a country's level of development.[24]

Furthermore, a growing body of research has also pointed towards the need to investigate how different movement behaviors over a 24-hour period, such as PA, sedentary behavior (SB) and sleep, influence each other.[25] Likewise, there is evidence that points towards the existence of a relationship between health-related behaviors, such as PA, SB and sleep, and urban and socioeconomic development.[26] Previous research has shown that the features of both the social environment (family, social cohesion, safety, noise and socioeconomic status) and the physical environment (light exposure, traffic, air pollution and walkability) may influence sleep.[27,28] However, the joint relationship between these factors and insomnia has not been explored.

OBJECTIVES

The objectives of the present study were: 1) to investigate the association between daily PA and insomnia, in a national sample of Brazilian adolescents; and 2) to verify whether this association varies according to sex and the HDI of the region of this country.

METHODS

Study design and sample

This was a cross-sectional analysis based on data from the National School-based Health Survey (PeNSE in Portuguese), conducted in Brazil between April and September 2015. This survey had the aim of assessing the risk and protective factors relating to the health of students enrolled in public and private schools throughout Brazil.[29] The sampling process and methods are detailed elsewhere.[29] Briefly, PeNSE 2015 was the third edition of this survey, with previous editions conducted in 2009 and 2012. Unlike the other editions, the PeNSE 2015 database was composed of two different samples, named: sample 1, which included students in the 9th grade of elementary school; and sample 2, composed of students aged 13 to 17 years, from the 6th grade of elementary school up to the 3rd grade of high school, in the reference year of this study.[29] This analysis focuses on sample 1, due to the greater representativeness of these data on the students' health.

For sample 1, students were selected through a complex cluster sampling process, which included schools in the 26 state capitals, plus the Federal District and 26 other municipalities, resulting in a total of 53 strata. In the capitals, the sampling process was carried out in two stages (schools as primary units and classes as secondary units), while in the other municipalities, stratification involved three stages (municipalities as primary units, schools as secondary units and classes as tertiary units). The sample size was calculated for each stratum, considering a sampling error of 3%, prevalence of 50% and confidence interval of 95%.[29]

Data were collected through a self-administered electronic questionnaire, composed of two main sections. The first section related to the school's characteristics and was filled out by the principal or coordinator. The second section was self-administered by students and assessed their individual characteristics. Based on the 2013 school census, 3160 schools were selected and invited to participate in the study, totaling 4159 classes. All students in the classes selected were invited. In total, 3040 public and private schools, with 124,227 students, were considered eligible to participate in the study. Among the students present on the day of data collection, 102,301 (82%) agreed to participate in the study.[29] Because of missing data, the current analysis considered data from 102,072 students (51.7% girls) aged from 11 to 19 years (mean age of 14.33 ± 1.06 years).

Informed consent was obtained from parents/legal guardians, and student assent was also obtained, as required by local ethics review boards. All procedures of PeNSE 2015 were approved by the National Research Ethics Committee of the National Health Council, and the study was conducted in accordance with the principles expressed in the Declaration of Helsinki (CONEP no. 1.006.467; dated March 30, 2015).

Insomnia

The prevalence of insomnia was obtained through self-reports, by means of the following question: *"In the past 12 months, how often have you been unable to sleep at night because something worried you a lot?*" The response options were "*Never*", "*Rarely*", "*Sometimes*", "*Most of the time*" or "*Always*". The first three options were categorized as "No" = "0". Individuals who

answered "Most of the time" or "Always" were classified as having insomnia and were categorized as "Yes" = "1". This categorization procedure was also used in a previous study.[20]

Physical activity

Daily physical activity was self-reported through a validated questionnaire,[30] using the following question: *"In the past seven days, on how many days did you exercise for at least 60 minutes a day?"* Daily physical activity was categorized according to the number of days reported (zero to seven).

Geographical regions

The analyses were stratified according to the Human Development Index (HDI) of Brazil's five macroregions. Thus, the Brazilian regions were classified as having low HDI (North = 0.667; Northeast = 0.663) = "0"; or as having high HDI (Southeast = 0.766; Center-West = 0.757; South = 0.754) = "1".[31] This form of classification is used in studies on regional inequalities in Brazil.[32]

Covariables

The following covariables were considered: a) age group (< 14 years or ≥ 14 years); b) ethnicity, which in the present study was dichotomized as "white" or "non-white" (black, Asian, brown/mixed or indigenous); c) bullying, obtained through the question: *"Have you ever been bullied?"*, with the answer options "yes" or "no". Those who answered "yes" were considered to be victims of bullying and were categorized as "1"; and d) television viewing, which was self-reported through the item: *"On an ordinary weekday, how many hours per day do you watch TV? (do not consider Saturday, Sunday or holidays)*". The response options ranged from "I don't watch TV" to "More than 8 hours per day" and the answers were categorized as "≤ 2 hours", "> 2 to ≤ 4 hours" or "> 4 hours".

Statistical analysis

Descriptive statistics were presented as absolute and relative frequencies, stratified according to sex, along with confidence intervals (95% CI). Crude and adjusted binary logistic regression models, stratified according to sex and HDI of the Brazilian regions, were constructed in order to estimate the odds ratio (OR) and 95% CI. Only covariates with a P-value < 0.2 in the crude analyses were included in the final model. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM, Armonk, New York, United States), with statistical significance taken to be P ≤ 0.05.

RESULTS

The descriptive characteristics of the sample according to sex are shown in **Table 1**. A total of 102,072 students (51.7% girls) participated in the study, with a mean age of 14.33 ± 1.06 years (ranging from 11 to 19 years), and most of them were "non-white" (> 65%). Almost 60% of the adolescents were from regions with low HDI. A greater proportion of the girls reported that they had been victims of bullying. Approximately one third of the adolescents reported watching TV for more than four hours per day. The prevalence of insomnia was more than twice as high for the girls (15.6%), compared with the boys. The proportion of the boys (13.4%) who declared that they had been active for at least 60 minutes/day, in the seven days prior to the survey, was three times higher than the proportion of the girls (4.3%).

In the crude and adjusted associations between daily PA and insomnia, according to sex and HDI of the Brazilian regions (**Table 2**), it was observed that, compared with their most inactive peers (zero/no active day), girls who accumulated at least 60 minutes/day of physical activity on up to three days/week were less prone to present insomnia, regardless of the region's HDI. After adjusting the analyses, this pattern of association was maintained only for those who lived in high HDI regions (OR = 0.87; 95% CI = 0.75-0.99). On the other hand, girls who accumulated at least 60 minutes/day of physical activity on seven days presented higher odds of insomnia, even after adjusting the analyses and regardless of the region's HDI (low HDI: OR = 1.17; 95% CI = 1.01-1.35; high HDI: OR = 1.25; 95% CI = 1.05-1.48). Among the boys, there was a positive association between the number of active days and protection against insomnia, especially for those who lived in high HDI regions.

DISCUSSION

The findings of the present study demonstrated that girls who were active for at least 60 minutes/day, on up to two days/week (low HDI) and on up to three days/week (high HDI) presented lower odds of insomnia. However, girls who achieved the daily guidelines for PA on all days presented greater odds of insomnia (regardless of the region's HDI). For boys, there was a positive association between the number of active days and protection against insomnia, mainly for those who lived in regions with high HDI.

Compared with their most inactive peers (no active day), girls who were active for at least two days/week and boys who were active for at least five days/week presented lower odds of insomnia. These results were similar to previous research conducted among adolescents, which found that higher levels of PA were associated with better sleep quality.[16,17,20] However, we found that this association varied according to the number of active days/week and according to the HDI of the region, which suggested that for this group of schoolchildren the association between PA and sleep did not depend on achievement of the international PA guidelines. This is especially important since previous research had

Table 1. Descriptive characteristics of the sample according to sex (n = 102,072)

Variables	n	Total sample % (95% CI)	n	Girls % (95% CI)	n	Boys % (95% CI)
Age						
< 14 years	68,871	67.5% (67.2-67.8)	37,968	71.9 (71.5-72.3)	30,903	62.7 (62.3-63.1)
≥ 14 years	33,201	32.5% (32.2-32.8)	14,814	28.1 (27.7-28.5)	18,387	37.3 (36.9-37.7)
Ethnicity						
White	33,775	33.1% (32.8-33.4)	16,779	31.8 (31.4-32.2)	16,996	34.5 (34.1-34.9)
Other	68,189	66.9% (66.6-67.2)	35,956	68.2 (67.8-68.6)	32,233	65.5 (65.1-65.9)
Bullying						
No	53,560	52.7% (52.4-53.0)	26,439	50.2 (49.8-50.6)	27,121	55.3 (54.9-55.8)
Yes	48,117	47.3% (47.0-47.6)	26,215	49.8 (49.4-50.2)	21,902	44.7 (44.2-45.1)
HDI Brazilian regions						
Low	60,271	59.0% (58.7-59.3)	31,589	59.8 (59.4-60.3)	28,682	58.2 (57.8-58.6)
High	41,801	41.0% (40.7-41.3)	21,193	40.2 (39.7-40.6)	20,608	41.8 (41.4-42.2)
TV viewing						
≤ 2 hours	42,635	41.8% (41.6-42.2)	21,543	40.8 (40.5-41.3)	21,092	42.9 (42.5-43.4)
> 2 to ≤ 4 hours	25,819	25.4% (25.1-25.6)	12,829	24.4 (24.0-24.7)	12,990	26.4 (26.1-26.8)
> 4 hours	33,353	32.8% (32.5-33.0)	18,306	34.8 (34.3-35.2)	20,122	30.7 (30.2-31.0)
PA (days with ≥ 60 minutes)						
0	34,854	34.3% (34.0-34.6)	23,870	45.5 (45.0-45.9)	10,984	22.4 (22.1-22.8)
1	15886	15.7% (15.4-15.9)	8,651	16.5 (16.2-16.8)	7,235	14.8 (14.5-15.1)
2	13,004	12.8% (12.6-13.0)	6,263	11.9 (11.6-12.2)	6,741	13.8 (13.5-14.1)
3	10,226	10.1% (9.9-10.3)	4,221	8.0 (7.8-8.3)	6,005	12.3 (12.0-12.6)
4	6,281	6.2% (6.0-6.3)	2,376	4.5 (4.3-4.7)	3,905	8.0 (7.7-8.2)
5	7,662	7.5% (7.4-7.7)	3,126	6.0 (5.8-6.2)	4,536	9.3 (9.0-9.5)
6	4,757	4.7% (4.6-4.8)	1,717	3.3 (3.1-3.4)	3,040	6.2 (6.0-6.4)
7	8,836	8.7% (8.5-8.9)	2,295	4.3 (4.2-4.5)	6,541	13.4 (13.1-13.7)
Insomnia						
No	89,905	88.5% (88.3-88.7)	44,413	84.4 (84.1-84.7)	45,492	92.9 (92.7-93.1)
Yes	11,699	11.5% (11.3-11.7)	8,230	15.6 (15.3-15.9)	3,469	7.1 (6.9-7.3)

CI = confidence interval; HDI = Human Development Index; PA = physical activity.

suggested that although the dose-response relationship between PA and mental health outcomes was uncertain, it could occur even at lower doses.[33-35] Likewise, a study conducted with a representative sample of European adolescents suggested that even those who did not reach the international PA recommendations, but who showed moderately increased activity, could achieve a meaningful improvement in wellbeing,[36] which might extend to better sleep quality.

Furthermore, studies that investigated the association between socioeconomic status and sleep quality among adolescents showed that individuals who lived in regions with greater social and economic vulnerability slept less than those who lived in more developed areas.[37-39] Thus, the present study has added important information regarding the impact of daily PA on the sleep quality of adolescents, suggesting that social and economic vulnerability may influence not only differences in PA recommendations, but also the association between PA and sleep.

The association between PA and sleep is based on mechanisms such as thermoregulation; increased metabolic rate and energy consumption; changes to heart rate, physical fitness levels and body composition;[15] and changes to the circadian cycle.[40] Furthermore, PA is associated with reduced anxiety and depression,

Table 2. Crude and adjusted associations between daily PA (≥ 60 minutes) and insomnia, according to sex and HDI of the Brazilian regions (n = 102,072)

Variables	Girls			
	Low HDI		High HDI	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
PA (days with ≥ 60 minutes)				
0	1	1	1	1
1	0.84 (0.77-0.92)	0.86 (0.78-0.94)	0.73 (0.65-0.82)	0.74 (0.66-0.83)
2	0.87 (0.79-0.97)	0.90 (0.81-0.99)	0.85 (0.75-0.95)	0.87 (0.77-0.98)
3	0.88 (0.78-1.00)	0.90 (0.79-1.02)	0.85 (0.74-0.98)	0.87 (0.75-0.99)
4	1.12 (0.96-1.30)	1.12 (0.97-1.31)	0.97 (0.82-1.15)	0.99 (0.83-1.18)
5	0.93 (0.81-1.07)	0.93 (0.81-1.07)	0.95 (0.81-1.11)	0.96 (0.82-1.12)
6	1.15 (0.97-1.36)	1.13 (0.96-1.34)	1.01 (0.83-1.24)	0.98 (0.80-1.21)
7	1.20 (1.04-1.39)	1.17 (1.01-1.35)	1.28 (1.08-1.52)	1.25 (1.05-1.48)
Boys				
PA (days with ≥ 60 minutes)				
0	1	1	1	1
1	0.73 (0.63-0.85)	0.76 (0.66-0.88)	0.69 (0.57-0.83)	0.71 (0.59-0.86)
2	0.70 (0.60-0.82)	0.74 (0.64-0.87)	0.58 (0.47-0.70)	0.61 (0.50-0.74)
3	0.68 (0.57-0.80)	0.72 (0.61-0.85)	0.70 (0.58-0.84)	0.73 (0.60-0.89)
4	0.74 (0.61-0.89)	0.77 (0.63-0.93)	0.76 (0.62-0.94)	0.82 (0.66-1.01)
5	0.77 (0.65-0.92)	0.80 (0.67-0.96)	0.69 (0.56-0.85)	0.73 (0.59-0.91)
6	0.81 (0.66-0.99)	0.83 (0.68-1.02)	0.75 (0.59-0.95)	0.78 (0.61-0.99)
7	0.93 (0.81-1.08)	0.96 (0.83-1.12)	0.79 (0.66-0.94)	0.83 (0.69-0.99)

HDI = Human Development Index; OR = odds ratio; CI = confidence interval; PA = physical activity.
Analysis adjusted for age group, ethnicity, bullying and TV viewing.

increased self-esteem and increased psychological wellbeing, which, in turn, may mediate the relationship between PA and sleep.[40]

Cross-sectional data from a previous survey carried out in the United States showed that only adolescents who were active for ≥ 60 minutes/day, on seven days per week, reported having sufficient amounts of sleep.[18] On the other hand, we observed that even adolescents who did not reach the weekly PA guidelines,[41] but who were active on at least two days/week (girls) and five days/week (boys), had better sleep quality, as also pointed out in other research.[15,19] In addition, our results reinforce the differences in the association between PA and insomnia according to sex, thus corroborating previous findings,[16,19] as well as highlighting the importance of planning tailored interventions that take into account the impact of social and economic vulnerabilities on health outcomes.

One interesting finding was that girls who were active for at least 60 minutes/day, on seven days per week, presented greater odds of insomnia, regardless of the HDI of the region in which they lived. This result is similar to that of previous studies,[20,36] in which it was concluded that the subgroup of girls with high PA levels might include adolescents who over-exercise and who are more susceptible to stressors, such as depression symptoms and anxiety,[36] which are associated with insomnia. Furthermore, an association among girls between over-exercise and sleep disorders has been documented among elite athletes,[42,43] such that a high training load was associated with higher prevalence of insomnia, compared with male athletes.[43]

Unfortunately, the PeNSE 2015 data did not allow investigation of the influence of potential mediators, such as social and physical environmental features, like noise and air pollution, traffic, light exposure and safety, which can mediate the relationship between PA and sleep quality.[27,28] Furthermore, the association among girls between over-exercise and insomnia occurred regardless of the region's HDI, and persisted even after controlling for possible confounding variables such as age, ethnicity, bullying and TV viewing, thus suggesting that other mediators that were not evaluated through PeNSE 2015 may be involved. Future research

should investigate other possible mediators between excessive PA and insomnia, especially among girls.

Despite the relevance of the results highlighted here, the present study had some limitations. First, the data analyzed were based on questionnaires, which are more subject to recall bias. Nevertheless, questionnaires are viable low-cost instruments and have become well established in epidemiological research worldwide.[44] Second, subjective sleep assessment did not allow analysis of other sleep outcomes, such as bedtime, sleep onset latency, waking time after sleep onset and total sleep time, or their possible associations with PA.[15] Third, the dichotomization of the study variables may have attenuated the power to detect associations.[45]

However, the study also had some strengths. First, this was one of the few studies to analyze the association between daily PA and insomnia among adolescents who were not living in developed countries, and it also took social and economic vulnerability into consideration. Second, given that this survey was based on a sample with national representation, the results can be generalized for the Brazilian population of school-age adolescents.[46]

CONCLUSION

Even amounts of physical activity that were lower than the weekly guidelines were associated with better sleep quality for Brazilian adolescents, especially girls, and even for those who were living in regions with greater social and economic vulnerability. Thus, the present study has important implications for policy makers. It highlights the need to consider regional inequalities and it shows that physical activity-based interventions can be targeted as a low-cost, non-pharmacological and widely viable alternative that may foster better sleep quality among adolescents. Further research should encourage use of prospective data to better understand the relationship between daily physical activity and sleep quality, taking into account the influence of social and economic vulnerability.

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COVID-19 pandemic in São Paulo: a quantitative study on clinical practice and mental health among medical residency specialties

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ABSTRACT

BACKGROUND: 2020 was a challenging year for all healthcare professionals worldwide. In São Paulo, Brazil, the virus SARS-CoV-2 took 47,222 lives up to December 29, 2020. The front line of medical professionals in São Paulo was composed of many residents, who were transferred from their rotations to cover the needs of the pandemic.

OBJECTIVE: To identify medical residents' mental health and clinical issues, regarding symptoms of burnout, depression and anxiety during the pandemic, and to compare them among specialties.

DESIGN AND SETTING: Quantitative study using a convenience sample of medical resident volunteers who responded to an anonymous online survey that was available during April 2020.

METHODS: This investigation collected sociodemographic information and used the Oldenburg Burnout Inventory (OLBI) to measure burnout, the Patient Health Questionnaire (PHQ-9) to measure depression and the General Anxiety Disorder (GAD-7) scale to measure anxiety symptoms. This study also developed a COVID-19 Impact Questionnaire (CIQ-19) to assess the residents' beliefs and clinical practices relating to COVID-19 patients.

RESULTS: The sample comprised 1,392 medical residents in São Paulo, Brazil. Clinical specialty physicians showed the highest rates of anxiety symptoms (52.6%) and burnout (51.2%), among the specialties.

CONCLUSION: Clinical specialty residents are at higher risk of anxiety, depression and burnout. The symptoms of anxiety and depression have worsened during the COVID-19 pandemic. There is a general need for mental health support interventions for medical resident physicians, which requires reinforcement during this worldwide crisis.

INTRODUCTION

In December 2019, a new disease caused by the virus SARS-CoV-2, popularly called coronavirus disease 2019 (COVID-19), was identified in Wuhan, China. This disease has high infectivity and transmissibility rates, with a reproductive number greater than one.[1] Since then, as stated by the World Health Organization (WHO), as of December 29, 2020, there were more than 79,231,893 cases and 1,754,574 deaths worldwide. Brazil was the epicenter of the pandemic with more than 7,448,560 cases and 190,488 deaths. São Paulo had 1,486,551 cases and 47,222 deaths up to December 29, 2020.[2]

Around the world, physicians of various specialties were called up to work in the fight against COVID-19.[3-6] Among these professionals, medical residents were reallocated from their rotations, to work in emergency departments, intensive care units and COVID-19 wards, in order to supply the need for medical personnel.[7,8]

São Paulo is the most populous city in Brazil and also the fourth largest city in the world by population. This city is an important focal point for the field of healthcare and has the highest concentration of physicians in the country, around 146,970 professionals. Among them, 18,236 were working as medical residents in 2019, which represented 33.9% of all medical residents in Brazil.[9]

Along with training and structural safety issues, the psychological effects on healthcare workers need to be discussed. During the last decade, motivated by alarming numbers of cases of mental illness and suicides in the medical community, the issues of mental health and the need for new perspectives of care have been highlighted.[10-12] Previous studies that analyzed the psychological effects of emerging virus outbreaks on healthcare workers found that staff in high-risk areas

exhibited increased levels of acute or posttraumatic stress and psychological distress.[13] The risk factors included younger age and less experience: two aspects that may be related to medical residents, a group that clearly needs guidance from more experienced staff to help them achieve the required knowledge and ethical maturity to deal with the difficulties and feelings inherent to this period, which can be an extremely rich learning experience.[14]

OBJECTIVE

The purpose of this study was to identify the mental health and clinical issues of medical residents in São Paulo, Brazil, regarding collective symptoms of burnout, depression and anxiety during the COVID-19 pandemic and compare them among medical specialties.

METHODS

Study design and procedures

A quantitative study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) parameters, to identify the clinical practice and mental health issues of medical residents in São Paulo, regarding their collective symptoms of burnout, depression and anxiety during the COVID-19 pandemic.

This study used a convenience sample from an anonymous online survey that was advertised through social media and distributed by means of e-mails from the residency committees of hospitals that are linked to universities and medical associations in São Paulo. Given that a convenience sample was used, no calculation of sample size was performed. Advertisement of the research was performed in line with the good practice guidelines.[15] There was no financial support for the volunteers who responded to the survey. The survey was available during the month of April 2020 in São Paulo.

Study measurements and analysis

This investigation collected sociodemographic information and used the Oldenburg Burnout Inventory (OLBI) to measure burnout, the Patient Health Questionnaire (PHQ-9) to measure depression and the General Anxiety Disorders (GAD-7) to measure anxiety symptoms.[16-18] All three scales had previously been adapted and validated for use in Brazilian contexts and populations. This study also developed a COVID-19 Impact Questionnaire (CIQ-19) to assess the residents' beliefs and clinical practices relating to COVID-19 patients, their behaviors concerning disease prevention and their substance use after the beginning of the pandemic. All fields were marked as mandatory, so a participant could move forward only after answering all questions. Therefore, all the participants included completed the entire questionnaire, and no data were missing. The protocol was reviewed and approved by the Universidade Federal de São Paulo (UNIFESP) Research Ethics Committee (Protocol #3,943,348; on March 20, 2020).

Exploratory analyses were conducted using basic contingency tables with analysis of variance (ANOVA), Mann-Whitney U test and Fisher's test. All analyses were controlled according to specialty areas: clinical specialties, surgical specialties and diagnostic and therapeutic support (i.e. pathology, radiotherapy and nuclear medicine). The residents' sociodemographic variables, gender and ethnicity characteristics, the nature of the hospital (public or private), year of medical residency and contact with COVID-19 patients were described. We also identified clinical issues and beliefs regarding COVID-19 and mental healthcare. Burnout was defined as positive if the total score on OLBI was 21; anxiety was defined as positive if the total score on GAD-7 was 10 or greater. For the variable "depression". three categories were used: no depression or mild depression (PHQ-9 score of nine or less), moderate (PHQ-9 score between 10 and 14) and severe depression (PHQ-9 score of 15 or higher).

The analyses were performed using SPSS Statistics for Windows, version 22.0 (released 2013; IBM Corp, Armonk, NY, United States) and the statistical significance level was taken to be 0.05. The results were presented as proportions and distributions of scores in the categories of each scale (frequencies).

RESULTS

This sample comprised 1392 residents in São Paulo, Brazil. The response rate represented approximately 8% of the medical residents in the state. These residents comprised 914 in clinical specialties, 336 in surgical specialties and 142 in diagnostic and therapeutic support. Most were women (72.5%), white (81.0%), first-year residents (35.4%), in a program provided by a public hospital (84.8%) and in close contact with COVID-19 patients (69.8%). The mean age of the sample was 27.9 years (standard deviation, SD: 3.0) (**Table 1**).

Our findings were significant with regard to mental health scales, COVID-19 aspects of clinical practice and mental healthcare among medical residents training in São Paulo.

Depressive symptoms were the most common (65.8%), followed by anxiety symptoms (49.7%) and burnout (49.2%) among these residents. We also observed anxiety symptoms (52.6%) and burnout (51.2%) among clinical specialties (**Table 2**).

In terms of aspects of COVID-19, residents in surgical specialties were less likely to feel that they themselves and their hospital were sufficiently prepared to treat patients with this disease (46.4% and 33.6%, respectively). The residents in these specialties also revealed that there was a lack of supervisor support for treating COVID-19 patients (55.6%).

Residents said that their personal protection equipment (PPE) was not efficacious (47.2%), felt that they would be better

Table 1. Descriptive statistics on medical residents in São Paulo, 2020

Descriptive		Specialty of medical residency[a]								P-value
		Clinical specialties n = 914		Surgical specialties n = 336		Diagnostic and therapeutic support n = 142		Total n = 1392		
		n	%	n	%	n	%	n	%	
Gender	Male	202	22.1	125	37.2	55	38.7	382	27.4	< 0.05
	Female	702	76.8	211	62.7	87	61.2	1010	72.5	
Ethnicity	White	746	81.6	271	80.6	111	78.1	1128	81.0	> 0.05
	Non-white	168	18.3	65	19.3	31	21.8	264	18.9	
Nature of hospital	Public	807	88.2	285	84.8	89	62.6	1181	84.8	< 0.05
	Private	107	11.7	51	15.1	53	37.3	211	15.1	
Year of residency	R1	325	35.5	119	35.4	49	34.5	493	35.4	< 0.05
	R2	269	29.4	95	28.2	43	30.2	407	29.2	
	R3	163	17.8	66	19.6	44	31.0	273	19.6	
	R4	122	13.3	27	8.0	4	2.8	153	11.0	
	R5	30	3.2	21	6.2	2	1.4	53	3.8	
	R6	5	0.5	8	2.3	-	-	13	0.9	
Do you have contact with COVID-19 patients?	Yes	674	73.7	201	59.8	98	69.0	973	69.8	< 0.05
	No	240	26.2	135	40.1	44	31.0	419	30.1	

[a]As described in the Methods section.

Table 2. Mental health scale scores for medical residents in São Paulo, 2020

Mental Health		Specialty of medical residency								P-value
		Clinical specialties n = 914		Surgical specialties n = 336		Diagnostic and therapeutic support n = 142		Total n = 1392		
		n	%	n	%	n	%	n	%	
Depression[a]	Absent or mild	287	31.4	137	40.7	51	35.9	475	34.1	< 0.05
	Moderate	244	26.6	93	27.6	46	32.3	383	27.5	
	Severe	383	41.9	106	31.5	45	31.6	534	38.3	
Anxiety[b]	Absent or mild	433	47.3	191	56.8	76	53.5	700	50.2	< 0.05
	Moderate or severe	481	52.6	145	43.1	66	46.4	692	49.7	
Burnout[c]	Absent or mild	446	48.7	182	54.1	78	54.9	706	50.7	< 0.05
	Moderate or severe	468	51.2	154	45.8	64	45.0	686	49.2	

[a]According to the Patient Health Questionnaire (PHQ-9); [b]According to the General Anxiety Disorder (GAD-7) scale; [c]According to the Oldenburg Burnout Inventory (OLBI).

professionals after the pandemic (80.3%), felt significantly worried about getting COVID-19 and transmitting it to their partners and families (90.5%) and had experienced impairment of personal relationships since the pandemic started (75.0%). There was no significant increase in substance use among them (**Table 3**).

Our sample revealed how the medical residents had been coping with their mental health. Residents in clinical and surgical specialties preferred to talk with family or friends (48.8% and 29.0%, respectively). Those in surgical specialties also chose to discuss matters with their team support (26.3%) when they need mental healthcare. On the other hand, this same group did nothing about their mental healthcare (17.8%), and only 4.0% among the residents in clinical specialties mentioned psychotherapy in relation to their mental healthcare (**Table 4**).

Table 3. Frequencies of perceptions regarding COVID-19 among medical residents in São Paulo, 2020

		Specialty of medical residency								P-value
		Clinical specialties n = 914		Surgical specialties n = 336		Diagnostic and therapeutic support n = 142		Total n = 1392		
		n	%	n	%	n	%	n	%	
COVID-19 clinical practice and beliefs	The hospital is prepared for treating patients with COVID-19	704	77.0	156	46.4	99	69.7	959	68.8	< 0.05
	Residents feel prepared for treating patients with COVID-19	453	49.5	113	33.6	92	64.7	658	47.2	< 0.05
	Supervisors do not provide the necessary support for treating patients with COVID-19	203	22.2	187	55.6	77	54.2	467	33.5	> 0.05
	Hospital provides personal protection equipment	449	49.1	120	35.7	88	61.9	657	47.2	< 0.05
	I feel I will be a better professional after the pandemic	744	81.4	269	80.0	106	74.6	1119	80.3	< 0.05
COVID-19 behaviors	Afraid of getting COVID-19 and transmitting it to my partner and family	841	92.0	303	90.1	117	82.3	1261	90.5	> 0.05
	Personal relationships impaired since the pandemic started	737	80.6	205	61.0	102	71.8	1044	75.0	< 0.05
Substance use after pandemic started	Increase in alcohol use	325	35.5	39	11.6	56	39.4	420	30.1	> 0.05
	Increase in tobacco use	350	38.2	71	21.1	42	29.5	463	33.2	< 0.05

Table 4. Frequency of mental healthcare among medical residents in São Paulo, 2020

		Specialty of medical residency								P-value
		Clinical specialties n = 914		Surgical specialties n = 336		Diagnostic and therapeutic support n = 142		Total n = 1392		
		n	%	n	%	n	%	n	%	
Mental healthcare[a]	Talking to friends/family	758	48.8	194	29.0	69	13.5	1021	37.4	< 0.05
	Team support	302	19.4	176	26.3	84	16.5	562	20.6	
	Physical activity	264	17.0	46	6.8	97	19.0	407	14.9	
	Nothing	111	7.1	119	17.8	69	13.5	299	10.9	
	Others	54	3.4	76	11.3	99	19.4	229	8.3	
	Psychotherapy	63	4.0	57	8.5	90	17.7	210	7.6	
Total responses		**1552**	**56.8**	**668**	**24.4**	**508**	**18.6**	**2728**	**100.0**	

[a]Multiple responses.

DISCUSSION

Three main findings emerged from this study among medical residents from a convenience sample in São Paulo: depression, anxiety and burnout are frequent among residents in clinical specialties working in the COVID-19 pandemic; exposure to COVID-19 patients may be related to changes in clinical practice, personal behavior and substance use in all three specialty areas; different fears, confidences and beliefs showed that there was low mental healthcare in the three specialty areas.

Medical residents' mental health was already a topic that worried medical educators worldwide, even before the pandemic scenario emerged. In the light of this worldwide scenario, we observed

that clinical specialties had higher rates of depression, anxiety and burnout symptoms than other ones. A previous study reported that the prevalence of depression or depressive symptoms among resident physicians was 28.8%, with a range from 20.9% to 43.2%.[11] In 2014, the prevalence rates for anxiety, depression and burnout were 41.3%, 21.6% and 58.4% respectively, among Brazilian residents. Thus, although the prevalence of burnout that was identified was similar to that of the pre-pandemic scenario, symptoms of anxiety were increased twofold and symptoms of depression exhibited an approximately threefold increase in the scenario of the COVID-19 pandemic.[19] These findings are similar to those of a survey of 1,257 healthcare workers who were in contact with COVID-19 patients in China, in which high rates of depression (50.4%), anxiety (44.6%) and distress (71.5%) were reported using the same instruments as those used in our study.[20] Mental distress was also reported in Italy, where only 20% to 25% of healthcare workers declared that they felt psychologically safe and only 48% reported having access to mental healthcare.[21]

Another study observed that the prevalence of burnout among surgical residents was 69%. This rate was associated with high levels of stress, depression and suicidal ideation. Surgical trainees have purposefully chosen a field with high baseline stress by definition, presumably due in part to the widely held belief among surgeons that not all stress is bad. Although burnout among them is known to be high, it is not clear whether stress and distress have the same strong associations with burnout, depression and anxiety symptoms, as seen in other medical specialties.[22]

Unfortunately, we did not find any Brazilian studies that compared medical specialties. To our knowledge, our study is the first to show a relevant difference among residents in medical specialties regarding the collective symptoms of burnout, depression and anxiety. Similar results have been found recently in studies among medical residents without comparing areas of specialties.[11,19] Two of these studies included Brazilian residents as participants. Given our findings relating to different behaviors among medical residents exposed to patients infected with or suspected of being infected with COVID-19, and the factors correlated with the development of mental disorder symptoms, it is necessary to develop interventional programs to prevent mental illness.

This investigation found that residents did not feel prepared to treat patients with COVID-19 and were afraid of getting it. Since these individuals believed that talking to colleagues and immediate line managers protected their mental health, it can be suggested that supervisors and peers should pay attention to residents with signs of at-risk behavior.[23] However, in the surgical specialty, the residents stated that there was a lack of support from supervisors during the treatment of these patients. Resident support groups can be a powerful resource for preventing psychological impacts, along with wider support networks, including the friends and family of medical residents, who may help them by keeping in touch through online resources. However, 10.9% of the residents stated that they had not had any care for their mental health during the COVID-19 pandemic.

There are only a few studies on medical residents' mental health during the COVID-19 pandemic. Although residents represent only a fraction of healthcare workers, their participation on the COVID-19 frontline is evident. A previous study highlighted that healthcare professionals suffer more stigma than the general population and are consistently more affected psychologically after quarantine.[24] Our participants reported that their personal relationships had become impaired since the pandemic started. This situation may lead to a greater chance of developing burnout, anxiety and depression symptoms.

A review on Brazilian medical residents indicated that in the state of São Paulo, most physicians are concentrated in the clinical specialty, in which supervisors are perceived to be important in the clinical practice process. That study also corroborates our findings, through stating that significant situations such as a pandemic or an outbreak of a certain disease make the medical professional realize the importance of residents' work and favors their professional growth. In our study, 80.3% of residents perceived this, in affirming they may become better professionals through their experience in the pandemic.[9]

The results from the present study suggested that there had not been any significant increase in substance use among these residents. However, another study found that residents in surgical specialties were more likely to present alcohol dependence than were residents in clinical specialties. Another study among practicing surgeons in the United States showed that alcohol abuse and dependence are a significant problem in that population. It is necessary to assess the relationship between substance dependence and personality among medical residents, since these are risk factors for this population.[25,26]

The cross-sectional design chosen for the present study was suitable for investigating associations and for providing wide-ranging data for discussion, but it does not allow inferences of causality. In addition, since our sample was restricted to one state in Brazil, further studies should investigate whether the trend cited above is replicable in other countries. Therefore, caution is needed with regard to generalizations of these results to distinct populations.

CONCLUSION

This study was conducted during the worldwide crisis of the COVID-19 pandemic. It is understandable that most of our sample of physicians undergoing training felt unprepared to deal with COVID-19 patients. This was one of the variables related to increased mental illness, such as depression, anxiety and burnout.

Residents in clinical specialties seem to be at higher risk of depression, anxiety and burnout during the pandemic, but previous studies that have been conducted outside of this scenario have shown the same results. Our findings from comparisons between specialties among Brazilian resident physicians highlights the need to better explore mental health in this population, since surgical specialties did not follow a trend towards higher rates, which was restricted to the clinical group.

This study demonstrates that there is a general need for better access to mental health professionals for resident physicians, which has been reinforced during the COVID-19 pandemic. Moreover, the feeling that support from staff is available appears to have a protective function in relation to mental health. Therefore, we suggest that support groups might give rise to the possibility of assessing mental health. We also emphasize that there is a need for more comparative studies between medical specialties.

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Women's health anxiety and psychological wellbeing during the COVID-19 pandemic. A descriptive study

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ABSTRACT

BACKGROUND: The rapid spread of the novel coronavirus (COVID-19) outbreak has led to extraordinary measures taken worldwide and has led to serious psychological disorders. With the measures taken, the difficulties in women's daily lives are increasing exponentially. This situation has caused women to experience more mental health problems.

OBJECTIVE: To identify the relationship between women's health anxiety and psychological wellbeing and the factors affecting these situations during the COVID-19 pandemic.

DESIGN AND SETTING: Descriptive study conducted online among women living in Adana, Turkey.

METHOD: This descriptive study was conducted among 623 married women between April 1 and April 20, 2020, using a SurveyMonkey online questionnaire. Data were collected using the link that was established. The questions comprised personal information, perceptions regarding the pandemic, the Health Anxiety Inventory (Short Form) and the Psychological Wellbeing Scale.

RESULTS: The women who participated were found to have a high level of anxiety and a moderate level of psychological wellbeing. A positive, moderate-level relationship was found between the scales.

CONCLUSIONS: The COVID-19 pandemic has had negative effects on both physical and psychological health. Support for women, to be provided within their holistic understanding of care, is of great importance for maintaining the psychological health of society.

INTRODUCTION

The novel coronavirus (COVID-19) emerged in Wuhan, China, in December 2019 and spread all over the world rapidly. It was declared to be a pandemic by the World Health Organization (WHO) on March 11, 2020 (WHO, 2020). When the first case was detected in Turkey, which was on the same date, the pandemic started to affect all parts of society dramatically.[1-4] Since then, it has caused many physical, psychological, social and economic changes to people's lives.[5] In many countries, including Turkey, people's practices within daily life have been interrupted by lockdown, social isolation or self-isolation.[6-8] Current studies on the COVID-19 pandemic have reported overreactions in society caused by common fear. In particular, it has been reported that individuals who survived and healthcare professionals experienced psychiatric disorders such as anxiety, depression and post-traumatic stress disorder.[9-12]

Health anxiety is defined as a constant, excessive and irrational worry that is present despite an absence of physical or psychological disease.[13] Women with high anxiety levels have difficulties in maintaining the activities of their daily lives, through experiencing uneasiness, difficulty in concentration, sleep disorders, fatigue and anger.

Psychological wellbeing is defined as pursuit of a meaningful life through having positive self-perceptions, managing oneself in times of difficulties and identifying strengths and limits for a meaningful life.[14] Worsening of women's levels of psychological wellbeing levels could lead to psychological problems, economic losses, exclusion from one's circles of friends, worsening of family relationships and increased stress levels. COVID-19 causes anxiety because it affects people's lives negatively and brings many uncertainties to society. Since the virus has a high rate of spreading from person to person, it causes pressure in personal relationships, and the anxiety increases due to uncertainties regarding how long the pandemic will last and how long its effects will continue.[5,15] Feelings of anxiety and stress in daily life during the pandemic also have negative effects on psychological wellbeing.[9,16]

It has been reported in the literature that women are exposed to more stress; they experience psychological problems more commonly; and, compared with men, the prevalence of life-long depression among women is 1.7 to 2.7 times higher.[17-20] Traditional patriarchal family structure is dominant in Turkey. For women, meeting their children's needs, doing housework, cleaning, cooking, etc. and continuing to work from home have increased women's responsibilities at home during the lockdown. This situation has increased women's risk of experiencing more psychological problems. Moreover, with the lockdown conditions caused by the pandemic and the social isolation precautions, the economic and social isolation experienced by women has become deeper day by day, and gender-based violence against women has increased incrementally.[12,21] Women's role in maintaining family life is highly important; hence, negative effects on their psychological health are somewhat inevitable in this process. Maintaining women's health is of great importance in terms of maintaining family life as well as community health.

A review of the literature relating to this topic indicated that numerous studies on people's psychological health in the COVID-19 pandemic have been conducted.[10,20,22-26] However, no studies at national level were found to have investigated women's health anxiety and psychological wellbeing in Turkey during the COVID-19 pandemic.

OBJECTIVE

The aim of this study was to identify the relationship between health anxiety and psychological wellbeing and the factors affecting this, among women aged between 18 and 60 years during the COVID-19 pandemic.

METHODS

Study design and setting

The present research was designed as a descriptive study. The study was conducted among married women living in Adana, Turkey, between April 1 and April 20, 2020.

Target population and sample

The target population of the study was 435,510 married women aged between 18 and 60 who were living in Adana.[27] The minimum sample size to represent the female population in this study was calculated using the method of the Australian Bureau of Statistics (with 95% confidence interval and 5% margin of error), which indicated a sample of 535 women.[28] Considering possible data loss, the sample size was increased by 25%, to become 625 people. During the study period, a total of 865 women living in Adana were approached. However, 142 questionnaires were not included in the analysis because the data had not been filled in accurately. Thus, the study was completed with 623 questionnaires. The study sample comprised volunteer female participants who had the necessary skills for filling in the online form, who were aged between 18 and 60, who were married, who were healthy and who had at least one child.

Data collection

The questionnaires were put into SurveyMonkey, which is an online questionnaire system (https://tr.surveymonkey.com/r/VGMMZR5). The questionnaire link was shared with women through WhatsApp. The online questionnaire system was set up such that it only allowed one participant per internet protocol address (IP number). Thus, only one questionnaire could be completed by each participant.

Data collection forms and tools

Data were collected using the link formed by https://tr.surveymonkey.com/r/VGMMZR5. The online data forms contained questions of four types: personal information; perceptions about the pandemic; the Health Anxiety Inventory (HAI) (brief version); and the Psychological Wellbeing Scale (PWS).

Personal information form

This form was prepared by the researchers in line with the literature and included eight questions about the women's sociodemographic features.[3,26]

Perceptions about the pandemic form

This form was prepared by the researchers in line with the literature[3,26] and was composed of nine questions on the women's perceptions about the COVID-19 pandemic. The participants responded to the questions in this form as "agree" or "disagree". The questions asked for responses to the following statements "COVID-19 is not as dangerous as it is said to be" (PP1); "COVID-19 is a fatal disease" (PP2); "COVID-19 can infect anyone" (PP3); "COVID-19 can infect men and women with equal probability" (PP4); "COVID-19 vaccination will soon be found" (PP5); "COVID-19 will not infect me if I am careful about my personal hygiene" (PP6); "COVID-19 will not affect me if I am careful about my diet" (PP7); "No matter how many precautions are taken, it might not be possible to prevent COVID-19 infection" (PP8); and "Preventive measures against COVID-19 that are being implemented in Turkey are sufficient" (PP9).

Health anxiety inventory

The health anxiety inventory (HAI) is an 18-item, self-report scale developed by Salkovskis et al.[29] Each item is scored between 0 and 3, and the total score ranges from 0 to 54. Higher scores indicate higher health anxiety. The HAI has two subscales, named "Hypersensitivity about Structural and Physical Symptoms" and "Anxiety and Fear of Illness". The "Hypersensitivity about

Structural and Physical Symptoms" subscale is formed by items 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14; and the "Anxiety and Fear of Illness" subscale is formed by items 15,16,17 and 18. The validity and reliability of the HAI for use in Turkey were assessed by Aydemir et al.[13] The Cronbach's alpha value of the HAI adapted to Turkish by Aydemir et al. was reported to be 0.918.[13] In our study, the Cronbach's alpha value of the HAI was found to be 0.773.

Psychological wellbeing scale

This scale, developed by Diener et al.[30] to measure women's psychological wellbeing, was adapted for use in Turkish by Özmete et al.[31] The scale consists of three subscales called "General Emotions", "Satisfaction with Economic, Family and Individual Conditions" and "Maintaining out-of-home activities". Items 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18 form the General Emotions subscale; items 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and 32 form the "Satisfaction with Economic, Family and Individual Conditions" subscale; and items 33, 34, 35 and 36 form the "Maintaining out-of-home activities" subscale. The responses to these items are recorded on a 5-point Likert scale as follows: 5 = I totally disagree; 4 = I disagree; 3 = I am not sure; 2 = I agree; and 1 = I totally agree. As some of the items in the scale (items 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 29, 30, 31, 32, 33 and 34) include negative meanings, these items are scored reversely. Each item is scored between 1 and 5, and the total scores can range from 36 to 180 points. High scores indicate a high level of psychological wellbeing.[31] The Cronbach's alpha values of the subscales of the Psychological Wellbeing Scale (PWS) adapted to Turkish by Özmete et al. were reported to be 0.86, 0.88 and 0.86.[31] In our study, we found the Cronbach's alpha values of the subscales of the PWS to be 0.75, 0.92 and 0.76.

Statistical analysis on the data

The data were analyzed using the IBM SPSS statistics software, version 22 (IBM SPSS, Turkey). The normality of the data distribution was assessed using the Shapiro-Wilk test, and the data were found to be distributed normally. The data analysis included descriptive statistical methods (means, standard deviations and frequencies) as well as inter-group assessments of quantitative data, such as through using the independent t test. Data analysis between more than two groups was performed using one-way analysis of variance (ANOVA) test. The groups that caused differences were identified using post-hoc tests. The analysis on relationships between the scales was performed using Pearson's correlation analysis. The statistical significance level was taken to be $P < 0.05$.

Ethical considerations

Academic committee approval was obtained from the Faculty of Health Sciences at our university. A formal document, indicating that no ethics committee approval was needed (since the study was a field study) was obtained from the Medical Faculty Non-Interventional Clinical Research Ethics Committee of our university (Number: 50243401/2020-6; June 2020). In addition, informed consent was obtained from the individuals who participated in the study.

RESULTS

This study found that 65% of the participating women had a university education or above, 76.7% had children aged 18 and below, 64.7% lived in the city, 62.3% worked and 69.5% perceived that they had a medium-level income (**Table 1**). The average age of the participating women was 38.9 ± 9.87 years (range: 18 to 60); the average number of children aged 18 and younger was 1.29 ± 0.846 (range: 0 to 4); and the average number of children aged 19 and older was 1.00 ± 0.909 (range: 0 to 6).

Table 1 also demonstrates the findings relating to comparison of the mean HAI and PWS scores according to the women's sociodemographic features. Significant differences in total mean HAI scores were detected in relation to the women's age, education level, income level and place of residence ($P < 0.01$). Through more detailed analysis, the results indicated that the total mean HAI scores were lower among women who were aged 30 and younger, who had an education level of university and above, whose perceived income was high and who lived in a village ($P < 0.05$). Significant differences in total PWS scores were found in relation to the variables of age, education level, income level and place of residence ($P < 0.01$). The more detailed analysis indicated that the total mean PWS scores were higher among women who were aged 30 and younger, who were primary/secondary school graduates, whose perceived income was medium and who lived in a village ($P < 0.05$).

A statistically significant difference in the women's total mean HAI scores was found in relation to responses to the question PP2 ($P < 0.05$). The health anxiety total scores of women who agreed with the statement "COVID-19 is a fatal disease" was found to be lower (**Table 2**). A statistically significant difference in the women's mean PWS scores was found in relation to responses to the questions PP2 and PP6 ($P < 0.05$) (**Table 2**). Psychological wellbeing was better among the women who agreed with the statements "COVID-19 is a fatal disease" and "COVID-19 will not infect me if I am careful about my personal hygiene" (**Table 2**).

The total mean HAI score of the participating women were found to be 44.00 ± 2.83, and the total mean PWS score was 102.27 ± 14.45 (**Table 3**). The mean scores for other subscales are presented in **Table 3**.

This study found that there was a positive high-level relationship between the PWS general emotions subscale and HAI total mean scores ($P < 0.01$). A positive medium-level relationship was detected between the total mean HAI score and the total mean PWS score ($P < 0.05$). Hence, the level of psychological wellbeing and the level on the general emotions subscale deteriorated as the mean health anxiety scores increased (**Table 4**).

DISCUSSION

This study examined the relationship between health anxiety and psychological wellbeing and the factors affecting them, among women during the COVID-19 pandemic.

Comparison of the total mean HAI and PWS scores according to the participating women's sociodemographic features indicated that the women's anxiety increased and their psychological wellbeing decreased with increasing age. Tutku et al. reported that women's health anxiety was significantly higher, and that anxiety levels increased with increasing age.[26] Oju et al. reported that young age was associated with low anxiety.[24] They also reported that especially among individuals aged 18 and younger, anxiety scores were low, which was considered to be associated with the facts that morbidity rates were lower among individuals aged younger than 18, they were affected by lockdown less and they were at lower risk of becoming infected. Oju et al. reasoned that since deaths due to COVID-19 were most common among elderly individuals,[24] higher anxiety and lower psychological wellbeing among these individuals were expected findings in their study. The findings from the present study are in line with those from studies in the literature, in that the levels of anxiety and psychological wellbeing during the pandemic varied depending on age, such that individuals were affected negatively with increasing age.

Table 1. Findings regarding comparison of HAI and PWS according to the women's sociodemographic characteristics (n = 623)

Demographic characteristics			Total HAI		HAI Hypersensitivity to structural and physical symptoms		HAI Fear of anxiety and disease		Total PWS		PWS General emotions		PWS Satisfaction with economic, family and individual conditions		PWS Maintaining out-of-home activities	
	n	%	χ ± SD	Statistical test	χ ± SD	Statistical test	χ ± SD	Statistical test	χ ± SD	Statistical test	χ ± SD	Statistical test	χ ± SD	Statistical test	χ ± SD	Statistical test
Age																
≤ 30	150	24.1	43.83 ± 2.70		37.16 ± 2.56		9.79 ± 1.46		103.33 ± 13.49		59.05 ± 12.72		30.86 ± 10.36		12.21 ± 3.24	
31-40	228	36.6	44.09 ± 2.75	F = 0.410 **P = 0.000****	37.56 ± 2.64	F = 1.237 P = 0.291	9.64 ± 1.48	F = 0.447 P = 0.640	102.11 ± 15.66	F = 1.261 **P = 0.000****	58.40 ± 12.90	F = 1.604 P = 0.202	30.59 ± 9.00	F = 0.071 P = 0.993	12.24 ± 3.48	F = 0.214 P = 0.808
≥ 41	245	39.3	44.02 ± 2.97		37.53 ± 2.59		9.67 ± 1.46		101.23 ± 14.61		60.39 ± 11.30		30.89 ± 9.085		12.05 ± 3.13	
Education																
Primary/ secondary school	75	12	44.08 ± 2.37		37.94 ± 3.19		9.84 ± 1.17		103.41 ± 17.00		56.26 ± 14.39		31.60 ± 9.83		12.18 ± 3.84	
High school	143	23	44.19 ± 3.83	F = 2.035 **P = 0.000****	37.52 ± 2.71	F = 1.448 P = 0.228	9.58 ± 1.51	F = 1.097 P = 0.350	101.72 ± 7.87	F = 0.707 **P = 0.000****	61.12 ± 10.72	F = 1.296 P = 0.275	28.52 ± 8.34	F = 1.145 P = 0.330	12.08 ± 3.16	F = 0.449 P = 0.718
University and above	405	65	43.83 ± 2.59		37.30 ± 2.43		9.68 ± 1.40		102.94 ± 12.94		59.32 ± 11.81		31.65 ± 10.36		12.43 ± 3.31	
Working status																
Employed	388	62.3	44.04 ± 2.82	t = 0.478	37.51 ± 2.62	t = 0.760	9.71 ± 1.39	t = 0.621	102.13 ± 13.85	t = -0.316	59.68 ± 12.47	t = 0.880	30.26 ± 8.51	t = -1.779	12.203.26	t = 0.385
Unemployed	235	37.7	43.93 ± 2.83	P = 0.633	37.35 ± 2.58	P = 0.447	9.66 ± 1.58	P = 0.686	102.51 ± 15.451	P = 0.213	58.78 ± 11.92	P = 0.379	31.63 ± 10.58	P = 0.076	12.093.32	P = 0.700
Perceived income level																
High	139	22.3	43.91 ± 2.73		37.54 ± 2.60		9.39 ± 1.34		100.96 ± 12.03		60.63 ± 11.97		28.37 ± 7.94		11.963.03	
Medium	433	69.5	43.95 ± 2.86	F = 1.642 **P = 0.000****	37.38 ± 2.61	F = 0.883 P = 0.435	9.74 ± 1.46	F = 5.670 P = 0.107	102.67 ± 14.89	F = 0.734 **P = 0.000****	59.18 ± 12.95	F = 1.607 P = 0.201	31.32 ± 9.34	F = 6.442 P = 0.102	12.163.25	F = 0.870 P = 0.419
Low	51	8.2	44.69 ± 2.76		37.84 ± 2.54		10.08 ± 1.69		102.49 ± 16.65		57.18 ± 14.21		32.65 ± 11.81		12.674.17	
Place of residence																
City	403	64.7	44.06 ± 2.68		37.47 ± 2.45		9.77 ± 1.47		102.45 ± 13.25		59.66 ± 12.24		30.63 ± 9.22		12.163.30	
Town	137	22.0	44.27 ± 2.81	F = 2.435 **P = 0.000****	37.79 ± 2.70	F = 2.475 P = 0.061	9.541 ± .42	F = 1.469 P = 0.222	101.69 ± 16.45	F = 0.459 **P = 0.000****	58.28 ± 12.15	F = 0.514 P = 0.673	31.21 ± 9.59	F = 0.280 P = 0.840	12.203.30	F = 0.271 P = 0.847
Village	83	13.3	43.27 ± 3.35		36.80 ± 3.98		9.57 ± 1.50		102.88 ± 15.90		59.73 ± 12.12		30.96 ± 9.82		12.193.19	

t = independent t test; F = one-way analysis of variance (ANOVA); **P < 0.001

HAI = Health Anxiety Inventory; PWS = Psychological Wellbeing Scale; SD = standard deviation.

In the present study, it was found that the anxiety level was lower and psychological wellbeing was moderate among women who had been educated to university and higher levels, i.e. that anxiety levels decreased with increasing education level. Differing from our study, Tutku et al. reported that individuals' anxiety levels increased with increasing education level.[26] Qui et al. also reported that individuals who had high education levels experienced high anxiety because they had high awareness about their health conditions.[32] In comparisons of COVID-19 pandemic management among various countries around the world, Turkey is considered to have managed the process successfully.[3,33] This might be a factor relating to the lower health anxiety and positive results regarding psychological wellbeing among women in the high-level education group of the present study, who would be expected to follow the media more closely.

The health anxiety of women living in villages was found to have lower scores in this study. Gao et al. found that anxiety was lower among women living in the countryside than among those living in cities.[34] People living in cities in Turkey were under lockdown on official holidays and at the weekends in April and May 2020. The city where the present study was conducted was a metropolitan city under lockdown. Hence, the majority of the women were exposed to lockdown, which is considered to increase their anxiety. This would explain the lower anxiety and higher psychological wellbeing of women living in villages.

This study found that women with the perception that they had high income had lower anxiety levels. Erdoğdu et al. investigated

Table 3. Mean scores for HAI and PWS among the women (n = 623)

Scales and sub-scales	Min-Max	$\chi \pm SD$
HAI subscales		
Hypersensitivity to structural and physical symptoms	28-48	37.00 ± 9.00
Fear of anxiety and disease	5-16	8.83 ± 1.78
Total HAI score	34-56	44.00 ± 2.83
PWS subscales		
General emotions	18-87	59.34 ± 12.26
Satisfaction with economic, family and individual conditions	14-70	30.77 ± 9.36
Maintaining out-of-home activities	4-20	12.16 ± 12.00
Total PWS score	36-177	102.27 ± 14.45

t = independent t test.
HAI = Health Anxiety Inventory; PWS = Psychological Wellbeing Scale; Min-Max = minimum-maximum; SD = standard deviation.

Table 2. Comparison of women's responses regarding their perception of the pandemic, in relation to the mean scores for HAI and PWS (n = 623)

Questions on perception of the pandemic	n	%	Total HAI		Total PWS	
			$\chi \pm SD$	Statistical test	$\chi \pm SD$	Statistical test
PP1						
Agree	104	16.7	43.73 ± 2.90	t =-1.111	102.13 ± 17.00	P = 0.915
Disagree	519	83.3	44.07 ± 2.80	P = 0.267	102.29 ± 13.94	t = -0.107
PP2						
Agree	513	82.3	43.88 ± 2.81	t = -2.265	102.02 ± 15.12	**P = 0.032***
Disagree	110	17.7	44.55 ± 2.87	**P = 0.025***	103.43 ± 10.80	t =-1.143
PP3						
Agree	598	96	44.01 ± 2.82	t = 0.291	102.24 ± 14.55	P = 0.819
Disagree	25	4	43.84 ± 3.00	P = 0.771	102.92 ± 12.09	t = -0.271
PP4						
Agree	461	74	43.99 ± 2.82	t = -0.185	102.34 ± 2.82	P = 0.830
Disagree	162	26	44.04±2.84	P = 0.853	10.06 ± 13.37	t = 0.214
PP5						
Agree	457	73.4	44.04 ± 2.79	t = 0.488	102.06 ± 14.15	P = 0.548
Disagree	166	26.6	43.91 ± 2.92	P = 0.625	102.85 ± 15.28	t = -0.601
PP6						
Agree	383	61.5	44.02 ± 2.91	t = 0.157	104.18 ± 12.57	**P = 0.009***
Disagree	240	38.5	43.98 ± 2.69	P = 0.876	101.08 ± 15.41	t = -2.619
PP7						
Agree	285	45.7	44.03 ± 2.92	t = 0.214	101.42 ± 15.16	P = 0.180
Disagree	338	54.3	43.98 ± 2.75	P = 0.831	102.99 ± 13.82	t = -1.343
PP8						
Agree	357	57.3	44.01 ± 2.75	t = 0.098	102.42 ± 13.08	P = 0.766
Disagree	266	42.7	43.99 ± 2.93	P = 0.922	102.07 ± 16.14	t = 0.298
PP9						
Agree	268	43	43.86 ± 2.97	t = -1.099	102.73 ± 15.65	P = 0.491
Disagree	355	57	44.11 ± 2.71	P = 0.272	101.92 ± 13.49	t = 0.690

t = independent t test; *P < 0.05.
HAI = Health Anxiety Inventory; PWS = Psychological Wellbeing Scale; SD = standard deviation.

Table 4. Relationship between the women's HAI and PWS scores (n = 623)

Scales and subscales		HAI Hypersensitivity to structural and physical symptoms	HAI Fear of anxiety and disease	HAI Total
PWS	r	0.063	-0.071	0.907
General emotions	P	0.117	0.075	**0.000****
PWS	r	0.003	-0.021	0.029
Satisfaction with economic, family and individual conditions	P	0.940	0.597	0.476
PWS	r	0.048	0.002	0.044
Maintaining out-of-home activities	P	0.228	0.956	0.229
PWS	r	0.066	-0.074	0.072
Total	P	0.098	0.066	**0.036***

Pearson's correlation analysis *P < 0.05; **P < 0.001.

HAI = Health Anxiety Inventory; PWS = Psychological Wellbeing Scale.

individuals' anxiety levels in Turkey and found that women who had the perception that they had a low level of income had high anxiety levels.[15] Sümen and Adibelli found that individuals who had low income also had low psychological health levels.[5] As economic worries were lower among people who perceived that their income was high, low levels of anxiety were an expected result. In line with the literature, this study indicated that these results were somewhat expected during the pandemic period, in which economic problems were triggered.

An analysis on the participating women's responses about the pandemic demonstrated that 82.3% agreed with the statement "COVID-19 is a fatal disease", and these women had high health anxiety and poor psychological wellbeing. Disease is a concept that is perceived negatively by people.[35] The women's anxiety levels and psychological wellbeing might have been affected negatively because of experiencing restrictive precautions and the individual, social and economic problems caused by them.

Among all the participating women, 61.5% agreed with the statement "COVID-19 will not infect me if I am careful about my personal hygiene". The psychological wellbeing of the women who agreed with this statement was found to be better than that of women who did not. The importance of personal hygiene in the pandemic process is frequently shown in public service announcements and media, and its importance is highly emphasized. Hence, the women's psychological wellbeing might have been affected by these factors positively.

The mean HAI score of the women was found to be 44.00 ± 2.83. Considering that the top score is 54, it can be concluded that the pandemic has caused high levels of anxiety among women. In studies on the pandemic process, Erdoğdu et al. and Alan et al. reported that women's anxiety scores were significantly higher than those of men.[1,15] In similar studies conducted during the COVID 19 pandemic period, anxiety levels were found to be high.[22,23,25]

The mean PWS score was found to be 102.27 ± 14.45 in our study. According to the assessment criteria for the PWS, the women's psychological wellbeing was moderate. In previous studies on the pandemic, it was reported to cause deep and tiring negative psychological effects on people. While the pandemic may have caused people without psychological problems to start to have such problems, it may also have worsened the effects on people who already had psychiatric problems.[36] Wang et al. found that stress, anxiety and depression during the COVID-19 pandemic were highly common, especially among women.[20] Gao et al. reported that the prevalence of mental health problems was high among their subjects during the COVID-19 pandemic.[32] Studies have shown that lockdown processes have negative effects on individuals' psychological wellbeing, particularly women's.[37-39] In a study investigating the effect of gender on psychological wellbeing, Ausin et al. reported that women's psychological wellbeing levels were significantly lower than those of men.[37] Fernandez-Abascal and Martin-Diaz reported that women's psychological wellbeing scores were lower than those of men.[38] Similar studies on this issue also reported that women had disadvantages in terms of their psychological wellbeing levels.[5,9,11,40]

In the present study, it was found that women's psychological wellbeing deteriorated as their health anxiety levels increased. Other recent findings have shown that the pandemic and lockdown precautions have increased anxiety levels and have had negative effects on psychological wellbeing. In a study involving 648 students, Sanal Karahan and Hamarta aimed to identify whether solution-oriented thinking had any effects on depression, stress, anxiety and psychological wellbeing. Their regression analysis indicated that solution-oriented thinking had a positive relationship with psychological wellbeing and a negative relationship with depression, anxiety and stress.[40]

Limitations of this study

This study had some limitations. The scales used in the study were based on the women's self-reports. Therefore, the responses were based on the women's subjective perceptions. In addition,

since the women's anxiety and psychological wellbeing levels were not identified before the pandemic, comparisons from before and to after the pandemic were not possible.

CONCLUSION

The aim of this study was to identify the relationship between health anxiety and psychological wellbeing among women during the COVID-19 pandemic. It was found that anxiety levels were high and psychological wellbeing was medium, among women during the pandemic. Furthermore, women's health anxiety and psychological wellbeing were found to be affected by several variables. In conclusion, the COVID-19 pandemic has had negative effects not only on physical but also on psychological health. Support provided to women by nurses and midwives within their holistic understanding of care is of great importance for maintenance of the psychological health of society. The results from the present study should be considered for use by policymakers, in formulating interventions to protect, improve and enhance women's psychological health during this pandemic period. Further studies, including a wider population and larger sample, are recommended.

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Lung function and stress echocardiography in pulmonary arterial hypertension: a cross-sectional study

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ABSTRACT

BACKGROUND: The mechanism of exercise limitation in idiopathic pulmonary arterial hypertension (IPAH) is not fully understood. The role of hemodynamic alterations is well recognized, but mechanical, ventilatory and gasometric factors may also contribute to reduction of exercise capacity in these individuals.

OBJECTIVE: To investigate whether there is an association between ventilatory pattern and stress Doppler echocardiography (SDE) variables in IPAH patients.

DESIGN AND SETTING: Single-center prospective study conducted in a Brazilian university hospital.

METHODS: We included 14 stable IPAH patients and 14 age and sex-matched controls. Volumetric capnography (VCap), spirometry, six-minute walk test and SDE were performed on both the patients and the control subjects. Arterial blood gases were collected only from the patients. The IPAH patients and control subjects were compared with regard to the abovementioned variables.

RESULTS: The mean age of the patients was 38.4 years, and 78.6% were women. The patients showed hypocapnia, and in spirometry 42.9% presented forced vital capacity (FVC) below the lower limit of normality. In VCap, IPAH patients had higher respiratory rates (RR) and lower elimination of CO_2 in each breath. There was a significant correlation between reduced FVC and the magnitude of increases in tricuspid regurgitation velocity (TRV). In IPAH patients, VCap showed similar tidal volumes and a higher RR, which at least partially explained the hypocapnia.

CONCLUSIONS: The patients with IPAH showed hypocapnia, probably related to their higher respiratory rate with preserved tidal volumes; FVC was reduced and this reduction was positively correlated with cardiac output.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by increased pulmonary arterial pressure as a consequence of remodeling of arterial pulmonary microcirculation. Idiopathic pulmonary arterial hypertension (IPAH) is diagnosed after ruling out pulmonary hypertension associated with left heart disease, hypoxic lung diseases, chronic pulmonary thromboembolic disease and some other conditions of PAH.[1]

Clinically, IPAH produces severe and progressive limitation on physical exercise and activities of daily living. The exercise limitation is usually explained by the progressive reduction in cardiac output (CO), but there are still many gaps in the understanding of the interrelationships between hemodynamic abnormalities and respiratory mechanics. Volumetric capnography (VCap), spirometry and blood gas analysis can reveal aspects of ventilatory patterns that are not routinely investigated. We hypothesized that some of these resting variables could have correlations with hemodynamic variables collected during stress Doppler echocardiography (SDE).

OBJECTIVE

In order to investigate this hypothesis, we sought to assess the resting breathing pattern among patients with IPAH, by means of VCap, arterial blood gases and spirometry. Patients were also evaluated during exercise by means of the six-minute walk test (6MWT) and SDE. We then sought to identify whether the variables obtained at rest would correlate with those collected during exercise.

METHODS

This was a single-center prospective observational study conducted at the Department of Pulmonology of a Brazilian university hospital. We considered for inclusion all patients with IPAH, of both sexes and over 18 years of age, who met the hemodynamic and clinical criteria stated in the latest PAH guidelines.[1] After reviewing the medical records, patients who fulfilled the inclusion criteria of the New York Heart Association (NYHA) functional class I-III and oxygen saturation (SpO_2) ≥ 90% were invited to participate. We excluded smokers (and ex-smokers), individuals who presented asthma or cardiac diseases and individuals who were unable to perform the tests. Inclusion of patients and data collection occurred between January 2011 and June 2015. The control group consisted of healthy non-smoker volunteers who were matched for age and sex with the group of patients, with no history or current heart or respiratory disease and with no regular physical training done.

This study was approved by a local research ethics committee (ruling 1129/2010; November 23, 2010). All the patients participating in the study signed a written informed consent statement.

All the subjects answered a questionnaire that asked about symptoms, medications used and functional class of dyspnea (NYHA). We also calculated their body mass index (BMI) and measured SpO_2 at rest. The tests were performed in the same sequence, with 15 minutes between them, and included VCap, blood sampling for gas analysis (only in patients), spirometry, 6MWT and exercise SDE.

VCap was performed using a CO_2SMOS Plus 8100 device (Dixtal/Novametrix Respironics, Murrysville, Pennsylvania, United States). The subjects remained breathing tidal volume for five minutes. During this time, the variables were measured and data was stored in a computer equipped with the Analysis Plus software 1996 (Respironics, Murrysville, Pennsylvania, United States). At the end of data collection, an offline sequence from the respiratory cycles of each subject was selected to accommodate variation of 15% for expiratory tidal volume and 5% for partial end-tidal CO_2 ($EtCO_2$) tension. Respiratory cycles that had slope 2 (Slp2) and slope 3 (Slp3) equal to zero were excluded.[2,3] The main variables analyzed were $EtCO_2$, Slp2, Slp3, inspiratory time (Ti), expiratory time (Te), expiratory volume (Ve) and tidal volume according to anatomical dead space (Vd/Vt aw). Both slopes were calculated using the Analysis Plus software.

Spirometry was performed (EasyOne-PC, NDD Medizintechnik AG, Zurich, Switzerland) in accordance with the Brazilian guidelines and reference values for the Brazilian population were used.[4] Values for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio were analyzed.

All subjects performed the 6MWT under supervision by the same technician, in accordance with the American Thoracic Society guidelines.[5] Baseline blood pressure and heart rate (HR) were measured, and SpO_2 was determined using a finger probe pulse oximeter (3100 Wrist-Ox wrist pulse oximeter; Nonin Medical, Plymouth, Minnesota, United States), three times: at rest, in the sixth minute (end of the test) and in the ninth minute (recovery). During the test, the patients were carefully observed to ensure that their exercise limits would not be dangerously exceeded. The distance was measured in meters and desaturation (ΔSpO_2) was calculated as follows: SpO_2 in the sixth minute minus initial SpO_2.

For stress echocardiography, a variable-load supine exercise bicycle [Movement 4000; Movement, São Paulo (SP), Brazil] was used and the test was always performed by the same physician (JRM) using a 3 mHz probe (Xario PST-30BT; Toshiba, Kyoto, Japan). The workload was increased by 25 W every two minutes until the submaximal HR was reached (85% of the predicted maximum HR), or the symptom-limited maximum. HR, SpO_2 and tricuspid regurgitation velocity (TRV) were analyzed twice: at rest and during stress. Systolic pulmonary arterial pressure (SPAP) was estimated from peak TRVs in accordance with the following equation: $SPAP = 4(V)^2$ + right atrial pressure, where V is the peak velocity (in m/s) of TRV. Pulmonary vascular resistance (PVR) was estimated using the formula: PVR = (simple ratio of peak tricuspid regurgitation velocity/right ventricular outflow tract velocity-time integral) x 10 + 0.16.[6] Cardiac output (CO) was determined using the following equation: CO = (systolic volume x HR)/1000.[7] The variations between rest (r) and stress (s) were calculated for TRV, SPAP, PVR and CO and were designated as $\Delta TRV = TRV_s - TRV_r$; $\Delta SPAP = SPAP_s - SPAP_r$; $\Delta PVR = PVR_s - PVR_r$; and $\Delta CO = CO_s - CO_r$, respectively. Echocardiographic assessments were performed in accordance with current guidelines.[8]

Data analysis

Exploratory data analysis was performed using summary measurements (mean, standard deviation, minimum, median, maximum, frequency and percentage). The groups were compared using the Mann-Whitney test or Fisher's exact test, as appropriate. The factors for ΔTRV and ΔCO were evaluated by means of linear regression, after transformation of the variables into ranks. Probability values of less than 0.05 were considered to be statistically significant. The analysis were performed using the SAS System for Windows (Statistical Analysis System, version 9.4; SAS Institute Inc., Cary, North Carolina, United States).

RESULTS

We evaluated the medical records of 99 patients with a previous diagnosis of IPAH who were being followed at our outpatient clinic. Of these, 24 met the inclusion criteria, but 10 declined to participate, leaving 14 patients who completed all the proposed tests. Fourteen control subjects who were matched for age and sex with the group of patients were also enrolled. The clinical

data are shown in **Table 1**, and there were no differences between the groups regarding age, sex or BMI. None of the subjects in the control group had any respiratory symptoms.

Data on lung function and functional capacity (6MWT) are shown in **Table 2.** In spirometry, the IPAH patients had lower FVC and lower FEV_1 than the control subjects.

In the VCap evaluation, the IPAH patients had lower values than the control group, in relation to VCO_2/br, Ti and Te. In addition, the respiratory rate was higher than in the control group. In blood gas analysis, all the IPAH patients presented hypocapnia at rest ($PaCO_2$ = 29.5 ± 4.6 mmHg).

In the 6MWT, the IPAH patients had significantly higher Borg index values before and at the end of the test, compared with the control group. They also walked shorter distances than the control group.

The stress Doppler echocardiography (SDE) results are shown in **Table 3**. All the IPAH patients discontinued the SDE test due to physical exhaustion, but all had a HR above 85% of maximal HR (220 beats per minute minus the patient's age). In the control group, the test was halted when submaximal HR was reached (above 80% of maximal HR).

The IPAH patients presented higher values for TRV than the control patients at rest (TRVr) and at exercise peak (TRVs). In addition, ΔTRV was higher in the patient group. Also, higher values for pulmonary vascular resistance and SPAP were observed in the IPAH group, compared with the control subjects. The two groups presented similar CO values at rest, but CO under stress and the difference between stress and rest (ΔCO) were significantly lower in the patient group than in the control group.

Table 1. Clinical data on idiopathic pulmonary arterial hypertension (IPAH) patients and control subjects

		IPAH group n = 14	Control group n = 14	P-value
Age (years)*		38.4 ± 9.1	38.5 ± 9.1	0.85
Sex (women, n/%)		11 (78.6%)	11 (78.6%)	1.00
Body mass index (kg/m²)*		24.0 ± 3.6	24.8 ± 23.6	0.66
New York Heart Association functional class (n/%)	I	0 (0.0%)	14 (100%)	
	II	9 (64.3%)	0 (0.0%)	
	III	5 (35.7%)	0 (0.0%)	

*Values expressed as mean ± standard deviation.

Table 2. Functional variables of idiopathic pulmonary arterial hypertension (IPAH) patients and control subjects

		IPAH group n = 14	Control group n = 14	P-value
Spirometry	FVC (liters)	3.0 ± 0.6	3.7 ± 0.6	0.018
	FEV_1 (liters)	2.5 ± 0.5	3.0 ± 0.5	0.017
	FEV_1/FVC (%)	81.5 ± 4.4	81.6 ± 6.9	0.35
	FVC < LLN (n/%)	6 (42.9%)	0 (0.0%)	0.016
Volumetric capnography (VCap)	RR (cycles/minute)	16.9 ± 4.2	13.4 ± 4.3	0.020
	Vd/Vt aw	0.3 ± 0.0	0.3 ± 0.1	0.40
	VCO_2 (mmHg)	178.4 ± 47.5	190.5 ± 56.9	0.066
	Ve (ml)	532.9 ± 151.3	643.4 ± 288.8	0.37
	T_i (minutes)	1.5 ± 0.4	2.0 ± 0.7	0.037
	T_e (minutes)	2.3 ± 0.8	3.0 ± 1.0	0.020
	$ETCO_2$	29.4 ± 8.1	33.9 ± 4.7	0.069
	VCO_2/br (mmHg/br)	10.6 ± 3.3	16.4 ± 7.7	0.012
	Slp3/Ve (mmHg/l)	0.0 ± 0.1	0.0 ± 0.0	0.87
Arterial blood	$PaCO_2$ (mmHg)	29.5 ± 4.6	-	-
Six-minute walk test (6MWT)	Borg at rest	1.4 ± 2.1	0.0 ± 0.1	0.023
	Borg end	4.4 ± 2.9	0.2 ± 0.5	< 0.0001
	HR at rest	84.1 ± 16.1	88.0 ± 14.9	0.45
	HR end	130.5 ± 24.7	125.9 ± 19.4	0.70
	SpO_2 at rest (%)	97.6 ± 1.7	95.4 ± 4.2	0.38
	ΔSpO_2 (%)	-3.9 ± 5.8	-0.9 ± 1.3	0.089
	6MWT (meters)	424.4 ± 139.4	595.1 ± 54.6	0.0001

Values expressed as mean ± standard deviation.

FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; LLN = lower limit of normality; RR = respiratory rate during VCap; Vd/Vt aw = ratio of tidal volume to anatomical dead space; VCO_2 = excretion of carbon dioxide; Ve = expiratory volume; Ti = inspiratory time; Te = expiratory time; $EtCO_2$ = end-tidal CO_2; VCO_2/br = excretion of CO_2 per respiratory cycle; Slp3/Ve = slope 3 normalized according to expired volume; $PaCO_2$ = partial pressure of carbon dioxide in the arterial blood; Borg = scale for evaluation of the degree of respiratory discomfort before (at rest) and at the end of 6MWT test; HR = heart rate; SpO_2 = oxygen saturation of hemoglobin; ΔSpO_2 = SpO_2 in the sixth minute minus initial SpO_2; 6MWT = six-minute walk test.

Table 3. Stress Doppler echocardiography (SDE) variables of IPAH patients and control subjects

			IPAH group n = 14	Control group n = 14	P-value
Stress Doppler echocardiography (SDE)	TRV (meter/second)	TRV at rest	3.5 ± 0.9	1.8 ± 0.2	< 0.0001
		TRV max	4.9 ± 1.2	2.4 ± 0.2	< 0.0001
		ΔTRV	1.4 ± 0.6	0.6 ± 0.3	0.0001
	PVR (dyn.s/cm^5)	PVR at rest	2.4 ± 0.9	1.3 ± 0.2	0.0003
		PVR max	3.2 ± 1.4	1.2 ± 0.5	< 0.0001
		ΔPVR	0.8 ± 1.0	-0.1 ± 0.5	0.011
	CO (ml/min)	CO at rest	3124.2 ± 989.1	3903.6 ± 980.3	0.094
		CO max	6989.0 ± 3063.8	11780.8 ± 2616.6	0.0002
		ΔCO	3864.8 ± 2605.0	7877.1 ± 2202.1	0.0004
	SPAP (mmHg)	SPAP at rest	61.9 ± 28.6	23.6 ± 2.7	< 0.0001
		SPAP max	109.3 ± 44.6	33.8 ± 4.4	< 0.0001
		ΔSPAP	47.4 ± 26.9	10.2 ± 4.8	< 0.0001

TRV = tricuspid regurgitation peak velocity; PVR = pulmonary vascular resistance; CO = cardiac output; SPAP = systolic pulmonary arterial pressure; ΔPVR = PVR under stress – PVR at rest; ΔSPAP = SPAP under stress – SPAP at rest; ΔCO = CO under stress – CO at rest.

In the correlation analysis, there were positive correlations between ΔTRV and FVC, pulmonary vascular resistance under stress (PVRs) and the variation in PVR during SDE (ΔPVR). Thus, the higher the values of ΔTRV were, the higher the values of PVR, ΔPVR and FVC also were. We also found positive correlations between ΔCO and the values for BMI and $PaCO_2$; and a negative correlation between ΔCO and Vd/Vt aw. (**Table 4**)

Table 4. Factors associated with variation of tricuspid regurgitation peak velocity (TRV) and cardiac output (CO) during stress Doppler echocardiography (SDE)

	R	Factors analyzed	P-value
ΔTRV	Positive correlation	ΔPVR	0.0354
	Positive correlation	PVRmax	0.0470
	Positive correlation	FVC	0.0293
ΔCO	Positive correlation	BMI	0.0005
	Positive correlation	$PaCO_2$	0.0024
	Negative correlation	Vd/Vt aw	0.0234

ΔTRV = change in TRV during SDE; ΔCO = change in CO during SDE; PVR = pulmonary vascular resistance; ΔPVR = change in PVR during SDE; PVR max = pulmonary vascular resistance under stress; FVC = forced vital capacity; BMI = body mass index; $PaCO_2$ = partial pressure of carbon dioxide; Vd/Vt aw = ratio of tidal volume to anatomical dead space during the evaluation of VCap.

DISCUSSION

The patients presented hypocapnia at rest and, in comparison with the control subjects, had lower FVC. A higher proportion of the patients had FVC below the lower limit of normality (42.9% versus 0%), even with FEV_1/FVC ratio > 0.8. In VCap, the IPAH patients presented a higher respiratory rate than the control subjects, with similar tidal volumes (Vi and Ve). Also, the VCO_2 eliminated at each expiration was lower in the patients. Taken together, these findings suggest a respiratory pattern at rest indicative of restrictive disorder and tachypnea.

The low $PaCO_2$ and higher respiratory rates measured in VCap suggested that the IPAH patients were hyperventilating even during rest, which could explain the hypocapnia. In fact, there is evidence that patients with PAH seem to hyperventilate during exercise, at rest and even during sleep.[9] Some authors found hypocapnia ($PaCO_2$ < 35 mmHg) in patients with pulmonary hypertension[10,11] and Hoeper et al. also showed that in IPAH patients, hypocapnia seemed to be an independent marker for mortality, whereas PaO_2 had no significant prognostic value.[10]

Patients with left heart failure and pulmonary hypertension (PH) have low cardiac outputs, but the effects of these conditions on the lungs are very different. The consequences of low CO for left heart failure are significant for peripheral organs and tissues, but the lungs are filled with fluid. Lungs with pulmonary edema have reduced compliance, and as expected from the mathematically inverse relationship, increased elastance.[12] In contrast, patients with PAH have less fluid in their lungs, as a result of remodeling of pulmonary microcirculation and increased pulmonary resistance. The reduction of the total amount of blood in the lungs of these individuals increases compliance and can make lung expansion easier. Increased compliance facilitates lung expansion and may alter the mechanisms of early discontinuation of lung expansion during inspiration. Along these lines, in a study on dynamic hyperinflation during exercise among patients with precapillary pulmonary hypertension, Richter et al. found a weak negative correlation between the change in inspiratory capacity and pulmonary vascular resistance.[11]

In spirometry, our patients had lower FVC and FEV_1 and a higher proportion of these individuals had FVC below the lower limit of normality, compared with the control group. These findings are similar to what was found by other authors.[11,13,14] Meyer et al.

evaluated lung function in patients with pulmonary hypertension (PH), compared with controls, and they identified signs of peripheral airway obstruction, seen as reductions in FVC and FEV_1/FVC, and increases in residual volume and the residual volume/total lung capacity ratio.[14] These authors postulated that there was evidence of premature airway closure, leading to reduction in FVC, perhaps due to impairment of lung elastic recoil.

In our study, we also found a positive correlation between ΔTRV (difference in tricuspid regurgitation velocity between rest and peak effort) and FVC (P = 0.029). Richter et al. described a negative correlation between the change in inspiratory capacity (IC) during exercise and the pulmonary vascular resistance. Moreover, they observed that the reduction in IC seemed to be related to a decrease in aerobic exercise capacity.[11] The same authors suggested that IC might have prognostic value among patients with PH: patients with better IC at rest (> 89% of predicted values) have significantly better survival rates than those with IC ≤ 89%.[15]

Laveneziana et al.[16] also identified signs of dynamic hyperinflation (DH) and reduction of IC as factors involved in exercise limitation among PAH patients.

Meyer et al. reported that residual volumes and the residual volume/total lung capacity ratios were significantly higher in PH patients than in controls, but that airway resistance was similar in the two groups. Those patients showed airflow limitation that could be explained by loss of elastic recoil.[14]

Considering that the reduction in FVC may be related to the reduction in resting inspiratory capacity, it can be speculated that this reduction of FVC may have some prognostic significance. The positive correlation between ΔTRV and FVC that we found in our study gives strength to this hypothesis, since exercise-induced increases in TRV and PSAP may be considered to be measurements of right ventricular contractile reserve. Using stress Doppler echocardiography, Grünig et al. demonstrated that exercise-induced increases in PSAP had clinical and prognostic relevance in PH patients, such that the lower the pressure increase was, the worse the prognosis also was.[17]

VCap evaluation showed that the IPAH patients had increased respiratory rates even at rest, without changes in expired volumes. Interestingly, they eliminated less CO_2 per breath (P = 0.012) and had lower $EtCO_2$, although this difference was not statistically significant (P = 0.069). Some investigators have shown that patients with PAH have low $EtCO_2$, and that they present a further decrease from baseline in cardiopulmonary exercise testing.[18-20]

As discussed above, the patients in this study had hypocapnia at rest, a condition that explains their low CO_2 values per breath (VCO_2/br) and low $EtCO_2$. There was no significant difference in the elimination of CO_2 per minute between the cases and controls, given that the patients had higher respiratory rates.

It is also noteworthy that CO_2 elimination is related to CO, and that VCap has been used to monitor the efficiency of cardiac resuscitation procedures. However, this relationship may not be linear. Smaller reductions in CO than those observed in cardiac arrest are probably not detected through VCap.

Although our results are tentative, they suggest that there is a characteristic ventilatory pattern in patients with IPAH. The reduction in FVC, the hypocapnia and the VCap findings might be associated with reduction in pulmonary perfusion and low right ventricular contractile reserve.

Limitations and strengths

One of the strengths of our study is that it searched for noninvasive methods for assessing patients with PH, such as VCap. Lung function has been poorly studied in patients with PH, and findings such as reduced vital capacity or hypocapnia may have clinical relevance as biomarkers. Considering the small number of patients studied here, the findings cannot be generalized to all patients with pulmonary hypertension. The unavailability of lung compliance and elastance analysis prevented confirmation of the hypothesis raised in this study. Our findings are tentative and need further investigation. Nevertheless, the idea is appealing and, from our perspective, deserves consideration.

CONCLUSIONS

Patients with IPAH showed hypocapnia, reduced FVC and reduced elimination of CO_2. These features could be explained as consequences of reduction in lung perfusion, which is a typical finding in IPAH.

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Systematic reviews on interventions for COVID-19 have rarely graded the certainty of the evidence

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Evidence-based medicine.
Public health.

AUTHORS' KEY WORDS:
Methodology.
Certainty of evidence.
Strength of recommendations.
Evidence-based healthcare.

ABSTRACT

BACKGROUND: Numerous systematic reviews on coronavirus disease-19 (COVID-19) treatment have been developed to provide syntheses of the large volume of primary studies. However, the methodological quality of most of these reviews is questionable and the results provided may therefore present bias.

OBJECTIVE: To investigate how many systematic reviews on the therapeutic or preventive options for COVID-19 assessed the certainty of the evidence through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

METHODS: We conducted a sensitive search in MEDLINE (via PubMed) and included all systematic reviews that assessed any intervention for COVID-19. The systematic reviews included were examined to identify any planned and/or actual assessment using the GRADE approach (or absence thereof) regarding the certainty of the evidence.

RESULTS: We included 177 systematic reviews and found that only 37 (21%; 37/177) assessed and reported the certainty of the evidence using the GRADE approach. This number reduced to 27 (16.2%; 27/167) when Cochrane reviews (n = 10), in which an evaluation using GRADE is mandatory, were excluded.

CONCLUSION: Most of the systematic reviews on interventions relating to COVID-19 omitted assessment of the certainty of the evidence. This is a critical methodological omission that must not be overlooked in further research, so as to improve the impact and usefulness of syntheses relating to COVID-19.

INTRODUCTION

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, large numbers of studies have been published in an attempt to find an effective treatment for this disease. Consequently, many systematic reviews have been developed on this topic, to provide syntheses of the large volume of primary studies. Healthcare professionals and policymakers commonly use systematic reviews to formulate recommendations and make practical decisions.[1]

However, the methodological quality of most of these systematic reviews is questionable. Hence, the results provided through these reviews may present bias.

Assessing the certainty of the evidence is an indispensable step in a systematic review. This is especially true within the current context, in which information is often misleading yet has been widely disseminated, both by scientific journals and by the traditional media. Thus, efforts need to be made by the authors of syntheses of the evidence on a given topic, to ensure that the degree of certainty that can be placed on the estimates of effect and clinical recommendations can be established.[1,2]

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a transparent approach to rating the certainty of the body of evidence in systematic reviews and other forms of synthesis, as a guide to making decisions.[3] This approach should be beneficial during the COVID-19 pandemic. It is entirely possible to perform GRADE assessments, even (or even more so) within an emergency context.[1,4]

OBJECTIVE

We carried out a critical appraisal study with the aim of investigating how many systematic reviews that have been published in relation to therapeutic or preventive options for COVID-19 made assessments of the certainty of the evidence through the GRADE approach.

METHODS

We conducted a sensitive search in MEDLINE (via PubMed) on January 20, 2021, using the MeSH term "Coronavirus" and its synonyms combined with the PubMed clinical queries filter for systematic reviews (Annex 1). Two authors independently screened all titles and abstracts through the Rayyan platform,[5] in order to include systematic reviews that assessed any intervention for COVID-19.

RESULTS

The systematic reviews included were analyzed in full text, to identify whether there was any planned and/or actual assessment of the certainty of the evidence using the GRADE approach (or absence thereof). The search strategy found 1,075 references, and 177 fulfilled the inclusion criteria. Of these, only 37 reviews (21%; 37/177) assessed the certainty of the evidence using the GRADE approach. This number reduced to 27 (16.2%; 27/167) when Cochrane reviews (n = 10), in which an evaluation using GRADE is mandatory, were excluded.

CONCLUSION

This result highlights the fact that most of the systematic reviews on interventions conducted in relation to COVID-19 omitted assessment of the certainty of the evidence. This is a critical methodological omission that must not be overlooked in further research, so as to improve the impact and usefulness of syntheses relating to COVID-19.

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Annex 1. Search strategy.

Database	Search strategy
MEDLINE (via PubMed)	#1 "Coronavirus"[Mesh] OR "Covid-19" OR (COVID) OR (Coronavirus) OR (SARS-CoV-2) OR (Coronaviruses) OR (Deltacoronavirus) OR (Deltacoronaviruses) OR "Munia coronavirus HKU13" OR (Coronavirus HKU15) OR (Coronavirus, Rabbit) OR (Rabbit Coronavirus) OR (Coronaviruses, Rabbit) OR (Rabbit Coronaviruses) OR "Bulbul coronavirus HKU11" OR "Thrush coronavirus HKU12" #2 (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt] #3 #1 AND #2

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Implementing healthcare professionals' training during COVID-19: a pre and post-test design for simulation training

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Health Personnel.
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AUTHORS' KEY WORDS:
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Knowledge acquisition.
Airway management protocol.

ABSTRACT

BACKGROUND: Coronavirus disease-19 (COVID-19) has imposed a new reality that presents several challenges for healthcare professionals. The main challenge has been the lack of proper training in relation to an unknown disease.

OBJECTIVE: To investigate healthcare professionals' acquisition of knowledge of a new airway management protocol for COVID-19 through their participation in simulation training.

DESIGN AND SETTING: Pre and post-test study with purpose sampling, carried out in a tertiary-level hospital in the city of Campinas, state of São Paulo, Brazil.

METHODS: This was a cross-sectional pre and post-test intervention among healthcare professionals working in the intensive care unit and emergency department of a large hospital. The training was carried out using an ***in situ*** simulation scenario and the participants answered pre and post-tests consisting of a 20-item questionnaire about the new protocol.

RESULTS: The paired-sample t test demonstrated that there was a significant increase in test score ($t = -19.06$; $P < 0.001$), from before the training ($M = 8.62$; standard deviation, $SD = 3.53$) to after the simulation training ($M = 17.02$; $SD = 1.76$).

CONCLUSIONS: The simulated training had a positive impact on the healthcare professionals' acquisition of the COVID-19 protocol. We also demonstrated that ***in situ*** simulation training was an efficient tool for implementing new protocols, thus bringing benefits to healthcare systems, professionals and patients.

INTRODUCTION

Coronavirus disease-19 (COVID-19) has imposed a new reality through the pandemic that it has caused, and this presents challenges to healthcare professionals and systems. The high rate of transmissibility of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), through droplets, aerosols and contaminated surfaces, has led to development of strict protocols for individual and collective protection for patient care,[1,2] which have been implemented throughout hospitals. Adaptations to protocols for procedures have been brought in, including use of alternative medications to minimize virus transmission in aerosol-producing procedures, donning and doffing of personal protective equipment (PPE) and other measures.

The implementation of these new protocols has required training for all front-line healthcare workers, without endangering them or their patients. Use of simulations may be an appropriate way for providing training since this replicates real-environment situations in a safe environment, and thus protects both patients and professionals from unnecessary risks. Simulation training has been widely used for continuing professional development, in order to train healthcare professionals in relation to new systems, thereby enabling them to remain up-to-date regarding new demands and protocols within their clinical practice.[3-7] Simulation has played a key role in testing and implementing new workflow structures, new protocols and cognitive resources,[8] through offering participants the possibility to practice rare and critical events in a controlled environment.[9]

In the current pandemic, simulation has been shown to be useful for testing healthcare systems, processes and new protocols.[10-15] Moreover, studies have shown that simulation is an appropriate teaching tool that has the capacity to quickly prepare frontline teams for changes that are necessary, through generating gains in knowledge and skills.[10,13,16,17]

Healthcare professionals have become protagonists in this new reality. For safe and effective care to be developed, it necessary to train these professionals in large numbers, in settings ranging from primary care to quaternary-level hospitals. Given the high rate of transmissibility of COVID-19, simulation training can ensure individual, team and system readiness[17] while increasing patient and professional safety.

OBJECTIVE

To investigate healthcare professionals' acquisition of knowledge of a new airway management protocol for COVID-19 through their participation in simulation training.

METHODS

This was a pre and post-test study with purpose sampling that was conducted between March 31 and April 14, 2020. The data for this study came from an institutional training protocol for healthcare professionals working in the intensive care unit and emergency department of a large hospital. The simulated training was carried out *in situ* using PPE and a high-fidelity simulator. Participants answered a pre-test and a post-test consisting of 20 questions with very short answers, on donning and doffing (five questions), oxygen therapy for patients with acute respiratory distress syndrome (ARDS) due to COVID-19 (four questions), orotracheal intubation (five questions), and choice of medication for starting mechanical ventilation (six questions) (**Appendix 1**). The maximum possible score for the test was 20.

The training offered to the participants consisted of the following steps:

1. Pre-test.
2. Simulation training on donning of personal protective equipment (PPE). The instructors carried out the demonstration and gave instructions to the participants. Then, the participants performed individual practical training.
3. Participation in an interdisciplinary simulation scenario. The participants received a briefing with the necessary instructions. The objective was to teach the new COVID-19 protocol, focusing on making a clinical diagnosis of likely COVID-19 infection and recognizing acute respiratory failure, followed by use of orotracheal intubation and choosing the medication for starting mechanical ventilation. This scenario is shown in **Appendix 2**.
4. Practical training on doffing of PPE. After the scenario had been described, the participants received instructions and a demonstration of the technique, and performed individual practical training.
5. Debriefing. After the doffing training, the participants discussed and reflected on contamination, the decision to intubate and the COVID-19 protocol, guided by instructors experienced in the COVID-19 protocol and the simulation methodology.
6. Post-test.

For data analysis, we used a paired-sample t test to investigate the difference between the pre and post-test scores. The data were analyzed using IBM-SPSS version 27.0 (IBM Corporation, Armonk, New York, United States)

This study was approved by our university's Ethics Committee (protocol number 3.943.505; date of approval March 30, 2020). Written informed consent was obtained from all participants.

The sample represented a small proportion of the total number of participants in the institutional training protocol. Due to the urgency of preparing the frontline team to face COVID-19, the managers of the hospital and the authors of this study came together to develop a training program for all doctors, nurses and physiotherapists. Since the physiotherapists were in the first training sessions, they were not included in the present study.

The training protocol started as a proposal from this hospital for coping with the COVID-19 pandemic. At a time when most of the employees had already undergone training, the authors submitted this study to the local Ethics Committee and obtained ethical approval for it during the final training phase, when a small number of employees were still waiting for training.

RESULTS

Forty-eight professionals participated in this study. Most of them were doctors (68.7%), followed by nurses (18.8%) and nursing technicians (12.5%). Among all the participants, 79.2% were female. The participants' ages ranged from 23 to 48 years, with an average of 31.96 years and a standard deviation of 7.11.

The paired-sample t test demonstrated that there was a significant increase in test score ($t = -19.06$; $P < 0.001$) from before the training ($M = 8.62$, standard deviation, $SD = 3.53$) to after the simulation training ($M = 17.02$; $SD = 1.76$). Significant increases from before to after the simulation training were also found in the subdomains (**Table 1**).

DISCUSSION

In this study, we investigated healthcare professionals' acquisition of a new airway management protocol for COVID-19 in a large hospital. We found evidence of a significant and considerable

Table 1. Mean, standard deviation (SD), t and P-value of the subdomains of the knowledge test

Subjects	Donning and doffing	Oxygen therapy	Medication	Orotracheal intubation
Before Mean (SD)	2.29 (1.01)	1.81 (1.00)	2.65 (2.19)	1.87 (1.38)
After Mean (SD)	4.67 (0.59)	3.10 (0.69)	5.62 (0.84)	3.62 (0.87)
t	-15.76*	-7.23*	-10.03*	-9.12*

*P < 0.001.

improvement from before to after training, which was in line with previous data in the literature.[4-7] Our data also corroborated studies that showed that simulation was essential for developing, testing, refining and implementing new workflows and protocols in healthcare.[8,10,11,18,19] This was also essential in the context of the COVID-19 pandemic, in which we trained healthcare professionals on the new protocol for safe and effective care of patients with COVID-19.

We chose *in situ* simulation because of the necessity to train healthcare professionals while they continued to do their clinical work. Thus, we organized training sessions in the mornings, afternoons and nights. *In situ* training also decreased the circulation of healthcare professionals throughout the university, thus avoiding exposing vulnerable people to the risks of COVID-19. Furthermore, these healthcare professionals remained close to their units, which allowed them to respond to any emergency when necessary. *In situ* simulation is a fast and efficient way for training a multidisciplinary team because training takes place during the team's hours of service, using the workplace resources.[19]

In this study, we decided to use questions with very short answers. Use of questions of this nature made it possible to assess the participants' knowledge without giving any clues about the correct answer. This was especially important because our sample was composed of experienced healthcare professionals who would have the capacity to deduce the correct answer by looking at the alternatives. Moreover, it was easier to grade the results than it would have been if essay questions had been used. Lastly, questions with very short answers have been shown to have the same psychometric properties as standard multiple-choice questions, while avoiding recognition of the correct answer.[20]

This study had some limitations. First, the purposing sample may have limited the generalizability of our findings. Another limitation was that we used a one-group pre and post-test design. Both the sampling and the study design were selected because of the importance of training frontline workers and we designed the simulation training based on the best evidence available.

Most importantly, we demonstrated the possibility and usefulness of simulation training during COVID-19. Lastly, we focused mostly on knowledge acquisition, since all the frontline workers were skillful with regard to airway management but lacked expertise relating to the new protocol.

CONCLUSIONS

The simulated training had a positive impact on the healthcare professionals' acquisition of the COVID-19 protocol. We also demonstrated that *in situ* simulation training was an efficient tool for implementing new protocols, thus bringing benefits to healthcare systems, professionals and patients.

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Appendix 1. Questions: pre and post-test.

Donning and doffing

1- During the donning, when should I put on the respiratory protection mask (PFF2/N95)?
2 - During the donning, when should I put on the gloves?
3 - How many times should hand hygiene be done BEFORE the donning?
4 - How many times should hand hygiene be done DURING the doffing?
5 - What are the necessary PPE for the intubation of a suspected COVID-19 patient?

Oxygen therapy for patients with severe acute respiratory syndrome (SARS) due to COVID-19:

6 - The device to be initially used to provide oxygen therapy to patients with SARS due to COVID-19 is:
7 - What is the oxygen saturation target to be obtained through initial oxygen therapy, for patients with COVID-19 and respiratory failure?
8 - Which device should be used for pre-oxygenation of a patient with suspected COVID-19?
9 - Which device should be installed between the mask and the bag, before pre-oxygenation, to minimize aerosol dispersion?

Choice of medication for rapid sequence intubation (RSI):

10 - What is the recommended drug for RSI in a patient with suspected COVID-19?
11 - How long should pre-oxygenation be performed on a patient with suspected COVID-19?
12 - Which drug is indicated for premedication before intubation?
13 - Which drug is indicated for induction (hypnosis)?
14 - Which drug is indicated for neuromuscular block?
15 - What is the average time needed for the premedication drug to be effective before administration of hypnosis?

Orotracheal intubation

16 – Since ventilation with bag-valve-mask (BVM) should be avoided among COVID-19 patients, how should they be ventilated when checking the orotracheal tube position?
17 - Since ventilation with BVM should be avoided among COVID-19 patients, which alternative method for checking the tube position can be used, if available?
18 - What is the potential complication of the tube clamping technique in the case of a patient with increased airway reactivity?
19 - After intubation, mechanical ventilation must be started. Which items should be attached between the tube and the Y-piece (which connects the inspiratory and expiratory limbs of the ventilator)?
20 - Which tidal volume should be set on the mechanical ventilator?

Appendix 2. Scenario of severe acute respiratory syndrome (SARS) due to coronavirus disease-19 (COVID-19).

Scenario title	**Severe acute respiratory syndrome (SARS) due to coronavirus disease-19 (COVID-19)**
Learning objectives	
- To recognize respiratory failure in a patient with severe acute respiratory syndrome (SARS); - To begin treatment for respiratory failure; - To recognize failure of the initial treatment; - To intubate the patient in the event of oxygen therapy failure.	
Materials	
- One high-fidelity mannequin; - One multiparametric monitor; - One gas panel; - Oxygen therapy devices - One airway material kit - Infusion therapy devices; - Water ampoules for injection, with the following identifications (one each): fentanyl, etomidate, midazolam, succinylcholine, ketamine, rocuronium, salbutamol, magnesium sulfate, dexamethasone, hydrocortisone and adrenaline	
Scenario overview	
The patient Alberto Ramos de Miranda, 52 years old, with a history of hypertension and type 2 diabetes, sought the emergency department with a complaint of four days of fever, dry cough, headache, diarrhea and dyspnea (which he noticed one day ago). The patient was first evaluated in the emergency department triage room and was referred to the emergency room (ER) due to severe hypoxemia and tachypnea. In the ER, the patient will not have an adequate (satisfactory) response to oxygen therapy, with maintenance of hypoxemia and elevated breathing effort, and with the need to institute invasive mechanical ventilation. Healthcare professionals should recognize the patient's respiratory failure and perform orotracheal intubation due to the failure of oxygen therapy.	
Participants	
Role in the scenario /participant	**Quantity**
Physician	1
Nurse	1
Nursing technician	1
Physiotherapist	1
Briefing	
You are a physician, nurse, nursing technician or physiotherapist in the emergency room. Upon entering the scene, you will receive the patient Alberto Ramos de Miranda, 52 years of age, who was brought in from the triage room with a main complaint of dyspnea. The patient has peripheral oxygen saturation measured at 86% and is under precaution regarding contact due to reports of flu-like symptoms preceding the current condition. You must perform patient care, handling the situation in the most appropriate way. Consider yourself donning to avoid droplets and aerosols.	
History of the actor/mannequin	
Alberto Ramos de Miranda, 52 years old, is undergoing treatment for hypertension and type 2 diabetes with hydrochlorothiazide and metformin. Four days ago, he noticed the start of a low fever, dry cough, malaise, body pain, and headache. He used analgesics, but without improvement of the condition and with worsening of symptoms. One day ago, he started to get tired with small efforts, so he came to the hospital today because he felt tired even when resting. He also reported having diarrhea and mild abdominal pain during this period. He says that he does not have any history of smoking or drinking. There are no other known comorbidities.	
Initial programming of the mannequin	
Sinus rhythm; HR 114 bpm; RR 34 bpm; SpO_2 86%; BP 168 x 96 mmHg	

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Screening for cognitive impairment among individuals aged 60 years or over: scoping review

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KEY WORDS (MeSH terms):
Cognitive dysfunction.
Mass screening.
Aged.
Dementia.
Cognition.

AUTHORS' KEY WORDS:
Primary care.
Elderly.
Cognitive impairment.

ABSTRACT

BACKGROUND: Growth in aging of the population has led to increasing numbers of elderly people presenting cognitive impairment and evolution to dementia. There is still no consensus within primary care on the best strategy for screening for cognitive impairment among elderly people. Standardization of a simple but reasonably accurate instrument for a brief cognitive test, in primary care environments, would enable healthcare professionals to identify individuals who require a more in-depth assessment of cognition.

OBJECTIVES: To investigate the instruments used by healthcare professionals in studies conducted worldwide and ascertain the most suitable instruments for screening for cognitive impairment among individuals aged 60 years or over, in the Brazilian population.

DESIGN AND SETTING: Scoping review developed at Pontifícia Universidade Católica de São Paulo, Brazil.

METHOD: A systematic search of the literature was conducted for primary studies using instruments to screen for cognitive impairment among individuals aged 60 years or over, in the MEDLINE, EMBASE, Cochrane Central and LILACS databases.

RESULTS: A total of 983 articles were identified by two independent reviewers, from which 49 were selected for full-text reading, based on the criteria defined for this review. From this, 16 articles adhering to the theme of screening for cognitive impairment among the elderly were selected for in-depth analysis.

CONCLUSION: The Mini-Mental State Examination was the instrument most cited in these studies. The Pfeffer Functional Activities Questionnaire and the Verbal Fluency Test (semantic category) present characteristics favoring further studies, for testing as screening instruments for cognitive impairment among elderly people in Brazil.

INTRODUCTION

Although substantial increases in the numbers of elderly people are now foreseen in all countries, greater growth is expected in developing regions such as Brazil, where the proportions are expected to become 18.8% in 2020 and 29.3% in 2050.[1,2]

Primary care is considered to be the front line for healthcare for the elderly and can provide regular contacts focused on preventing disabilities resulting from chronic health conditions, such as classification of cognitive impairment in this age group.[3]

Healthcare professionals are faced with the challenge of evaluating the limit of normality among elderly people's cognitive alterations. Within the concept of senescence, they need to differentiate the expected changes for this age group from the pathological conditions of aging that constitute senility. If such conditions are seen at the prodromal stage, reversal or mitigation may still be possible.[4,5]

Development of dementia in elderly people is a measurable risk. Thus, the pathological transition to this, from a mild stage of cognitive impairment, forms a "gray zone" between normality and initial dementia.[4]

Screening for cognitive impairment among elderly people can be achieved through instruments that have already been translated and validated for application in Brazil.[6]

Bustamante et al.[7] suggested that cognitive tests and functional scales should be used in combination, in populations with educational heterogeneity. This would improve the accuracy of cognitive screening among mild to moderate cases of dementia because, when used together, they

bring more information than when used separately. The functional scales of questionnaires are less influenced by the interviewee's age, education level or other sociocultural factors.[7]

So far, there is no consensus regarding the best strategy within primary care for screening for cognitive impairment among elderly patients. However, several brief instruments for screening for cognitive impairment have been recommended.[8,9]

No specific drug therapy for treating mild cognitive impairment (MCI) is currently approved. Nonetheless, it was recommended through the FINGER (Finnish Intervention Study to Prevent Cognitive Decline and Disability) study that healthy lifestyle factors such as leisure activities, social interaction, cognitive stimulation, Mediterranean diet and regular physical activity, both for elderly people in general and for those with MCI, should be encouraged as possible protectors against neurodegenerative diseases of aging.[10]

Most individuals and their caregivers would rather know about a diagnosis of dementia as early as possible. This knowledge allows such individuals to make decisions regarding future plans while they still have the ability to do so.[11,12]

In Brazil, around 75% of the population receives its medical care through the public healthcare system (Sistema Único de Saúde, SUS). In this, care is centered on general practitioners, who play an increasingly important role in screening for cognitive impairment among elderly people, which is often neglected within primary care. Moreover, many primary care providers have difficulty in diagnosing dementia accurately. Particularly at the mild stage, dementia is poorly recognized.[13,14]

Thus, instruments for cognitive screening that are quick to apply but relatively accurate are needed, so that healthcare professionals working within primary care can identify individuals who may require a more in-depth evaluation of cognition, at an early stage, and refer them to secondary care.[15]

The present study consisted of a scoping review, in which instruments for screening for cognitive impairment that have been used in studies in the literature, as applicable to individuals aged 60 years or over, were assessed.

OBJECTIVES

To investigate the cognitive screening instruments used by healthcare professionals in studies conducted worldwide and ascertain which of these are most suitable for use in screening for cognitive impairment among individuals aged 60 years or over, in the Brazilian population.

METHODS

The PICO technique (Population, Intervention, Comparison, Outcome) was used to define the question and the development of the research, as follows:

P: Population aged 60 years or over.

I: Use of a screening instrument for cognitive impairment in this population.

C: Comparison between screening instruments for cognitive impairment in this population.

O: Verification of the most suitable instruments for screening for cognitive impairment among elderly people, in the Brazilian population.

Design

This study consisted of a scoping review of the literature. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology.[16]

Search strategy

The searches were conducted in June 2020 in following databases: MEDLINE (Medical Literature Analysis and Retrieval System Online); EMBASE (Excerpta Medica Database); Cochrane Library; and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde).

The descriptors were chosen and identified in accordance with the Medical Subject Heading (MeSH) and Descritores em Ciências da Saúde (DeCS) lists of descriptors, as follows: cognitive dysfunction; mass screening; and elderly.

The same search strategies were used in all databases. The search was refined by specifying randomized clinical trial (RCT) and the elderly age group, or studies that included individuals aged 60 years or over, depending on the filter for searching the information sources for articles, as described in **Table 1**. No limit was placed on the date of publication or the languages of these documents. For cases in which an update was found, the latest version was considered.

Criteria for inclusion in the scoping review

We only included studies that met the following criteria: randomized clinical trials (RCTs) that had been duly registered or observational studies with random sampling; individuals aged 60 years or over who had been recruited from the general population or from primary healthcare attendees, for random sampling, with absence of any reports of presence of pathological conditions or previous treatments; and application of instruments for screening for cognitive impairment and their implications and results. We considered any outcomes that had been assessed and reported by the original authors.

Selection of studies

The selection process was performed by two authors (MRLR, PRPF), who independently screened all titles and abstracts that had been found through the electronic search. These authors checked their eligibility in relation to the inclusion criteria.

Table 1. Search strategy

DATABASE	STRATEGY	n	ACCESS
MEDLINE	(("Cognitive Dysfunction"[Mesh] OR (cognitive dysfunctions) OR (dysfunction, cognitive) OR (dysfunctions, cognitive) OR (cognitive impairments) OR (cognitive impairment) OR (impairment, cognitive) OR (impairments, cognitive) OR (mild cognitive impairment) OR (cognitive impairment, mild) OR (cognitive impairments, mild) OR (impairment, mild cognitive) OR (impairments, mild cognitive) OR (mild cognitive impairments) OR (mild neurocognitive disorder) OR (disorder, mild neurocognitive) OR (disorders, mild neurocognitive) OR (mild neurocognitive disorder) OR (neurocognitive disorder, mild) OR (eurocognitive disorders, mild) OR (cognitive decline) OR (cognitive declines) OR (decline, cognitive) OR (declines, cognitive) OR (mental deterioration) OR (deterioration, mental) OR (deteriorations, mental) OR (mental deteriorations))) AND ("Mass Screening"[Mesh] OR (mass screenings) OR (screening, mass) OR (screenings, mass) OR Screening*) **Filters:** Randomized Controlled Trial, Humans, Middle Aged + Aged: 45+ years, Middle Aged: 45-64 years, Aged: 65+ years, 80 and over: 80+ years	134	PubMed
EMBASE	(('cognitive dysfunction' OR 'cognitive dysfunctions' OR 'dysfunction, cognitive' OR 'dysfunctions, cognitive' OR 'cognitive impairments' OR 'cognitive impairment' OR 'impairment, cognitive' OR 'impairments, cognitive' OR 'mild cognitive impairment' OR 'cognitive impairment, mild' OR 'cognitive impairments, mild' OR 'impairment, mild cognitive' OR 'impairments, mild cognitive' OR 'mild cognitive impairments' OR 'mild neurocognitive disorder' OR 'disorder, mild neurocognitive' OR 'disorders, mild neurocognitive' OR 'mild neurocognitive disorders' OR 'neurocognitive disorder, mild' OR 'neurocognitive disorders, mild' OR 'cognitive decline' OR 'cognitive declines' OR 'decline, cognitive' OR 'declines, cognitive' OR 'mental deterioration' OR 'deterioration, mental' OR 'deteriorations, mental' OR 'mental deteriorations') AND ('mass screening' OR 'mass screenings' OR 'screening, mass' OR 'screenings, mass' OR screening*)) AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de) AND ([aged]/lim OR [very elderly]/lim)	245	Elsevier
LILACS	("Disfunção cognitiva" OR "Comprometimento Cognitivo" OR "Comprometimento Cognitivo Leve" OR "Declínio Cognitivo" OR "Deficiências Cognitivas" OR "Deterioração Mental" OR "Distúrbio Neurocognitivo Leve" OR "Transtorno Neurocognitivo Leve") AND ("Programas de rastreamento" OR "Exame Coletivo" OR "Identificação Sistemática" OR rastreamento OR screening OR "Triagem de Massa") AND (db:("LILACS") AND limit:("aged"))	88	Bireme
Cochrane Library	(((Cognitive Dysfunction*) OR (Dysfunction, Cognitive) OR (Dysfunctions, Cognitive) OR (Cognitive Impairments) OR (Cognitive Impairment) OR (Impairment, Cognitive) OR (Impairments, Cognitive) OR (Mild Cognitive Impairment) OR (Cognitive Impairment, Mild) OR (Cognitive Impairments, Mild) OR (Impairment, Mild Cognitive) OR (Impairments, Mild Cognitive) OR (Mild Cognitive Impairments) OR (Mild Neurocognitive Disorder) OR (Disorder, Mild Neurocognitive) OR (Disorders, Mild Neurocognitive) OR (Mild Neurocognitive Disorders) OR (Neurocognitive Disorder, Mild) OR (Neurocognitive Disorders, Mild) OR (Cognitive Decline) OR (Cognitive Declines) OR (Decline, Cognitive) OR (Declines, Cognitive) OR (Mental Deterioration) OR (Deterioration, Mental) OR (Deteriorations, Mental) OR (Mental Deteriorations)) AND ((Mass Screening*) OR (Screening, Mass) OR (Screenings, Mass) OR (Screening*)) and ((AGED) OR (AGED, 80 AND OVER)))	516	Wiley

Any disagreements in the selection process were resolved through reaching a consensus or by consulting a third author (JEM). To assess the methodological quality of the studies included, the Downs & Black checklist was used,[17] with adaptation for RCTs and observational studies. For the RCTs, all questions from this tool were used, with a maximum score of 28 points. For the observational studies, the 17 questions from the original list were used, totaling a maximum of 18 points.

RESULTS

Selection of articles

We found 983 articles in the first stage of article selection, but 244 articles were excluded due to duplication in the research databases. Thus, 739 articles were retained for assessment of eligibility. In the next phase, articles that did not have the research topic in the title or abstract were excluded. Thus, a further 690 articles were excluded and 49 were selected for assessment of eligibility. Of these, only 16 articles met the objectives of this scoping review (**Figure 1**). **Tables 2** and **3** provide details on the studies included, so that readers can make their own judgments about the research in these studies.

Results from blinded randomized clinical trials (RCTs)

The RCTs (**Table 2**) were conducted on a total population of 10,445 people, with a weighted average age of 77.49 years. The educational level was only recorded in the study by Fowler et al.[18]

In these studies, four instruments were used, which were all cognitive assessment tests: memory impairment screening (MIS), Mini-Cog, DemTect and clock drawing test[19] (CDT).

The RCT by Fowler et al.[18] did not detect any differences in healthcare, quality of life or harm from symptoms of depression and anxiety among individuals who were screened as positive for dementia, through application of MIS or Mini-Cog.[18]

Reiner et al.[20] compared positive results from cognitive screening using DemTect with the results obtained through the CDT.[19] They suggested that the CDT[19] was not a suitable instrument for detection of probable dementia within primary care.[20]

Results from observational studies (OS)

The sample size in the 14 observational studies (OS) ranged from 50 to 15,051. It was in the range of up to 100 in one article; 101 to 1,000 in seven articles; 1,001 to 10,000 in five articles and more than 10,000 in one article. The total population of the OSs was 35,010 individuals (Table 3).

The participants' cognitive status was classified as follows: cognitively normal (CN); cognitive impairment with no dementia (CIND); mild cognitive impairment (MCI); and dementia in its respective clinical stages of evolution.

Among the observational studies, 19 instruments (14 cognitive assessment tests and five functional assessment scales) were used to screen the cognition of individuals aged 60 years or over (Tables 4 and 5).

DISCUSSION

The criteria used for analysis in this scoping review, on the instruments that might be best suited for use in the Brazilian population, were the following: quick application, validation for use in primary care locations or in the community; adequate psychometric properties; ease of application by members of the healthcare team; the least possible influence from the subject's educational and cultural level; and whether elderly people's interest in the evaluation was aroused. The sensitivity and specificity of screening instruments for cognitive impairment among the elderly were also considered.

Use of indiscriminate screening, i.e. for the entire elderly population, irrespective of any cognitive complaints, has been controversial. This is not only because of the need for adaptations to instruments, for them to be applied (given the lack of standardization),[21] but also because positive results could lead to harm such as anxiety and depression among individuals without any proven dementia. Nonetheless, in the RCT conducted by Fowler et al.,[18] no harm due to symptoms of depression and anxiety was found after positive screening for dementia.[18]

DemTect[22], the instrument used by Reiner et al.[20] is composed of the following tests that are already used in the Brazilian population: immediate memory of a word list, late evocation of the same list, a numerical coding test, a span digit test and a semantic verbal fluency test.[23] Those researchers did not consider that screening by means of the CDT[19] to detect probable dementia was an adequate method.[24] Although the CDT[19] is easy to apply, it is vulnerable to different interpretations of the final result, given that different ways to analyze the clock that was drawn have been found. It cannot be used among people with visual or motor difficulties that prevent them from properly handling paper and pen, to make the drawing. There is no consensus on whether the CDT[19] can distinguish MCI from dementia, even though this test can assess memory, motor and executive function and verbal comprehension, and has been shown to differentiate dementia from normal cognition in review studies.[25]

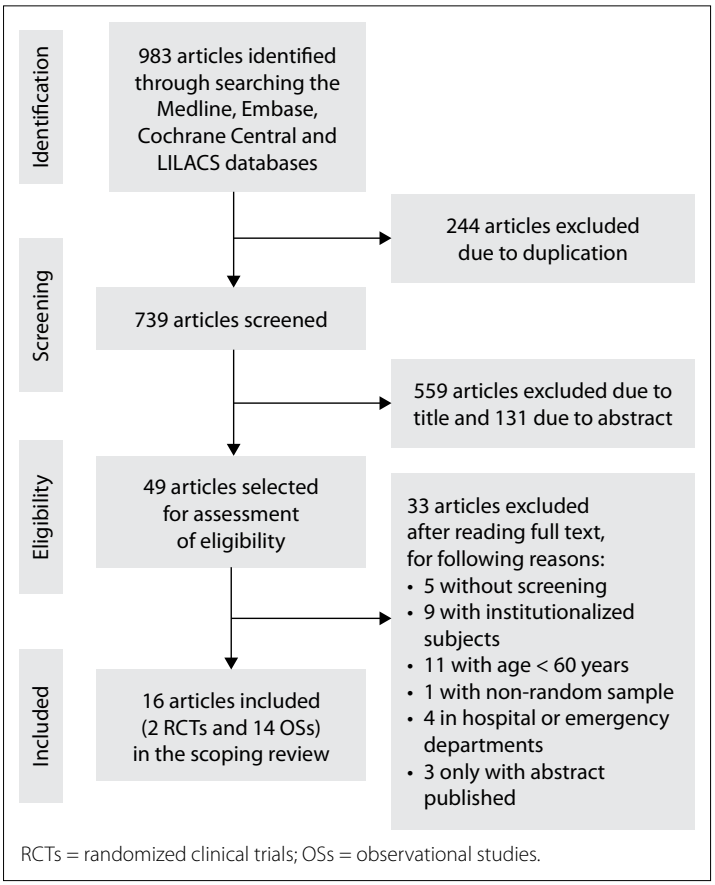

Figure 1. Flowchart for identifying and selecting articles for this scoping review.

The Mini-Cog[26] includes the CDT,[19] with its characteristics as described above, along with immediate and late evocation of three repetitions of words. In the study by Fowler et al.,[18] Mini-Cog was applied together with MIS. Those authors concluded that Mini-Cog was suitable for routine screening within primary care. However, this test has not been recognized as a good tool for cognitive screening among elderly people in the Brazilian population with less than five years of formal education. [27]

The memory impairment screening (MIS)[28] test was recommended for use in the Medicare Annual Wellness Visit as a preliminary test in conjunction with other screening tools. It can be effectively applied within four minutes to identify cognitive impairment,[29] and does not require the ability to write. However, an ability to read is required, which thus means that the results from this test are influenced by the subject's educational level.[30]

The Montreal Cognitive Assessment (MoCA)[31] is a test that was designed to screen for MCI and to differentiate it from dementia.[31] Although it covers all cognitive domains, it is significantly influenced by age and level of formal education. MoCA[31] may be

Table 2. Randomized Clinical Trials

Authors, year and country	Study design	Population and setting	Intervention	Comparison	Main findings	Down & Black (maximum score: 28)
Reiner et al.,[20] 2018; Germany	Cluster-randomized controlled intervention trial; ClinicalTrials.gov identifier NCT01401582	6,440 primary care patients systematically screened for dementia	DemTect and clock drawing test (CDT)	1,601 subjects (41.6% men and 58.4% women); mean age 76 ± 5.3 years (range 70 to 95 years); after DemTect screening, they were assessed using CDT	DemTect is a dementia screening instrument used in Germany with sensitivity of 100% and specificity of 92%; 17.3% (n = 1,117) of the total sample (n = 6,440) were categorized as presenting probable dementia (DemTect score < 9). The sensitivity and specificity of CDT were 84.4% and 45.6% respectively. CDT cannot be regarded as a suitable instrument for detection of probable dementia in primary care. Multi domain tests like DemTect should be considered more appropriate for identifying probable dementia in primary care	25 points/28
Fowler et al.,[18] 2019; United States	Single-blinded, two-arm, randomized controlled trial; ClinicalTrials.gov identifier NCT01699503	4,005 primary care patients; mean age of the overall study population was 74.1 (± 6.9); 2,256 (66%) were female	Memory impairment screening (MIS) and Mini-Cog	2,008 patients randomized to screening for Alzheimer disease and related dementias (ADRD) and 1,997 patients randomized to no ADRD screening. Primary measurements were health-related quality of life at 12 months and symptoms of depression and anxiety at 1 month	A total of 134 participants (7.7%) in the screening arm screened positive in either MIS or Mini-Cog. Symptoms of depression and anxiety were not harmed through screening and their scores were similar between screened and non-screened ADRD groups. No differences in healthcare utilization, advance planning of care or ADRD recognition by physicians were detected at 12 months	26 points/28

not an suitable instrument for identifying CIND among individuals with lower levels of education, according to a study by César et al.[32] However, Cecato et al.[33] found that MoCA was the test with the highest predictive value for differentiating Alzheimer's dementia (AD) from MCI and also for differentiating cases of MCI from normal individuals. Furthermore, MoCA has been shown to have significant correlations with the age variable in the mini-mental state examination (MMSE),[34] Cambridge Cognitive Examination (CAMCOG),[35] CDT,[19] verbal fluency test (VFT)[36] and Pfeffer Functional Activities Questionnaire (PFAQ),[37] which are instruments that have already been validated and are widely used in the Brazilian population.[33] Although MoCA[31] has the disadvantage of taking longer to apply than MMSE[34] and presents limitations with regard to the capacity for illiterate individuals to perform the proposed tasks, it is a tool that provides a superior overall assessment in the early stages of cognitive decline.[38]

Burkart et al.[39] compared the selective reminding procedure[40] (SRP) with MMSE[34] and concluded that the SRP was not recommendable for cognitive screening for dementia.[40] The Fuld Object Memory Evaluation (FOME)[41] assesses memory and learning through the SRP and can be applied to elderly people with a low level of formal education. It uses late evocation after distraction and is applied through a semantic VFT.[36] In Brazil, the only studies found involved a professional trained in psychology as the evaluator of this test.[42,43]

The MMSE[34] was the instrument most cited and used in this scoping review, thus corroborating other findings reported in the literature.[21,44] It has been validated for application both in the community and in primary care in many countries, with the aim of increasing the recognition of cognitive impairment. It has been accepted both by patients and by interviewers, even without assessment of executive function.[29]

Despite being widely used in Brazil, MMSE[34] needs adjustments to its cutoff scores, which are variable, because it can be influenced by age and level of formal education.[45] It is a screening tool that can be applied rapidly, and it addresses the main cognitive domains with high specificity and sensitivity for dementia. A wide variety of healthcare professionals have the capacity to use it.[46]

The criteria used in the MMSE[34] make it highly capable of screening for moderate and severe cognitive impairment. However, its ability to signal milder or earlier degrees of cognitive decline is significantly lower. It is not suitable for screening for the initial phases of dementia and can lead to higher rates of false negative results, since it does not evaluate executive function.[47]

Table 3. Observational studies

Authors, year and country	Study design	Population and setting	Intervention	Comparison	Main findings	Down & Black (maximum score: 18)
Morales et al.,[55] 1997; Spain	Cross-sectional	Urban sample of 97 subjects (48.5% men and 51.5% women); mean age ± SD = 75.2 ± 6.1 years (range 66-92); 17.9% illiterate. Rural sample of 160 subjects (31.9% men and 68.1% women); mean age ± SD = 73.5 ± 8.2 years (range 61-96); 28.2% illiterate. (Community-dwelling elderly people)	Spanish translation of the Mini-Mental State Examination (MMSE) and Spanish version of the Informant Questionnaire on Cognitive Decline in the Elderly (S-IQCODE)	MMSE and S-IQCODE	Eleven subjects in the urban sample were found to be mild dementia cases (prevalence rate 11.3%) and 23 subjects in the rural sample were dementia cases (prevalence rate 14.4%). S-IQCODE had higher accuracy than MMSE, especially when applied to mild dementia cases, and had higher specificity than MMSE when applied to population-based samples. In the urban sample, S-IQCODE had accuracy of 89% (cutoff ≥ 85 points) versus 77% for MMSE (cutoff ≤ 21 points); and sensitivity of 82% (versus 73% for MMSE). In the rural sample, S-IQCODE had accuracy of 83% (cutoff ≥ 86) versus 75% for MMSE (cutoff ≤ 21); sensitivity was 83% in both tests; and S-IQCODE had specificity of 83% (versus 74% for MMSE)	18 points/18
Dartigues et al.,[66] 1997; France	Prospective cohort study	2,726 subjects (59.8% women and 40.2% men); mean age 74.8 ± 6.9 years (range 65-101); 4.3% had never gone to school; 61.2% had a grade school level and 5.7% a university level of education. (Community-dwelling elderly people)	French version of MMSE, Benton's visual retention test (BVRT) and Isaac's set test (IST)	MMSE < 24, BVRT < 9 and IST < 23. Comparison between expected Alzheimer disease (AD) cases was based on the number of low values among the three tests, thus leading to a score of values 0, 1, 2 or 3	2043 subjects (75%) had at least one complete follow-up screening at 1 or 3 years. At first year of follow-up, 21 subjects were classified as incident cases of dementia (13 as possible or probable Alzheimer's Disease (AD) and 8 as other dementia). At the third year of follow-up, 63 subjects were classified as incident cases of dementia (46 as possible or probable AD and 17 as other dementia). Among the 3 tests (MMSE, BVRT and IST), when cutoff level was 1, the sensitivity for diagnosing AD was 90.8% and specificity was 52.2%; When the level was 2, the sensitivity was 81.2% and specificity was 80.4%. When the level was 3, the sensitivity was 52.2% and specificity was 91.3%	18 points/18
Burkart et al.,[39] 2000; Germany	Cross-sectional	256 subjects. (Community-dwelling elderly people)	A modified German version of the selective reminding procedure (SRP), Mini-Mental State Examination (MMSE) and verbal fluency test (VFT)	MMSE and SRP	23 (9%) of the 256 probands received the diagnosis of dementia (87% female; mean age 87 ± 7.3 years; mean formal education 9.1 ± 1,7 years). MMSE performed better than all SRP scores in terms of sensitivity and specificity. SRP cannot be recommended for dementia screening. MMSE with cutoff of ≤ 23 had sensitivity of 87% and specificity 99%; with cutoff of ≤ 24, sensitivity was 91% and specificity 97%. SRP score cutoffs with specificity of 95% or above had sensitivities below 50%	17 points/18

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Table 3. Continuation

Authors, year and country	Study design	Population and setting	Intervention	Comparison	Main findings	Down & Black (maximum score: 18)
Silva et al.,[65] 2002; Sri Lanka	Cross-sectional	380 subjects of mean age 68.2 (SD = 7,17); 33.1% males and 66.9% females; 54.2% had less than six years of formal education; 11.6% had no formal education; and 5.5% were illiterate. (Community-dwelling elderly people)	Translated Sinhalese versions of the MMSE and Cambridge Cognitive Examination (CAMCOG)	MMSE cutoff score ≤ 17 or > 17 points; and CAMCOG	29 of the 33 subjects who screened positive in MMSE showed evidence of dementia. Among the 24 randomly selected subjects who screened negative in MMSE, 22 showed no evidence of dementia while two scored below cutoff in CAMCOG and showed evidence of dementia. The Sinhalese translation of the MMSE is a useful and sensitive instrument for screening for cognitive impairment in Sri Lanka. MMSE cutoff of 19 points had sensitivity of 100% and specificity 84.6%; with cutoff of 17 points, it had sensitivity of 93.5% and specificity 84.6%	15 points/18
Jeong et al.,[64] 2004; South Korea	Cross-sectional	235 subjects; mean age 73.5 ± 6.7 years; 50.2% had no formal education; and 66.4% were women. (Community-dwelling elderly people)	Korean Mini-Mental State Examination (K-MMSE); Korean version of modified Mini-Mental State Examination (K-mMMSE); Korean version of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), using short form of Samsung Dementia Questionnaire (S-SDQ); Korean Instrumental Activities of Daily Living (K-IADL); and Korean version of Expanded Clinical Dementia Rating (CDR)	K-MMSE and K-mMMSE	Among the 235 participants, 46 (19.6%) were classified as having dementia and 54 (22.9%) as having cognitive impairment with no dementia (CIND). K-mMMSE is more sensitive to all levels of CIND and dementia than K-MMSE. At the cutoff of 59/60, K-mMMSE had sensitivity of 0.91 (0.79-0.98) and specificity of 0.78 (0.72-0.84). At the cutoff of 18/19, K-MMSE had sensitivity of 0.91 (0.79-0.98) and specificity of 0.76 (0.69-0.82) to distinguish between demented and normal individuals	16 points/18
Rait et al.,[44] 2005; United Kingdom	Cross-sectional survey as part of a cluster randomized trial	15,051 subjects; 61.5% were female and 47% were aged between 75 and 79 years. (Community- dwelling elderly people)	Mini-Mental State Examination (MMSE)	MMSE at cutoffs of 23/24 and 17/18	The prevalence of cognitive impairment was 18.3% at cutoff of 23/24 and 3.3% at 17/18 in MMSE	18 points/18
Laks et al.,[63] 2005; Brazil	Cross-sectional	870 subjects 65.9% were female; 40.1% were illiterate; 53.4% had 1-8 years of schooling; 5.3% had 9-11 years of schooling; and 1.2% subjects had more than 12 years of schooling. Mean age 72.14 ± 7.26 years. (Community-dwelling elderly people)	Mini-Mental State Examination (MMSE) and Pfeffer Functional Activity Questionnaire (PFAQ)	MMSE and PFAQ	Cognitive and functional impairment was observed in 19.2% of the total sample. Functional impairment without cognitive decline was found in 5.3% of the subjects. Functional impairment was correlated with cognitive impairment. This may be an easier feature for families to recognize and for healthcare professionals to screen for dementia, with assessment of both cognitive and functional status, in combination	18 points/18

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Table 3. Continuation

Authors, year and country	Study design	Population and setting	Intervention	Comparison	Main findings	Down & Black (maximum score: 18)
Tatsch et al.,[62] 2006; Brazil	Cross-sectional	1,563 subjects. (Community-dwelling elderly people)	Mini-Mental State Examination (MMSE); Fuld Object Memory Evaluation (FOME); Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); Activities of Daily Living-International Scale (ADL-IS); Cambridge Examination for Mental Disorders of the Elderly (CAMDEX); Cambridge Cognitive Examination (CAMCOG; cognitive section of CAMDEX); and Clinical Dementia Rating Scale (CDR)	Combination of screening with MMSE, FOME, IQCODE and ADL-IS was tested prior to diagnostic evaluation with CAMDEX, CAMCOG and CDR	Prevalence of dementia was 6.8%. Alzheimer disease and CIND were diagnosed in 64 and 25 subjects, respectively	18 points/18
Ortega et al.,[67] 2012; Honduras	Cross-sectional	50 subjects; 52% were female and 44% were aged between 71 and 80 years. (Community-dwelling elderly people)	Mini Mental State Examination (MMSE)	MMSE	According to MMSE, 18% were classified as possible cases of dementia	14 points/18
Jiang et al.,[53] 2014; China	Cross-sectional	1,773 subjects; mean age of participants 72 years; majority female. (Community-dwelling elderly people)	Montreal Cognitive Assessment (MoCA)	MoCA	About 13% (233) of the elderly subjects were identified as having mild cognitive impairment (MCI). The study results suggested that MCI is associated with not doing housework	17 points/18
César et al.,[61] 2015; Brazil	Cross-sectional epidemiological study	630 subjects; mean age of 71.3 years (± 7.99); range 60-98 years; median 70 years; mean education level 4.9 years (± 4.54) with median of 4 years; 14% of participants were illiterate and 28.9% had 1-3 years of education. (Community-dwelling elderly people)	Mini-Mental State Examination (MMSE); Brief Cognitive Screening Battery (BCSB); semantic and phonemic verbal fluency test (VFT); clock drawing test (CDT); Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); and Pfeffer Functional Activity Questionnaire (PFAQ)	MMSE; BCSB/VFT/CDT; IQCODE; and PFAQ	110 individuals were diagnosed with dementia and 135 individuals were diagnosed with cognitive impairment without dementia (CIND). The prevalence of dementia found in this study was 17.5% and the prevalence of CIND was 19.5%	18 points/18

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Table 3. Continuation

Authors, year and country	Study design	Population and setting	Intervention	Comparison	Main findings	Down & Black (maximum score: 18)
Han et al.,[68] 2018; South Korea	Prospective cohort study	6,818 subjects; mean age 70.5 ± 7.10 years; 57.5% were women; mean education level was 7.8 ± 5.38 years; illiteracy rate in reading was 4% (n = 275) and illiteracy rate in writing was 4.7% (n = 323). (Community-dwelling elderly people)	Korean version of Short Informant Questionnaire on Cognitive Decline in the Elderly (SIQCODE); Korean version of Consortium to Establish a Registry for Alzheimer's Disease, neuropsychological assessment package (CERAD-K-N); digit span test (DST); executive clock drawing task (CLOX); Frontal Assessment Battery (FAB); Severe Cognitive Impairment Rating Scale (SCIRS); Disability Assessment for Dementia (DAD); and Clinical Dementia Rating (CDR)	The baseline evaluation was conducted over two years from November 2010 to October 2012. Follow-up evaluations were conducted every two years from November to October, from 2012 to 2018	In the baseline evaluation (November 2010 to October 2012), there were 4572 individuals with normal cognition, 1903 individuals with CIND and 343 individuals with dementia	18 points/18
Vega Alonso et al.,[21] 2018; Spain	Descriptive observational study	4,624 subjects. (Primary care)	Mini-Cog; Mini-Mental State Examination (MMSE); and Alzheimer Questionnaire (AQ)	Mini-Cog screened positive, plus MMSE/AQ	356 patients (8.2%) had a history of dementia or mild cognitive impairment (MCI). Cognitive impairment was confirmed using MMSE or AQ in 67.2% of the cases in which Mini-Cog screened positive. Total number of known cases plus confirmed cases was 806 (18.5%). Prevalence of cognitive impairment was 21.3% among women and 14.8% among men, and it increased with age, reaching maximum values at ages of 85 years or over	18 points/18
César et al.,[32] 2019; Brazil	Cross-sectional epidemiological study	630 subjects; mean age 71.3 years (± 7.99); range 60-98 years; median 70 years; mean education level was 4.9 years (± 4.54) with median of 4 years; 14% of participants were illiterate and 28.9% had 1-3 years of education. (Community-dwelling elderly people)	Montreal Cognitive Assessment (MoCA); Mini-Mental State Examination (MMSE); Brief Cognitive Screening Battery (BCSB); semantic verbal fluency test (VFT), animal category; clock drawing test (CDT); Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE); Pfeffer Functional Activity Questionnaire (PFAQ); and Clinical Dementia Rating (CDR)	MoCA and MMSE total scores stratified into educational levels within each age group	Among the 630 participants, 385 were classified as cognitively normal (CN), 135 as having cognitive impairment with no dementia (CIND) and 110 as having dementia. The MoCA test may not be an adequate tool for identifying individuals with CIND, among those with lower education, but this tool may be used to detect dementia, especially among individuals with more than five years of education, if a lower cutoff score is used, such as 15 points. For MoCA cutoff score 15, CN versus dementia presented sensitivity 90% and specificity 77%; for MoCA cutoff score 19, CN versus CIND presented sensitivity 84% and specificity 49%.	18 points/18

Table 4. Cognitive assessment test

Cognitive test	n = sample	Cognitive domains
MoCA[31] (Montreal Cognitive Assessment)	n = 630 [32] n = 1773 [53]	Attention, orientation, language, immediate and delayed memory, constructive praxis, calculation, executive functions, visual-spatial ability
MMSE[34] (Mini-Mental State Examination)	n = 630 [32 61] n = 4335 [21] n = 1563[62] n = 870 [63] n = 15051[44] n = 235 [64] n = 380 [65] n = 256 [39] n = 2792 [66] n = 257 [55] n = 50 [67]	Attention, orientation, language, immediate memory, constructive praxis, calculation
BCSB[50] (Brief Cognitive Screening Battery)	n =630 [32 61]	Attention, language, immediate and delayed memory, constructive praxis, executive functions, visual-spatial ability
Mini-Cog[26]	n = 4335 [21]	Attention, language, immediate and delayed memory, constructive praxis, executive functions, visual-spatial ability
CERAD[51] (Consortium to Establish a Registry for Alzheimer's Disease)	n = 6818 [68]	Attention, orientation, language, immediate and delayed memory, constructive praxis, executive functions, visual-spatial ability, calculation
FOME[41] (Fuld Object Memory Evaluation)	n = 1563 [62]	Episodic memory, language, executive functions, learning
CAMCOG[35] (Cambridge Cognitive Examination)	n = 1563 [62] n = 380 [65]	Attention, orientation, language, immediate and delayed memory, constructive praxis, executive functions, visual-spatial ability, calculation
Digit span	n = 6818 [68]	Attention, working memory, executive functions, concentration, learning
CDT[19] (clock drawing test)	n = 6818 [68]	Attention, constructive praxis, executive functions, visual-spatial ability
FAB[69] (Frontal Assessment Battery)	n = 6818 [68]	Executive functions
SRP[40] (selective reminding procedure)	n = 256 [39]	Immediate and delayed memory, learning
BVRT[70] (Benton's visual retention test)	n = 2792 [66]	Memory, executive functions, constructive praxis, visual-spatial functions
IST[36] (Isaac's set test)	n = 2792 [66]	Language, memory, executive functions
VFT[36] (verbal fluency test)	n = 256 [39]	Language, memory, executive functions

Source: Observational studies.

Table 5. Functional evaluation scale

Functional scale	n = sample	Cognitive and functional domains and activities of daily living
IQCODE[54] (Informant Questionnaire on Cognitive Decline in the Elderly)	n = 630 [32 59] n = 1563 [60] n = 257 [53]	Memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care
PFAQ[37] (Pfeffer Functional Activity Questionnaire)	n = 630 [32 59] n = 870 [61]	Memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care
CDR[56] (Clinical Dementia Rating)	n = 630 [32 59] n = 1563 [60]	Memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care
AQ[71] (Alzheimer's Questionnaire)	n = 4335 [21]	Memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care
SCIRS[72] (Severe Cognitive Impairment Rating Scale)	n = 6818 [66]	Memory, orientation, motor function, visuospatial function, language

Source: Observational studies.

Changes in executive function may be present early in cases of dementia syndrome, and even as the only manifestations. It needs to be emphasized that the MMSE[34] should not be used in isolation to assess cognitive performance.[48,49]

Use of the semantic VFT[36] was also seen among the studies reviewed. This enables evaluation of language, memory and executive function, through asking individuals to verbally list categories of colors, animals, fruits or cities. Although it was considered separately only in one study, it was used in other articles in this scoping review, within the FOME[41] and CAMCOG[34] tests, the Brief Cognitive Screening Battery[50] (BCSB), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[51] battery and the MoCA[31] test (phonology version).

VFT[36] is a simple test that can easily be applied. It presents screening results that classify cognition with precision comparable to that of MMSE,[34] given that it is very effective in evaluating

executive function and language ability, mainly due to its semantic approach, which seems to require a high level of thought process. The semantic and phonological versions of VFT[36] can be considered to be indicators of executive functions since this test requires the ability to self-regulate working memory through the ability to search for and retrieve information that is stored in long-term memory. VFT[36] is considered to be quite accurate for dementia screening and relatively sensitive for assessing earlier stages of cognitive impairment. The levels of resistance or refusal to participate are low because listing words for one minute is not particularly intimidating. This test is free of charge and easy to administer. It does not require any materials other than a device to keep track of the time and a means for recording the number of words produced. VFT[36] appears to be able to distinguish between individuals with or without normal cognition. Performance in this test may be influenced by the subject's level of education and age, which therefore needs to be taken into account.[8,52]

Jiang et al.[53] suggested that changes to instrumental activities of daily living (IADLs) for domestic work may occur in individuals with MCI and, therefore, use of functional scales is also recommendable. Furthermore, according to Rait et al.,[44] individuals with CIND presented higher levels of functional deficit than people with intact cognition.

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[54] is a questionnaire (via an interview) that is applied to an individual who accompanies a patient. This companion is asked to quantify the patient's current performance in different activities of daily living (ADLs), in comparison with the same situations 10 years ago. Morales et al.[55] showed that the IQCODE[54] scale presented greater precision of results than the MMSE,[34] in cases of MCI.

PFAQ[37] was the functional assessment questionnaire that was most used among the studies reviewed here. It was also aimed at accompanying informants, who were asked to answer 10 simple questions about the performance of elderly people regarding their ADLs. These results can provide direct sensitive information, within the primary care setting, regarding the companion's suspicion that the patient may present dementia. Use of PFAQ[37] combined with VFT[36] showed sensitivity of 88.3% and specificity of 76.5% in a study by Jacinto et al.,[5] thus suggesting that these tests are useful for screening for cognitive impairment among elderly people.

The Clinical Dementia Rating (CDR)[56] scale assesses behavior and cognition among elderly people and ascertains the degree of dementia when present. It is capable of identifying individuals for whom the criteria for dementia have not yet been established, but who present cognitive impairment. This instrument is divided into six cognitive and behavioral functions, in order to assess the influence that cognitive impairment can have on the functional capacity to perform ADLs.[57]

The articles selected for the present review showed certain limitations. These included the rate of losses and the short follow-up period for the patients in the RCTs.[18,20] There was also selection bias in the subsample categories, when tests at different times of assessment were compared. Furthermore, there was no reassessment of participants with a negative result from screening for cognitive impairment.[53] Evaluation of a sample of patients from primary care and not from the community in general was criticized in some studies,[18,20,21] but this met the inclusion criteria of this scoping review. In addition, given that cognitive impairment can begin many years before dementia syndromes are diagnosed,[58] further studies on cognitive screening among younger individuals are needed. For example, individuals aged 40 to 60, who may or may not have subjective cognitive complaints, could be assessed. The instruments that were relevant in this review, such as MMSE,[34] VFT[36] and PFAQ,[37] could be used in such studies.

CONCLUSIONS

The MMSE[34] was the test most frequently found, and its use and limitations were discussed here. The findings from this scoping review suggest that additional studies on the use of the PFAQ,[37] in combination with the VFT,[36] for screening for cognitive impairment among elderly people in the Brazilian population, should be conducted. The positive characteristics of these tools include the reliability of their results; the lower influence of the level of formal education, compared with other instruments; and their ease of application. These additional studies should comprise randomized clinical trials and observational studies to assess the application of PFAQ[37] and VFT[36] within primary care, given the diversity of educational and cultural levels in Brazil.

It also necessary to create new cognitive screening instruments for future studies, with the characteristics common to the MMSE,[34] VFT[36] and PFAQ,[37] such as ease of application, in order to obtain standardized results. General practitioners within primary care services can then apply such instruments to elderly people, in order to be able to refer them for wide-ranging and timely evaluation in specialized services, when necessary.

In the context of aging of the population, it is important that professionals should screen for cognitive impairment,[59,60] as a routine procedure within primary healthcare. Through this, preventive interventions can be provided in order to avoid or minimize the negative effects of dementia on elderly people's health.

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COVID 19 repercussions in ophthalmology: a narrative review

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ABSTRACT

BACKGROUND: The new coronavirus of 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally and has repercussions within ophthalmological care. It has caused ocular manifestations in some patients, which can spread through eye secretions.

OBJECTIVES: The purpose of this review was to summarize the currently available evidence on COVID-19 with regard to its implications for ophthalmology.

DESIGN AND SETTING: Narrative review developed by a research group at Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil, and at Ludwig-Maximilians-Universität, Munich, Germany.

METHODS: We searched the literature on the repercussions of COVID-19 within ophthalmological care, using the MEDLINE and LILACS databases, with the keywords "COVID-19", "ophthalmology" and "coronavirus", from January 1, 2020, to March 27, 2021. Clinical trials, meta-analysis, randomized controlled trials, reviews and systematic reviews were identified.

RESULTS: We retrieved 884 references, of which 42 were considered eligible for intensive review and critical analysis. Most of the studies selected reported the evidence regarding COVID-19 and its implications for ophthalmology.

CONCLUSIONS: Knowledge of eye symptoms and ocular transmission of the virus remains incomplete. New clinical trials with larger numbers of patients may answer these questions in the future. Moreover, positively, implementation of innovative changes in medicine such as telemedicine and artificial intelligence may assist in diagnosing eye diseases and in training and education for students.

INTRODUCTION

The outbreak of the new coronavirus (COVID-19) that started in Wuhan, China, has spread all over the world and has had a great impact on eye care.[1] It is a ribonucleic acid (RNA) virus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may have ocular manifestations in some patients.[2]

This is a single-stranded RNA virus with a genome of about 30 kb in length. The RNA genome encodes its proteins. The proteins are spike protein S, membrane protein M, envelope protein E and nucleocapsid protein N. Protein S is responsible for attachment to host receptors; protein M helps to shape virus particles and their binding to the nucleocapsid; protein E acts in the assembly of particle release; and protein N acts on genome binding and replication.[3]

The new coronavirus shows 96% genetic similarity to the bat-type coronavirus SARS BatCovRaTG13, and its spike surface protein (S) binds to angiotensin-converting enzyme 2 (ACE2) on the cell surface. ACE2 expression can be found in respiratory, intestinal, renal, cardiac and immune cells. Its main transmission routes are through respiratory droplets, fomites and fecal-oral routes. Some patients have had an episode of conjunctivitis before pneumonia, thus raising the hypothesis that the ocular mucosa is a possible transmission route for SARS-CoV-2, since the cornea and conjunctiva show expression of the ACE2 receptor, which is responsible for entry of the virus cells.[4] Presence of the ACE2 infection receptor in the aqueous humor of humans has also been described.[5] ACE2 is a crucial receptor for SARS-CoV-2 in vivo: in an experiment on mice, an injection of SARS-CoV spike worsened acute lung failure in vivo, which was then attenuated by blocking the renin-angiotensin pathway.[6,7]

OBJECTIVE

The objective of this narrative review was to summarize the currently available evidence on COVID-19 with regard to its implications for ophthalmology.

METHODS

We conducted a review of the literature considering the period from January 1, 2020, to March 27, 2021. We used the MEDLINE database (via PubMed) and LILACS (via Virtual Health Library) to identify relevant articles on the repercussions of COVID-19 within ophthalmological care, without restrictions on languages. Different combinations of keywords and MeSH terms were used as search strategies in order to ensure a broad search strategy: "ophthalmology", "COVID-19" and "coronavirus". The titles and abstracts of citations identified through these search strategies were screened for eligibility. We selected the main articles that reported on ophthalmological manifestations of coronavirus and how the pandemic was impacting ophthalmological care and education. We also selected articles that presented alternative solutions for eye care, such as the use of telemedicine and artificial intelligence. The details of the search strategy are shown in **Table 1**.

RESULTS

From the search in the databases, two clinical trials, 11 meta-analyses, one randomized controlled trial, 158 reviews and 27 systematic reviews were identified. After screening the titles and abstracts, removing duplicates and screening the citations, 42 studies were considered eligible for critical analysis. The article selection process is detailed in **Figure 1**.

Ophthalmological manifestations

The main symptom reported by infected patients was viral conjunctivitis (hyperemia, eye pain, photophobia and tearing), which lasted for 2 to 24 days (average of 6 days). The incubation period for this viral infection is 2 to 14 days.[8]

In a study conducted among a total of 535 patients with COVID-19, 5.0% had conjunctival congestion, 29.6% had conjunctival discharge, 22.2% had watery eyes and 18.5% had ocular pain. Eye symptoms were usually present in patients with more severe symptoms of the disease. In that study, no viral nucleic acid was detected in the conjunctival swabs taken from the patients.[9] In another study on 1,099 patients, presence of conjunctival congestion was detected in 0.8% of the patients. Conjunctivitis in these patients usually has follicles and mucoid secretion.[10,11] Children can be affected by conjunctivitis, as well as adults, and they may present a picture of eyelid dermatitis.[12] The viral load of conjunctival sac secretions in patients with COVID-19 is relatively low and is usually proportional to the severity of the disease.[13]

Xia et al. reported that SARS-CoV-2 existed only in the conjunctival and lacrimal secretions of a patient with conjunctivitis and that patients without ocular manifestations would not be a source of infection via this transmission route.[14] However, another study demonstrated the presence of the virus in the eye secretions of patients without conjunctivitis.[15] Therefore, ophthalmological examinations need to be carried out in a ventilated place and all possible measures should be taken to avoid cross-infection among ophthalmic patients. Patients should be advised not to touch their eyes because of the risk of contamination by the virus. The recommended treatment for viral conjunctivitis is supportive, and most cases are self-limiting. However, some recommendations for decreasing transmission rates should be followed, such as frequent hand washing and avoidance of touching one's eyes.

The coronavirus epidemic has changed the criteria for corneal donation in some countries. In these, exclusion of suspected or confirmed cases has been started.[16] Coronavirus patients may present with hyperreflective lesions at the level of ganglion cells and in the inner plexiform layer. This condition may be associated with hemorrhages and cottony exudates.[17] Cases of changes in ocular motility after coronavirus infection have been described.[18] Clinical findings such as conjunctivitis, retinitis, anterior uveitis and optic neuritis have been recognized in animal models. Thus, awareness of these possible manifestations in humans is needed.[19]

Ophthalmological services

Because ophthalmological care is administered close to patients' faces, ophthalmologists are exposed to tears and eye discharges. These medical specialists are therefore at high risk of contracting COVID-19. Protective measures for the mouth, nose and eyes need to be implemented, with use of personal protective equipment (N95, FFP2 or FFP3 masks, goggles and face shields).

Reduction of the number of patients scheduled should be sought, along with greater distance (at least 1.5 meters) between patients in the waiting room. Online prescription programs for patients can be implemented. Patients should have their temperature measured before entering the doctor's office and must wear a mask for the entire period of stay in the doctor's office. If the patient's temperature is above 37.5 °C, the appointment should be postponed unless it is an eye emergency.

Table 1. Details of the search strategy

Database	Search strategies	Papers found
MEDLINE (via PubMed)	#1- ("ophthalmology") AND ("coronavirus")	872
	#2-("COVID-19" [Mesh Terms) AND ("ophthalmology" [MeSH Terms])	220
LILACS (via Biblioteca Virtual em Saúde, BVS)	#1- ("ophthalmology") AND ("coronavirus")	300
	#2- ("COVID-19" [Mesh Terms) AND ("ophthalmology" [MeSH Terms])	7

The examination room needs to be well ventilated, and the ophthalmic devices should be disinfected immediately after use, with 0.1% sodium hypochlorite or 70% ethanol for at least one minute before and after examination of the patient. Use of a non-contact tonometer should be avoided because of the micro-aerosols that are generated. The tips of the Goldman tonometer need to be disinfected.[20,21]

Examinations using direct ophthalmoscopy should be avoided due to the proximity to the patient. This can be replaced by retinography, which allows greater distancing from the patient. Acrylic shields need to be installed in the slit lamp, so as to reduce contact with aerosols generated by patients. Ophthalmological examinations should be conducted as soon as possible. Elective procedures should be postponed during this period. Emergency surgery for infected patients should be performed preferably in operating rooms with negative pressure. Moreover, surgery with general anesthesia should be avoided, given that intubation can generate an aerosol.

So far, there is no evidence to contraindicate use of contact lenses by patients. However, because it is known that the virus can be isolated in tears and conjunctiva, it is advisable to avoid

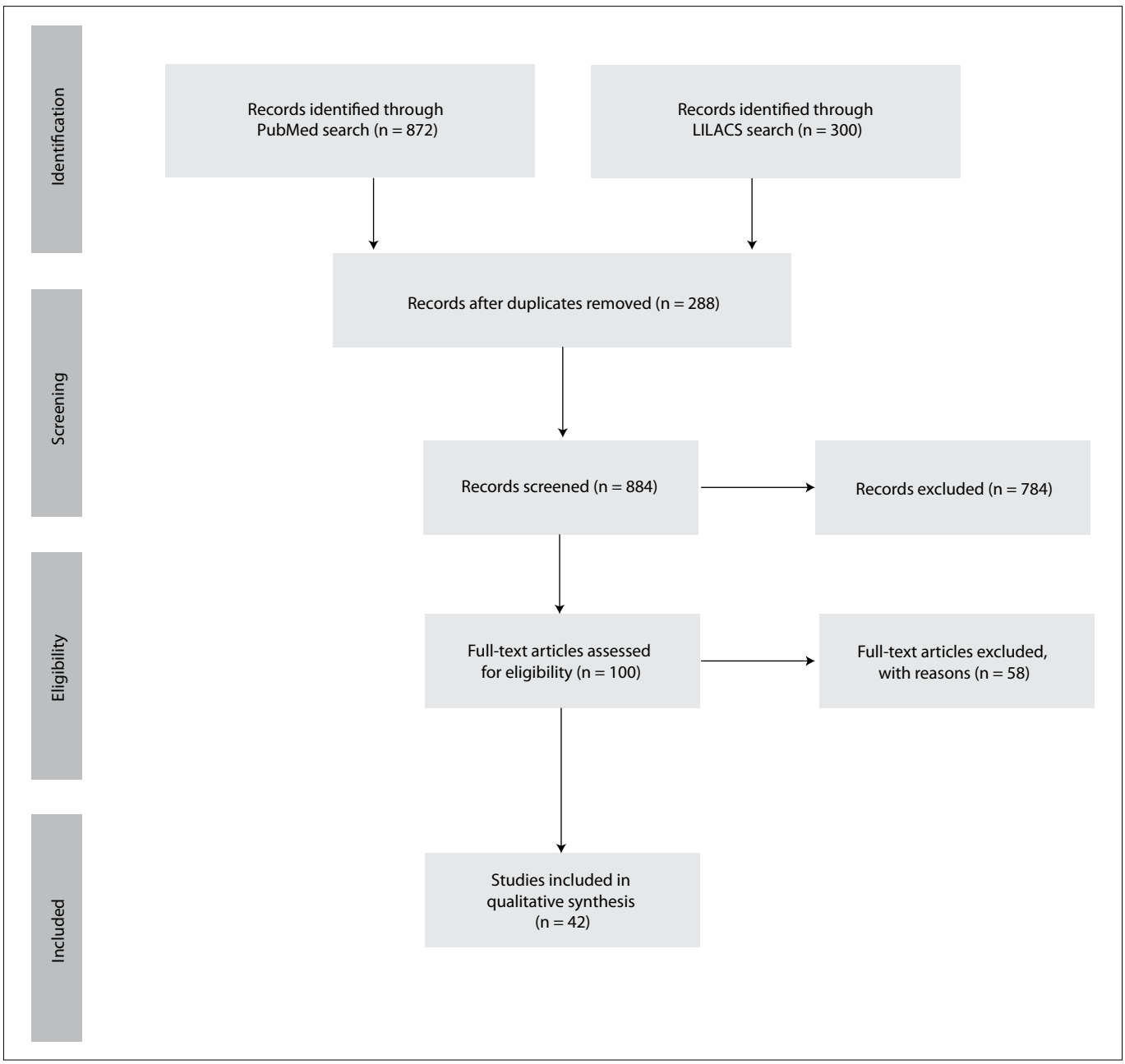

Figure 1. Flow diagram of the study selection process.

adaptation to contact lenses during this period. The main objectives of these measures are to minimize cross-infection between employees and patients, and to ensure a safe working environment.

Telemedicine

The training of ophthalmology students has been greatly affected during the pandemic period, since most appointments and elective surgeries have been canceled.[22] Telemedicine with use of distance training has become an option for training clinical staff during this period. The teleguidance for ophthalmological patients has also been used, with the aims of correctly directing emergencies to hospitals and preventing patients from unnecessarily looking for hospitals, which might increase their risk of contamination. During this period, use of training models and simulators has proven to be useful in training these students for surgery and eye examination.[23-25]

Patients can also be assisted through teleophthalmology, which can be improved with appropriate training for healthcare professionals. Quality images can be captured and sent to ophthalmologists in other locations. In special pandemic situations, some images can even be captured by patients using smartphones.[26,27] The COVID-19 pandemic has transformed some leading telehealth platforms, which have reported that virtual visits by patients have increased by between 257% and 700%.[28]

For evaluation of macular diseases, there are applications and devices to monitor the central 10 degrees of the field of view, such as the hyperacuity perimeter ForSee device (Notal Vision).[29] There are already smartphones capable of capturing images of the retina, but they have not yet been designed for patients to use at home.[30]

During this period of global health emergency, rapid communication and international collaboration are essential, in order to achieve better outcomes from the pandemic, and telemedicine has collaborated in this process. Teleophthalmology plays an important role in rural areas and in places with few specialists, but during this pandemic it has become useful even in areas with enough ophthalmologists, in order to promote social isolation and reduce the rate of virus transmission.

Artificial intelligence

In this scenario of difficult access to eye care, artificial intelligence seems to be an alternative for facilitating the diagnosis and monitoring eye diseases. Through the development of artificial intelligence, it has become possible to develop algorithms that are able to identify lesions in ophthalmic examinations without human intervention. This enables analysis of the large amounts of data that are generated, in an automatically supervised, semi-supervised or unsupervised manner. Development of algorithms with real-time cloud database analysis may be useful for controlling and monitoring eye diseases. Thus, incorporation of machine-learning technology in ophthalmology can improve medical care for the population in regions with limited medical resources, thereby reducing some social inequalities that already existed before the coronavirus epidemic and became more evident.

Development of algorithms in smartphone applications helps in identifying contacts with contaminated people (contact tracing). These algorithms cross-reference information about patients' locations and symptoms. They are responsible for notifying people who have been in contact with infected individuals regarding the need for quarantine, so as to reduce the risk of spreading contamination across society. Artificial intelligence is providing new ways to enable contact tracking, through using Bluetooth to track nearby phones, keep records of these contacts and alert people to others with whom they have been in contact. An individual can test positive and then the algorithms start a cascade of notifications from all recent contacts. Alternatively, an individual may be notified that he was in the vicinity of another anonymous person who tested positive. This big data can be used by public healthcare systems. Some problems still need to be overcome, such as maintaining data confidentiality and the fact that not all people have smartphones and internet access.[31-35] In China, the Alipay Health app on Alipay indicates the possibility of getting around a city, based on three categories: green (without restrictions), yellow (7-day quarantine) and red (14-day quarantine).[36] An application developed in South Korea warns people by text message if they were close to people diagnosed with COVID-19.[37] In Italy, the application "Immuni" combines clinical information with the possible contacts of infected people.[38]

The WellAI COVID-19 app uses deep neural networks to learn from a big dataset about COVID-19 and to summarize existing knowledge. These algorithms are based on unsupervised learning.[39] SciSight is an algorithm that uses artificial intelligence to explore associations between concepts that appear in the COVID-19 dataset. It is available at https://SciSight.apps.allenai.org/.[40] These algorithms and large databases (big data) are valuable within research and development relating to medical knowledge. Artificial intelligence tools are expected to accelerate development of the diagnosis, treatment and prevention of COVID-19, at a time when humanity needs rapid responses in order to minimize the damage of the pandemic.

DISCUSSION

The COVID 19 epidemic has had a major impact on the volume of eye care. The reduction in the volume of care that has occurred has hindered the teaching of ophthalmology residents and the follow-up of several ophthalmic diseases. Use of technology in telemedicine and development of artificial intelligence algorithms can reduce the impact of COVID-19 on the care of ophthalmic patients.[41]

The policies of lockdown and social distancing have hindered the ophthalmological follow-up of many patients. Many elective eye surgeries have been canceled and treatments for many patients have been delayed.[42] During the period of greatest social isolation, some hospitals even reported a reduction of 63% in the number of ophthalmological consultations and 67% in the number of surgeries. On the other hand, they reported an increase of 1800% in the number of telemedicine consultations.[42] The impact on the population's eye health can only be clarified through future studies that may document what this loss of ophthalmological monitoring may have caused.

The period of social isolation and the large number of deaths caused by the coronavirus pandemic have caused a major change to the mental health of ophthalmologists. The numbers of psychiatric complaints among them, such as depression, anxiety and insomnia, have increased.[43] Since ophthalmologists perform examinations very close to patients' faces, they are at high risk of contamination. In a survey conducted at Moorfields Eye Hospital, 80% of the ophthalmologists were found to be at high risk of contamination by coronavirus.[44] The main concerns were the lack of adequate protective masks and the risk of contaminating family members. Many patients have reported fear of loss of vision during the pandemic due to loss of eye care.[45] Thus, not only is patients' health impaired through social isolation, but also ophthalmologists' health is impaired through the risk of contamination and mental health problems.

The new forms of assistance by means of telemedicine and with the use of artificial intelligence have limitations in countries that do not have an adequate internet infrastructure and where the population does not have access to this technology.[46]

However, a study has shown that most patients like this new form of telemedicine care. Thus, this new service can continue to be used even after the end of the coronavirus pandemic.[47] Telemedicine consultations can reduce the number of unnecessary consultations with ophthalmologists. This reduces the risk of infection, reduces the cost of healthcare and increases the degree of patient satisfaction.

Future perspectives

Because COVID-19 is a new virus, further studies will be needed to characterize the main ophthalmological symptoms and whether the ocular route can provide a gateway for the virus, as a primary infection site. Through new studies, more can be learned about the pathophysiology of this disease and a better theoretical basis for better orientation of the population can be established. Development of new artificial intelligence algorithms and devices for capturing ophthalmological images, which can be used by patients themselves, can facilitate the monitoring of ophthalmic diseases in areas with few specialists or in situations that require social isolation, such as epidemics.[48-51] Academic medical centers should take this opportunity to modify their curricula, including training in data science, computing, virtual reality and telemedicine. The expectation is that, with increasing levels of vaccination in the population, eye care and the number of surgeries will be able to return to normal within a short time.[52]

Strengths and limitations

The articles included in this review generated heterogeneous data because of the diversity in the design of the studies (clinical trials, meta-analysis, randomized controlled trials, reviews and systematic reviews). The main limitation of this review was the lack of tools for methodological assessment of the reviews. This narrative review does not provide quantitative answers to specific questions about the ophthalmic manifestations of coronavirus. The selection of studies and the interpretation of information may have been influenced by the authors' subjectivity.

CONCLUSION

Since 2002, coronaviruses have seemed to pose a continuous threat to humanity, such that there is a need to always be on the lookout for new outbreaks. Knowledge of eye symptoms and ocular transmission of the virus remains incomplete. New clinical trials with larger numbers of patients may answer these questions in the future. Moreover, positively, implementation of innovative changes in medicine such as telemedicine and artificial intelligence may assist in diagnosing eye diseases and in training and education for students.

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3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports;
4. 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 in the PROSPERO database. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details

to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

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 "doi" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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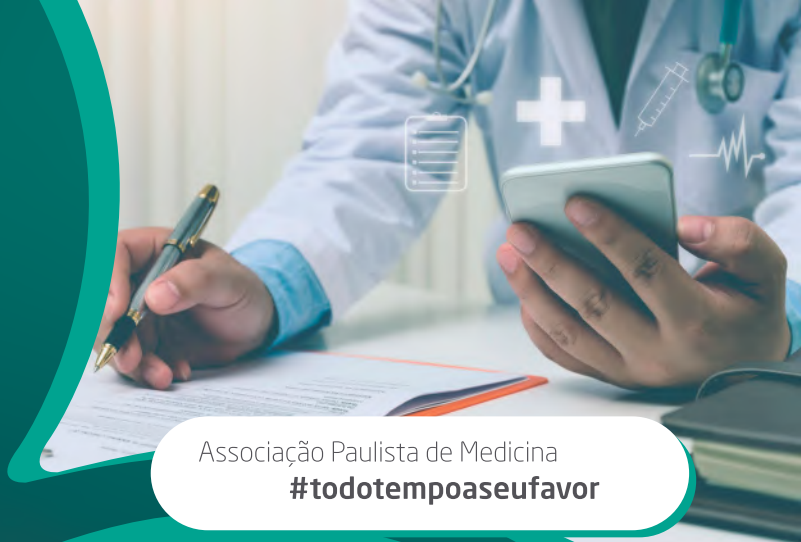

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