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Editorial
- Undergraduate Medical Research

Cross-sectional study
- Time to initiation of dialysis and length of stay in hospitalized patients with kidney damage

Systematic review
- Intensity-modulated radiation therapy for early-stage breast cancer

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Undergraduate Medical Research

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Following World War II, several countries started programs to advance medical, scientific, and technological development through research funding. Despite Brazil's abundance of strategic mineral resources, the country lacked both the technology and specialized workforce required for their exploitation.

In 1946, Admiral Álvaro Alberto da Motta e Silva, a military officer and engineer representing Brazil in the newly established UN Security Council's Atomic Energy Commission, proposed establishing a National Research Council. The National Research Council (CNPq) was founded in 1951, when then President Eurico Gaspar Dutra recognized the strategic value of science and the need to create formal programs to support and promote research in Brazil.

Álvaro Alberto referred to Law No. 1.310 of January 15, 1951, which established CNPq, as the "Golden Law of Brazilian Research." Its purpose was to promote and stimulate scientific and technological development through research funding, researcher and technician training, partnerships with Brazilian universities, and international institutional exchanges. Since then, CNPq has carried out its broad mission, making invaluable contributions to the country's scientific and technological progress. Its institutional mission is summarized as follows: "*CNPq aims to promote and foster scientific and technological development in the country while contributing to the formulation of national science and technology policies*."

Currently, under the name of the National Council for Scientific and Technological Development, CNPq provides approximately 80,000 research grants across various categories and supports research in virtually all fields of study. This investment ensures Brazil's presence in key foreign institutions while safeguarding national sovereignty through the strategic placement of Brazilian researchers in remote locations, including distant archipelagos and Antarctica.

Since their inception, Undergraduate Research Programs (UR) have provided annual grants to support undergraduate research activities. This CNPq initiative was later adopted by state research foundations across Brazil such as FAPESP, FAPERJ, and FAPERGS, as well as universities that provide funding for undergraduate students through UR programs.

CNPq's Institutional Program for Undergraduate Research (PIBIC) was the first such program established in Brazil. Since then, PIBIC has served public and private educational and/or research institutions, with undergraduate research grants awarded directly to institutions through an open call for proposals. The institutions themselves are responsible for selecting the projects.

However, despite the steady increase in undergraduate research scholarships over the years, the CNPq acknowledges that the number of grants remains limited compared to the country's advisory capacity and growing university enrollment.

In medicine, undergraduate research programs offer a monthly grant of R$700 for one year, with the possibility of extension at the discretion of the institution and advisor. According to the CNPq website, the program aims to spark scientific interest and nurture talent among undergraduate students through research projects under the guidance of qualified researchers.

Undergraduate researchers who are scholarship holders tend to have higher grade point averages in their degree programs. Several factors contribute to this, including exposure to a scientific research environment and interaction with researchers and advisors, who provide them with new learning opportunities based on their own experience in their research projects. This set of factors likely enhances academic performance during undergraduate studies, leading

to a well-rounded education through the acquisition of specialized scientific knowledge.

Medical students participating in PIBIC programs typically aim to enhance their qualifications during undergraduate studies. The prospect of personal growth acts as a natural filter, as truly interested individuals tend to seek out programs rather than wait to be recruited by current ones.

The involvement of undergraduate researchers in clinical or experimental research projects provides numerous opportunities and new experiences. Undergraduate researchers' interaction with their advisor and project team demystifies research, teaching them scientific investigation processes, research methodology, results interpretation, and potential clinical applications. Throughout this process, undergraduate researchers are encouraged to formally present their project methods and results through seminars, events, and scientific papers. This learning cycle ends when students complete the program by submitting an activity report and reflecting on their progress.

This experience is life-changing for medical students, often distinguishing them from their classmates, particularly when they perform well throughout the program. For high achievers, this experience substantially impacts their future choices, influencing both how they pursue opportunities and their drive for comprehensive training, ultimately helping them choose their medical specialty and career path.

Participating in undergraduate research programs during medical school considerably affects students' academic performance. This improvement is largely due to advisors, who encourage students to actively seek information and make critical contributions to their scientific development beyond the formal curriculum. This transformative experience fundamentally shapes future career paths, helping them become more well-rounded and dedicated physicians, surgeons, researchers, and educators throughout their professional journey.

As a final note to undergraduate research supervisors, accepting this role means objectively and fully committing to shaping qualified future professionals who can become mentors, innovators, thought leaders, and knowledge disseminators for generations to come. It is, therefore, a great responsibility and a rewarding experience for advisors to contribute to and follow their PIBIC program graduates throughout their careers.

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The relationship between insulin resistance and fibroblast growth factor 23 in patients with non-diabetic pre-dialysis chronic kidney disease: a cross-sectional study

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AUTHORS' KEY WORDS:
Pre-dialysis chronic kidney disease.
Soluble klotho.
Homeostasis model assessment of insulin resistance.

ABSTRACT

BACKGROUND: Insulin resistance often occurs in patients with chronic kidney disease (CKD) owing to mineral and bone metabolism disorders. Fibroblast growth factor (FGF)-23 and soluble klotho (s-KL) play crucial roles in linking CKD with mineral and bone metabolism.

OBJECTIVE: This study aimed to examine the relationship between insulin resistance and FGF-23 and s-KL in patients with non-diabetic pre-dialysis patients with CKD.

DESIGN AND SETTING: This research was conducted in the Ankara Bilkent City Hospital Nephrology Clinic. Ankara,Turkey.

METHODS: This study included 133 male and 150 female patients with pre-dialysis CKD. The patients were compared with 80 healthy individuals. FGF-23 and s-KL levels were determined using enzyme-linked immunosorbent assay kits. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to determine insulin resistance.

RESULTS: Creatinine, urine protein/creatinine ratio (UPCR), $\log_{10}$ FGF-23, $\log_{10}$ s-KL, and HOMA-IR were notably higher, while glomerular filtration rate was notably lower, in patients than in healthy individuals. Stage 5 CKD, $\log_{10}$ FGF-23, creatinine, and UPCR were significantly higher in patients with HOMA-IR > 3.06 compared to those with HOMA-IR ≤ 3.06. No difference was observed in s-KL levels between the two groups. Univariate and multivariate logistic regression analyses revealed an increase in HOMA-IR and $\log_{10}$ FGF-23 values.

CONCLUSIONS: Insulin resistance, serum FGF-23, and s-KL levels increased in patients compared with healthy individuals. Higher creatinine, proteinuria, and FGF-23 levels were associated with greater insulin resistance. The study highlighted a significant relationship between insulin resistance and FGF-23.

INTRODUCTION

Insulin mainly targets the liver, skeletal muscle, and fat cells, and regulates glucose metabolism through the insulin receptor. Insulin resistance is defined as at decrease in the sensitivity of targeted organs to circulating insulin. Consequently, the pancreas produces more insulin, which results in hyperinsulinemia. Insulin resistance begins to develop very early in patients with chronic kidney disease (CKD) and becomes more prominent with disease progression disease these patients approach end-stage kidney disease.[1] Increased visceral fat, accumulation of nitrogenous compounds, metabolic acidosis, vitamin D deficiency, anemia, and physical inactivity lead to the development of insulin resistance in patients with CKD.[2] Insulin resistance is a risk factor for the progression of renal failure and decreased glomerular filtration rate (GFR). In a study using kidney tissues insulin resistance was demonstrated to be associated with interstitial fibrosis and arteriolosclerosis of renal blood vessels.[3] Insulin resistance in patients with CKD is also responsible for cardiovascular (CV) diseases that cause mortality.

Fibroblast growth factor-23 (FGF-23) is a hormone that is most frequently synthesized by osteocytes and osteoblasts, less frequently by the spleen and brain, and plays a role in maintaining normal serum phosphate (P) balance. FGF-23 causes renal P excretion by inhibiting sodium-P-2a and sodium-P-2c, which are sodium-dependent P carriers in the proximal tubule.[4] It also reduces serum 1.25-hydroxy vitamin D3 levels by inhibiting 1-alpha hydroxylase. Klotho (KL) gene is found mainly in the kidneys, parathyroid gland, and choroid plexus.[5] KL protein reaches the cell membrane from the intracellular endosome, and the extracellular domain of KL is released to circulation as soluble klotho (s-KL). FGF-23 exerts biological activity by binding to fibroblast

growth factor receptors in the kidney via an s-KL-dependent pathway. FGF-23 is associated with vascular calcification, inflammation, left ventricular hypertrophy, kidney disease progression, and secondary hyperparathyroidism in patients with CKD.

The association of FGF-23 with atherosclerosis and CV diseases is well-documented; however, only a few previous studies have investigated its association with insulin resistance in pre-dialysis patients with CKD, and the results are contradictory. Therefore, we aimed to investigate the relationship between insulin resistance and FGF-23 levels in patients with non-diabetic pre-dialysis CKD.

OBJECTIVES

This study aimed to examine the relationship between insulin resistance and FGF-23 and s-KL levels in patients with non-diabetic pre-dialysis CKD.

METHODS

Selection of patients

This study was conducted with a total of 283 patients with pre-dialysis CKD, 133 (47%) males and 150 (53%) females, with a mean age of 47.49 ± 9.57 years, who were followed up in the Nephrology Outpatient Clinic. The patients were compared with 80 healthy individuals of a similar age and sex ratios who had no known comorbid diseases or drug use history. Patients with glucose intolerance, fasting blood glucose ≥ 126 mg/dL and/or using antidiabetic drugs, active malignancy, active infection, pregnancy, previous renal transplantation or dialysis history, and who did not want to participate in the study were excluded from the study. After the first urination in the morning, a second urine sample was collected in a container, and the spot urine protein/creatinine ratio (UPCR) was calculated. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. The glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[6] The patients were divided into three different CKD stages according to their GFR levels. Those with GFR values between 89-60 mL/min/1.73 m^2 were evaluated as pre-dialysis stage 3, between 59-30 mL/min/1.73 m^2 as pre-dialysis stage 4, and those with GFR < 15 mL/min/1.73 m^2 and those who did not require renal replacement therapy were evaluated as pre-dialysis stage 5. The purpose of the study was explained to all the participants, and the study was approved by the Ethics Committee of the Ankara City Hospital on May 22, 2024 (TABED 1-24-227).

Determination of laboratory parameters

Venous blood samples were taken from the patients after 8-10 hours of night fasting and 4°C or 10 minutes and stored at -80°C. The levels of creatinine, calcium (Ca), phosphate (P), total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) in the collected blood samples were determined using the spectrophotometric method and Beckman Coulter commercial kits in Beckman Coulter AU5800 (Beckman Coulter Inc. CA, USA) autoanalyzer. Low-density lipoprotein cholesterol (LDL-C) levels were calculated according to the formula described by Friedewald et al.[7] Parathyroid hormone (PTH) levels were determined using a Beckman Coulter Dxl 800 autoanalyzer (Beckman Coulter Inc. CA, USA).1-25-hydroxy (OH) Vitamin(Vit)D_3 levels were determined using a LIAISON (DiaSorin, MN, USA). Homeostatic model assessment of the insulin resistance (HOMA-IR) value was calculated according to the formula developed by Matthews et al.[8]

HOMA-IR = [Fasting glucose (in mg/dL) x Fasting insulin (in uIU/mL)]/405[8]

Glycosylated hemoglobin (HbA1c) levels were calculated using high-performance liquid chromatography. Fasting insulin and C-peptide levels were measured via chemiluminescence using a Beckman Coulter DxI800 (Beckman Coulter, Inc. CA, USA) device. Fibroblast growth factor (FGF)-23 and soluble klotho (s-KL) levels were determined using enzyme-linked immunosorbent assay. The measurement range for s-KL was 0.29-18 ng/mL, the measurement sensitivity was 0.15 ng/mL, and the measurement range for FGF-23 was 14.3-895 pg/mL, and the measurement sensitivity was calculated as 8.36 pg/mL.

Statistical analysis

Data were analyzed using the IBM SPSS software. Conformity to a normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare data that were not normally distributed among the paired groups. The relationship between groups and categorical variables was examined using Pearson's Chi-square test, and multiple comparisons were performed using the Bonferroni-corrected Z test. The relationship between non-normally distributed HOMA-IR, clinical characteristics, and laboratory values was examined using Spearman's rho correlation coefficient. The Kruskal-Wallis H test was used to analyze non-normally distributed variables according to three or more groups. Factors affecting the HOMA-IR levels were examined with the logistic regression model. When all variables were included in the multivariate analysis, in line with the classical method, most results could not be obtained because of inadequate number of observations or the relationship between the independent variables. Therefore, the forward stepwise Wald's method was used in order to determine the most effective variables. The results of the analyses were presented as frequency (percentage) for categorical variables and as mean ± standard deviation for the quantitative data. The statistical significance level was accepted as 0.05.

RESULTS

Patient characteristics

A total of 238 patients with pre-dialysis CKD, 133 males (47%) and 150 females (53%), with a mean age of 47.49 ± 9.57 years were included in the study. The patients were compared with a healthy control group consisting of 80 individuals of similar age and sex. Hypertension was observed in 270 patients (95.4%). Specifically, 49 (17.3%) patients used angiotensin-converting enzyme inhibitors, 137 (48.4%) were on angiotensin II receptor blockers, 119 (42%) were on calcium canal blockers, 70 (24.7%) were on beta-blockers, 22 (7.8%) were on alpha-blockers, 26 (9.2%) were on diuretics, and 30 (10.6%) were on other antihypertensive drugs. According to CKD stages, 150 (53%) patients had stage 3, 84 (29.7%) had stage 4, and 49 (17.3%) had pre-dialysis stage 5. The mean $\log_{10}$ FGF-23 was 2.63 ± 0.33 pg/mL, while $\log_{10}$ s-KL was 1.28 ± 0.09 ng/mL. The mean HOMA-IR was 3.06 ± 2.92 mg/dL.

When compared to healthy individuals, creatinine, UPCR, PTH, P, $\log_{10}$ FGF-23, $\log_{10}$ s-KL, triglyceride, HbA1c, C-peptide (all $P < 0.001$), fasting insulin, and HOMA-IR ($P = 0.040$) levels were found to be significantly higher in patients,whereas GFR ($P < 0.001$) was significantly lower. BMI, Ca, and 25-(OH)-Vit D_3 were similar in both groups ($P > 0.005$) (**Table 1**).

Mean insulin resistance values

Compared to those with HOMA-IR ≤ 3.06, stage 5 CKD ($P = 0.002$), BMI, UPCR ($P < 0.001$), creatinine ($P = 0.002$), PTH ($P = 0.025$), and $\log_{10}$ FGF-23 ($P = 0.003$) were significantly higher in those with HOMA-IR > 3.06, whereas GFR, Ca, P, and 25(OH) $VitD_3$ values were significantly lower ($P < 0.001$). Both groups had similar s-KL levels (**Table 2**).

The relationship of insulin resistance with FGF-23 and s-KL

In the univariate logistic regression analysis, as BMI increased, HOMA-IR levels increased 1.212 times OR = 1.212, 95% CI 1.128–1.302). As the $\log_{10}$ FGF-23 value increased, the HOMA-IR values increased 2.425 times (OR = 2.425, 95% CI 1.032–5.698) (**Figure 1**). An increase in the UPCR value led to an increase of 1.002 times in the HOMA-IR values (OR = 1.002, 95%CI 1.002–1.003). As PTH levels increased, HOMA-IR levels increased by 1.006 times (OR = 1.006, 95% CI 1.000–1.011). As the GFR value increased, a decrease of 0.962 times was observed in the HOMA-IR levels (OR = 0.962, 95% CI 0.939–0.987) (**Figure 2**). As the P- value increased, HOMA-IR levels decreased by 0.414 times (OR = 0.414, 95% CI 0.266–0.645). As the 25(OH)$VitD_3$ value increased, a decrease of 0.899 times was observed in the HOMA-IR levels (OR = 0.899, 95% CI 0.865–0.933). No relationship was found between HOMA-IR and s-KL levels ($P > 0.05$) (**Figure 3**).

According to the multivariate logistic regression analysis using the forward stepwise Wald's method, as the BMI increased, HOMA-IR levels increased 2.933 times (OR = 2.933, 95% CI 2.073–4.150). As the $\log_{10}$ FGF-23 value increased, this led to a decrease of 0.002 times in HOMA-IR levels (OR = 0.002, 95%CI = 0.000–0.033). As the PTH level increased, a decrease of 0.963 times was observed in

Table 1. Comparison of clinical, demographic and laboratory characteristics of the patient and healthy control group

	Patients (n = 283) Mean ± SD/n(%)	Healthy control group (n = 80) Mean ± SD/n(%)	P value
Age (years)	47.49 ± 9.57	46.21 ± 7.05	0.236*
Male /Female	133 (47%)/ 150 (53%)	40 (50%)/40(50%)	0.635**
BMI (kg/m²)	27.63 ± 3.9	26.91 ± 4.49	0.271*
HT	270 (95.4%)		
Use of antihypertensive medications			
ACEinh/ARB	49(17.3%)/ 137(48.4%)		
Calcium channel blocker	119 (42%)		
Beta blocker	70 (24.7%)		
Alpha blocker	22 (7.8%)		
Diuretic	26 (9.2%)		
Others	30 (10.6%)		
CKD			
Stage 3	150 (53%)		
Stage 4	84 (29.7%)		
Pre-dialysis stage 5	49 (17.3%)		
Creatinine (mg/dL)	2.13 ± 0.77	0.84 ± 0.1	**< 0.001***
GFR (mL/dk/1.73 m²)	33.27 ± 11.49	91.24 ± 6.83	**< 0.001***
UPCR (mg/dL)	514.15 ± 540.5	45.15 ± 53.8	**< 0.001***
PTH (mg/dL)	107.17 ± 48.32	52.52 ± 23.32	**< 0.001***
Ca (mg/dL)	9.35 ± 0.38	9.36 ± 0.4	0.743*
P (mg/dL)	3.76 ± 3.9	2.96 ± 0.62	**< 0.001***
25-(OH)-$VitD_3$ (ng/mL)	21.37 ± 13.26	20.88 ± 10.13	0.981*
Log_{10} FGF-23 (pg/mL)	2.63 ± 0.33	2.08 ± 0.28	**< 0.001***
Log_{10} s-KL (ng/mL)	1.28 ± 0.09	1.13 ± 0.1	**< 0.001***
HbA1c	6.16 ± 1.16	5.59 ± 0.43	**< 0.001***
Fasting insulin (pg/mL)	9.46 ± 6.44	7.44 ± 3.48	**0.040**
Total cholesterol (mg/dL)	201 ± 38.57	194.25 ± 41.27	0.106*
Triglyceride (mg/dL)	154.6 ± 61.21	139.06 ± 87.42	**< 0.001***
LDL-C (mg/dL)	115.66 ± 38.03	118.65 ± 32.45	0.764*
HDL-C (mg/dL)	54.37 ± 25.24	49.15 ± 14.59	0.209*
C-peptide (ng/mL)	4.58 ± 2.82	2.77 ± 1.14	**< 0.001***
HOMA-IR (mg/dL)	3.06 ± 2.92	1.86 ± 1.03	**0.040**

Mann-Whitney U test, Pearson chi-square test, Mean ± standard deviation, Frequency (%). SD = standard deviation; BMI = body mass index; HT = hypertension; ACEinh = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; GFR = glomerular filtration rate; FGF-23 = fibroblast growth factor-23; UPCR = urine protein-to-creatinine ratio; PTH = parathyroid hormone; Ca = calcium, P = phosphate; 25(OH)$VitD_3$ = 25-hydroxy vitamin D_3; s-KL = soluble klotho; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HbA1c = glycosylated hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance.

the HOMA-IR levels (OR = 0.963, 95% CI 0.947–0.979). As the Ca level increased, the HOMA-IR levels decreased by 0.053 (OR = 0.053, 95% CI 0.015–0.183). As the P-value increased, a decrease of 17.239 times was observed in HOMA-IR levels (OR = 17.239, 95%CI 2.848–104.366). As the 25(OH)VitD_3 increased, the HOMA-IR levels decreased by 0.836 (OR = 0.836, 95%CI 0.784–0.891). The common effects of the other parameters on the HOMA-IR levels were not statistically significant (P > 0.05) **(Table 3)**.

Table 2. Comparison of clinical and laboratory features according to mean homeostasis model assessment of insulin resistance levels

	HOMA-IR ≤ 3.06 (n = 209)	HOMA-IR > 3.06 (n = 74)	P value
BMI (kg/m²)	29.82 ± 5.14	26.85 ± 3.01	**< 0.001***
CKD			
Stage 3	123 (58.9%)[a]	27 (36.5%)[b]	
Stage 4	57 (27.3%)[a]	27 (36.5%)[a]	**0.002****
Pre-dialysis stage 5	29 (13.9%)[a]	20 (27%)[b]	
Creatinine (mg/dL)	2.01 ± 0.66	2.47 ± 0.94	**0.002***
GFR (mL/dk/1.73 m²)	34.52 ± 11.35	29.76 ± 11.23	**< 0.001***
UPCR (mg/dL)	352.49 ± 373.03	970.74 ± 667.78	**< 0.001***
PTH (mg/dL)	103.54 ± 46.02	117.43 ± 53.27	**0.025***
Ca (mg/dL)	9.37 ± 0.41	9.29 ± 0.26	**< 0.001***
P (mg/dL)	3.05 ± 0.61	2.71 ± 0.6	**< 0.001***
25-(OH)-VitD_3 (ng/mL)	24.2 ± 14.1	13.83 ± 6.11	**< 0.001***
Log_{10} FGF-23 (pg/mL)	2.6 ± 0.31	2.69 ± 0.36	**0.003***
Log_{10} s-KL (ng/mL)	1.29 ± 0.09	1.27 ± 0.11	0.075*

Mann -Whitney U test, Pearson chi-square test, a-b: There is no difference between groups with the same letter (Z test with Bonferroni correction), Mean ± standard deviation, Frequency (%).
BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate; UPCR = urine protein-to-creatinine ratio; PTH = parathyroid hormone; Ca = calcium, P = phosphate; 25(OH)VitD_3 = 25-hydroxy vitamin D_3; s-KL = soluble klotho; HOMA-IR = homeostasis model assessment of insulin resistance; FGF-23 = fibroblast growth factor-23.

DISCUSSION

In this study, elevated insulin resistance development and elevated serum FGF-23 and s-KL levels were observed in patients with CKD in comparison to healthy individuals. Higher creatinine levels, proteinuria, and serum FGF-23 levels were observed in patients with high insulin resistance than in those with lower levels. A significant relationship, independent of serum P levels, was observed between insulin resistance and FGF-23 levels.

Insulin resistance is characterized by a deteriorated physiological response of peripheral tissues to the metabolic effects of insulin; and occurs due to a decrease in insulin receptor expression in tissues that play a role in energy homeostasis. Insulin resistance in patients with CKD is a metabolic feature and an independent determinant of mortality in the early and late stages of CKD. In this study, increased insulin resistance development identified with HOMA-IR was determined in patients with CKD compared to healthy individuals. It was also determined that as renal function disorders and proteinuria progressed, insulin resistance increased. Arroyo et al. reported that insulin resistance determined by HOMA-IR was high in patients with stage 3-4 CKD.[9] Duong et al. reported in their study that HOMA-IR was high among patients who received dialysis and that it correlated with inflammatory markers.[10] Du et al. reported the occurrence of insulin resistance starting from the early CKD stages.[11] In contrast

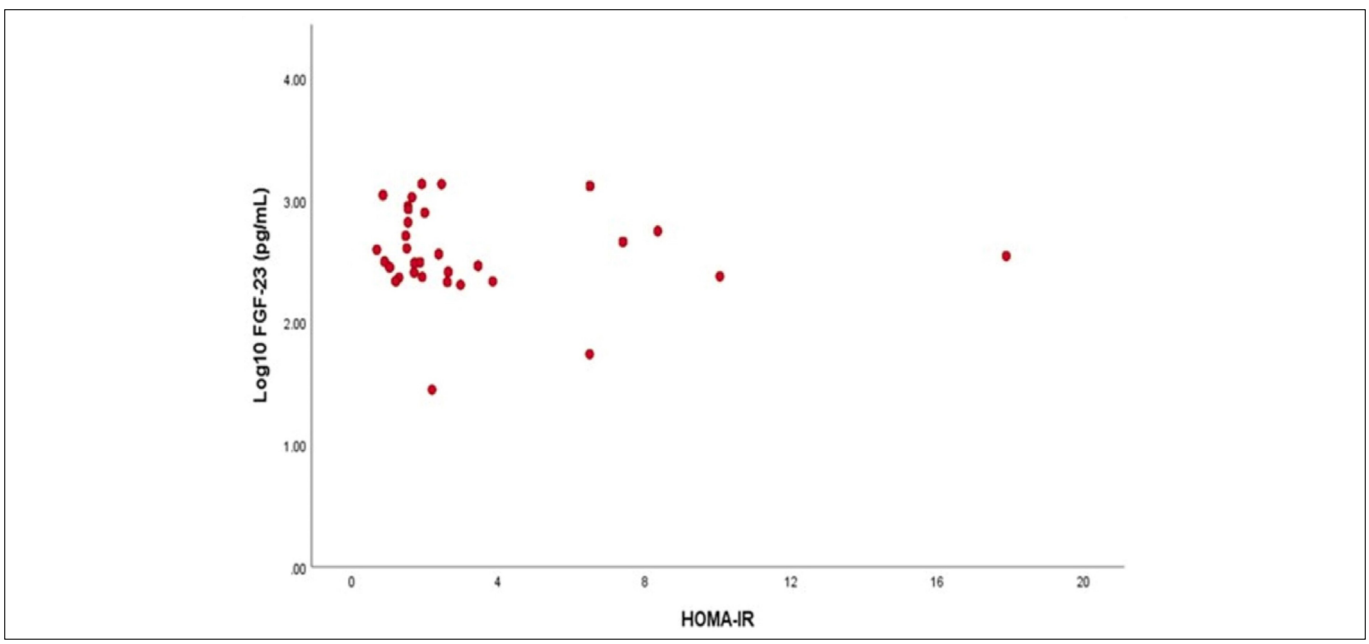

Figure 1. Relationship between homeostasis model assessment of insulin resistance and fibroblast growth factor-23.

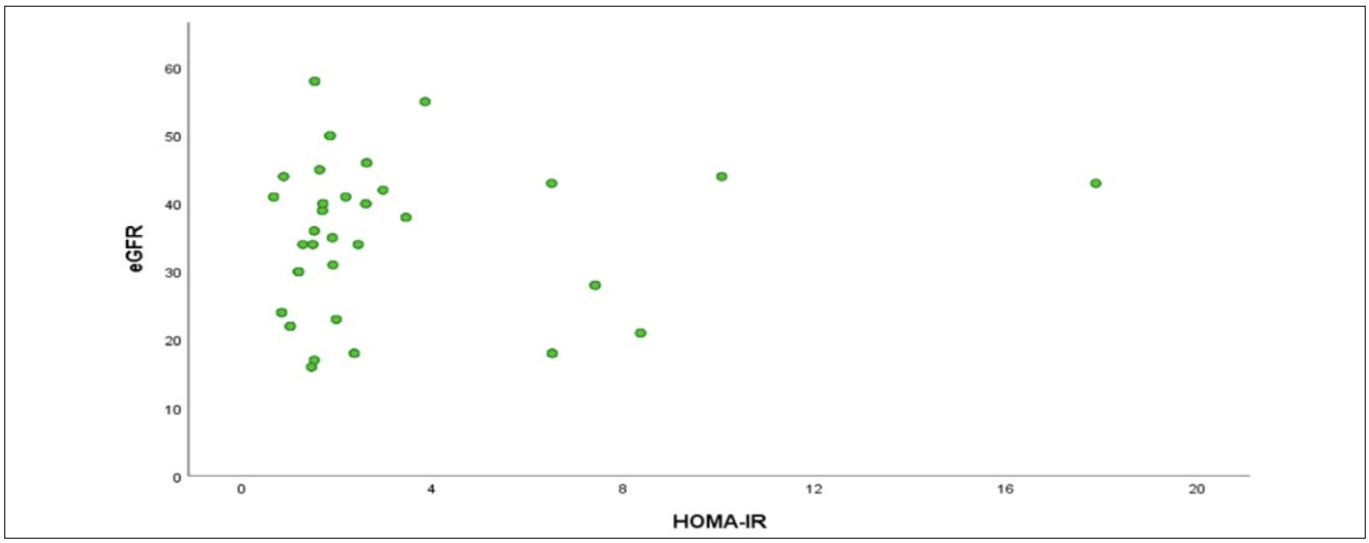

Figure 2. Relationship between homeostasis model assessment of insulin resistance and glomerular filtration rate.

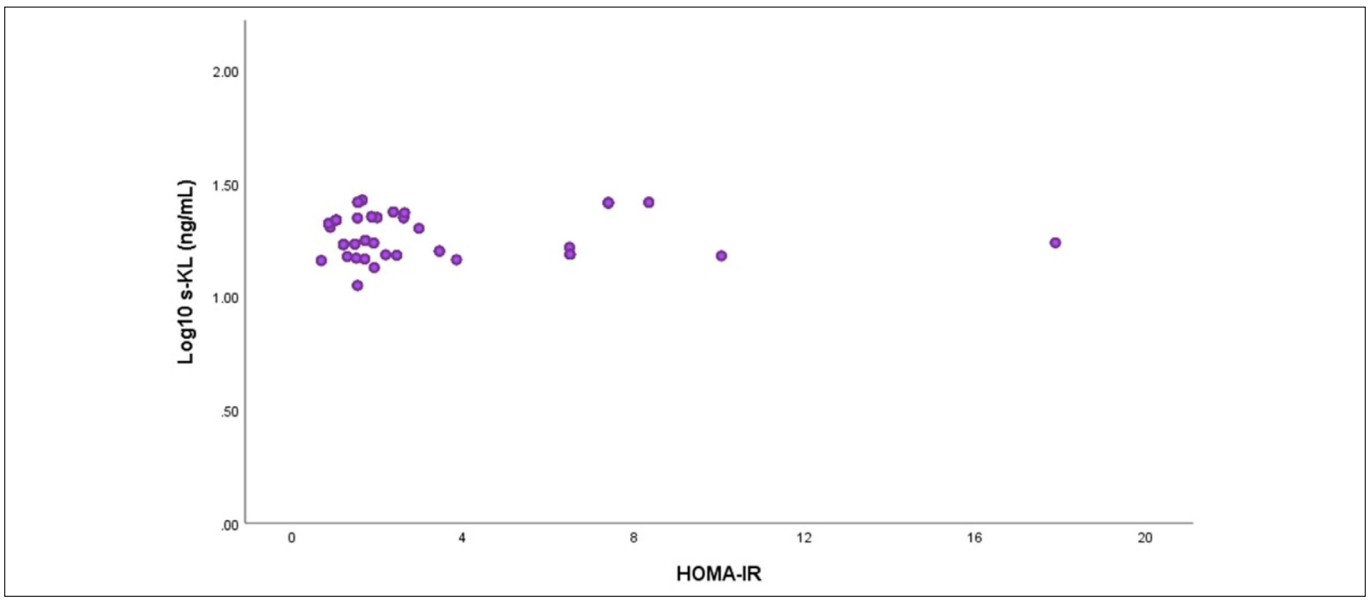

Figure 3. Relationship between homeostasis model assessment of insulin resistance and soluble klotho.

Table 3. Factors independently affecting homeostasis model assessment of insulin resistance

	Univariate		Multivariate[fwald]	
	OR (%95 CI)	**P**	**OR (%95 CI)**	**P**
BMI (kg/m^2)	1.212 (1.128 - 1.302)	**< 0.001**	2.933 (2.073 - 4.15)	**< 0.001**
GFR (mL/dk/1.73 m^2)	0.962 (0.939 - 0.987)	**0.003**		
UPCR (mg/dL)	1.002 (1.002 - 1.003)	**< 0.001**		
PTH (mg/dL)	1.006 (1 - 1.011)	**0.035**	0.963 (0.947 - 0.979)	**< 0.001**
Ca (mg/dL)	0.593 (0.299 - 1.176)	0.135	0.053 (0.015 - 0.183)	**< 0.001**
P (mg/dL)	0.414 (0.266 - 0.645)	**< 0.001**	17.239 (2.848 - 104.366)	**0.002**
25-(OH)-VitD_3 (ng/mL)	0.899 (0.865 - 0.933)	**< 0.001**	0.836 (0.784 - 0.891)	**< 0.001**
Log_{10} FGF-23 (pg/mL)	2.425 (1.032 - 5.698)	**0.042**	**0.002 (0 - 0.033)**	**< 0.001**
Log_{10} s-KL (ng/mL)	0.084 (0.005 - 1.412)	0.085		

OR = Odds ratio, CI = Confidence interval, fwald = Forward Wald Method, Accuracy = 0.963; BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate; UPCR = urine protein-to-creatinine ratio; PTH = parathyroid hormone; Ca = calcium, P = phosphate; 25(OH)VitD_3 = 25-hydroxy vitamin D_3; s-KL = soluble klotho; HOMA-IR = homeostasis model assessment of insulin resistance; FGF-23 = fibroblast growth factor-23.

to these aforementioned studies, Park et al., in their large-scale study including 17.157 individuals, reported that GFR decrease was not associated with the increase in insulin resistance.[12] Chen et al. reported in their study that there was a significant relationship between insulin resistance and GFR in patients with CKD. However, this relationship disappeared after conductng a multivariate analyses, which included BMI as correction factor.[13]

FGF-23 is a hormone synthesized by osteocytes and osteoblasts and plays a role in controlling serum P levels. s-KL is synthesized by the epithelial cells of the kidney tubules, most frequently from the distal tubule. When FGF-23 binds to s-KL in the kidneys, fibroblast growth factor receptors become activated, inhibiting renal P reabsorption and leading to a decrease in serum 1.25(OH)(Vit) D_3 by inhibiting the 1-alpha-hydroxylase enzyme. As the P load per nephron increases in patients with CKD, serum FGF-23 levels increase to counterbalance this load. In the present study, serum FGF-23 and s-KL levels were observed to be higher in patients with CKD than in healthy individuals. Lima et al. reported that there was an increase in serum FGF-23 levels in patients with CKD starting from the early stages.[14] Manou et al. reported in their study that as the renal failure stage progressed in patients with CKD, the increase in serum FGF-23 levels was accompanied by a decrease in the coreceptor s-KL levels.[15] Shou et al. reported that increased serum FGF-23 levels in patients with advanced-stage CKD were accompanied by an increase in serum PTH levels, along with a decrease in 1. 1.25(OH)(Vit)D_3 levels.[16]

Kutluturk et al. conducted a study including 46 obese children and adults in which they observed that serum insulin and glucose levels increased, while FGF-23 and s-KL decreased. They identified an inverse relationship between insulin resistance and FGF-23. They claimed that insulin resistance-related hyperinsulinism and/or low 1.25(OH)(Vit)D_3 levels may lead to a decrease in FGF-23 generation and serum levels. This study focused on adolescents with a mean age of 14 years and no renal failure,[17] Wojcik et al. reported an inverse correlation between insulin resistance and FGF-23.[18] In another study they conducted on obese adolescents with insulin resistance and without renal failure, they reported lower FGF-23 levels when compared to obese controls who did not have insulin resistance. They claimed that lower insulin resistance was correlated with higher FGF-23 levels.[19] Hanks et al. reported that insulin resistance determined by HOMA-IR was associated with FGF-23, especially in those who had normal renal functions, but that this relationship was not observed in patients with CKD. They claimed that FGF-23 in circulation modulated the bonding of s-KL and thus indirectly affected insulin signal.[20] Holecki et al. reported in their study on 3115 elderly individuals that there was no relationship between insulin resistance and FGF-23.[21] Mirza et al. reported in The Prospective Investigation of the Vasculature in Uppsala Seniors Cohort (PIVUS) and The Osteoporotic Fractures in Men Study Cohort (MrOS) studies that one standard deviation increase in FGF-23 was associated with 8% and 12% higher insulin and HOMA-IR values. However, in the multivariate analysis, they reported no correlation between insulin resistance and FGF-23.[22] Unlike these studies, in our study, higher serum FGF-23 levels and lower serum P levels were observed in patients with high insulin resistance. No difference was observed in the s-KL levels between patients with high and low insulin resistance. Winther et al. reported that hyperinsulinemia increased serum FGF-23 levels in patients with type 2 DM.[23] Marchelek-Mysliwiec reported that FGF-23 was a significant determinant of insulin resistance in patients with CKD.[24] Fernandez-Real et al. determined the relationship between HOMA-IR and FGF-23 in their study on 314 individuals with renal failure. They reported that HOMA-IR and FGF-23 levels decreased in 10 males after losing about 20 kg and that insulin resistance affected FGF-23 levels.[25] Garland et al. reported higher FGF-23 levels in those with high insulin resistance in their study on 72 patients with stage 3-5 CKD. They reported a relationship between insulin resistance and P balance, and found a significant and independent relationship between insulin resistance and FGF-23. They argued that insulin resistance contributes to the deterioration of renal P homeostasis in patients with CKD and that this could be determined clinically with increased FGF-23 levels.[26] In the present study, while a significant relationship was observed between insulin resistance and FGF-23, an inverse correlation with P was found. No relationship was observed between insulin resistance and s-KL levels. This suggests that the relationship between insulin resistance and FGF-23 levels in patients with CKD may result from mechanisms other than P metabolism. However further studies are required to confirm this hypothesis.

The varying results of these previous studies can be attributed to various reasons. FGF-23 was divided into two kits intact and C-terminal. However, the FGF-23 kits used in these studies may have been different. It is thought that C-terminal FGF-23 better reflects the biologically functional FGF-23 molecule that reduces the reabsorption of P in kidney tubules.[27] In their study on 81patients with CKD younger than 25 years, Yasin et al. reported that FGF-23 levels varied depending on age.[28] The type of FGF-23 kits used, the ages of the patients included, and their growth status may have yielded different results. The demonstration of the effect of insulin on FGF-23 release through the hyperinsulinemic-euglycemic clamp technique[23] suggests that high insulin levels are required for FGF-23 synthesis. The insulin levels in these aforementioned studies could have been too low to cause this effect.

Certain limitations affect the results of our study. First, as the study was conducted using a cross-sectional design, the temporal results of the relationship between insulin resistance and FGF-23 in patients with CKD were not examined. Second, instead of the hyperinsulinemic-euglycemic technique, which is the gold standard

method for determining insulin resistance, the HOMA-IR formula was used. Third, the FGF-23 values, which are FGF subgroups that regulate glucose metabolism in patients with CKD,[29] were not included in the study. Fourth, although the relationship between FGF-23, insulin resistance, and inflammatory parameters, such as interleukin, vascular cell adhesion molecule, and tumor necrosis factor, is known, these markers have not been studied. Fifth, although the anti-phosphaturic activities of insulin and FGF-23 are known, their effects on serum and urine levels have not been investigated.

CONCLUSION

Increased insulin resistance development and increased serum FGF-23 and s-KL levels were observed in patients with pre-dialysis CKD when compared with healthy individuals. Higher insulin resistance was observed in patients with stage 5 CKD than in those with stage 3 CKD. More renal function disorders and higher serum FGF-23 levels were observed in patients with high insulin resistance. Although a significant relationship was found between insulin resistance and FGF-23 levels, an inverse correlation was found with P. As few studies have been conducted in this regard, further multicenter studies with larger number of patients are needed.

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Diagnosis and treatment of latent tuberculosis infection among household contacts in inland Bahia, Brazil: a cross-sectional follow-up study

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Tuberculosis control.
Epidemiology.

ABSTRACT

BACKGROUND: The diagnosis and treatment of latent tuberculosis infection (LTBI) are crucial for tuberculosis (TB) control. Household contacts (HHC) of patients with pulmonary TB are at a high risk of LTBI due to their close proximity to source cases.

OBJECTIVE: To describe the diagnosis and treatment of LTBI among HHC.

DESIGN AND SETTING: This cross-sectional follow-up study was conducted in the municipality of Paulo Afonso, northeastern Brazil, between 2013 and 2022.

METHODS: We retrieved secondary data from the medical records of HHC who were followed up at a specialized referral center for TB. LTBI prevalence estimates were calculated and are presented with 95% confidence intervals (CIs).

RESULTS: In total, 622 HHC were screened for LTBI, with 620 evaluated using the tuberculin skin test (TST). Of these, 40 (6.5%) did not return for TST reading. The overall prevalence of LTBI was 53.1% (95% CI: 49–57.1%), with a high prevalence among females and individuals aged 25–34 years. The overall LTBI treatment initiation rate was 26.1% (95%CI: 21.5–31.3%), and 64.2% (95%CI: 53.3–73.8%) of HHC who initiated treatment completed their course.

CONCLUSION: This study revealed a high prevalence of LTBI among HHC, particularly among women and individuals aged 25–34 years, underscoring the ongoing TB transmission within the community. Only 26.1% of the diagnosed HHC initiated treatment, with approximately 64% completing their course. This highlights the challenges in managing LTBI and emphasizes the need for targeted screening and interventions for high-risk groups.

INTRODUCTION

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, primarily affects the lungs but can also manifest in extrapulmonary sites.[1] In 2019, TB impacted 10 million people worldwide, resulting in 1.5 million deaths and 85,338 new cases in Brazil. The emergence of coronavirus disease 2019 (COVID-19) has further complicated TB control, as reflected in Brazil's 2021 statistics showing 78,833 new cases and a 16% increase in deaths.[2,3]

In Brazil, the Northeast region, including the state of Bahia, faces a high TB burden, primarily affecting vulnerable populations in areas with limited healthcare access.[4] Notably, the municipality of Paulo Afonso, situated 480 km from the capital of Bahia, had a TB incidence rate of 33 cases per 100,000 inhabitants in 2021, surpassing the state average.[5] The challenge of disease control, particularly given the COVID-19 pandemic, which has exacerbated the TB epidemiological situation, requires a comprehensive plan of action across various fronts. This includes increased efforts to screen, diagnose, and treat latent TB infections (LTBI) as an integral component of public health interventions.

Approximately one-quarter of the world's population is infected with *M. tuberculosis*. In general, these individuals remain asymptomatic, and approximately 5–10% develop the active form of the disease, with a higher risk of illness within the first 2 years after the initial infection. Although individuals with LTBI do not transmit *M. tuberculosis*, they remain reservoirs of the bacteria, which can be reactivated when immune system competence is compromised. Reactivation of LTBI is responsible for a large proportion of active TB cases, contributing to the perpetuation and maintenance of the disease transmission chain.[6,7]

Therefore, diagnosing and treating LTBI are pivotal for reducing and eliminating TB, particularly within high-risk groups, such as people living with HIV (PLHIV); those undergoing immunosuppressive therapy, including TNF-α inhibitors; homeless persons; prisoners; illicit-drug users; healthcare workers; immigrants from high-TB-burden countries; and household contacts (HHC) of patients with pulmonary TB.[8] HHC of patients with TB are at a higher risk of TB infection and disease due to prolonged and close exposure to the source case.[9] A recent study noted that contacts accounted for more than 57.2% of LTBI treatment notifications.[10] Sagili et al.[11] found that a significant proportion of HHC of patients with TB in low- and middle-income countries have LTBI, with estimates suggesting that more than 50% of these contacts are infected. In a cross-sectional study conducted in Brazil, 48% of contacts of patients with pulmonary TB tested positive on the tuberculin skin test (TST), thereby meeting the criteria for LTBI treatment.[12] Furthermore, factors, such as recurrent exposure, malnutrition, and a compromised immune system are known to influence infection rates among these high-risk populations.[13]

Given the significance of infection in the development of active disease, and in alignment with the international 'End TB Strategy' and national elimination goals, Brazil implemented the LTBI online surveillance vigilance system in 2018 to record LTBI diagnoses and treatment, along with a 'Protocol for Latent Tuberculosis Infection Surveillance'. These initiatives have established ambitious goals and actions that have facilitated the expansion of screening coverage, diagnostic practices, and the implementation of shortened treatment regimens for LTBI.[14,15] Although these changes represent significant advances in TB control, the prevalence of LTBI remains unknown in most Brazilian regions due to the scarcity of studies.

OBJECTIVE

To describe the diagnosis and treatment of LTBI among HHC who were followed up at a specialized reference center for TB in the municipality of Paulo Afonso, northeastern Brazil. The study aimed to generate information that best represents the local context, thereby aiding decision-making by managers in the control of LTBI and, consequently, avoiding the development of active TB.

METHODS

Study design and setting

This was a cross-sectional follow-up study. Initially, a retrospective cross-sectional analysis was conducted by examining the medical records of all HHC who underwent screening between 2013 and 2022 to determine the prevalence of LTBI. Subsequently, HHC diagnosed with LTBI were followed up longitudinally to monitor treatment progress according to the prescribed regimen.

This study was conducted at the 'Dermatology and Sanitary Pneumology Service' (SEDERPAS), a reference center for TB located in the municipality of Paulo Afonso, northeastern Brazil. The health unit serves as a referral center for the municipality of Paulo Afonso and neighboring regions, providing specialized services for comprehensive care in the management of leprosy and TB. It also conducts screening, diagnosis, and treatment of LTBI and is responsible for administering all skin tests in the region.

Paulo Afonso is located in the north of the state of Bahia, an important region bordering the states of Pernambuco, Alagoas, and Sergipe. According to the Brazilian Institute of Geography and Statistics (IBGE), the municipality has an estimated population of 112,870 inhabitants distributed in an area of 1,545.19 km^2. According to the Health Department of Bahia, Paulo Afonso boasts 88% primary healthcare coverage, with a Human Development Index of 0.674.[16]

Study population

The study population comprised HHC of patients with pulmonary TB residing in the Paulo Afonso municipality or nearby regions. An HHC was defined as an individual who resided in the same dwelling unit or plot of land as the index patient and shared the same housekeeping arrangements.[17]

Selection criteria and follow-up

As part of the routine investigation at the specialized referral center, all HHC identified during the TB case investigation were invited for a screening visit. LTBI screening was performed using the TST, which was conducted by trained staff in accordance with the recommendations of the Brazilian Ministry of Health. The TST was conducted by intradermal injection (Mantoux method) of two tuberculin units of a purified protein derivative per 0.1 mL. The transverse induration diameter was measured 48–72 hours later. A TST with a cut-off point ≥ 5 mm was considered a positive result in the absence of clinical and radiographic signs of TB.[18] Additionally, a chest X-ray was conducted to exclude active TB, and the absence of signs and symptoms was confirmed among the HHC.

The HHC underwent TST between 2013 and 2022, and their treatment followed the therapeutic regimen outlined by the guidelines of the Brazilian Ministry of Health.[18] All individuals with a positive TST result were encouraged to initiate LTBI treatment. However, the patient made the final decision on whether to undergo treatment. Three treatment regimens were considered in this study: i) 6-month daily isoniazid at a dose of 5–10 mg/kg, with a maximum of 300 mg and at least 180 doses; ii) 4-month daily rifampicin at a dose of 10 mg/kg, with a maximum of 600 mg and at least 120 doses; or iii) 3-month weekly rifapentine (900 mg/week) plus isoniazid (900 mg/week), with at least 12 doses.[18] Individuals

undergoing LTBI treatment were asked to return every 30 days for refills. HHC who did not return for a follow-up clinical visit or any drug supply refills were considered lost to follow-up.

Data collection

All data were extracted from the medical records housed at SEDERPAS. To achieve this, variables of interest were collected by double data entry to ensure reliability and accuracy in data collection. The study included variables such as sex (male or female), age group (in years: 0–4; 5–9; 10–14; 15–24; 25–34; 35–44; 45–54; or 55+), TST results (positive, negative, or did not return for TST reading), LTBI treatment regimen (isoniazid, rifampicin, or rifapentine + isoniazid), and outcome (completed treatment or non-completed treatment). Incomplete or missing data were excluded from analyses.

Statistical analysis

For statistical analysis, the data were tabulated in Microsoft Excel spreadsheets and analyzed using the statistical software SPSS (version 22.0; IBM Corporation, Armonk, United States) and GraphPad Prism (version 8.0; GraphPad Software, San Diego, United States). Categorical variables are presented as absolute values or relative frequencies and were compared using Fisher's exact test or the Chi-square test. The estimated prevalence of LTBI, along with the 95% confidence interval (CI), was calculated, as were the treatment initiation and completion rates. Quantitative variables are presented as mean and standard deviation (SD) and were compared using either Student's t-test or Pearson's correlation coefficient. Differences were considered statistically significant at P values < 0.05.

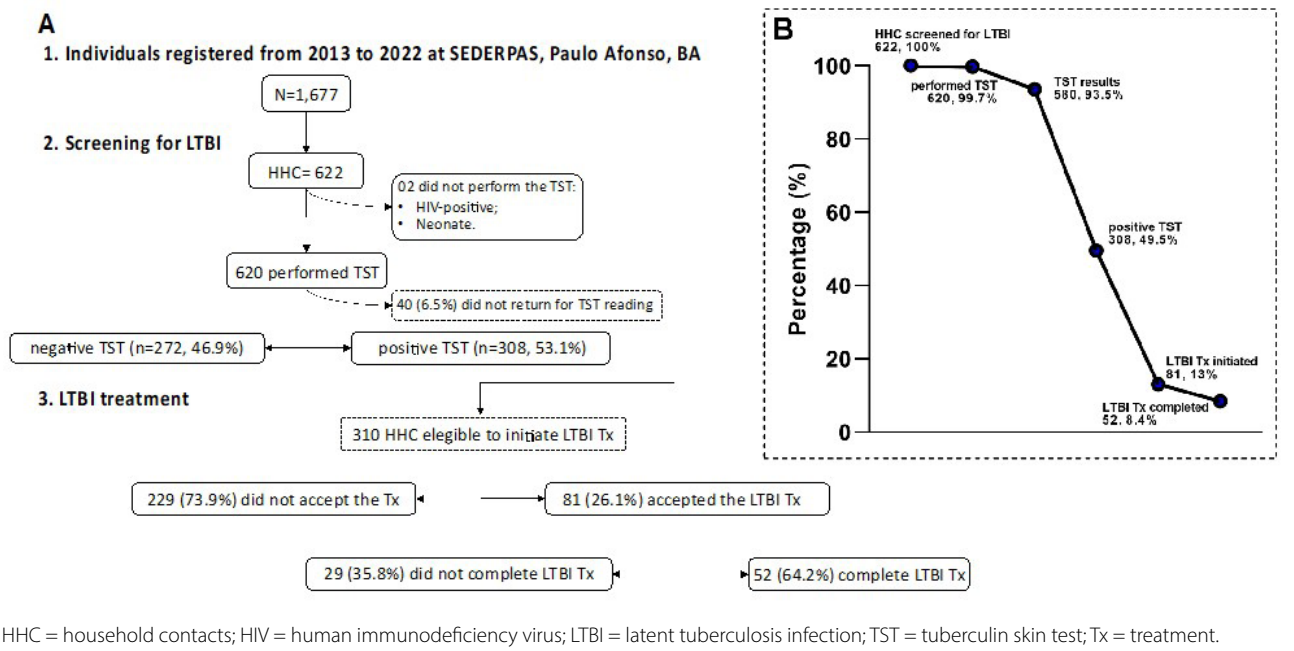
Ethical considerations

This study was approved by the Research Ethics Committee (CEP) of the University Center of Rio São Francisco (UniRios) under opinion no. 4,858,939, in compliance with Resolution no. 466/2012 of the National Health Council. The requirement for informed consent was waived because the present study relied solely on secondary data. Authorization was obtained from the Municipal Health Department.

RESULTS

A total of 1,677 individuals were included in this study. Among these, 622 (37.1%) were HHC of patients with pulmonary TB who underwent screening for LTBI. On average, approximately 62.2 ± 48.1 HHC were investigated per year. Two HHC did not undergo TST because they were HIV-positive and neonates. Of the 620 HHC who underwent TST, only 40 (6.5%) did not return for the reading (**Figure 1**). The demographic profiles of HHC who did and did not return for the TST reading were not significantly different (age, P = 0.72; sex, P = 0.42, data not shown).

Valid TST results were available for 580 (93.5%) of the 620 HHC. Using a cut-off of ≥ 5 mm of induration, 308 (53.1%) HHC



HHC = household contacts; HIV = human immunodeficiency virus; LTBI = latent tuberculosis infection; TST = tuberculin skin test; Tx = treatment.

Figure 1. Flowchart illustrating the enrollment, latent tuberculosis infection diagnosis, and treatment of the study population (A). The chart shows the percentage of household contacts screened for latent tuberculosis infection, tuberculin skin test assessment, treatment initiation, and outcomes (B). Paulo Afonso, Brazil, 2013–2022.

had positive TST results. No significant differences in age were observed between the negative (26.7 ± 21.7 years) and positive TST groups (29.4 ± 20.2 years, P = 0.12), nor in sex distribution (negative TST, M/F = 112/160; positive TST, M/F = 122/186; P = 0.73). Similarly, no correlation was found between the TST results and the age of the HHC (r = 0.06, P = 0.14; **Figure 2B**).

The overall prevalence of LTBI among the HHC of patients with TB was 53.1% (95%CI: 49–57.1%). The prevalence according to sex and age group is shown in **Figure 2A** and **Table 1**.

Among the 308 HHC with positive TST results, only 79 (25.6%) agreed to undergo LTBI treatment. Additionally, two HHC with treatment indications did not have TST results available. Thus, the overall LTBI treatment initiation rate was 26.1% (81/310; 95%CI: 21.5–31.3%), while the majority, 73.9% (229/310; 95%CI: 68.7–78.5%), declined treatment (**Figure 1**). No significant differences were found in terms of sex or age between individuals who consented to LTBI treatment and those who refused treatment. Interestingly, a slight difference was observed in the TST results between those who accepted treatment initiation and those who declined treatment (**Table 2**).

Of the 81 HHC who initiated LTBI treatment, 59 (72.8%) received isoniazid monotherapy, seven (8.6%) received a rifampicin-containing regimen, and 15 (18.5%) received a combination of rifapentine and isoniazid. At the end of the follow-up period, 52 (64.2%) patients had completed treatment, and 29 (35.8%) were lost to follow-up (**Figure 1**, **Table 3**). The overall LTBI treatment completion rate was 64.2% (95%CI: 53.3–73.8%). Furthermore, no significant differences in sex, age, TST results, or treatment regimen were observed between individuals who abandoned or completed treatment (P > 0.005; **Table 3**).

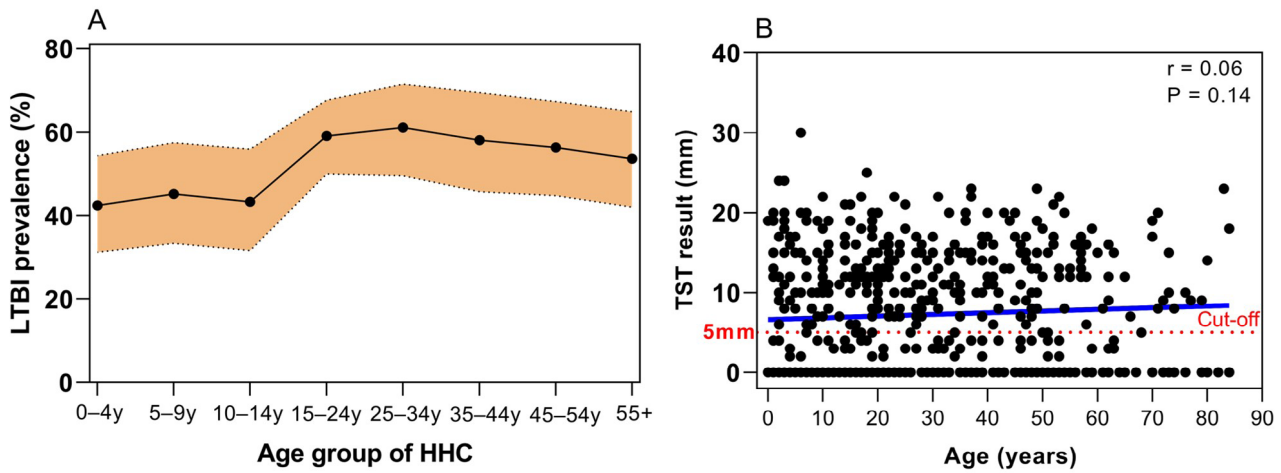
DISCUSSION

Studies providing knowledge and information about LTBI are crucial and necessary to achieve the goals of the WHO's 'End TB Strategy' (2016–2035) and the Brazilian National Plan to End Tuberculosis proposed by the Brazilian National Ministry of Health. Therefore, this study was the first to estimate the prevalence of LTBI among HHC in the municipality of Paulo Afonso,

Table 1. Prevalence of latent tuberculosis infection among household contacts by sex and age groups. Paulo Afonso, Brazil, 2013–2022

Characteristics	n (%)	LTBI	
		Prevalence	95%CI
Sex			
Male	122 (39.6)	52.1	45.8–58.4%
Female	186 (60.4)	53.8	48.5–58.9%
Age groups*			
0–4 years	28 (9.1)	42.4	31.2–54.4%
5–9 years	28 (9.1)	45.2	33.4–57.5%
10–14 years	26 (8.5)	43.3	31.6–55.9%
15–24 years	68 (22.1)	59.1	50.0–67.7%
25–34 years	44 (14.3)	61.1	49.6–71.5%
35–44 years	36 (11.7)	58.1	45.7–69.5%
45–54 years	40 (13.0)	56.3	44.8–67.2%
55+ Years	37 (12.1)	53.6	42.0–64.9%

*Data not available for one household contacts; LTBI = latent tuberculosis infection.



The solid line represents the overall estimate of LTBI prevalence, and the dotted lines represent the 95% confidence interval by age group of HHC (A). The solid blue line depicts the linear correlation curve between the TST result and age of HHC, with a Pearson correlation coefficient of 0.06, P = 0.14. The red dotted line corresponds to the TST cutoff (B). HHC = household contacts; LTBI = latent tuberculosis infection; mm = millimeters; TST = tuberculin skin test.

Figure 2. Prevalence rates of latent tuberculosis infection among household contacts by age groups and the correlation between tuberculin skin test results and the age of household contacts. Paulo Afonso, Brazil, 2013–2022.

Table 2. Comparison of sex, age, and tuberculin skin test results between latent tuberculosis infection treatment acceptance and refusal among household contacts. Paulo Afonso, Brazil, 2013–2022

Variables	LTBI treatment, n (%)		P value
	Yes (n = 81)	Refused (n = 229)	
Sex			
Male	35 (43.2)	88 (38.4)	
Female	46 (56.8)	141 (61.6)	0.50
Age*			
0–4 years	6 (7.4)	23 (10.1)	
5–9 years	7 (8.6)	21 (9.2)	0.76
10–14 years	7 (8.6)	20 (8.8)	0.75
15–24 years	15 (18.5)	53 (23.2)	0.99
25–34 years	12 (14.8)	32 (14.0)	0.59
35–44 years	12 (14.8)	24 (10.5)	0.28
45–54 years	15 (18.5)	25 (11.0)	0.19
55+	7 (8.6)	30 (13.2)	0.99
TST (mm)			
Mean ± SD	14.4 ± 4.4	12.6 ± 4.7	**0.003**

*Age information was not available for one household contacts who declined LTBI treatment; LTBI = latent tuberculosis infection; mm = millimeters; SD = standard deviation; TST = tuberculin skin test.

Table 3. Latent tuberculosis infection treatment initiation among household contacts. Paulo Afonso, Brazil, 2013–2022

Variables	LTBI Treatment, n (%)		P value
	Complete (n = 52)	non-completion (n = 29)	
Sex			
Male	19 (36.5)	16 (55.2)	0.16
Female	33 (63.5)	13 (44.8)	
Age			
Mean (years) ± SD	29.4 ± 17.0	30.1 ± 20.0	0.87
0–4 years	2 (3.8)	4 (17.4)	0.55
5–9 years	5 (9.6)	2 (8.7)	
10–14 years	6 (11.5)	1 (4.3)	
15–24 years	9 (17.3)	4 (17.4)	
25–34 years	9 (17.3)	2 (8.7)	
35–44 years	9 (17.3)	3 (13.0)	
45–54 years	9 (17.3)	5 (21.7)	
55+	3 (5.8)	2 (8.7)	
TST (mm)			
Mean ± SD	14.8 ± 4.3	13.8 ± 4.6	0.32
Treatment regimen			
Isoniazid	37 (71.2)	22 (75.9)	0.69
Rifampicin	4 (7.7)	3 (10.3)	
Rifapentine + isoniazid	11 (21.2)	4 (13.8)	

LTBI = latent tuberculosis infection; mm = millimeters; SD = standard deviation; TST = tuberculin skin test.

Bahia, Brazil. This research is particularly important for HHC, who are at high risk of LTBI and progression to active TB.[8,9,19]

Our study identified an overall LTBI prevalence of 53.1% among HHC using a 5-mm TST cut-off. These results are consistent with those of a previous study conducted in Belém (Pará), where 52.3% of HHC who underwent TST yielded positive results.[20] Conversely, other studies on LTBI prevalence in Brazil, conducted by Jones-López et al.[21] and Fernandes et al.,[22] reported higher prevalence rates of 62.4% and 66.4%, respectively. However, these studies used a ≥ 10 mm TST cut-off for their assessments. It is reasonable to assume that the differences in prevalence may be linked to the contagiousness of the index case. Although bacilloscopy data of the index case were not available in our study, Acuña-Villaorduña et al.[23] investigated the relationship between HHC infection and the number of colony-forming units (CFU) of *M. tuberculosis* cultured in cough-generated aerosols from index TB patients in Vitória (Espírito Santo). They found that the frequency of TST ≥ 5 mm in contacts increased in a dose-response pattern with increasing aerosol CFU: aerosol negative (66%), aerosol low (69%), and aerosol high (79%).

In a meta-analysis that included studies from 36 countries, the overall population prevalence estimates were 24.8% (95%CI: 19.7–30%) and 21.2% (95%CI: 17.9–24.4%), based on the Interferon-Gamma Release Assay (IGRA) and a 10-mm TST cut-off, respectively.[24] However, according to a systematic review and meta-analysis by Sagili et al.,[11] the prevalence of LTBI among HHC of patients with TB was higher than that in the general population, estimated at 41% (95%CI: 33–49%). These findings underscore the need to prioritize LTBI screening for HHC, given that its prevalence in this group is higher than that in the general population.

The results based on sex and age group showed that the prevalence of LTBI is similar between men and women; however, some studies suggest that the prevalence may be slightly higher among men.[25] On the other hand, a trend toward a higher LTBI prevalence was evident among individuals aged 25–34 years, regardless of sex. This age group includes individuals of reproductive and active working age, who are generally at a higher risk of *M. tuberculosis* exposure.[26]

The cut-off point for measuring skin induration in the TST was set at < 5 mm, with indurations of ≥ 5 mm indicative of *M. tuberculosis* infection. This measurement corresponds to the largest transverse diameter of the induration perpendicular to the forearm, and its correct reading is crucial because LTBI treatment is based on this cutoff point. TST results can be influenced by BCG vaccination or non-tuberculous mycobacteria (NTM) in the environment.[18] However, the lack of BCG vaccination records among HHC in the present study hindered a more in-depth analysis. Nonetheless, despite the limitations of TST in identifying eligible individuals, a positive result likely indicates prior infection with *M. tuberculosis* and is not affected by BCG vaccination or NTM infection in endemic regions.[27]

Another limitation of the TST is the requirement for a second clinic visit after 48–72 hours to read the results. In such cases, a

second test can be performed as soon as possible. According to our results, 6.5% of the participants did not return for the TST reading, most likely due to economic barriers, lack of time, non-adherence to the recommendations of health professionals, and poor knowledge about the importance of the TST.[28] Similarly, Mendes et al.[20] reported that only 2.3% of patients did not return for TST reading. Although a low frequency was observed, this does not reflect the reality in the municipalities of the country, in which the return rate ranges from 8.4% to 13.3%.[27,29–31] These differences may be attributed to health professionals adopting a patient-centered approach and providing sufficient guidance during the test, which increases the quality of care.[19]

In the present study, no significant differences in sex or age were observed between individuals with negative and positive TST results. These findings are consistent with those of a study conducted at the Maruípe Health Unit in Vitória (Espírito Santo), where no significant differences were observed in sex and age between TST reactors and non-reactors.[32] Similar results were also reported by Rogerio et al.[33] These results suggest that sex and age did not significantly influence the TST outcome.

Treatment for LTBI has been recommended in Brazil since 1995 and is currently included in pillar 1 of LTBI surveillance as a crucial action to achieve its goals. However, most HHC in our study did not initiate LTBI treatment (73.9%) despite it being offered free of charge by the Brazilian Unified Health System.[15] Unfortunately, the LTBI treatment initiation rate has been suboptimal in most studies, ranging from 33.9% to 87.8%.[12,34]

Treatment was successfully completed by 64.2% of the HHC. This rate aligns with an estimated pooled rate of 65% (95% CI: 54–74%) reported in a systematic review and meta-analysis conducted by Sagili et al.[11] Nevertheless, studies conducted in Brazil indicated a more favorable outcome, with success rates ranging from 53% to 83%.[12,34] No characteristic was found to be significant among those who completed treatment. However, according to Araújo et al.,[30] a higher prevalence was observed among women.

Sociodemographic factors, including high transportation costs and limited social support, may have impacted treatment completion. Furthermore, factors such as medication palatability and extended treatment duration have been linked to a decreased likelihood of treatment completion.[11] Moreover, inadequate health education, exemplified by recurrent communication gaps between healthcare professionals and individuals with LTBI, may also contribute to this issue.[35]

Despite the use of isoniazid and rifapentine as alternatives to shorten the treatment duration and mitigate the risk of treatment abandonment, the present study did not find any significant difference. This treatment regimen is recommended by the guidelines because of its effectiveness and short duration. However, further research is necessary to investigate local factors that may influence treatment outcomes and adherence among HHC.

This study has two primary limitations. First, the study relied on secondary data, which may have limitations in terms of accuracy and completeness. However, this study analyzed all reported cases of LTBI among HHC in the municipality, which enhanced the validity of the results. Second, the study analyzed a limited number of variables. Other critical factors that may influence treatment initiation and completion rates, such as socioeconomic status and educational level, were not investigated. A more comprehensive exploration of these modifiable factors is essential to develop effective interventions aimed at improving treatment uptake and adherence in at-risk populations. Additionally, IGRA, a more recent technology for diagnosing and assessing the prevalence of LTBI, was not employed in this study. This omission occurred because the Brazilian Ministry of Health continues to recognize TST as the preferred marker of infection in Brazil.

CONCLUSION

This study provides important insights into the prevalence of LTBI and treatment uptake among HHC. The observation of an increased LTBI prevalence among women aged 25–34 years recently exposed to infectious TB in their households underscores the need for targeted interventions to address the needs of this group. Additionally, the low rates of LTBI treatment initiation and completion emphasize the urgency of identifying the reasons for these barriers and developing effective strategies to overcome them. Thus, to achieve TB control in municipalities, treating all individuals diagnosed with LTBI is crucial, as this can reduce TB transmission and prevent the development of active TB in high-risk populations.

Future research should investigate strategies to address barriers to LTBI treatment initiation and completion. Evaluating the effectiveness of targeted interventions and their impact on treatment outcomes will be essential for refining TB control strategies and enhancing public health efforts.

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Retrospective study of factors associated with the clinical severity of covid-19 in older adults in Minas Gerais: structural equation modeling

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ABSTRACT

BACKGROUND: Studies have shown an association between the clinical severity of coronavirus disease (COVID-19) and sociodemographic and clinical variables in older adults. However, few studies have described the explanatory factors of the relationship between these variables and the clinical severity of COVID-19 using structural equation modeling.

OBJECTIVE: To analyze the factors directly and indirectly associated with the clinical severity of coronavirus disease (COVID-19) among older adults in Minas Gerais, Brazil.

DESIGN AND SETTING: Retrospective epidemiological study.

METHODS: This study included 51,141 elderly adults with COVID-19 living in Minas Gerais, Brazil. Data were collected through the Individual Registration Form – Hospitalized Cases of Severe Acute Respiratory Syndrome from January 28, 2020, to January 27, 2022.

RESULTS: Older age ($P < 0.001$), male sex ($P < 0.001$), dyspnea ($P < 0.001$), change in chest X-ray examination findings ($P < 0.001$), greater number of risk factors/comorbidities ($P < 0.001$), and longer hospitalization time ($P < 0.001$) were directly associated with the clinical severity of COVID-19. Female sex, mediated by the greater number of risk/comorbidity factors ($\beta = -0.02$, $P < 0.001$), and younger age, mediated by longer hospitalization time ($\beta = -0.01$; $P < 0.001$), were indirectly associated with the clinical severity of COVID-19.

CONCLUSION: Demographic and clinical variables were directly associated with increased disease severity. In addition to the direct effect, a greater number of risk/comorbidity factors and longer hospitalization time mediated the association between demographic variables and outcomes.

INTRODUCTION

Population aging is a global phenomenon.[1] In Brazil, older adults, characterized by age equal to or greater than 60 years, correspond to 13.8% of the population.[2] Specifically, in the state of Minas Gerais, where the current study was developed, the elderly population represents 15.4%[2] and has the highest aging rate in the country.[3]

Due to the physiological changes that occur with the human aging process and affect the immune system, as well as the greater number of complications resulting from chronic diseases, the older adults are more vulnerable to the clinical severity of the coronavirus disease 2019 (COVID-19), which includes the highest proportion of admissions to the intensive care unit (ICU), use of invasive ventilatory support, and death,[4,5] when compared to younger individuals.[4,6] Corroborating these findings, in Minas Gerais, it was observed that the occurrence of deaths from COVID-19 increased with advancing age, with 22.3% among older adults aged 60 to 69 years, 26.3% from 70 to 79 years, and 29.9% from 80 years or older.[7]

According to studies carried out among older adults, there is evidence of an association between the clinical severity of COVID-19 and advanced age;[6] the presence of morbidities;[8] male sex;[9,10] frailty;[11-13] malnutrition;[14-16] obesity[17] and clinical and laboratory test alterations related to inflammatory manifestations and deterioration of immune function.[11,18,19] In this sense, the investigation of these factors contributes to the detection of risk situations, in addition to the implementation of adequate care plans for the health demands of older adults during the COVID-19 pandemic.

However, it is not clear which of these factors acts directly or through mediation, given the scarcity of studies that describe the explanatory factors of the relationship between sociodemographic and clinical variables and the clinical severity of COVID-19 among older adults,[6] using structural equation modeling models.

Scientific knowledge on the subject in question is limited and structural equation modeling models have the potential to identify the dependence and interaction of multiple variables, as well as to estimate the direct effects and those mediated by other factors that are part of the causal network of the outcomes of interest.[20] Therefore, this study aims to analyze the factors directly and indirectly associated with the clinical severity of COVID-19.

OBJECTIVE

The objective of this study was to analyze the factors directly and indirectly associated with the clinical severity of COVID-19 among older adults in the state of Minas Gerais.

METHODS

A retrospective epidemiological study was conducted using the information obtained through the Individual Record Form – Cases of Severe Acute Respiratory Syndrome Hospitalized for the state of Minas Garais. The data was obtained from a Microsoft Office Excel® version 10 (Redmond, Washington) datasheet available on the Integrated Health Surveillance Platform of the Ministry of Health (http://plataforma.saude.gov.br/coronavirus/dados-abertos/), specifically within the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe).[21]

Data from a two-year period (January 28, 2020, to January 27, 2022) were used, starting from the date of the first notification of suspected COVID-19 in the state. The study included hospitalized adult patients aged 60 years or older with confirmed COVID-19 (form classification: option 5 - severe acute respiratory syndrome (SARS) due to COVID-19). Cases with incomplete data were excluded as they did not meet the study's criteria.

Of the total number of COVID-19 cases diagnosed in the state of Minas Gerais in the two-year period (n = 212,275), 102,029 were hospitalized older adults. Of these, 50,888 were excluded due to incomplete data (**Figure 1**). Thus, a total of 51,141 older adults met the established criteria and constituted the final sample for the study (**Figure 1**).

The independent variables were demographic: sex (female; male), age (mean years of complete life), color/race (white; non-white); and clinical: risk factors/comorbidity: chronic cardiovascular disease; chronic hematologic; chronic liver disease; asthma; diabetes mellitus; chronic neurological; chronic lung disease; immunodeficiency/immunosuppression; chronic renal; obesity; others (mean number of risk factors/comorbidity); chest X-ray (normal; abnormal); dyspnea (yes; no) and length of hospital stay (mean number of days of hospitalization). The dependent variable, which was defined based on previous studies, was the clinical severity of COVID-19, which included the use of ventilatory support (yes or no), ICU stay (yes or no), and death (yes or no).[4-5]

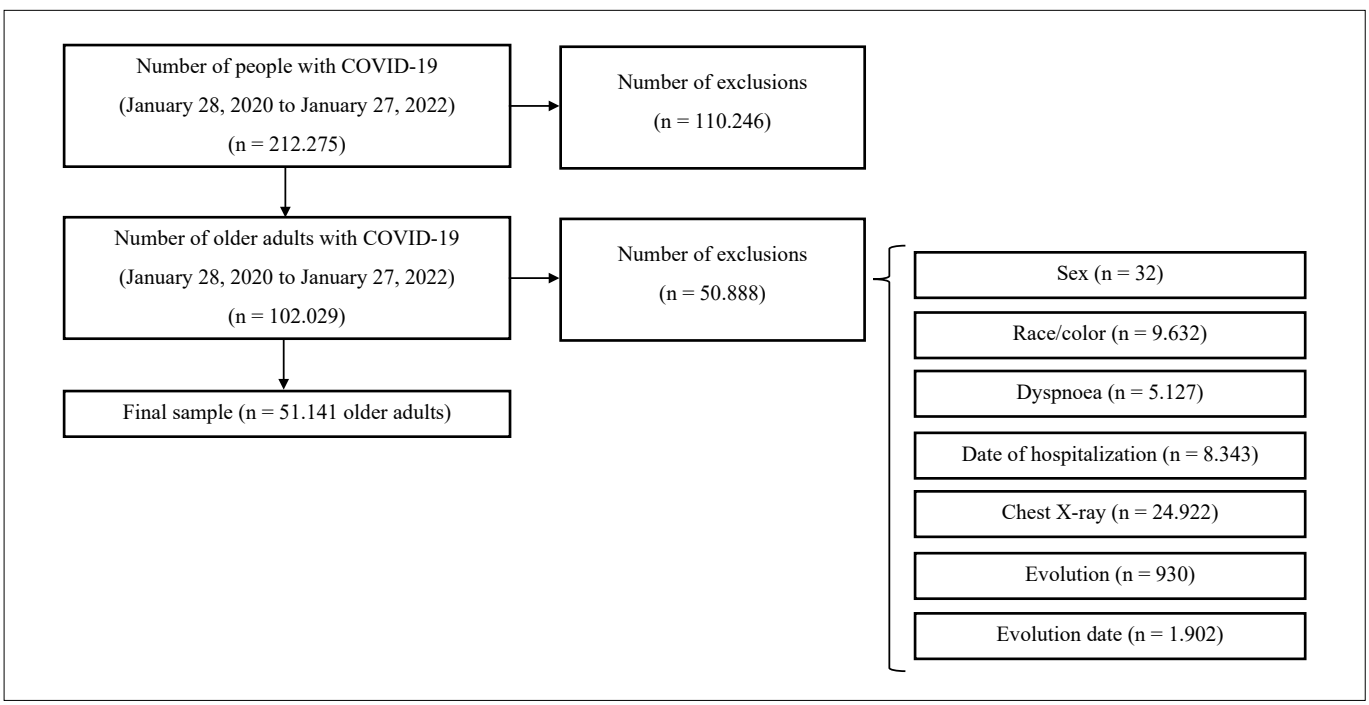


Figure 1. Sample composition.

After selecting the variables, the database was imported to the SPSS (version 24.0; IBM Corp, Armonk, New York, United States) and Analysis of Moment Structures (AMOS), version 24.0 (Armonk, New York, United States).

Data were subjected to descriptive analysis using absolute and relative frequencies for categorical variables, and means and standard deviations for quantitative variables.

For the construction of the structural model, based on the scientific literature, it was considered that demographic and clinical characteristics were associated with the clinical severity of COVID-19,[4,5] through direct and indirect trajectories. Thus, a hypothetical model was developed (**Figure 2**) and tested through the analysis of trajectories composed of observed variables, represented by rectangles, and classified as endogenous or exogenous. Endogenous variables receive directional arrows and measurement errors are attributed, specified by the letter "e" in the models.[20]

From the hypothetical model (**Figure 2**), the steps for the analysis of structural equation modeling were as follows: data collection, model estimation, and evaluation of the goodness of fit. The parameters were estimated by the Free Asymptotic Distribution method and the fit qualities of the models were evaluated according to: Chi-square test (χ^2) $P > 0.05$; goodness of fit index (GFI) ≥ 0.90; comparative fit index (CFI) ≥ 0.90 and root mean error of approximation (RMSEA) ≤ 0.05.[20] The model was tested and, subsequently, respecifications were performed (elimination of non-significant pathways ($P > 0.05$) and calculations of modification indices (≥ 11)).[20]

Direct associations were presented by the estimates of the standardized coefficients of the trajectories between demographic variables, health conditions, and clinical severity of COVID-19. Indirect standardized coefficients were obtained by multiplying the coefficients of the direct paths between variables, and significance was evaluated using the Goodman test. In all tests, the type I error was fixed at 5% (P value < 0.05).[20]

Submission to and approval by an ethics committee was not necessary, given that the present study analyzed the data without identifying registered cases. These are open-access and freely available public secondary data.[21]

RESULTS

Among the older adults included in the study, there was a predominance of men (50.8%), self-reported non-white skin color/race (51.3%), normal chest radiographs (60.6%), and dyspnea (77.8%) (**Table 1**). Regarding variables related to the clinical severity of COVID-19, the majority used ventilatory support (82.5%), were not admitted to the ICU (63.9%), and were discharged from the hospital (54.4%). However, it is important to emphasize that 45.6% of older adults died (**Table 1**).

The distributions of the demographic variables, health conditions, and clinical severity included in the model are shown in **Table 1**.

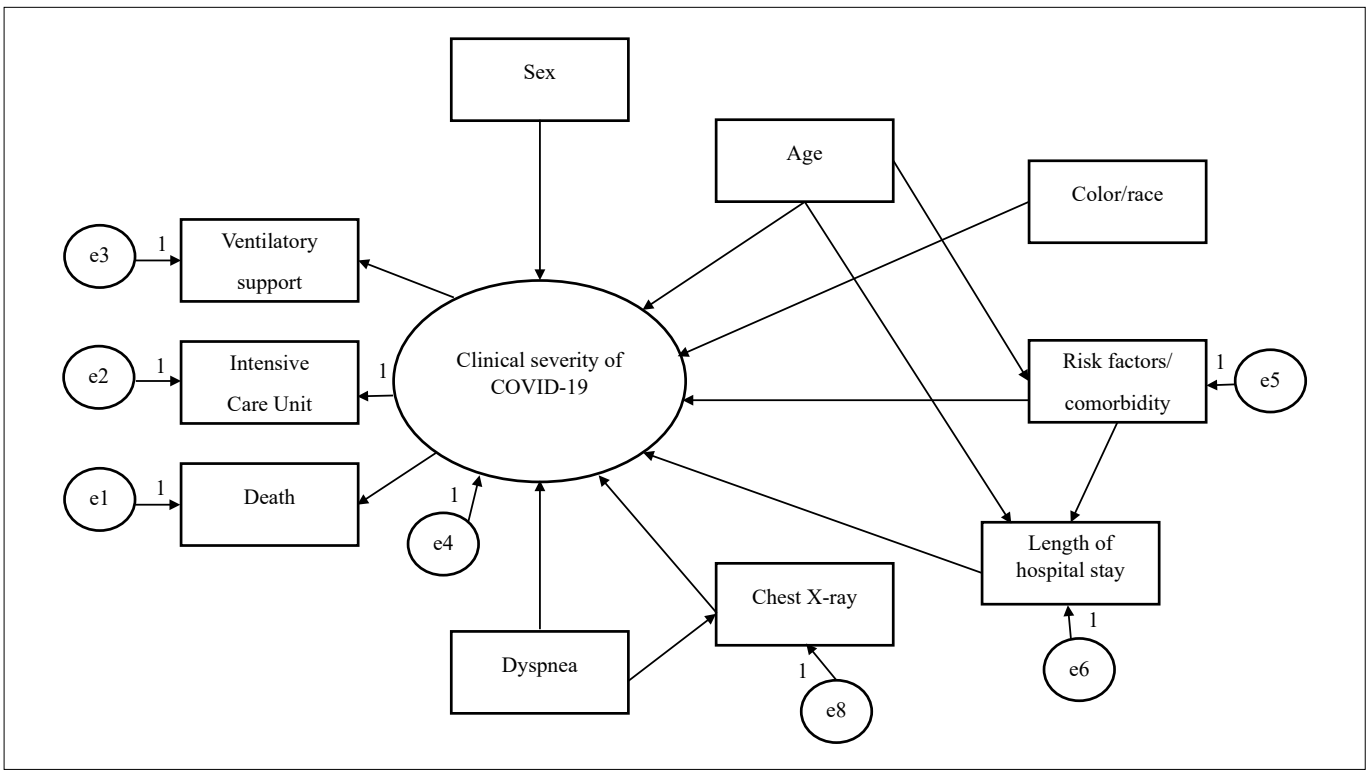


Figure 2. Hypothetical model.

Older age (P < 0.001), male sex (P < 0.001), report of dyspnea (P < 0.001), change in chest X-ray examination (P < 0.001), greater number of risk factors/comorbidities (P < 0.001), and length of hospital stay (P < 0.001) were directly associated with the clinical severity of COVID-19 (**Table 2**). Furthermore, it was observed that female sex (β = -0.02), mediated by the greater number of risk factors/comorbidity, and younger age (β = -0.01), mediated by longer hospitalization time, were associated with indirectly to the clinical severity of COVID-19 (**Table 2**).

The direct and indirect estimators of the associations between the tested variables and clinical severity among older adults diagnosed with COVID-19 in the two-year period (2020-2022) in the state of Minas Gerais are shown in **Table 2**.

Six direct and indirect associations were identified with the clinical severity of COVID-19. The number of risk factors/comorbidities and length of hospital stay were found to have direct and indirect associations with outcomes. Female sex was directly associated with the outcome but was also indirectly associated with risk factors/comorbidities (**Figure 3**).

Figure 3 presents the model with direct and indirect associations between the tested variables and clinical severity among older adults diagnosed with COVID-19 in the two-year period (2020-2022) in Minas Gerais.

Table 1. Distribution of demographic variables, health conditions, and clinical severity, included in the model among older adults diagnosed with COVID-19 in a two-year period (2020-2022) in the state of Minas Gerais, Brazil, 2022

Variables	n = 51,141	%	Mean	Standard deviation
Sex				
Male	25998	50.8	-	-
Female	25143	49.2	-	-
Age	-	-	73.46	9.21
Color/race				
Non-white	27170	51.3	-	-
White	23971	46.9	-	-
Risk factors/comorbidity	-	-	1.49	1.09
Chest X-ray				
Normal	31006	60.6	-	-
Abnormal	20135	39.4	-	-
Dyspnea				
Yes	39765	77.8	-	-
No	11376	22.2	-	-
Length of hospital stay	-	-	12.38	9.48
Clinical severity of COVID-19				
Ventilatory support				
Yes	42196	82.5	-	-
No	8945	17.5	-	-
ICU stay				
Yes	18440	36.1	-	-
No	32701	63.9	-	-
Death				
Yes	23313	45.6	-	-
No	27828	54.4	-	-

ICU = intensive care unit; COVID-19 = coronavirus disease 2019.

DISCUSSION

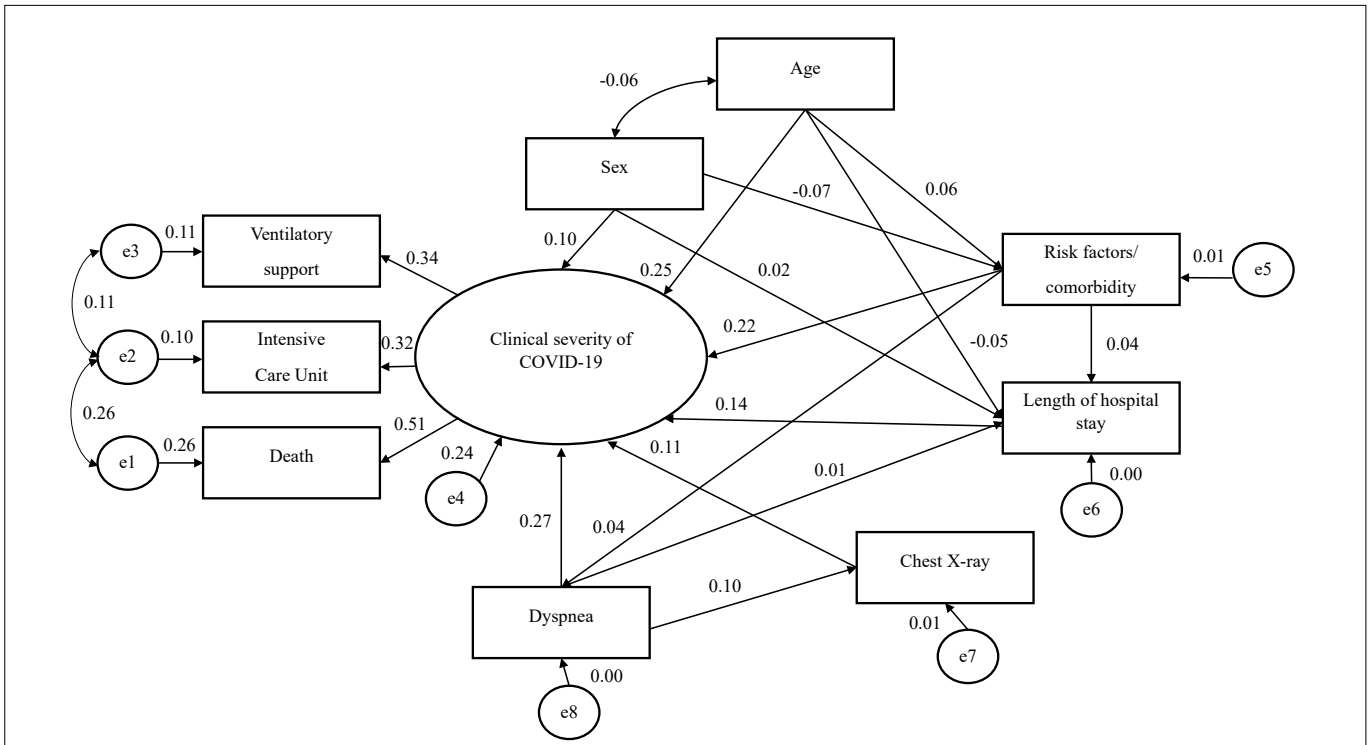
The present study shows the factors that directly or indirectly influenced the clinical severity of COVID-19 in the older adults, through structural equation modeling, based on data from the state of Minas Gerais, the second most populous in Brazil.[3] The factors that were directly associated with the clinical severity of COVID-19 were older age, male sex, greater number of risk/comorbidity factors, longer hospitalization time, altered chest X-rays and the presence of dyspnea. The factors that were indirectly associated were female sex, mediated by a greater number of risk/comorbidity factors, and younger age, mediated by longer hospitalization times.

These results help to understand the factors associated with clinical severity, not only reinforcing that older people, especially men, and those with certain clinical conditions should be prioritized in the implementation and maintenance of preventive measures, but also advance the explanation of factors that can mediate the clinical severity of COVID-19 in women and younger older adults, which can assist in decision-making and public health policy-making.

Table 2. Direct and indirect standardized estimators for variables associated with clinical severity among older adults diagnosed with COVID-19 in a two-year period (2020-2022) in the state of Minas Gerais, Brazil, 2022

Direct and indirect associations	Estimator	P*
Direct associations		
Age → Clinical severity of COVID-19	0.25	< 0.001
Sex → Clinical severity of COVID-19	0.10	< 0.001
Dyspnea → Clinical severity of COVID-19	0.27	< 0.001
Chest X-ray → Clinical severity of COVID-19	0.11	< 0.001
Number of risk factors/comorbidity → Clinical severity of COVID-19	0.22	< 0.001
Length of hospital stay → Clinical severity of COVID-19	0.14	< 0.001
Indirect associations		
Sex female → Risk factors/comorbidity → Clinical severity of COVID-19	-0.02	< 0.001
Minor age → Length of hospital stay → Clinical severity of COVID-19	-0.01	< 0.001

* P < 0.05; COVID-19 = coronavirus disease 2019.



Fit quality indices (χ^2 (gl = 16) = 2143,3; P = 0.001; CFI = 0.90; GFI = 0.99; RMSEA = 0.05).

Figure 3. Model with direct and indirect associations between the tested variables and clinical severity among older adults diagnosed with COVID-19 over a two-year period (2020-2022) in the state of Minas Gerais.

The association between older age and the clinical severity of COVID-19 corroborates previous research,[23-25] including advanced age being described as one of the main factors associated with infection by the new coronavirus.[6,24,25] In the multicenter study HOPE COVID-19, older adults aged 75 years or older had a higher occurrence of death, in addition to the need for oxygen therapy and ICU admission, when compared to the age group of 65 to 74 years.[23] A systematic review with meta-analysis showed that the proportion of people aged over 65 years was higher in the group of patients with critical and fatal evolution of COVID-19 (Odds Ratio [OR] = 6.01; 95%CI: 3.95-9.16; P < 0.001).[25]

Furthermore, physiological changes inherent to the aging process help to understand, in part, the association between advanced age and clinical severity,[24,26] as for example, impairment of the immune system and mitochondrial and hormonal functions.[26] Besides, the presence of underlying comorbidities, prevalent in older adults, can also negatively affect the clinical evolution of the disease.[24-26] These findings confirm the greater vulnerability to the disease associated with age, indicating the need to reinforce preventive measures,[23] with the aim of minimizing the negative repercussions of COVID-19 in this age group.

Regarding male sex and its association with the clinical severity of COVID-19, a study found that men are more affected by the infection[24] and are more likely to develop critical conditions, represented by the demand for ventilatory support and ICU admission,[24,25] in addition to presenting higher mortality when compared to women.[24,25,27]

Similar to advanced age, the association between male sex and the outcome of interest can be explained by immunological characteristics, such as lower responsiveness to infection by the new coronavirus.[24,28] It is noteworthy that certain diseases and conditions related to severe cases of COVID-19 are more prevalent among men,[25] such as cardiovascular diseases.[25,26] In addition to these issues, behavioral factors related to lifestyle among men, such as alcoholism and smoking,[25,28] and lower adherence to preventive measures, can increase the risk of infections and predispose them to negative outcomes.[28]

International studies have found associations between dyspnea[29] and alterations in chest X-rays[30] with the clinical severity of COVID-19 among older adults, corroborating the findings of the present study in which such variables were directly associated with the outcome. Research has shown that patients with a greater extent of alveolar opacities identified on chest radiographs, in general, had a higher mean age,[30] and more intense respiratory distress,[31] which is a strong predictor of death.[32] Such unfavorable circumstances are possibly related to changes in the senescent immune system,[24,26] and to a higher prevalence or occurrence of morbidities among older adults.[24-26] Therefore, detailing the characteristics

of older adults with a higher risk of adverse outcomes can provide early interventions that postpone the worsening of positive cases.

Multiple comorbidities as a risk for the clinical severity of COVID-19 were also evidenced in a survey carried out in Belo Horizonte-MG, predisposing older adults to a greater chance of death (OR = 1.16); this risk factor has been linked to a worse prognosis for hospitalized patients.[33] International studies have observed that a greater number of health problems increased the risk of in-hospital mortality among adults and older people (1.8 times the risk in people with ≥ 3 versus no underlying condition),[30] and also only among older people (1.93 times the risk in people with ≥ 5).[34] From this fact emerges the need for special attention to individuals with multimorbidity, highlighting chronic diseases, a frequent condition among older adults.

The association between the clinical severity of COVID-19 and the length of stay is consistent with a national study that observed a decrease in survival: on average, 2.3% per day for hospitalization and 3.3% per day for ICU stay. For older adults, the probability of survival reached 50% after the thirteenth day, and, on the twenty-third day, patients aged ≥ 85 years had a survival rate of 24%.[35] It is noteworthy that hospitalization, especially for people older or with comorbidities affected by COVID-19, is one of the signs of the severity of the disease, as approximately 7.2% of hospitalized patients die.[35]

Despite the scientific literature on the subject[24-25,27] and current findings showing an association between male sex and the clinical severity of COVID-19, the present study advances our understanding of the repercussions of the disease by showing that the outcome is also associated with female sex, mediated by the presence of risk factors and comorbidities.

The greater life expectancy among women[1] can expose this population to adverse conditions, such as NCDs,[36] in agreement with studies that found a higher prevalence of multimorbidity for females in general.[37,38] In addition, data from the Brazilian Longitudinal Study of Aging (ELSI-Brazil) showed that the prevalence of one or more chronic conditions considered at risk for severe COVID-19 was higher for women (86.4%) than for men (74.3%).[39]

Thus, considering that multimorbidities contribute negatively to the clinical evolution of COVID-19,[24-26] resulting in financial expenses, it is necessary to invest in the approach, diagnosis, and management of these conditions to better use resources and provide care,[37] mainly for the female population exposed to multiple diseases, violence, and socioeconomic inequalities.[36]

An association was identified between the clinical severity of COVID-19 in younger older adults based on the mediation of longer hospitalization times. Although the period of hospitalization is often longer in older age groups,[29,40] a multicenter study found a longer average length of stay (P = 0.05) among older people aged 65-74 years (9.4 ± 7.3 days) when compared to those aged 75 years or older (8.6 ± 6.9 days).[23] This fact, found in other investigations,[6,19,33] is related to immunological issues[19,26] and the presence of risk factors, such as multimorbidities,[19,23,33] that require intensive[24] and prolonged care. However, the results of the present study reinforce the repercussions of longer hospital stay on worse prognoses, including mortality,[32] regardless of age. Thus, it is essential that health services direct efforts and resources to improve their approach and treatment, with the aim of reducing the negative consequences of longer hospital stays.

The present study has limitations, such as the non-inclusion of aspects related to vaccination; that is, the study scope possibly included older adults who received some dose of the vaccine, which may have influenced the outcome. Another limitation refers to wave peaks, as in these periods' hospitalizations have been associated with higher mortality, as demonstrated by a national study.[41] Furthermore, the exclusion of 50,888 cases with incomplete data may have influenced the results, highlighting the importance of completing notification forms.

The strengths of this study include the use of a state database and the performance of structural equation modeling analysis, which allowed us to understand the characteristics and health factors that determine the clinical severity of COVID-19.

CONCLUSION

Demographic characteristics, such as older age and male sex, and clinical characteristics, including the highest number of morbidities, length of hospital stay, change in X-ray examination, and dyspnea, were directly associated with the clinical severity of COVID-19, that is, ICU admission, use of ventilatory support, or death. Female sex, mediated by a greater number of risk/comorbidity factors, and younger age, mediated by a longer hospitalization time, were indirectly associated with the clinical severity of COVID-19. The results of this study can help identify groups at risk of adverse outcomes and make decisions to prioritize older adults who may need more care owing to COVID-19, considering previous health information.

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Prevalence of depressive disorders among pregnant women in Brazil in 2019: A descriptive cross-sectional study

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ABSTRACT

BACKGROUND: Prenatal depression threatens maternal and child well-being and interferes with issues prioritized by the 2030 agenda for the Sustainable Development Goals.

OBJECTIVES: This study aimed to estimate the prevalence of depressive disorders during pregnancy using the Patient Health Questionnaire-9 (PHQ-9).

DESIGN AND SETTING: A cross-sectional study using a sample of pregnant Brazilian women, representative of Brazil as a whole.

METHODS: Data were obtained from the National Health Survey 2019 (PNS-2019), as coordinated by the Instituto Brasileiro de Geografia e Estatística (IBGE). Women aged 18-49 years who were pregnant during PNS-2019 data collection were included. The prevalence of depressive disorders and 95% confidence intervals (95%CI) were calculated.

RESULTS: The prevalence of depression before the current pregnancy was 6.03% (95%CI: 3.80%; 8.25%). Using the PHQ-9, the prevalence of Major Depressive Disorder (MDD) in the current pregnancy was estimated to be 17.39% (95%CI: 12.70%–22.06%) among pregnant women who were targeted by the PNS-2019. Moreover, MDD was 15.26% (95%CI: 10.54%; 19.97%) among those who were free from depression history and in half of the pregnant woman population with depression history. Suicidal ideation has been reported in almost 23% of pregnant women with a history of depression. The two items from Patient Health Questionnaire-2 (PHQ-2) (anhedonia and depressed mood) with a cutoff of ≥ 3 presented similar results.

CONCLUSIONS: Depression during pregnancy affects a non-negligible proportion of pregnant women, thus constituting an important public health problem. Therefore, it is crucial to discuss the implementation of regular screening for depression during prenatal care programs in Brazil.

INTRODUCTION

The 2030 agenda for the Sustainable Development Goals established the following as its 3rd objective: "to ensure a healthy life and promote well-being for all at all ages". Linked to this objective is a list of subheadings directly related to maternal and child health, including item 3.4, which is aligned with promoting mental health and well-being.[1] Throughout the life cycle, well-being and mental health are threatened by risk factors shared by the mother and child in various developmental phases: preconception, perinatal and postnatal, adolescence, and youth.[2]

During the gestational period, women experience physical, psychological, and emotional changes as permeated by stressful situations, few sleep hours, hormonal oscillations, and tiredness, thereby making it difficult to suspect and diagnose depression.[3] Analysis of the current nationwide Brazilian data indicates that the underdiagnosis of depression is more frequent among pregnant women (88.1%), as compared to non-pregnant women (68.0%).[4] Women of reproductive age are common users of health services, especially during pregnancy, a scenario that provides an opportunity to track depressive symptoms and make referrals to specialized professionals.[4]

When screening for depressive disorders, the American Psychiatric Association (APA) recommends investigating the frequency of nine symptoms, provided that they differ from the previously perceived functioning, occur nearly every day, and persist over the previous two-week period.[5] The investigated symptoms should correspond to the items in the Patient Health Questionnaire-9 (PHQ-9), a tool proposed to diagnose mental disorders among primary healthcare users.[6] The PHQ-9 is an instrument validated across different scenarios and is used in people with different health conditions and age characteristics.[7]

The PHQ-9 has proven to be reliable in tracking suspected cases of Major Depressive Disorders (MDD) among the general population in Brazil,[8] and has revealed acceptable reliability and validity for screening depressive symptoms among pregnant women.[9] It is included as one of the modules of the National Health Survey, a population-based survey representing the Brazilian population.[10] It provides population-based information and measures the frequency of prenatal depression, which interferes with several issues prioritized by the Sustainable Development Goals, and can contribute to the planning and implementation of actions aimed at achieving the 2030 Agenda.

OBJECTIVE

This study aimed to estimate the prevalence of depressive disorders among pregnant women in Brazil by using data from the National Health Survey (PNS-2019).

METHODS

This descriptive study addressed the research question, "what is the prevalence of depression during pregnancy in Brazil?". The data was obtained from the National Health Survey-2019 (PNS-2019).[10] The PNS has the merit of providing public access to information regarding the health conditions of populations residing in private households within the national territory, which is not made available by the country's information systems.[11] The original project of the PNS-2019 was approved by the National Commission for Ethics in Research (CONEP) under the National Health Council (CNS), with the approval number: No. 3.529.376, dated 23rd August 2019.

Access to the 2019 PNS microdata

The microdata was imported using the online option via the "PNSIBGE" package and the R program, as recommended by IBGE.[12] The microdata was derived from the "questionnaire of the selected resident", which gathered the questions asked only to the randomly selected residents in the selected household. The steps were followed in order to facilitate the analysis via the "survey" package.

Sampling plan

Details of the sampling plan can be retrieved from the article, "National Health Survey 2019: history, methods and perspectives".[11] In summary, the method considered the effects of the selection scheme applied in the complex sampling plan, as well as the measures of error of the estimates and the originally applied post-stratification estimator.[12]

Participants

The target population of the PNS-2019 included people aged ≥ 15 years who lived in permanent private households in rural or urban areas. This allowed for the disaggregation of (i) macro-regions, (ii) federative units (UF), (iii) Capitals and (iv) Metropolitan Regions. This study used PNS-2019 data to produce estimates for the target population of women aged 18–49 years. The subset included women with a confirmed pregnancy during PNS data collection.

Variables of interest selected from the PNS-2019

a) Module: general characteristics: age in years (18-24, 25-34, and 35-49); ethnicity/race (white, black, yellow, brown, and indigenous); having a spouse or partner living in the same household (yes versus no).
b) Module: lifestyle: pregnancy status (yes versus no) at the time of the interview [Question P005. Are you currently pregnant?]
c) Module: chronic diseases: History of a medical diagnosis of depression [Question Q092. Had a doctor or mental health professional [such as a psychiatrist or psychologist] ever diagnosed you with depression?
d) Module: perception of health status: symptoms within the last two weeks that could have affected the respondent in a different way than usual. Symptoms were assessed using the PHQ-9, which is a self-reporting instrument composed of nine items with four response options as follows: 0 (none of the days), 1 (less than half of the days), 2 (more than half of the days), and 3 (almost every day).[6] The PNS-2019 applied the PHQ-9 items in the following order: N010 (trouble falling or staying asleep, or sleeping too much), N011 (feeling tired or having little energy), N012 (little interest or pleasure in doing things), N013 (trouble concentrating on things), N014 (poor appetite or overeating), N015 (moving or speaking so slowly, or the opposite), N016 (feeling down, depressed, or hopeless), N017 (feeling bad about yourself, or that you are a failure or have let yourself or your family down), and N018 (thoughts that you would be better off dead or of hurting yourself).

Definition and measurement of depressive manifestations

Depressive manifestations were measured as follows:

(i) Frequency of a history of depression, as diagnosed by a healthcare professional according to question Q092 (Had a doctor or mental health professional [such as a psychiatrist or psychologist] ever diagnosed you with depression?). The answer options were "yes" versus "no", indicating positive or negative previous depression before the current pregnancy.
(ii) Frequency of depressive symptoms in the last 15 days according to the responses to the PHQ-9,[6] considering:
    a) Firstly, the PHQ-9 was interpreted as a continuous scale in which the sum varied from 0 to 27; a cutoff point of ≥ 10 suggested MDD.
    b) Subsequently, we scrutinized two questions ("lack of pleasure in doing things" and "depressed mood")

comprising the PHQ-2.[13] The PHQ-2 interpretation was based on summed scores ranging from 0 to 6; a cutoff point of ≥ 3 suggested depression disorders.[13] In our study, the N12 (lack of pleasure in doing things) and N16 (depressed mood) items were used to check the distribution of pregnant women in the different cutoff points and to obtain the estimates of prevalence affecting those with a cutoff point of ≥ 3, which were suspected with depression disorders.

The frequency of depression was calculated considering the following participants of the PNS-2019:

1) All pregnant women as a whole;
2) The subgroup of pregnant women restringing those with previous depression (Question Q092 with a positive response);
3) The subgroup of pregnant women restringing those without previous depression (Question Q092 with a negative response);

This allowed for the calculation of the prevalence of depressive disorders that manifested during the gestational period of: (i) pregnant women as a whole, (ii) pregnant women with a previous medical diagnosis of depression, and (iii) pregnant women without a history of depression.

Statistical analysis

Data analysis was performed online according to the recommendations of the IBGE for complex samples.[12] The Survey package was used; the function, design = subset, and the argument, selected = TRUE, were performed. This was followed by the calculation of prevalence and 95%CIs.

RESULTS

The data analyzed in this study were representative of a contingent of women expected to be pregnant (n = 1,402,399) at the time of data collection (from 2019-August to 2019-December 2019) of the National Health Survey in Brazil. The results indicated a prevalence of 6.03% (95%CI: 3.80%; 8.25%) for a previously self-reported medical diagnosis of depression. Most pregnant women reported living with a partner at home, regardless of a history of depression. **Table 1** summarizes the demographic characteristics of the pregnant women analyzed in this study.

Prevalence of depression symptoms via PHQ-9 items

The symptoms captured by each PHQ-9 item indicated that suicidal ideation had the lowest positivity. The will to die was confirmed in < 5% of pregnant women as a whole (4.47%) and of those without a history of depression (3.31%). However, 22.51% of participants with a history of depression reported suicidal thoughts (**Table 2**).

Prevalence of MDD by a cutoff point of ≥ 10

Using the PHQ-9 items as a continuous scale, the mean total score for pregnant women was 4.62 (95%CI: 3.98; 5.26). The lowest and highest means were 4.26 (95%CI: 3.63; 4.89) for the pregnant women subgroup without a history of depression and 10.26 (95% CI: 7.47; 13.05) for those with a history of depression, respectively. The estimates based on a cutoff point of ≥ 10 suggested that MDD could be present in approximately 17.39% (95%CI: 12.70%; 22.06%) of pregnant women who were targeted by the PNS-2019. The prevalence of MDD was 15.26% (95%CI: 10.54%; 19.97%) among those who were free from previous depression

Table 1. Demographic characteristics of the target population of women aged 18 to 49 years who were pregnant at the time of the National Health Survey (PNS-2019) data collection, Brazil, 2019

	Total (n = 1,402,399)		With a previous depression diagnosis (n = 84,569)		Without a previous depression diagnosis (n = 1,317,830)	
	Prevalence	95%CI	Prevalence	95%CI	Prevalence	95%CI
Age						
18 a 24	34.6	29.1; 40.2	17.4	4.2; 30.6	35.7	29.9; 41.5
25 a 34	42.5	36.7; 48.3	36.9	18.2; 55.7	42.8	36.7;48.8
35 a 49	22.9	17.5; 28.3	45.6	27.2; 63.9	21.4	15.8; 27.0
Skin Color						
White	33.3	27.6; 39.0	54.4	36.2;72.6	31.9	26.0; 37.8
Black	15.9	11.2; 20.5	9.8	-15.1; 21.2	16.3	11.3; 21.1
Yellow	0.5	-0.3;1.4	0.0	0.0; 0.0	0.5	-0.3; 1.4
Mixed	49.9	43.7; 56.1	35.7	19.1; 52.3	50.8	44.2; 57.2
Indigenous	0.4	-0.02; 0.9	0	0.0; 0.0	0.5	0.0; 0.9
Living with partner						
Yes	78.7	73.8; 83.6	73.9	56.1; 91.7	79.1	73.9; 84.1
No	21.3	16.4; 26.1	26.1	8.2; 4.4	20.9	15.8; 26.0

Data source: National Health Survey, 2019. Instituto Brasileiro de Geografia e Estatística. CI = confidence interval.

Table 2. Frequency of depressive symptoms, as measured by the Patient Health Questionnaire-9 administered to pregnant women participants in the National Health Survey (PNS-2019), in Brazil, 2019

Pregnant women group/PHQ-9-symptoms	None of the days	Less than half of the days	More than half of the days	Almost everyday
	(%)	(%)	(%)	(%)
All pregnant women together				
N010 (sleep problems)	55.56	20.72	8.89	14.83
N011 (low energy)	47.29	25.75	12.79	14.16
N012 (anhedonia)	55.18	27.27	7.59	9.95
N013 (concentration difficulties)	75.97	13.92	5.50	4.59
N014 (appetite changes)	67.61	15.63	6.75	9.99
N015 (moving or speaking so slowly)	77.67	12.73	4.29	5.28
N016 (depressed mood)	67.52	22.19	5.15	5.13
N017 (feeling bad about yourself)	84.45	10.63	1.42	3.48
N018 (suicidal thoughts)	95.53	3.08	0.61	0.76
Pregnant women with a previous depression diagnosis				
N010 (sleep problems)	18.65	21.13	10.69	49.53
N011 (low energy)	23.89	26.35	11.34	38.42
N012 (anhedonia)	35.31	30.54	13.32	20.83
N013 (concentration difficulties)	51.38	15.26	7.93	25.43
N014 (appetite changes)	48.17	18.03	9.17	24.63
N015 (moving or speaking so slowly)	52.23	18.11	5.48	24.18
N016 (depressed mood)	43.78	23.83	8.45	23.93
N017 (feeling bad about yourself)	56.74	18.88	11.23	13.15
N018 (suicidal thoughts)	77.49	9.47	9.52	3.52
Pregnant women without a previous depression diagnosis				
N010 (sleep problems)	57.92	20.70	8.77	12.61
N011 (low energy)	48.79	25.72	12.89	12.60
N012 (anhedonia)	56.45	27.06	7.23	9.26
N013 (concentration difficulties)	77.55	13.84	5.35	3.26
N014 (appetite changes)	68.87	15.48	6.60	9.05
N015 (moving or speaking so slowly)	79.31	12.39	4.22	4.07
N016 (depressed mood)	69.05	22.08	4.94	3.92
N017 (feeling bad about yourself)	86.23	10.10	0.80	2.87
N018 (suicidal thoughts)	96.69	2.67	0.04	0.59

Data Source: National Health Survey 2019. Instituto Brasileiro de Geografia e Estatística. 95% Confidence Intervals were omitted.

and among approximately half (95%CI: 31.98%; 69.01%) of pregnant women with previous depression.

Depressive disorder as measured by PHQ-2 [symptoms of anhedonia (N012) and depressed mood (N016)]

The mean scores of the two PHQ-2 items was 1.20 (95%CI: 1.01; 1.39), 2.32 (95%CI: 1.37; 3.26), and 1.13 (95%CI: 0.94; 1.31), among pregnant women as a whole, those with previous depression, and those without depression, respectively. The positivity for depressive disorders according to different cutoff points indicated that the higher the cutoff point, the lower the prevalence of depression. Moreover, estimates with a cutoff point of ≥ 3 suggested that 16.61% (all pregnant women), 32.22% (group with depression history), and 15.61% (group without depression history) of pregnant women in Brazil may have positive depressive symptoms (**Table 3**).

The overlapping of the 95%CIs of the estimates captured via the PHQ-9 items (dichotomized at a cutoff point of ≥ 10) as compared to those from the PHQ-2 items (dichotomized at a cutoff point of ≥ 3), which are displayed in **Table 3**, suggested no difference between the two methods in terms of capturing depressive disorders during pregnancy, regardless of previous depression, among Brazilian women.

DISCUSSION

This study focused on the mental health of pregnant women and showed that symptoms suggestive of depression during pregnancy may be present in > 15% of the population. The estimates derived from the PHQ-9 indicated that among pregnant women, MDD may be present in 17.39% (pregnant women as a whole), 15.26% (pregnant women, without previous depression), and 50.00% (pregnant women, with previous depression) of the

Table 3. Positivity of Patient Health Questionnaire-2, considering two-item scores (N012-anhedonia and N016-depressed mood) and different cutoff points among pregnant women with and without previous depression

Pregnant women/ Cutoff points	Positivity (n)	Prevalence (%)	95%CI
All together (n = 1,402,399)			
≥ 1	739,347	52.72	46.92; 58.51
≥ 2	465,544	33.19	27.46; 38.92
≥ 3	**232,964**	**16.61**	**12.02; 21.20**
≥ 4	138,840	9.90	5.89; 13.90
≥ 5	64,981	4.63	2.31; 6.95
With a previous depression diagnosis (n = 84,569)			
≥ 1	60,889	72.00	56.11; 87.88
≥ 2	45,050	53.27	34.76; 71.77
≥ 3	**27,255**	**32.22**	**13.50; 50.95**
≥ 4	26,046	30.79	12.04; 49.55
≥ 5	19,519	23.08	4.87; 41.28
Without a previous depression diagnosis (n = 1,317,8300)			
≥ 1	678,457	51.48	45.42; 57.54
≥ 2	420,493	31.90	25.94; 37.87
≥ 3	**205,709**	**15.61**	**10.91; 20.30**
≥ 4	112,794	8.55	4.52; 12.58
≥ 5	45,461	3.44	1.38; 5.51

Data Source: National Health Survey, 2019. Instituto Brasileiro de Geografia e Estatística; CI = confidence intervals.

subgroups analyzed. The two PHQ-2 items with a cutoff point of ≥ 3 showed similar results.

Significant public investment in Brazil has been made to improve obstetric and perinatal outcomes. Despite the harmful effects caused by maternal depression on various aspects of women's and children's health and family relationships, it remains underdiagnosed and inadequately studied in Brazil.[14] To reduce the literature gap in the context of national representation, the hospital-based survey, "Nascer no Brasil", estimated a post-partum depression frequency of 26.3%, based on information collected through telephone calls between 6 and 18 months after child birth.[15] The collected information led to the creation of a risk model for post-partum depression, wherein the predictor, "previous history of mental disorders", constituted the strongest risk factor after final model adjustments.[15]

In line with the aforementioned results, the present study detected a prevalence of 6.05% for depression, as self-reported by PNS-2019 participants who were diagnosed before pregnancy. Moreover, data from 6814 mother-child pairs, which were analyzed to investigate associations between maternal mental health disorders before and during pregnancy, showed that depression increased the risk of anxiety disorders during pregnancy and pediatric healthcare utilization.[16] In addition to these issues, the present study detected a high frequency of symptoms, thereby indicating that MDD affects pregnant women with (50.0%) and without (15.2%) a history of depression. These figures suggest a need to implement depression-screening measures, regardless of mental health status before pregnancy.

Therefore, the PHQ-2 appears to be an effective and sensitive alternative when screening for depressive disorders. This instrument comprises two core PHQ-9 items and has been recommended for use in high demand scenarios, wherein healthcare professionals are overloaded and have little time to carry out everyday tasks.[13] A study conducted in the United States using the PHQ-2 on a sample size of 218 pregnant women with a gestational age of up to 16 weeks showed sensitivity and specificity measures of 77% and 59%, respectively, with a cutoff point of ≥ 3 and the Composite International Diagnostic Interview as reference measures.[17] In Spain, the performance of the PHQ-2 was evaluated in a study that included 1019 pregnant women in their first trimester.[18] The instrument showed sensitivity and specificity measures of 85.4% and 79.5%, respectively, when utilizing a cutoff point of ≥ 2 and the PHQ-9 as the gold standard, with excellent discriminatory ability (84%).[18]

In addition to the long list of implications attributed to perinatal depression,[19,20] it is crucial to draw attention to the fact that almost 5.0% and 23.0% of pregnant Brazilian women, as a whole and among those with previous depression, respectively, may be living with suicidal thoughts and are at risk for non-fatal and fatal outcomes. This result was extracted from a PHQ-9 component item (N018-suicidal thoughts) that was analyzed in isolation. This item was also analyzed in a study on pregnant women in Spain, which showed the occurrence of suicidal ideation in 2.6% of those interviewed in their first trimester.[21]

Suicidal thoughts may manifest from the beginning of the gestational period and may extend into the post-partum period. Results from a study with a sample of 831 low-income Brazilian women who were pregnant between the 20th and 30th weeks estimated a 6.3% prevalence of antenatal suicidal ideation.[22] Pooled measures from a meta-analysis that included 71 studies showed that the prevalence of suicidal ideation was 10% during the gestational period, 7% in the post-partum period, and 8% in both groups. In addition, the studies reported a higher frequency (13%) in low- and middle-income countries, including five studies conducted in Brazil.[23]

Although rarely practiced, suicide attempts were also measured by a meta-analysis that gathered 14 studies and indicated that the act has been detected during pregnancy (prevalence 95%CI: 0.10%; 4.69%) and the first post-partum year (prevalence 95%CI: 0.01%; 3.21%).[24] A retrospective cohort study conducted with data from 712 hospitals in Japan included 1202 pregnant women admitted during the pre-partum period and 111 re-admissions within 1-year post-partum, of which all admissions were due to suicide attempts.[25] In addition, prenatal psychiatric disorders, including depression, were among the potential risk factors for peripartum suicide attempts.[25] Suicide attempts among women in reproductive age are increasing

in Brazil.[26] However, the magnitude of these events practiced during the gestational period demands further studies for better understanding and urgent proposal of intervention measures.

The present study used data from a representative sample of women residing in Brazil to provide measures on the prevalence of depressive disorders during pregnancy. However, this study has some limitations. First, the data analyzed corresponded to a subset of selected residents derived from a complex sampling process that included age classes in the definition of expansion factors,[10] whose limits were not fully equivalent to the age group of the study. Nevertheless, we believe that the estimated parameters facilitate population inferences for women aged 18–49 years who were pregnant according to the PNS-2019. Another issue that must be pointed out relates to the investigation of symptoms that are commonly present in some general medical conditions, as well as in pregnancy.[5] In general, gestation is physiologically characterized by changes in appetite and sleep, which are also investigated by two PHQ-9 items. Bearing in mind the equivalence of the measures provided by the different structures involving appetite and sleep investigation, it is possible that such a limitation may have been circumvented to some extent. Finally, it is important to point out that despite the practicality of using the PHQ-2 to identify people suspected of suffering from depressive disorders, it is only a screening instrument that indicates whether the person needs evaluation using more appropriate instruments and/or specialized professionals. Despite the adequacy demonstrated in capturing cases of depression among women,[27] the performance of the instrument still requires further evaluation among pregnant women. Checking of validity and reliability of PHQ-9 and PHQ-2 in Brazilian pregnant women deserves consideration in future research.

CONCLUSION

In conclusion, the present study shows that the symptoms of suicidal ideation in isolation and MDD are highly prevalent conditions during pregnancy, thus supporting the formulation of guidelines for regular screening during prenatal care. The equivalence of the estimates, as measured by the PHQ-9 items interpreted in two different ways, suggests that the two questions about depressive mood and anhedonia could constitute a screening tool for gestational depression, as they allow for rapid administration and are suitable for use in high-demand environments, such as primary care in Brazil.

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Time to initiation of dialysis and length of stay in hospitalized patients with kidney damage: a cross-sectional study

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ABSTRACT

BACKGROUND: Universal healthcare is a cornerstone of Brazil's public health system. However, delayed diagnosis and treatment of chronic kidney disease (CKD) remain substantial issues. The scarcity of outpatient dialysis facilities contributes to extended hospital stays. This study aimed to examine how the time to dialysis initiation (TID) impacts mortality in patients with renal disease.

OBJECTIVES: This study aimed to evaluate the correlation between variables affecting TID and mortality in hospitalized patients with renal disease.

DESIGN AND SETTING: A cross-sectional study was conducted at Santa Marcelina Hospital in São Paulo.

METHODS: This cross-sectional study was conducted in a tertiary hospital, involving adults with kidney disease who were referred to the emergency department between 2014 and 2017. Primary outcomes included TID and mortality rates.

RESULTS: Among the 402 patients studied, the average age was 58.6 years, and 59.4% were men. The median hospital stay was 44.5 d. Notably, 28.1% of the patients began dialysis under emergency conditions. Diabetes and hypertension were the most prevalent causes of renal disease. A positive correlation was found between age and TID (P = 0.007).

CONCLUSIONS: Primary care in Brazil often fails to effectively detect and manage CKD, leading to a higher incidence of emergency dialysis, particularly among older adults. This delay correlates with increased mortality rates. Older age is associated with delayed TID, prolonged hospital stays, and consequently higher mortality. These findings highlight the need for better primary care to effectively manage CKD and reduce hospitalization and mortality.

INTRODUCTION

Universal access to healthcare is a significant topic of debate worldwide. Both politicians and the general population recognize the importance of creating a sustainable and cost-effective system to support the treatment and prevention of serious health conditions. Brazil, a country of continental proportions, established its Unified Health System (SUS) in the 1980s.[1] The system ensures that every Brazilian citizen has the right to receive medical treatment, not only for chronic conditions but also for preventive care, medication distribution, and diagnostic testing. Since its implementation, the SUS has improved access to healthcare for low-income individuals, particularly in areas such as prenatal care and vaccination. However, challenges remain, including inequitable coverage, conflicting ideologies and goals, and limitations in financing, infrastructure, and human resources.[2]

Chronic kidney disease (CKD) is a public health issue with increasing prevalence over recent decades. Its leading causes, hypertension and diabetes, continue to grow in prevalence. To understand the economic burden of this disease, the 2022 annual report from the United States Renal Data System indicated that in 2020, total fee-for-service expenses for all beneficiaries reached $85.4 billion, accounting for 23.5% of all Medicare expenditures.[3] Brazil has the third-largest population of patients with end-stage renal disease on hemodialysis globally, with the SUS primarily supporting this care. Despite a budget allocation of $ 80 million for initial dialysis care, the system struggles to prevent the progression of CKD.[4] Despite the growing number of patients initiating dialysis, estimated at 133,464 by the Brazilian Nephrology Society, these figures do not capture the full burden of in-hospital dialysis costs incurred by public hospitals under the SUS and by the private healthcare sector.[2,5] The need for hospitalization to initiate renal replacement therapy increases the risk of death and raises the overall cost of CKD care. However, data on these factors not well-documented in Brazil.

OBJECTIVE

This study aimed to evaluate the correlation between variables affecting the time to initiate dialysis (TID) and mortality in hospitalized patients with renal disease at a major hospital in São Paulo.

METHODS

This cross-sectional study was conducted at a major tertiary hospital in São Paulo, Brazil, between 2014 and 2017. All medical records of hospitalized adult patients admitted during this period with kidney damage and no previous renal replacement therapy were analyzed. A review of these records revealed the study participants' demographics and baseline clinical characteristics. No personal information was shared during the review of medical records. A flowchart explaining the patient selection process is provided in the Supplemental Material.

The primary diagnosis at admission was considered to address the etiology of renal dysfunction, preexisting conditions, and patient demographic information. In Brazil, patients with a permanent indication for renal replacement therapy are discharged from the hospital only when an external dialysis facility has seats available to continue treatment. The TID in this study referred to the time when the patient was admitted to the external dialysis facility and not to the in-hospital indication of renal replacement therapy. In the public system, external dialysis facilities must have available seats for patients. This study followed and revised the checklist principles for items that should be included in reports of observational studies (STROBE).

Kidney damage evaluation followed the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[4] Acute kidney injury (AKI) diagnosis followed the 2012 KDIGO criteria, where a significant rise in serum or plasma creatinine of at least 0.3 mg/dL within 48 h, or suspected to have occurred within the preceding 48 h, compared to baseline serum creatinine levels, was used to make the diagnosis.[6] For individuals who developed hospital-acquired AKI, the baseline reference was a consistent serum creatinine level obtained during the patient´s hospital stay before the diagnosis of AKI. Evaluation of the medical records was triggered by a call to the nephrology team in the emergency room and involved tracking the patient's clinical origin and kidney function. For individuals admitted from the community, the study team searched for reference serum creatinine levels in the following order of preference: the most recent value recorded within 3 months before hospital admission. If this was not accessible, the value obtained within 3 to 12 months prior to hospital admission was considered. If this was also unavailable, serum creatinine levels upon hospital admission were recorded. If the patient had no renal abnormalities, their medical record was excluded from the evaluation.

The evaluation of CKD was based on a sustained decrease in the estimated glomerular filtration rate for at least 12 weeks, according to KDIGO guidelines for CKD management.[4] Persistent albuminuria or structural kidney alterations observed in imaging tests were also considered for CKD diagnosis and staging. The etiology of kidney failure was classified into six categories: glomerulonephritis, arterial hypertension, diabetes, oncology-associated, sepsis-related, and other causes, such as drug-induced renal dysfunction. The study team did not influence the indications for renal replacement therapy, which were solely determined by the hospital nephrology staff. Discharge or transfer to an external dialysis facility was also managed by the hospital team. The primary outcome was the TID in days after the diagnosis of renal dysfunction, as well as death from any cause. The length of stay (LOS) was analyzed as a secondary outcome, correlated with death.

Descriptive analyses were conducted by measuring central tendency and dispersion. Proportion measures were used to describe qualitative variables. After confirming the normality of the variables using simple histograms, parametric tests were performed. The TID was compared between the groups (survivors and deceased) using the Student's t-test. LOS and TID were evaluated using linear regression and Pearson's correlation tests. Multivariate analysis was performed with the best baseline characteristic variables against TID and LOS. An alpha error rate of 5% was assumed. The statistical software used was XLStat for Windows. The study was approved on 03/13/2019 by the Faculdade de Medicina do ABC (FMABC) review board, under reference number 94759218.4.0000.0082.

RESULTS

The study population included 402 patients with complete medical records during data collection. Most patients were between 18 and 60 years of age, and 60% of men had kidney damage during the period analyzed. There was significant variability in the LOS, ranging from 3 to 410 d, with a median LOS of 44.5 d. The majority of the patients (78.6%) stayed for a maximum of 30 d. The prevalence of hypertension and diabetes as causes of renal dysfunction was higher than that of other categories, as shown in **Table 1**. Approximately 52.5% of the patients had previously consulted a nephrologist, and 53.3% had kidney damage identified in the emergency room.

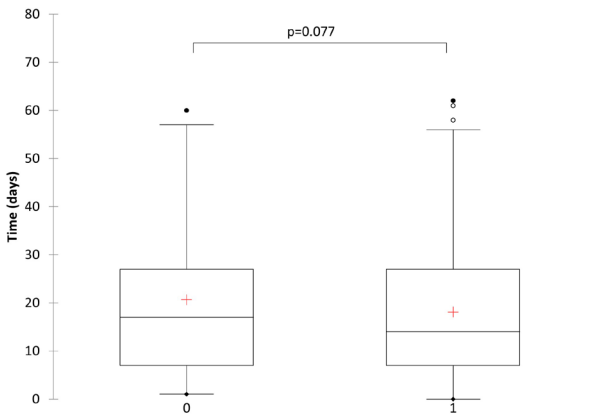
The comparison between TID and death using the Student's t-test was not statistically significant, as shown in **Figure 1**. Pearson's univariate analysis revealed a positive correlation between age and TID ($P = 0.007$) (**Figure 2**).

Multivariate analysis was used to evaluate the possible explanatory variables tested against dialysis initiation time (**Table 2**). None of the patient characteristics (age, prior nephrologist consultation, kidney damage etiology, or the patient's origin) were significantly correlated. Age was the most influential factor in the TID model.

TID and LOS were tested against the etiology of kidney damage in each of the five categories (diabetes and arterial hypertension,

Table 1. Demographics and clinical characteristics of the sample

	n	%
Age (years)		
18–59	208	52
60–79	174	43
> 80	19	5
Sex		
Men	234	60
Women	168	40
Length of stay (days)		
01–30	316	78.6
31–60	41	10.2
> 60	45	11.2
Admission creatinine (mg/dL)		
< 1.0	97	24.2
1.0–3.0	176	35.3
> 3.0	163	40.5
Renal dysfunction etiology		
Diabetes	96	24
Hypertension	165	41
Sepsis	20	5
Cancer	25	6
Glomerulonephritis	80	20
Other causes	16	4



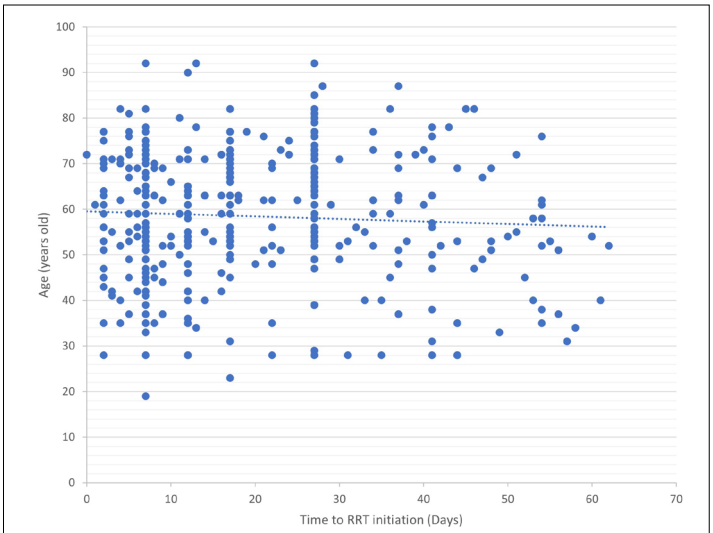
0 = Alive; 1 = Dead; TID = time to initiate dialysis.

Figure 1. TID and death in patients hospitalized with kidney damage.

oncology-associated, glomerulonephritis, sepsis-related, and other causes), as shown in **Figure 3**. All causes analyzed using the Kruskal–Wallis test showed a P value of 0.822. Individual etiologies related to TID and LOS were also analyzed using the Steel–Dwass–Critchlow–Fligner test (**Figure 3**).

DISCUSSION

In this cross-sectional study conducted at a tertiary hospital in São Paulo, patients with renal dysfunction admitted for treatment were evaluated to identify the variables that contributed to



RRT = renal replacement therapy. * Pearson´s correlation test.

Figure 2. Univariate analysis between age and time to initiation of dialysis in hospitalized patients.

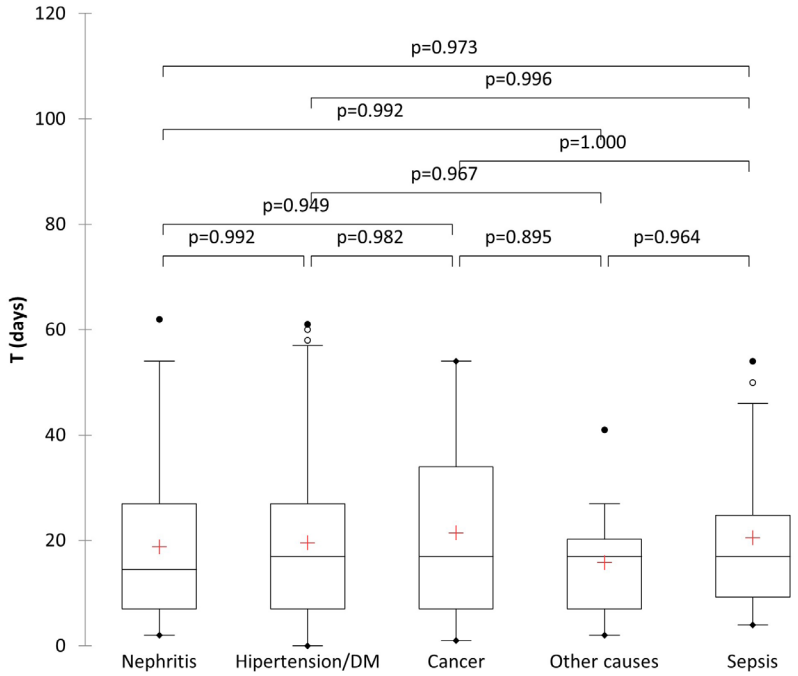
Table 2. Multivariate analysis between selected variables and time to initiate dialysis vs. length of stay

Variable	P
Age	0.226
Previous nephrologist consultation	0.442
Origin of the patient (ER x Community)	0.365
Kidney damage etiology	0.801

ER = emergency room.

their prognosis and their influence on TID and LOS. During the observation period, most admitted patients had previously consulted a nephrologist, and age was identified as the primary factor contributing to delayed TID in this cohort.

Over the past 50 years, CKD has transitioned from a neglected disease to a critical public health issue.[7] However, in developing countries, there is a lack of oversight regarding the management of renal disease, from screening to dialysis or organ transplantation. In Brazil, studies have reported a gap in primary care physicians' knowledge of kidney disease identification and diagnostic screening.[7-9] This situation is exacerbated in the Brazilian public health system (SUS) due to the uneven distribution of nephrologists across the country, with more developed regions and cities having a higher concentration of specialists, whereas less wealthy areas face delays in accessing nephrology care. The hospital where the study was conducted is located in São Paulo, Brazil's largest city, but in a less affluent neighborhood, receiving patients from distant regions with limited access to medical specialists. In our sample, many patients had not previously consulted a nephrologist. Moreover, the average LOS for patients with kidney damage was 44 d, which is consistent with the findings of Cruz et al., who



LOS = length of stay; TID = time to initiate dialysis; DM = diabetes; * Individual analysis performed using the Steel–Dwass–Critchlow–Fligner test; **Full model analysis performed using the Kruskal–Wallis test (P = 0.822).

Figure 3. Etiology of renal dysfunction and time to initiation of dialysis.

reported that late referral to a nephrologist was associated with higher mortality and prolonged hospital stays.[10]

A late indication for dialysis might influence the LOS. In this cohort, the hospital staff determined dialysis indications according to standard clinical and metabolic criteria. Neurological symptoms, such as uremia, refractory metabolic acidosis, hyperkalemia, and fluid overload, are the most critical clinical indications for urgent dialysis initiation. However, the indication for dialysis can be subjective, and other criteria, such as the patient's age, diuresis, and the intuition of a reversible cause of kidney damage might delay this decision. A strict clinical approach to renal dysfunction rather than early initiation of dialysis may increase the risk of an urgent start. A recent review showed that the cost of urgent dialysis was USD 6,092 per patient over 6 months.[11] In this cohort, 28.18% of the patients required urgent dialysis initiation during the observation period. As there was a significant proportion of patients without proper nephrology treatment before hospitalization, delayed TID negatively affected patients needing more time to stabilize and who lacked definitive vascular access, such as a venous fistula. From the data gathered, we identified a direct relation between longer LOS due to the late release of the outpatient hemodialysis bed and higher mortality, especially among older people. This finding was corroborated by Cruz et al., who reported that patients older than 70 years had a higher mortality rate when starting renal replacement therapy.[9]

This study has several strengths. It is the first Brazilian study to provide real-world evidence of delayed TID in an outpatient dialysis facility for hospitalized patients with end-stage renal disease. The leading causes of renal dysfunction in this cohort were consistent with the main etiologies of preventive care: arterial hypertension, diabetes, and sepsis, within the hospital environment. We did not have access to the individual costs for each patient to show the burden of delays in initiating external dialysis. This was a single-center study, and some findings might reflect the nephrology staff's standard of care practices, which could have impacted dialysis indications. Critical care patients and those who underwent elective surgery were not analyzed, as this was not the main objective of this study. Data were retrieved from the electronic medical records. However, the study team manually inserted the data, which could have caused some inconsistencies, even with a double-check safety procedure for each data insertion.

CONCLUSION

In summary, in this cross-sectional study, aging was positively correlated with late TID and longer LOS in patients hospitalized for renal disease. The number of external dialysis seats available for the public system must increase rapidly as the prevalence of CKD continues to rise in Brazil and worldwide. Despite being conducted in a single-center hospital, this study provides future directions for

a broader, multicenter evaluation to understand all the variables involved in reducing LOS and contributing to early discharge for end-stage renal disease patients. Moreover, it highlights the importance of primary care in renal function screening, thereby reducing the burden on these patients during hospital care.

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Changes in the prevalence of severe anxiety and depression symptoms and the associated factors in adults living in Manaus: a comparison of two cross-sectional studies conducted in 2015 and 2019

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ABSTRACT

BACKGROUND: Emotional distress increases, also affected by the setting.

OBJECTIVE: To estimate changes in prevalence of severe anxiety and depressive symptoms and associated factors.

DESIGN AND SETTING: This cross-sectional study included adults living in Manaus selected through a three-stage probability sampling in 2015 and 2019.

METHODS: This is an analysis of two surveys conducted. The outcomes were assessed by Generalized Anxiety Disorder 7-item (≥ 15 points) and Patient Health Questionnaire 9-item (≥ 20), and changes were tested by chi-square goodness-of-fit. Prevalence ratios (PR) with 95% confidence intervals (95%CI) were calculated by Poisson regression.

RESULTS: Severe anxiety symptoms increased from 3.3% (95%CI = 2.7–3.9) in 2015 (n = 3,479) to 8.7% (95%CI = 7.5–9.8) in 2019 (n = 2,321); severe depressive symptoms changed from 2.5% (95%CI = 2.0–3.0) to 8.5% (95%CI = 7.3–9.6). Variations were more pronounced in social vulnerability (P < 0.05). Outcomes were higher in women (anxiety: PR = 1.27; 95%CI = 1.20–1.34, depression: PR = 1.35; 95%CI = 1.27–1.44), low-income individuals (anxiety: PR = 1.90; 95%CI = 1.20–3.00, depression: PR = 1.98; 95%CI = 1.22–3.19), less educated individuals (anxiety: PR = 2.20; 95%CI = 1.16–4.18, depression: PR = 2.37; 95%CI = 1.23–4.60), and individuals with poor health status (anxiety: PR = 9.06; 95%CI = 6.72–12.21, depression: PR = 8.99; 95%CI = 6.67–12.12).

CONCLUSION: Severe anxiety and depression tripled in Manaus, potentially reflecting Brazilian socioeconomic crises.

INTRODUCTION

Mental health is influenced by social, economic, cultural, racial, psychological, and behavioral factors, which mediate suffering and can trigger disorders such as anxiety and depression.[1] From the onset of symptoms to the treatment of these conditions, individuals encounter numerous challenges, including limited access to specialists, a constrained therapeutic arsenal, and inadequate social care. These barriers can contribute to the chronicity of symptoms associated with anxiety and depression.[2]

The global prevalence of affective disorders is rising, with depressive states increasing by approximately 50% since the 1990s, predominantly affecting women.[3] In Brazil, depressive symptoms are associated with a high prevalence of non-communicable chronic diseases, as the daily limitations imposed by chronically ill exacerbate mental suffering, leading to depressive symptoms.[4]

Since 2016, Brazil has been experiencing increases in unemployment rate, income inequality, and reductions in public support for basic social programs due to ongoing economic and political crises.[5] These measures included reforms in the healthcare system and reductions in social spending.[6] In this social insecurity setting, stress and fear, among other feelings of restlessness, impair mental health at the individual and collective levels.[7]

The Brazilian Amazon is one of the country's least developed regions, with significant income inequality and limited research on mental health and its social effects.[8] In 2015, a survey was

carried out in the Manaus Metropolitan Region.[9] In 2019, another population-based survey was conducted exclusively in Manaus.[10] Anxiety and depressive symptoms affected over 20% of *Manauaras* adults in 2019.[11] Meanwhile, the prevalence was < 10% in the whole metropolitan area in 2015,[12,13] indicating an increase in mental suffering in this population. Comparing the population of the same city in these two periods would help identify the predictors of mental health disorders and assess the effects of the social context in the Brazilian Amazon.

OBJECTIVE

This study aimed to estimate the changes in the prevalence of severe anxiety and depressive symptoms from 2015 to 2019 and identify the factors associated with severe symptomatology among adults living in Manaus.

METHODS

Study design

Two cross-sectional population-based studies conducted in adults (≥ 18 years old) living in Manaus, Brazil, in 2015 and 2019 were analyzed. The 2015 survey examined the metropolitan area of Manaus and seven other cities. In the present analysis, the sample was restricted to adults residing in Manaus to enable comparison with the results of the 2019 survey, which focused exclusively in the capital.[14]

Setting

This study was conducted in Manaus, the capital of the state of Amazonas, which is the most economically and densely populated city in the state, housing over half of its inhabitants in 2018. In the same year, the state ranked fourth in terms of income inequality (Gini index 0.523) and had a high percentage of public healthcare demand (84%).[14] Manaus is one of the Brazilian cities with the largest gross domestic product (78 billion Brazilian reais, accounting for 1% of the gross national product in 2018). However, this wealth is unevenly distributed, resulting in significant social inequalities.[14]

Participants

Probabilistic sampling was conducted in three stages to select participants for both surveys. In the first stage, census tracts were randomly selected. In the second stage, households were chosen through systematic sampling. A number from 1 to 20 was randomly assigned to determine the first household to be visited, ensuring that 1 out of every 20 households was visited. All residents present in the household were registered in the electronic devices used for the interview. One participant was selected based on predefined quotas for age and sex according to the proportions estimated by the Brazilian Institute of Geography and Statistics for each time point to ensure population representativeness.[9,10]

Variables

The primary outcomes were the prevalence and severity of anxiety and depressive symptoms. The independent variables were sex (men or women), pregnancy (yes or no), age (18–24, 25–34, 35–44, 45–59, or ≥ 60 years), ethnicity (White [White and Asian] or Black [Black, Brown, and Indigenous]), the presence of a partner (yes or no), education (higher education or above, high school, elementary school, or less than elementary school), occupation (formal worker, informal worker, retired, student, or unemployed/housewife), social class (A/B, C, or D/E, where A refers to the wealthiest and E refers to the poorest based on the Brazilian Economic Classification Criteria of each year),[15,16] and self-reported health status (good, fair, or poor).

Data sources and measurement

A team of trained and experienced interviewers collected data from the participants using questionnaires preconfigured in the SurveyToGo software, with the aid of electronic devices (Tab3 SM-T110 Samsung® Galaxy, in 2015 and Intel TabPhone 710 Pro, in 2019). Data were collected offline and subsequently transmitted to a research database via the Internet.

Anxiety symptoms were assessed using the validated version of the Generalized Anxiety Disorder 7-item (GAD-7).[17,18] The questionnaire comprises seven items that assess the symptoms observed in the last two weeks, with a total score ranging from 0 to 21. The anxiety symptoms were categorized as minimal or none (0–4), mild (5–9), moderate (10–14), or severe (15–21).[19] A cut-off value of ≥ 10 points was used to indicate the presence of anxiety symptoms, with sensitivity and specificity greater than 80% compared with the mental health professionals' clinical diagnosis. Severe anxiety was defined as a GAD-7 score of ≥ 15.[20]

The validated version of the nine-item Patient Health Questionnaire 9-item (PHQ-9) was used to assess depressive symptoms.[21] Based on the instrument's nine questions, depressive symptoms were categorized as minimal or none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), or severe (20–27), with the total scores ranging from 0 to 27. A score of ≥ 10 points indicated the presence of depressive symptoms, with a sensitivity of 78% and a specificity of 87% (compared to the clinical diagnosis made by a psychiatrist).[22] Severe depressive symptoms were considered present if the final score of PHQ-9 was ≥ 20.[23]

Bias

To avoid biases related to the research instrument, several precautions were taken. The data were automatically tabulated by transmitting the questionnaires completed on the tablets to the online

database. Face-to-face interviews were conducted using validated instruments to measure the main outcomes and variables, which increased the response rate and data reliability. The questionnaire was pre-tested with 150 participants from various social levels to ensure comprehension. To allow reliability of data collection, part of interviews were audio recorded by the electronic device and 20% of interviews were audited by telephone.

Study size

The sample size was determined based on the population estimates for each period. In the 2015 survey, 4,000 of the 2,106,322 adult inhabitants were planned to be interviewed across the Manaus Metropolitan Region. This estimate was based on an anticipated 50% healthcare service usage, 95% confidence level, 2% absolute accuracy, and a design effect of 1.5.[9] In 2019, 2,300 interviews were planned considering the results of the previous study, which found that 20% of the participants reported seeking health services in the last 15 days, 2,145,444 adults living in Manaus and similar parameters to the previous survey.[10]

Statistical methods

The prevalence of severe anxiety and depressive symptoms and the corresponding 95% confidence intervals (95%CI) were estimated and described according to the independent variables. The differences in absolute (Δ) and relative (ratio) frequencies from 2015 to 2019 were calculated, and significance was assessed using the chi-square goodness-of-fit test. The outcomes were stratified by year, sex, and health status, and the Pearson's correlation coefficient (r) was estimated to examine the relationship between the GAD-7 and PHQ-9 scores.

A Poisson regression with robust variance was performed to assess the factors associated with severe anxiety and depressive symptoms. Prevalence ratios (PR) and 95%CI of severe anxiety and depression symptoms were calculated and adjusted for year of research, sex, and age, in separate models. All analyses employed a complex sampling design (*svy* command) and were performed using the Stata statistical package (version 12.4).

Ethics

Both surveys were approved by the Universidade Federal do Amazonas Research Ethics Committee (opinion letter No. 974,428 of March 3, 2015, and Certificate of Presentation for Ethical Assessment [CAAE]: 42203615.4.0000.5020; 2019: opinion letter No. 3,102,942 on December 28, 2018, and CAAE: 04728918.0.0000.5020). All participants signed an informed consent form prior to the interviews.

RESULTS

We included 5,800 participants (3,479 in 2015 and 2,321 in 2019). The prevalence of severe anxiety symptoms were 3.3% (95%CI = 2.7%–3.9%) in 2015 and 8.7% (95%CI = 7.5%–9.8%) in 2019. Similarly, the prevalence of severe depressive symptoms increased from 2.5% (95%CI = 2.0%–3.0%) in 2015 to 8.5% (95%CI = 7.3%–9.6%) in 2019. Comparisons between the 2019 with 2015 survey results suggested a relative increase in the prevalence of both severe anxiety and depressive symptoms (**Figure 1**).

The prevalence of severe anxiety symptoms was higher in women (4.8% in 2015 and 11.6% in 2019), those belonging to the lower social classes (4.3% in 2015 and 9.6% in 2019), and those with poor health (16.7% in 2015 and 31.7% in 2019). Severe depressive symptoms were more frequent in women (4.2% in 2015; 11.0% in 2019), individuals from the lower social classes (3.7% in 2015; 9.6% in 2019), and individuals with poor health (13.9% in 2015; 31.4% in 2019) (**Table 1**). Higher absolute

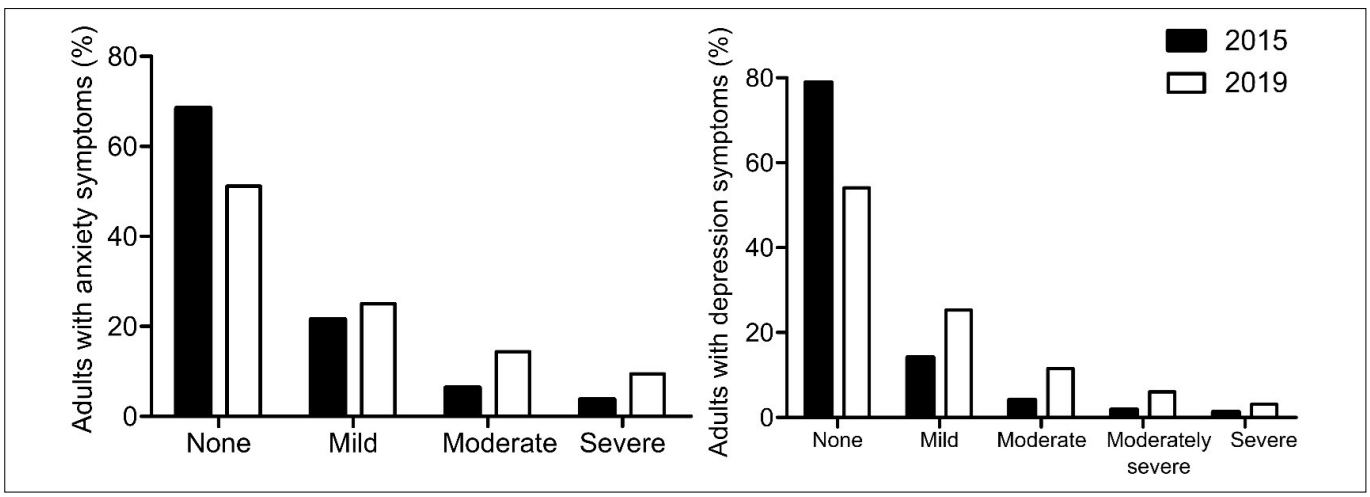


Figure 1. Distribution of anxiety and depression symptoms in adults living in Manaus, according to the severity, in 2015 (n = 3,479) and 2019 (n = 2,321).

changes (Δ) in the prevalence of severe anxiety and depressive symptoms were observed among women (anxiety and depression: 6.8%), individuals with lower educational levels (5.9% and 7.3%, respectively), and those with poor health status (15.0% and 17.5%). Conversely, the highest ratio of prevalence between 2015 and 2019 was observed in the youngest adults (5.8 and 6.6; **Table 1**). The prevalence rates of anxiety symptoms (of any severity) were 9.1% (95%CI = 8.2%–10.1%) in 2015 and 22.4% (95%CI = 20.7%–24.1%), in 2019. Meanwhile, depressive symptoms affected 6.3% (95%CI = 5.5%–7.1%) of the adults in 2015 and 19.9% (95%CI = 18.2%–21.5%) in 2019.

After adjustment, the prevalence of severe anxiety and depressive symptoms was significantly higher in 2019 in women (anxiety: PR = 1.27; 95%CI = 1.20–1.34, depression: PR = 1.35; 95%CI = 1.27–1.44), individuals with lower income (anxiety: PR = 1.90; 95%CI=1.20–3.00, depression: PR = 1.98; 95%CI = 1.22–3.19), and less educated individuals (anxiety: PR = 2.20; 95%CI = 1.16–4.18, depression: PR = 2.37; 95%CI = 1.23–4.60), and in those with worse health status (anxiety: PR = 9.06; 95%CI = 6.72-12.21, depression: PR = 8.99; 95%CI = 6.67–12.12) (**Table 2**). The prevalence of severe anxiety was also higher in individuals who only finished elementary education (PR = 1.96; 95%CI = 1.01–3.79) compared

Table 1. Main characteristics of the participants, prevalence, absolute and relative differences of severe anxiety and depression symptoms in Manaus, 2015 (n = 3,479) and 2019 (n = 2,321)

Variables	Total, n (%)		Severe anxiety symptoms, n (%)				Severe depressive symptoms, n (%)			
	2015	2019	2015	2019	Δ	Ratio	2015	2019	Δ	Ratio
Sex										
Men	1,623 (47.9)	1,088 (47.8)	26 (1.6)	59 (5.4)	3.8	3.4	11 (0.7)	61 (5.6)	5.0	8.4
Women	1,856 (52.2)	1,233 (52.2)	88 (4.8)	144 (11.6)	6.8	2.4	77 (4.2)	137 (11.0)	6.8	2.6
Pregnant										
No	1,657 (89.9)	1,091 (88.3)	79 (4.9)	131 (11.9)	7.1	2.4	66 (4.1)	125 (11.4)	7.3	2.8
Yes	199 (10.1)	142 (11.7)	9 (4.5)	13 (9.3)	4.8	2.1	11 (5.5)	12 (8.4)	2.9	1.5
Age group (years)										
18–24	716 (19.6)	405 (19.3)	11 (1.5)	35 (8.5)	7.0	5.8	10 (1.4)	37 (9.0)	7.7	6.6
25–34	1,010 (27.5)	586 (25.1)	29 (2.8)	41 (7.0)	4.2	2.5	28 (2.7)	44 (7.5)	4.8	2.8
35–44	744 (22.4)	553 (22.9)	24 (3.2)	53 (9.5)	6.3	3.0	13 (1.7)	52 (9.3)	7.6	5.4
45–59	674 (20.2)	526 (21.2)	31 (4.6)	53 (10.0)	5.4	2.2	24 (3.6)	48 (9.1)	5.5	2.5
≥ 60	335 (10.3)	251 (11.6)	19 (5.7)	21 (8.4)	2.8	1.5	13 (3.9)	17 (6.8)	2.9	1.8
Ethnicity										
White	674 (19.3)	349 (15.1)	19 (2.8)	34 (9.6)	6.8	3.4	17 (2.5)	28 (8.0)	5.5	3.2
Black	2,805 (80.7)	1,972 (85.0)	95 (3.4)	169 (8.5)	5.1	2.5	71 (2.5)	170 (8.5)	6.0	3.4
Marital status										
Without partner	1,636 (47.0)	1,005 (44.1)	43 (2.7)	89 (8.7)	6.0	3.2	40 (2.5)	99 (9.7)	7.2	4.0
With partner	1,843 (53.0)	1,316 (56.0)	71 (3.8)	114 (8.6)	4.8	2.2	48 (2.6)	99 (7.5)	4.9	2.9
Educational level										
Higher education or above	131 (3.8)	153 (6.5)	2 (1.5)	8 (5.3)	3.8	3.5	3 (2.2)	7 (4.7)	2.5	2.2
High school	1,695 (48.3)	1,171 (50.4)	37 (2.2)	91 (7.7)	5.5	3.5	28 (1.6)	89 (7.6)	5.9	4.6
Elementary school	562 (16.0)	432 (18.9)	20 (3.6)	41 (9.4)	5.8	2.6	16 (2.8)	38 (8.8)	6.0	3.1
Less than elementary	1,091 (31.9)	565 (24.2)	55 (5.0)	63 (10.9)	5.9	2.2	41 (3.8)	64 (11.1)	7.3	2.9
Economic classification										
A/B	555 (16.0)	282 (12.2)	8 (1.4)	14 (5.0)	3.6	3.5	6 (1.0)	14 (5.0)	3.9	4.8
C	2,006 (57.4)	1,244 (53.6)	66 (3.4)	112 (8.9)	5.6	2.7	47 (2.4)	106 (8.5)	6.1	3.6
D/E	918 (26.5)	795 (34.1)	40 (4.3)	77 (9.6)	5.2	2.2	35 (3.7)	78 (9.6)	5.9	2.6
Occupation										
Formal job	651 (18.8)	419 (17.9)	13 (2.0)	36 (8.6)	6.6	4.3	7 (1.1)	30 (7.2)	6.1	6.7
Informal job	978 (28.5)	661 (28.1)	27 (2.7)	39 (5.8)	3.1	2.2	18 (1.8)	48 (7.3)	5.5	4.1
Retired	271 (8.2)	162 (7.2)	20 (7.5)	18 (10.9)	3.5	1.5	14 (5.2)	13 (7.8)	2.6	1.5
Student	315 (8.7)	124 (5.7)	5 (1.6)	9 (7.1)	5.5	4.5	5 (1.5)	9 (7.2)	5.6	4.7
Unemployed/housewife	1,264 (35.7)	955 (41.0)	49 (3.9)	101 (11.0)	7.0	2.8	44 (3.5)	98 (10.2)	6.6	2.9
Health status										
Good	2,243 (64.1)	1,498 (64.8)	33 (1.5)	53 (3.5)	2.0	2.4	21 (0.9)	60 (4.0)	3.1	4.5
Fair	1,012 (29.3)	671 (28.8)	44 (4.3)	102 (15.1)	10.9	3.5	36 (3.5)	90 (13.3)	9.8	3.8
Poor	224 (6.6)	152 (6.5)	37 (16.7)	48 (31.7)	15.0	1.9	31 (13.9)	48 (31.4)	17.5	2.3
Total	3,479 (100)	2,321 (100)	114 (22.5)	203 (50.3)	27.9	7.8	88 (18.3)	198 (48.7)	30.4	10.6

with those who achieved a higher education. Age, pregnancy in the previous year, ethnicity, the presence of a partner, and occupation were not associated with the outcomes (**Table 2**).

Comparison between the 2019 and 2015 survey results revealed an increase in the prevalence of severe anxiety and depression symptoms, with a moderate to high correlation between the GAD-7 and PHQ-9 scores in 2015 (r = 0.726) and 2019 (r = 0.732; **Figure 2**).

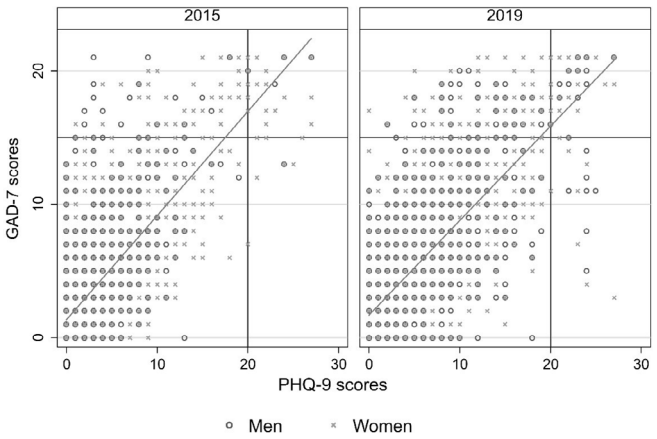
DISCUSSION

In 2019, the prevalence of severe anxiety and depression increased from 3% in 2015 to 9%. This increase was more pronounced in socioeconomically disadvantaged individuals, such as those with lower educational levels. The prevalence of severe anxiety and depressive symptoms was notably higher in 2019 among women, individuals with poor health status, and middle-class people. Pregnant women and informal workers had a lower prevalence of severe anxiety.

Table 2. Unadjusted and adjusted prevalence ratios (PR) with 95% confidence intervals (95%CI) of severe anxiety and depression symptoms by independent variables

Variables	Severe anxiety symptoms				Severe depressive symptoms			
	PR unadjusted (95%CI)	P value	PR adjusted (95%CI)	P value	PR unadjusted (95%CI)	P value	PR adjusted (95%CI)	P value
Year								
2015	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001
2019	2.63 (2.09–3.28)		1.27 (1.20–1.34)		3.35 (2.62–4.30)		1.35 (1.27–1.44)	
Age group (years)								
18–24	1.00		1.00		1.00		1.00	
25–34	0.95 (0.66–1.39)		0.96 (0.66–1.39)		0.95 (0.66–1.38)		0.96 (0.67–1.38)	
35–44	1.27 (0.89–1.83)	0.045	1.25 (0.87–1.78)	0.094	1.07 (0.74–1.56)	0.733	1.05 (0.73–1.51)	0.733
45–59	1.46 (1.02–2.08)		1.42 (1.00–2.02)		1.22 (0.85–1.75)		1.18 (0.82–1.69)	
≥ 60	1.40 (0.92–2.14)		1.30 (0.85–1.97)		1.03 (0.65–1.62)		0.94 (0.60–1.49)	
Sex								
Men	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001	1.00	< 0.001
Women	2.32 (1.81–2.98)		2.31 (1.81–2.95)		2.38 (1.83–3.09)		2.38 (1.83–3.09)	
Pregnant								
No	1.00	0.431	1.00	0.905	1.00	0.661	1.00	0.940
Yes	0.84 (0.54–1.30)		0.97 (0.62–1.53)		0.91 (0.59–1.40)		0.98 (0.62–1.55)	
Ethnicity								
White	1.00	0.862	1.00	0.767	1.00	0.401	1.00	0.815
Black	1.03 (0.77–1.38)		0.96 (0.72–1.28)		1.15 (0.83–1.58)		1.04 (0.76–1.42)	
Marital status								
Without partner	1.00	0.336	1.00	0.747	1.00	0.178	1.00	0.045
With partner	1.12 (0.89–1.39)		1.04 (0.83–1.30)		0.85 (0.68–1.07)		0.78 (0.62–0.99)	
Educational level								
Higher education or above	1.00		1.00		1.00		1.00	
High school	1.29 (0.68–2.45)	0.006	1.51 (0.80–2.84)	0.007	1.27 (0.66–2.42)	0.014	1.48 (0.78–2.82)	0.002
Elementary school	1.71 (0.88–3.33)		1.96 (1.01–3.79)		1.64 (0.83–3.22)		1.85 (0.94–3.63)	
Less than elementary	1.93 (1.02–3.66)		2.20 (1.16–4.18)		1.87 (0.97–3.58)		2.37 (1.23–4.60)	
Economic classification								
A/B	1.00		1.00		1.00		1.00	
C	2.04 (1.30–3.19)	< 0.001	1.81 (1.16–2.82)	0.021	1.94 (1.21–3.10)	< 0.001	1.71 (1.07–2.73)	0.019
D/E	2.44 (1.54–3.86)		1.90 (1.20–3.00)		2.54 (1.57–4.09)		1.98 (1.22–3.19)	
Occupation								
Formal job	1.00		1.00		1.00		1.00	
Informal job	0.81 (0.56–1.16)		0.72 (0.50–1.04)		1.10 (0.74–1.64)		1.00 (0.67–1.49)	
Retired	1.71 (1.13–2.59)	< 0.001	1.58 (0.96–2.60)	0.115	1.55 (0.95–2.53)	0.002	1.60 (0.88–2.88)	0.482
Student	0.73 (0.40–1.32)		0.74 (0.39–1.41)		0.93 (0.50–1.73)		0.87 (0.46–1.65)	
Unemployed/housewife	1.42 (1.03–1.95)		1.00 (0.72–1.39)		1.73 (1.21–2.47)		1.19 (0.82–1.72)	
Health status								
Good	1.00		1.00		1.00		1.00	
Fair	3.92 (3.01–5.11)	< 0.001	3.79 (2.90–4.96)	< 0.001	3.37 (2.55–4.45)	< 0.001	3.37 (2.56–4.44)	< 0.001
Poor	9.64 (7.25–12.82)		9.06 (6.72–12.21)		9.02 (6.72–12.11)		8.99 (6.67–12.12)	

PR = prevalence ratios; CI = confidence interval.



Vertical and horizontal lines indicate the threshold for severe symptoms for each outcome.

Figure 2. Depression and anxiety symptom scores from the Generalized Anxiety Disorder 7-item (GAD-7) and Patient Health Questionnaire 9-item (PHQ-9), for each year, according to sex.

Our study was not primarily designed as a comparative analysis between the two surveys. The similar methodologies employed in each year enabled us to compare the changes in the study's outcomes in these two distinct periods. Probabilistic sampling was adopted in both surveys to minimize selection bias, but all measurements were based on self-reports. Anxiety and depressive symptoms were assessed using two validated tools with strong psychometric properties that allow reliability when measuring these outcomes.[18,21] Conservative cut-off points with higher sensitivity and specificity were used to determine the presence of anxiety and depressive symptoms.[20,24,25] The present study reflects the status before the COVID-19 pandemic, which has since had a significant impact on mental health.[26] Despite these limitations, our analysis provides valuable insights into the early effects of austerity measures on mental health in Manaus.

The prevalence of severe anxiety and depressive symptoms in our study, particularly in the 2019 survey, was higher than that reported in other countries. For example, a 2011–2014 study of 5,355 German adults reported a prevalence of severe anxiety symptoms of 4%.[27] Similarly, an analysis of 13,829 adults living in Australia in 2020 showed a lower prevalence of severe depressive symptoms (4.5%).[28,29] A representative survey from the United Kingdom (n = 17,152), conducted in 2014, reported severe depressive symptoms in only 3.3% of the population.[30]

The increase in the prevalence of severe anxiety and depressive symptoms was more pronounced among vulnerable individuals. In 2018, a cross-sectional study conducted in the United States with 22,682 adults found that financial concerns exacerbated mental health issues, particularly among the unemployed and low-income families due to daily exposure to stressors and the higher vulnerability of this group to stress.[31]

Our findings also indicate a higher prevalence of severe anxiety and depression in women than in men. Globally, women have consistently shown a higher prevalence and burden of depression and anxiety from 1990 to 2019.[32] The psychosocial risk factors that can contribute to anxiety and depression are more frequent in women, such as domestic violence, gender harassment, employment and income inequalities, educational disparities, which increases stress.[33,34]

Symptom reporting is closely associated with the perception of poor health status, with a higher prevalence of symptoms correlating with greater dissatisfaction with one's health conditions.[35] Severe anxiety and depressive symptoms were higher among individuals with poorer self-reported health. A study of 1,241 patients from 28 primary care units in Spain in 2014–2017, using the same assessment tools as our research, found that anxiety and depressive symptoms were associated with lower quality of life.[36] The overlapping diagnoses of mental disorders significantly worsens the quality of life.[37] In a South Korean cohort including 1,204 community-dwelling older adults with anxiety and depression followed from 2001 to 2003, both conditions were associated with a higher incidence of comorbidities.[38] The simultaneous presence of anxiety and depression exacerbated the physical disorders and disabilities after a 2-year follow-up period.[38]

Middle-class individuals exhibited a high prevalence of severe anxiety and depression. However, the poorest individuals had a higher probability of experiencing these conditions. A 2013 study conducted in 2,229 German adults found a significant correlation between socioeconomic status and clinically significant anxiety and severe anxiety.[39] Another German cohort study that followed 12,484 adult individuals for 2.5 years identified socioeconomic status as a strong predictor of elevated depressive symptoms among individuals without these conditions at baseline.[40] Depression and anxiety may also result in economic consequences and financial burdens. Individuals with lower socioeconomic status experience more depression- and anxiety-related absences from work.[41] This mental distress can amplify social disadvantage, creating a vicious cycle where poorer individuals experience limited access to better employment opportunities and higher incomes, thus exacerbating the burden of mental disorders.[42]

Informal employment does not necessarily result in worse health outcomes but can expose underlying vulnerabilities.[43] Informal workers have a lower prevalence of severe anxiety than formal workers. These results contrast with previous analyses, which suggest that informal work is associated with poorer health outcomes compared with formal work, particularly in low- and middle-income countries.[44,45] A cross-sectional study of 8,680 non-agricultural workers from Spanish-speaking Central American countries, conducted in 2011, found a significant association between informal work and poor mental health.[46] A previous analysis of the

2015 survey in the Manaus Metropolitan Region indicated that the health-related quality of life (measured using the European Quality of Life 5-Dimensions 3-Level instrument, which includes an anxiety/depression dimension) was lower among informal workers than among formal workers.[47] The lack of labor and social protections may lead to poor working conditions, irregular income opportunities, barriers to healthcare access, and vulnerability to serious health shocks.[48]

CONCLUSIONS

The prevalence of severe anxiety and depression symptoms tripled during the study period. The observed increase in mental distress may reflect the contextual changes, such as rising unemployment and difficulties in accessing health services. Positive variations in both outcomes were particularly pronounced among the most vulnerable individuals, underscoring the pivotal influence of social inequalities on the prevalence of mental disorders in the region. Ideally, further research should prospectively investigate the incidence of these outcomes and triggering factors that may increase mental distress in Manaus. Societal and health services improvements are also needed to address mental health comprehensively.

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Assessment of detraining through a six-minute walk test in patients with heart disease

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ABSTRACT

BACKGROUND: Detraining can partially or completely reduce training-induced metabolic adaptations. However, the duration for which the rehabilitation effects persist after detraining, especially in patients with heart disease, remains unclear.

OBJECTIVES: To evaluate the principle of reversibility/detraining in patients with heart disease via the 6-minute walk test (6MWT) after a period of rest.

DESIGN AND SETTING: A retrospective cohort study developed at the Rehabilitation Center of the Universidade Federal do Triângulo Mineiro in Uberaba/MG, Brazil.

METHODS: This clinical, retrospective longitudinal study involved 20 patients with heart disease who underwent 5 months of supervised cardiac rehabilitation (CR). The mean age of participants was 64.05 ± 9.25 years. The initial rehabilitation was followed by an interruption period and rehabilitation for another 5 months. Functional capacity was assessed using the 6MWT.

RESULTS: In the specific analysis of the distance covered, values of P = 0.03 and P = 0.01 were obtained on comparing post-training (669.64 ± 58.80 meters) with post-detraining (640.82 ± 101.23 meters) and post-detraining with post-retraining (650.82 ± 96.28 meters), respectively. No significant difference was observed for the comparison between training and retraining (P = 0.83).

CONCLUSION: Cardiovascular rehabilitation positively stimulates functional capacity, whereas detraining significantly reduces it. The 6MWT is effective in measuring changes in physical capacity.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, accounting for a 21.1% surge in total deaths from 2007 to 2017.[1,2] Primary prevention strategies for CVDs involve lifestyle modification (e.g., smoking cessation and increased physical activity) and drug therapy.[3]

Epidemiological findings have demonstrated an association between physical inactivity and a higher prevalence of most CVD risk factors, including dyslipidemia, high blood pressure (BP), metabolic syndrome, obesity, and type 2 diabetes.[4]

Cardiovascular rehabilitation (CR) is a chronic disease management program that provides structured exercises, patient education to promote behavioral changes, and psychological support to lessen the burden of risk factors and optimize secondary prevention.[5] Notably, CR increases functional capacity with continued gains over the following months.[6]

Continuous rehabilitation through physical exercise is vital for patients with heart disease to reduce limitations and ensure a better quality of life. The suspension or reduction of this training can cause deconditioning, affect performance, and decrease physical capacity.[7]

This interruption, called the principle of reversibility or detraining (DT), can occur due to an injury, aging, voluntary discontinuation, and/or as part of the annual training cycle to train for other skills.[8]

DT can be assessed through the 6-minute walk test (6MWT). Notably, disease progression and the risk of hospitalization or mortality can be assessed by measuring the distance covered,[9,10] and the variables measured in the 6MWT exhibit a strong correlation with the cardiopulmonary test, which is the gold standard for assessing physical capacity.[11] Although many studies have examined the effects of CR in patients with heart disease, the duration for which the rehabilitation effects

persist after the DT stage remains unclear. In addition, studies on DT have been mainly conducted on the athlete population than the non-athlete population.[12]

Therefore, more studies, especially involving patients with heart disease, considering both adherence and the importance of continuing physical training to chronically maintain the benefits achieved via training, are necessary. DT may lead to a partial or complete reduction in training-induced physiological adaptations and performance.

OBJECTIVES

The present study primarily aimed to assess the principle of reversibility/detraining via the 6MWT in patients with heart disease undergoing CR after a period without training. We also reassessed the patients after a new training period.

METHODS

This retrospective study involved patients assisted at a rehabilitation center. This center operates in different areas, including physiotherapy rehabilitation, medical screening consultations, occupational therapy, nutrition, nursing, and psychology. The participants were selected from a convenience sample of 20 patients who underwent CR.

Patients with CVDs of both sexes, aged > 18 years, who regularly participated in our institution's CR program for at least 5 consecutive months were included in the study. Patients who did not undergo the 6MWT and those with a participation frequency of < 80% were excluded from the study.

The patients included in this retrospective analysis followed the institutional protocol of the CR program, as follows: initially, all program patients were evaluated by a cardiologist specializing in ergometry and rehabilitation who, following a thorough clinical assessment, including the review of complementary examinations and medication optimization, when necessary, performed a conventional limited physical exertion ergometric test. This test was conducted by a cardiologist before the patient was enrolled in the rehabilitation program to assess signs and symptoms during physical exertion, cardiovascular risk classification, and the initial prescription of physical training intensity based on heart rate (HR). Subsequently, all patients included in our rehabilitation program underwent follow-up re-evaluations through the 6MWT whenever they were about to interrupt the program for any reason or were progressing to the next phase.

All patients were explained about the study, and signed informed consent was obtained from all participants with consent to allow the use of the results of their evaluations. The study was approved by the Research Ethics Committee of the Universidade Federal do Triângulo Mineiro (UFTM) (protocol 3.378.424; 06/07/2019).

Evaluation Period

Three evaluations were performed, as follows:

- First evaluation (post-training): At the end of 5 months of CR (n = 20).
- Second evaluation (post-DT): After 45 days of interruption, with no loss of the sample (n = 20).
- Third assessment (post-retraining): At the end of the 5-month rehabilitation period (retraining period) involving individuals who were able to attend and were actively attending the program (n = 11) (**Figure 1**). Of the 20 patients, 9 were excluded from the study because they did not adhere to the treatment or did not show up for evaluation.

Therefore, the study was divided into two phases. The first phase involved the assessment of the effect of detraining on the physical capacity of the patient, measured by comparing the distance covered in the post-training and post-DT tests after the second evaluation (n = 20). The second phase involved comparing the distance covered at three time points: post-training, post-DT, and post-retraining after the third evaluation (n = 11).

Study Protocol

Cardiovascular rehabilitation

The CR lasted 60 minutes, as follows: a warm-up characterized by stretching large muscle groups (10 minutes); aerobic conditioning in ergometers, such as a treadmill or bicycle (30 minutes); peripheral muscular resistance training of the upper and lower limbs using dumbbells and anklets (10 minutes); and ending with a cool-down (10 minutes). The conditioning intensity was determined through an ergometric test, with 60–80% of the reserve HR of the maximum HR reached in the test calculated using the Karvonen method. This test was performed routinely at the rehabilitation center for all individuals prior to the start of rehabilitation.

During the 45-day interruption of the CR program, patients were advised to maintain their usual activities and were counseled regarding the benefits of physical training. However, unsupervised training was not prescribed during this period.

Six-minute walk test

The 6MWT was always performed in the morning, and patient information, including registration number, sex, height and weight (for calculating the body mass index [BMI]), age, waist circumference, BP, and HR, was collected.

Data were collected from the medical records of the 6MWT, which is routinely performed at our rehabilitation center, prioritizing the same evaluator to guarantee the reliability of the test. The test was performed in accordance with the guidelines of the

American Thoracic Society,[13] requiring a corridor with a minimum length of 30 m free of human circulation, two cones to delimit the route, and a stopwatch to record the time. The participants were instructed to walk on the track as quickly as possible for 6 minutes. Before performing the test, the patients rested for at least 10 minutes, after which resting BP was evaluated using a Bic aneroid sphygmomanometer and Littmann Classic 3m stethoscope, and resting HR was evaluated using a Polar heart rate monitor, model FS2. The patients were given instructions on how to perform the test.

The patients underwent two tests with a minimum interval of 15 minutes. Notably, the test with the greatest distance covered in 6 minutes was considered for rest and normalization of vital data. After performing the test, the distance walked, defined as the maximum distance that the patient was able to cover during the test, was evaluated, along with the level of effort using the Borg Scale, BP of recovery, and HR of recovery immediately after completion. Notably, two measurements were taken at 2 and 4 minutes after the test was interrupted, and the predicted distance covered by each patient was calculated.[14]

Statistical Analysis

Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, New York, United States). Descriptive analysis was performed by calculating the central tendency (mean and median) and dispersion (standard deviation [SD]). The Shapiro–Wilk test was used to verify the normality of the data. Paired Student's t-test and Wilcoxon test were used for variables with normal and non-normal distributions, respectively. The Friedman test with multiple comparisons of the averages of orders was used to compare the variables at specific time points (post-training, post-DT, and post-retraining). The significance level was set at 5%.

RESULTS

Twenty individuals who underwent CR participated in this study. The mean age was 64.1 ± 9.3 years, with a prevalence of 70% and 30% in males (n = 14) and females (n = 6), respectively. The most frequent comorbidity was systolic hypertension (70%, n = 14), followed by acute myocardial infarction (45%, n = 9). Notably, only 5% (n = 1) of the participants were smokers, and 25% (n = 5) have smoked in the past (**Table 1**).

No sample loss occurred between the post-training and post-detraining periods. A significant reduction was observed in HR at rest (P = 0.04) and distance covered (P = 0.02; **Table 2**).

During retraining, 9 patients were dropped out owing to their absence from rehabilitation, and 11 patients finally participated in all stages of data collection. A significant difference was only observed in the distance covered when comparing the results of the post-training, post-DT, and post-retraining periods (n = 11, Friedman test, P = 0.03; **Table 3**). Comparisons of the training period with post-DT and post-DT with post-retraining exhibited P = 0.03 and P = 0.01, respectively, in the specific analysis of the distance covered. No significant difference was observed between the post-training and post-retraining periods (P = 0.83).

DISCUSSION

The results of the present study revealed that the distance covered in the 6MWT was an effective parameter for documenting the reduction in physical capacity after a 45-day period of interruption of supervised training in patients with CVD. Additionally, the individuals reattained the pre-interruption training parameter values after a period of 5 months of retraining.

Regular exposure to long-term exercise (physical training) promotes a set of morphological and functional adaptations involving intrinsic and extrinsic mechanisms of the heart, thus increasing the capacity of the body to respond to exercise stress.[15] Furthermore, regular physical training can promote various adaptations, including the growth, proliferation, and function of cardiomyocytes; mitochondrial biogenesis; improved lipid and glucose metabolism; changes in the morphology and function of the microcirculation; prevention of cardiac fibrosis; control of systemic and cardiac inflammation; beneficial changes in the microbiome; and positive adaptations in all body systems.[16] Conversely, an interruption or reduction of this training leads to a deconditioning process, with a reduction in the gains obtained.[7]

Table 1. Patient characteristics (n = 20)

Variables	P value
Age, years	64.1 ± 9.3
Sex	n (%)
Female	6 (30.0)
Male	14 (70.0)
Comorbidities/intervention	
Hypertension	14 (70.0)
Acute myocardial infarction	10 (50.0)
Coronary transluminal angioplasty	10 (50.0)
Cardiomyopathy	7 (35.0)
Diabetes mellitus	6 (30.0)
Dyslipidemia	6 (30.0)
Familial hypercholesterolemia	5 (25.0)
Previous smoking	5 (25.0)
Myocardial revascularization surgery	3 (15.0)
Arterial fibrillation	2 (10.0)
Obesity	2 (10.0)
Heart valve diseases	2 (10.0)
Angina	2 (10.0)
Hypothyroidism	1 (5.0)
Left ventricular aneurysm	1 (5.0)
Infective endocarditis	1 (5.0)
Metabolic syndrome	1 (5.0)
Smoker	1 (5.0)
Physical activity on vacation	6 (30.0)

Table 2. Comparison of variables between post-training and post-DT (n = 20)

Variables	Post-training	Post-DT	P value
BMI (Kg/m²)	28.3 ± 5.5	28.4 ± 5.6	0.69
Abdominal circumference (cm)	98.4 ± 11.0	94.55 ± 22.95	0.76
SP rest (mmHg)	121. 5 ± 15.0	111.5 ± 16.3	0.07
SP recovery (mmHg)	138.5 ± 32.2	138.5 ± 25.4	1
DP rest (mmHg)	84.5 ± 15.4	83.0 ± 10.3	0.95
DP recovery (mmHg)	84.0 ± 9.9	85.0 ± 9.5	0.52
HR rest (bpm)	72.7 ± 11.8	68.6 ± 9.1	**0.04***
HR recovery (bpm)	108.7 ± 18.1	107.7 ± 19.7	0.71
Distance covered (m)	618.9 ± 94.9	583.6 ± 120.4	**0.02***
Borg effort scale	2.5 ± 0.9	2.8 ± 0.9	0.08
Predicted distance covered (m)	505.8 ± 75		--

SD = standard deviation; BMI = body mass index; SP = systolic pressure; DP = diastolic pressure; HR = heart rate; rest = evaluated before the test; recovery = evaluated at the end of the test; *P < 0.05.

Table 3. Comparison of variables among post-training, post-DT, and post-retraining (n = 11)

Variables	Post-training	Post-DT	Post-retraining	P-value
BMI (Kg/m²)	27.2 ± 2.9	27.1 ± 2.9	27.4 ± 2.6	0.67
Abdominal circumference (cm)	95.4 ± 5.8	89.3 ± 27.4	94.0 ± 6.0	0.35
SP rest (mmHg)	122.7 ± 15.6	115.5 ± 12.9	120.9 ± 19.7	0.15
SP recovery (mmHg)	137.3 ± 37.2	140.0 ± 29.7	140.5 ± 36.1	0.64
DP rest (mmHg)	89.1 ± 18.1	84.6 ± 5.2	79.1 ± 8.3	0.12
DP recovery (mmHg)	86.4 ± 8.1	88.2 ± 4.0	80.0 ± 12.6	0.07
HR rest (bpm)	71.6 ± 13.4	65.7 ± 9.2	73.1 ± 11.2	0.21
HR recovery (bpm)	109.5 ± 20.4	109.0 ± 19.1	112.0 ± 25.0	0.92
Distance covered (m)	669.6 ± 58.8*	640.8 ± 101.2	650.8 ± 96.3#	**< 0.05**
Borg effort scale	2.4 ± 0.8	2.6 ± 0.8	2.1 ± 1.4	0.33

SD = standard deviation; BMI = body mass index; SP = systolic pressure; DP = diastolic pressure; HR = heart rate; rest = evaluated before the test; recovery = evaluated at the end of the test; Friedman test *P = 0.03 compared withpost-DT, and #P = 0.01 in compared withpost-DT.

According to the World Health Organization,[17] approximately 600 million people exhibit high BP, which may increase by 60% by 2025. Notably, this is consistent with the results of the present study, wherein the most frequent comorbidity was systolic arterial hypertension (70%, n = 14). According to the 2017 Surveillance System of Risk and Protective Factors for Chronic Diseases by Telephone Survey, the prevalence of self-reported hypertension increased from 22.6% in 2006 to 24.3% in 2017.[18] Notably, reducing salt intake and encouraging physical activity and healthy eating are the most effective measures to reduce BP.[19]

Our findings revealed a significant decrease (P = 0.02) in the distance covered after the initial detraining (from 618.9 ± 94.9 meters to 583.6 ± 120.4 meters), indicating a loss in the functional capacity of the individual acquired through CR. This result corroborates the findings of the study by Seemann et al.,[20] involving the assessment of the influence of detraining in older women who underwent a functional gymnastics program, which reported a decrease in performance, as evaluated through the 6MWT, after 3 months of interruption in the functional gymnastics sessions.

Detraining occurs quickly, even after a few weeks of interruption, along with significant reductions in the ability to perform work and almost total loss after a few months.[21] Additionally, some factors, such as the decline in cardiac output, arteriovenous difference, oxidative enzymes, hemoglobin concentration, density of myocytic mitochondria, and muscle capillarization, occurring alongside detraining may contribute to the reduction in aerobic fitness.[22,23]

According to Sousa et al.,[24] 8 weeks of aerobic and resistance training are sufficient to verify improvements, whereas only 4 weeks of detraining results in a marked reduction in physical performance, with the variables returning to their initial values. These results align with those of other studies, which reported that training-induced gains can be compromised with a short-term detraining period (6 weeks), leading to a decrease in performance and return to baseline values.[25,26] This information can be useful for health professionals to encourage individuals not to interrupt training, as the acquired capacities are lost and interfere with their physical fitness.

Despite detraining, the patients covered a good distance in the 6MWT. The average predicted distance covered by the patients was 505.8 ± 75 m, with the distance covered in the post-training test being 125.5% higher than predicted. Similarly, the distance covered in the post-DT test was also higher than predicted (115.5%), despite significantly lower values than post-training.

This result highlights that a 45-day period without supervised physical training is sufficient to significantly reduce physical capacity

in patients with CVD participating in a CR program. However, patients could still cover a good distance (greater than the predicted distance) in 6MWT.

In this study, we calculate the predicted distances using the formula described by Enright and Sherrill.[14] However, other formulae are also available in the literature. Iwama et al.,[27] in their study involving 134 healthy Brazilians of both sexes, aged between 13 and 84 years, described an equation to predict the distance covered and documented the existence of variances among the other formulas described in the literature.

However, we used the equation by Enright and Sherrill[14] in our study based on another study that tested this formula in a population of Brazilian adults with cardiac comorbidities. Moreover, Costa et al.[28] documented a significant correlation between the actual distance covered and the distance estimated using this equation.

In the present study, no significant difference was observed (P = 0.83) on comparing the distance walked after the training period (669.6 ± 58.8 meters) with the distance walked at the end of the retraining (650.8 ± 96.3 meters). Although the results did not return to the initial values, the functional capacity lost during the detraining period was recovered after 5 months of training.

Lee et al.,[29] on comparing functional fitness in the older individuals 12 months after training, 12 months after detraining, and 3, 6, and 9 months after retraining, found improvement in aerobic resistance post-training, whereas functional fitness of the participants decreased by 16.59% post-detraining. Notably, a refreshment period of ≥ 9 months was necessary to gradually recover the post-training condition. A study by Tokmakidis et al.,[30] involving combined training (aerobic and strength) for 9 months, followed by 3 months of detraining and 9 months of retraining, revealed that the discontinuation of exercise also led to negative changes; however, all beneficial adaptations were restored during the retraining period.

In the present study, functional capacity in patients with CVD was increased after 5 months of rehabilitation (P = 0.01), as evidenced by an increase in the distance covered post-DT (640.8 ± 101.2 meters) than post-retraining (650.8 ± 96.3 meters). These findings align with the findings of Silva et al.,[31] who compared the functional capacity of patients with cardiac disease before and after a 60-minute training for 8 weeks, totaling 16 sessions. Based on the 6MWT results, conventional CR positively influenced the physical capacity of individuals.

The study of Lima et al.,[32] investigating the effects of a 12-week aerobic training program involving moderate-intensity aerobic activities (warm-up, stretching, walking, stretching, and relaxing) for 50 minutes on the functional capacity of sedentary women with hypertension during the menopausal period, revealed an increase in the distance covered in the 6MWT after the practice period. Therefore, aerobic training may improve functional capacity. Bustamante et al.,[33] through a survey including 277 individuals who were integrated into phase II of CR, which lasted 36 sessions (approximately 12 weeks), revealed a significant improvement of 10% (mean, 56.4 meters) in the distance covered in the 6MWT.

Although physical training improves maximal aerobic power, it does not significantly modify maximal HR. Notably, patients undergoing aerobic training achieve the same maximum HR as before training, but more intense efforts are required to reach maximum HR.[34]

Evaluating the effects of detraining is challenging, and consensus remains lacking in the literature owing to different types of training with different intensities, frequencies, and durations. Notably, divergent findings have been reported from similar studies, indicating the existence of many variables that can influence the final result. Consequently, further studies evaluating different detraining times in patients with cardiac disease are necessary to better understand the changes in functional capacity in this population.

The results of the present study demonstrate that the 6MWT, a simple and low-cost tool, is effective for training and detraining assessments. Moreover, as the 6MWT has shown a strong correlation with cardiopulmonary exercise testing,[11,35] which is considered the gold standard for assessing physical capacity, the 6MWT becomes an effective tool for serial evaluations. Notably, a small sample (n = 20) is one limitation of this study, with a more pronounced decrease in the sample size following the loss of nine participants over the 5-month retraining period.

CONCLUSION

Detraining reduced the training-induced gains in the study participants, negatively influencing the functional capacity of patients with CVD. The 6MWT was effective in measuring changes in physical capacity.

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Brazilian version of the Kerlan-Jobe orthopedic clinic shoulder and elbow score: translation and cross-cultural adaptation

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ABSTRACT

BACKGROUND: The Kerlan-Jobe Orthopedic Clinic (KJOC) Shoulder and Elbow Score is commonly used to assess the functional status of athletes with conditions affecting the shoulder and elbow. However, a Brazilian Portuguese version of the KJOC questionnaire is currently unavailable.

OBJECTIVES: This study aimed to develop a Brazilian Portuguese version of the KJOC questionnaire.

DESIGN AND SETTING: This translation and cultural adaptation study was conducted at the Federal University of Paraíba, Brazil.

METHODS: The procedures adopted in this study followed guidelines recommending translation by two independent translators, synthesis of the translations, back-translation performed by two native English-speaking translators, analysis by an expert committee, and pre-testing. The Portuguese version was tested with 32 athletes to assess their understanding of the assessment tool. Items were deemed adequate if they were understood by at least 90% of the athletes.

RESULTS: The terms and expressions of some original items were modified to achieve better comprehensibility in the Brazilian context. No further modifications were necessary after the pre-test; all terms were comprehensible to over 90% of athletes.

CONCLUSION: The translation and cultural adaptation of the KJOC questionnaire into Portuguese were completed, resulting in a Brazilian version of the scale. Further studies are needed to evaluate the reliability and validity of this scale.

INTRODUCTION

Musculoskeletal injuries are common among athletes, resulting from high physical demands, including movements with high load and speed, abrupt changes in direction, and physical contact with other athletes.[1,2] In overhead athletes (athletes participating in a sport that requires movements of the upper arm over the head), the decelerating phase of throwing gestures, which generates shoulder distraction forces up to 1.5 times the athlete's body weight, and the repetitive tensile loading in posterior structures may cause structural changes in the shoulder.[3] In addition, the rotational speed of the arm may exceed 7000°/s during a throw with a distraction force of 947 N (108% body weight) at the glenohumeral joint.[4] Other factors may be associated with injury occurrence, such as age, sex, history of previous injuries, poor physical fitness, insufficient muscle strength, improper training, increased training volumes, short rest periods, type of training surface, and lack of preventive measures.[5,6]

Upper limb injuries have a high incidence and prevalence in overhead athletes, accounting for approximately 8 to 13% of all sports-related injuries and approximately 75% of injuries associated with sports involving throwing. The shoulder and elbow joints are most commonly affected.[7–10] Shoulder pain affects approximately 50% of baseball players during their careers,[11] and 44% of volleyball players.[7] The prevalence of shoulder injuries among handball players is high, ranging from 19.6%, in Norway,[12] to 36% in Iran.[13] Furthermore, the reported incidence of shoulder injuries is 44% in Brazil.

These conditions can directly affect athletes' performance, causing clinically significant dysfunction that may result in reduced dexterity, missed training sessions and games, loss of sponsorships, and even early retirement.[7,9] The evaluation of shoulder and elbow injuries and its impact on function and sports performance is crucial. Proper assessment can assist therapists in

characterizing athletes, identifying functional deficits, analyzing prognosis, establishing criteria for return to sport, and verifying treatment effectiveness.[8,14]

The main patient-reported outcome measures for evaluating shoulder function in athletes are the Kerlan-Jobe Orthopedic Clinic (KJOC) Shoulder and Elbow Score,[15–18] Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire,[19] Functional Arm Scale for Throwers (FAST),[8] Penn Shoulder Score,[20] and the American Shoulder and Elbow Surgeons Evaluation Form (ASES).[21] However, the DASH questionnaire and ASES have few questions that assess the specificities of overhead sports, and the FAST focuses only on throwing athletes and has not yet been translated into Brazilian Portuguese.[8,22,23]

The KJOC questionnaire was developed in English and is considered an important tool for assessing the shoulder and elbow in overhead athletes, being specifically validated in this population.[14,22] The KJOC questionnaire is a patient-reported outcome measure that assesses athletes' performance, symptoms, and function, including sports-related interpersonal interactions. The final score enables sensitive observation of changes in the function and performance of overhead athletes.[14,17,24]

Although it has been translated and validated for use in various countries such as Germany,[25] Spain,[15] Finland,[14] Norway,[17] Greece,[26] Korea,[18] Turkey,[27] and Italy,[16] and has already been used as a tool in randomized studies,[28] quasi-experimental studies,[24] and longitudinal studies,[29] this questionnaire has not been translated and culturally adapted for use in Brazil.[30]

OBJECTIVES

The current study aimed to translate and culturally adapt the KJOC questionnaire into Brazilian Portuguese.

METHODS

Study Design

This cross-sectional study followed guidelines for translation and cultural adaptation.[31–33] The study was approved by the Research Ethics Committee (CAAE No. 67423323.3.0000.5188, on April 25, 2023) of the Universidade Federal da Paraíba (UFPB). All individuals who agreed to participate signed an informed consent form.

Participants

This study included athletes of both sexes, aged between 18 and 60 years, with at least one year of competitive practice in an overhead sport, who were either asymptomatic or had shoulder or elbow pain. Asymptomatic athletes were included in this study based on previous reports demonstrating that the KJOC questionnaire can assess functional status in asymptomatic athletes.[29,37] Participants were required to maintain a regular regimen with training at least twice a week and participate in sports for competitive purposes, which involved participation in championships and tournaments, regardless of the level (college, regional, state, or national).[34–36] Athletes with cognitive impairments that would preclude them from completing the assessment were excluded from the study.

Procedures

The translation and adaptation process of the KJOC questionnaire for Brazilian athletes was based on the following steps: 1) translation, 2) synthesis of translations, 3) back-translation to the original language, 4) committee analysis, and 5) pre-testing.[31–33]

The author of the original version of the KJOC questionnaire authorized this study via e-mail. The KJOC questionnaire was translated by two independent translators who were fluent in both Brazilian and English. The first translator, with expertise in the health sciences, was informed of the research objectives. The second translator, without expertise in health sciences, was not informed of the concepts being assessed. Each translator produced versions of the questionnaire, V1 and V2. These versions were read and discussed by both the translators and the researchers to synthesize V1 and V2 into a single version (V3).

V3 was translated back into English by two independent native English-speaking translators fluent in Portuguese, resulting in two independent versions: B1 and B2. The back translators were blinded to the original version of the questionnaire and did not have a medical background. Subsequently, a committee composed of back-translators, translators, two physical therapy students, one physiotherapist, and two professors with PhDs in physical therapy discussed the differences between all versions (V1, V2, V3, B1, and B2) and the original questionnaire, aiming to produce the final version used in the pre-testing phase. The discussions identified sentences that required modifications and were rewritten to enhance the comprehensibility and semantic, conceptual, idiomatic, and cultural equivalence of the tool, resulting in the version used in the pre-test (pre-test version).

The pre-test was conducted with 32 athletes from different overhead sports. The sample size was determined based on the recommendation of Beaton et al. [32], which considers 30 individuals to be adequate. The athletes completed the KJOC questionnaire without further explanation beyond the initial instructions to prevent any potential influence on their responses. Athletes were instructed to: 1) read and respond to the pre-test version; 2) indicate if they understood the questions (Yes or No question); 3) and provide suggestions for each item, if any. The items that obtained a "non-understanding" level above 10% were reformulated to create the final version, which was then sent to the author of the KJOC questionnaire for approval.[38–40]

Scoring Calculation

The KJOC questionnaire consists of 19 items divided into two sections. The first section, comprising 9 items, included questions about the history of the current injury, a description of the current competition level, and the current state of the arm. The second section includes 10 questions, measured with a ten-centimeter Visual Analog Scale (VAS), about physical functioning, playing, and practice conditions, and specific questions regarding the competition level in the relevant sport. The total score was obtained by summing the scores obtained from all items in the second section, resulting in a total score between 0 and 100 points. Higher scores indicate better arm function.[14,18]

RESULTS

This study included 32 overhead athletes, and their characteristics are shown in **Table 1**. In the translation stage, the committee analyzed and discussed all questions from versions V1 and V2 to formulate the consensus version, V3 (**Table 2**).

The consensus version (V3) was back-translated into versions B1 and B2, which are described in **Table 3**. After back-translation, the differences between all versions and the original questionnaire were discussed with the entire committee to culminate in a version with semantic, idiomatic, and cultural equivalence to the original.

During the pre-test, all items achieved comprehensibility above 90%, and there were no suggestions for removing or adding questions to the questionnaire. However, during the observation of the responses, it was noticed that a few athletes had difficulty understanding the horizontal line. Therefore, in the discussion with the expert committee, the 10 cm horizontal line was replaced by an 11-point numerical rating scale to optimize the understanding of these items. Additionally, a few athletes suggested changing question 1 from "Tempo normal de aquecimento" to "Se sente solto (relaxado(a)) durante tempo normal de aquecimento", and question 7 from "Perdi toda a força, alterei minha técnica de arremesso ou deixei de ser um atleta de bolas rápidas e me tornei um arremessador de longa-distância" to "Perdi toda a minha força e velocidade. Tive que alterar minha técnica". The final version of the questionnaire is presented in **Supplementary Material 1** https://osf.io/9puxg/?view_only=05246b5e7b3e48aba5aedf3fdc37e114.

Table 1. Characteristics of the included individuals

Characteristics	n = 32
Sex, n (%)	
Male	22 (69)
Female	10 (31)
Age, years	31.8 ± 10.53
Body Mass Index, kg/m²	77.5 ± 20.35
Years of Sports Practice	13.3 ± 11.22
Sport Modality, n (%)	
Baseball	17 (53)
Volleyball	14 (44)
Handball	1 (3)
Asymptomatic individuals	11 (34.4%)
Symptomatic individuals	21 (65.6 %)
Educational Level, n (%)	
Elementary School	1 (3)
High School	12 (38)
Higher Education	17 (53)
Postgraduate	2 (6)

Continuous data were described as mean ± standard deviation, and categorical data were described as frequency (%).

DISCUSSION

The translation and cultural adaptation of the KJOC questionnaire for use in Portuguese was conducted, and a Portuguese version for use in Brazil was developed. This process followed the methods recommended by Beaton et al.[32], previously used in the translation and adaptation of various questionnaires in various countries, such as the ABILHAND-Kids, the revised Foot Function Index (FFI-R), the Bournemouth questionnaire,[38–40] and the KJOC questionnaire.[17,25]

Throughout the process, the primary translations and subsequent back-translations into English resulted in minor linguistic inconsistencies that were resolved during the synthesis group and committee meetings. A few terms were translated non-literally to achieve cultural equivalence with the study population. For example, the phrase "switched to short races" in question eight was originally translated to "corrida de curtas distâncias" (short-distance race). During the discussion, it was identified that the term did not make sense in Portuguese; therefore, it was modified to "passei a ter menos tempo de jogo" (started to have less playing time) to make it understandable and maintain its original meaning. Moreover, there were changes regarding the adaptation of the American Sports Classification system to the Brazilian system in question 6, which resulted in the translation of 'Professional Minor League' to "Profissional da Segunda Divisão" (Second Division Professional), for example. Additionally, a numerical rating scale was added, as previously reported, to facilitate athletes' understanding of how to complete the questionnaire.[18] Question 7 was revised to "Perdi toda a minha força e velocidade," as reported in another translation and cultural adaptation.[17]

After the modifications, the questionnaire was subjected to a pre-test application, a practice commonly adopted in similar studies, such as those conducted by Schulz et al.[25] and Sukanen et al.,[14] who applied a preliminary version of the questionnaire to 10 athletes. In the Brazilian context, this approach is already widely used and plays a fundamental role in the cultural adaptation process, as it allows for the assessment of how the target population interprets the questionnaire items.[40] The pre-test version was employed to

Table 2. Comparison of translations and development of the consensus version

Original	V1 e V2	V3
Name... Age... Sex... Dominant Hand (R) (L) (Ambidextrous)... Date of Examination... Sport... Position... Years Played	V1 - Nome... idade... sexo... mão dominante (D) (E)... (Ambidestro)... Data do teste... Esporte... Posição... Há quanto tempo pratica... V2 - Nome... Idade... Sexo... Mão dominante... (D) (E) (Ambidestro)... Data do exame... Esporte... Posição... Anos em ativa	Nome... idade... sexo... mão dominante (D) (E) (Ambidestro)... Data do teste... Esporte... Posição… Anos em ativa
Please answer the following questions related to your history of injuries to YOUR ARM ONLY:	V1 - Por favor responda às seguintes questões relacionadas ao seu histórico de lesões, BRAÇO APENAS. V2 - Por favor responda às seguintes questões relacionadas ao seu histórico de lesões APENAS DO SEU BRAÇO.	Por favor responda às seguintes questões relacionadas ao seu histórico de lesões APENAS DO SEU BRAÇO.
1. Is your arm currently injured?	V1 - Seu braço está lesionado atualmente? V2 - Seu braço está lesionado no momento?	1. Seu braço está lesionado atualmente?
2. Are you currently active in your sport?	V1 - Você está ativo(a) no seu esporte atualmente? V2 - Você está ativo no seu esporte?	2. Você está ativo(a) no seu esporte atualmente?
3. Have you missed game or practice time in the last year due to an injury to your shoulder or elbow?	V1 - Você já perdeu alguma partida ou treinamento, no último ano, por causa de uma lesão no ombro ou cotovelo? V2 - Você perdeu algum jogo ou treino no último ano devido a uma lesão no seu ombro ou cotovelo?	3. Você perdeu alguma partida (jogo) ou treino, no último ano, devido a uma lesão no seu ombro ou cotovelo?
4. Have you been diagnosed with an injury to your shoulder or elbow other than a strain or sprain? If yes, what was the diagnosis?	V1 - Você já foi diagnosticado com alguma lesão no ombro ou cotovelo além de tensão muscular ou torção? Se sim, qual foi o diagnóstico? V2 - Você foi diagnosticado com uma lesão no seu ombro ou cotovelo além de um estiramento ou entorse? Se sim, qual foi o diagnóstico?	4. Você já foi diagnosticado com alguma lesão no ombro ou cotovelo além de estiramento ou entorse? Se sim, qual foi o diagnóstico?
5. Have you received treatment for an injury to your shoulder or elbow? If yes, what was the treatment? (Check all that apply): Rest... Therapy... Surgery (please describe)	V1 - Você já recebeu algum tratamento para lesões em seu ombro ou cotovelo? Se sim, qual foi o tratamento? (Marque todos que se aplicam)... Descanso... Terapia... Cirurgia (por favor descreva) V2 - Você recebeu tratamento para alguma lesão no seu ombro ou cotovelo? Se sim, qual foi o tratamento? (Marque todas que se aplicam)... a. Descanso... b. Terapia... c. Cirurgia (por favor especifique)	5. Você já recebeu algum tratamento para lesões em seu ombro ou cotovelo? Se sim, qual foi o tratamento? (Marque todos que se aplicam)... a. Descanso... b. Terapia... c. Cirurgia (por favor especifique)
Please describe your level of competition in your current sport: (Use Professional Major League, Professional Minor League, Intercollegiate, High School as the choices)	V1 - Por favor descreva sua categoria de competição no seu esporte atual: (Use Profissional das Grandes Ligas, Profissional da Segunda-divisão, Intercolegial, Ensino Médio como as opções) V2 - Por favor, descreva seu nível de competição no seu esporte atual: (Use: Liga Principal Profissional, Liga Menor Profissional, Intercolegiado, Escolar)	Por favor, descreva seu nível de competição no seu esporte atual: (Use como opções: Profissional das Grandes (principais) Ligas, Profissional da Segunda-divisão, Intercolegial, Escolar).
6. What is the highest level of competition you've participated at?	V1 - Qual a categoria de competição mais alta que você já participou? V2 - Qual é o maior nível em que você já competiu?	6. Qual é o maior nível de competição em que você já participou?
7. What is your current level of competition?	V1 - Qual sua categoria atual? V2 - Qual o nível em que você está competindo atualmente?	7. Qual o nível em que você está competindo atualmente?
8. If your current level of competition is not the same as your highest, do you feel it is due to an injury to your arm?	V1 - Se a sua categoria atual não é a mesma que a categoria mais alta que já atingiu, você sente que seja por causa de uma lesão no braço? V2 - Se o seu nível de competição não é o mesmo que o maior em que você já competiu, você sente que é devido à lesão no seu braço?	8. Se o seu nível atual de competição não é o mesmo que o maior em que você já competiu, você sente que é devido à lesão no seu braço?
Please check the ONE category only that best describes your current status: Playing without any arm trouble... Playing, but with arm trouble... Not playing due to arm trouble	V1 - Por favor marque apenas UMA opção que melhor descreva sua situação atual: Jogando sem nenhum problema no braço... Sem jogar por causa de um problema no braço... Jogando, mas com problema no braço. V2 -Por favor marque a ÚNICA categoria que descreve melhor seu estado atual: Jogando sem nenhum problema no braço... Jogando, mas com problema no braço... Sem jogar devido a um problema do braço.	Por favor marque apenas UMA opção que melhor descreva sua situação atual: Jogando sem nenhum problema no braço... Jogando, mas com problema no braço... Sem jogar por causa de um problema do braço

It continues...

Table 2. Continuation

Original	V1 e V2	V3
Section II		
Instructions to athletes: The following questions concern your physical functioning during game and practice conditions. Unless otherwise specified, all questions relate to your shoulder or elbow. Please answer with an X along the horizontal line that corresponds to your current level.	V1 - Instrução para os atletas: As perguntas a seguir são acerca de seu funcionamento físico durante jogos e práticas. A menos que caso contrário seja especificado, todas as perguntas são relacionadas aos seus ombros e cotovelos. Por favor, responda com um X sobre a linha horizontal da forma que você ache que melhor corresponde ao seu nível atual. V2 - Instruções para atletas: As questões a seguir se referem ao seu funcionamento físico durante jogos e treinos. Todas as questões estão relacionadas ao seu ombro ou cotovelo, a não ser que especifiquem o contrário. Por favor responda com um X no espaço da linha que corresponde ao seu nível atual.	Instruções para atletas: As questões a seguir se referem ao seu funcionamento físico durante jogos e treinos. Todas as questões estão relacionadas ao seu ombro ou cotovelo, a não ser que seja especificado o contrário. Por favor, responda com um X sobre o espaço da linha horizontal que melhor corresponde ao seu nível atual.
1. How difficult is it for you to get loose or warm prior to competition or practice? Never feel loose during games or practice; Normal warm-up time	V1 - O quão difícil é para você relaxar ou se aquecer antes de uma competição ou prática? Nunca me sinto relaxado(a) durante jogos ou práticas; Tempo normal de aquecimento. V2 - Quão difícil é para você aquecer ou se soltar antes de uma competição ou treino? Nunca se sente solto durante jogos ou treino; Tempo normal de aquecimento.	1. Quão difícil é para você aquecer ou se soltar (relaxar) antes de uma competição ou treino? Nunca se sente solto (relaxado(a)) durante jogos ou treino; Tempo normal de aquecimento
2. How much pain do you experience in your shoulder or elbow? Pain at rest; No pain with competition	V1 - Quanta dor você sente em seu ombro ou cotovelo? Dor no descanso; Sem dor na competição. V2 - Quanta dor você sente no seu ombro ou cotovelo? Dor mesmo descansando; Sem dor em competições	2. Quanta dor você sente em seu ombro ou cotovelo? Dor no descanso; Sem dor na competição
3. How much weakness and/or fatigue (ie, loss of strength) do you experience in your shoulder or elbow? Weakness or fatigue preventing any competition; No weakness, normal competition fatigue	V1 - Quanta fraqueza e/ou fadiga (ou seja, perda de força) você experiencia em seu ombro ou cotovelo? Fraqueza ou fadiga impedindo qualquer competição; Sem fraqueza, fadiga de competição normal V2 - Quanta fraqueza e/ou fadiga (leia-se, perda de força) você sente no seu ombro ou cotovelo? Fraqueza ou fadiga que me impede de competir; Sem fraqueza, sinto uma fadiga normal de competição	3. Quanta fraqueza e/ou fadiga (ou seja, perda de força) você sente no seu ombro ou cotovelo? Fraqueza ou fadiga que me impede de competir; Sem fraqueza, sinto uma fadiga normal de competição.
4. How unstable does your shoulder or elbow feel during competition? "Popping out" routinely; No instability	V1 - Quão instável seu ombro ou cotovelo fica durante as competições? "latejando"; Sem instabilidade V2 - Quão instável seu ombro ou cotovelo parece durante a competição? Desloca rotineiramente; Sem instabilidade	4. Quão instável seu ombro ou cotovelo fica durante as competições? Desloca (instável) rotineiramente; Sem instabilidade.
5. How much have arm problems affected your relationship with your coaches, management, and agents? Left team, traded or waived, lost contract or scholarship; Not at all.	V1 - O quanto os problemas do seu braço afetaram seu relacionamento com seus treinadores, empresários e agentes? Saí do time, trocado ou dispensado, perdi contato ou bolsa de estudos; Nem um pouco. V2 - O quanto problemas no braço têm afetado seu relacionamento com seus treinadores, diretores e agentes? Saí do time, fui trocado ou despedido, perdi um contrato ou bolsa de estudos; Nem um pouco	5. O quanto os problemas do seu braço têm afetado seu relacionamento com seus treinadores, gestores e agentes? Saí do time; fui trocado ou despedido; perdi um contrato ou bolsa de estudos; Nem um pouco
The following questions refer to your level of competition in your sport. Please answer with an X along the horizontal line that corresponds to your current level.	V1 - As seguintes perguntas são referentes a sua categoria de competição no seu esporte. Por favor, responda com um X sobre a linha horizontal da forma que você ache que melhor corresponde ao seu nível atual. V2 - As seguintes perguntas são referentes a sua categoria de competição no seu esporte. Por favor, responda com um X sobre a linha horizontal da forma que você ache que melhor corresponde ao seu nível atual.	As seguintes perguntas são referentes a sua categoria de competição no seu esporte. Por favor, responda com um X sobre a linha horizontal da forma que você ache que melhor corresponde ao seu nível atual.
6. How much have you had to change your throwing motion, serve, stroke, etc, due to your arm? Completely changed, don't perform motion anymore; No change in motion.	V1 - O quanto você teve que mudar seu movimento de arremesso, saque, rebatimento, etc., por causa de seu braço? Mudou completamente, não faço o movimento mais; Sem mudança no movimento. V2 - Quanto você teve que mudar seu movimento de arremesso, saque, rebate, etc, devido ao seu braço? Mudei completamente, não faço mais nenhum desses movimentos; Sem mudanças no movimento	6. O quanto você teve que mudar seu movimento de arremesso, saque, rebatimento, etc., por causa de seu braço? Mudou completamente, não faço mais o movimento mais; Sem mudança no movimento

It continues...

Table 2. Continuation

Original	V1 e V2	V3
7. How much has your velocity and/or power suffered due to your arm? Lost all power, became finesse or distance athlete; No change in velocity/power.	V1 - Quanto a sua velocidade e/ou força mudaram por causa de seu braço? Perdi todo o poder, tornei delicado ou atleta de longa distância; Sem mudança na velocidade/força V2 - Quanto sua velocidade e/ou força diminuíram devido ao seu braço? Perdi toda a força, me tornei um atleta de jogos estratégicos ou longa-distância; Sem mudanças na velocidade/força	7. Quanto sua velocidade e/ou força diminuiu devido ao seu braço? Perdi toda a força, alterei minha técnica de arremesso ou deixei de ser um atleta de bolas rápidas e me tornei um arremessador de longa-distância; Sem mudanças na velocidade/força.
8. What limitation do you have in endurance in competition due to your arm? Significant limitation (became relief pitcher, switched to short races for example); No endurance limitation in competition.	V1 - O quão limitada é a sua resistência em competições por causa de seu braço? Limitação significativa (me tornei arremessador reserva, troquei para corrida de curta distância por exemplo); Sem limitação de resistência em competições V2 - Que limitações você tem em relação a resistência em competições devido ao seu braço? Limitações significativas (me tornei substituto, mudei para corridas curtas, por exemplo); Sem limitações de resistência em competições	8. Qual é a limitação da sua resistência em competições por causa de seu braço? Limitação significativa (me tornei arremessador reserva, passei a ter menos tempo de jogo, por exemplo); Sem limitação de resistência em competições
9. How much has your control (of pitches, serves, strokes, etc.) suffered due to your arm? Unpredictable control on all pitches, serves, strokes, etc; No loss of control	V1 - Quanto o seu controle (de arremessos, saques, rebatimento, etc.) sofreu por causa de seu braço? Controle imprevisível em todos os arremessos, saques, rebatimentos, etc.; Sem perda de controle V2 - Quanto seu controle diminui devido ao seu braço? Controle imprevisível em arremessos, saques, rebates, etc; Sem perda de controle	9. Quanto o seu controle (de arremessos, saques, rebatimento, etc.) sofreu por causa de seu braço? Controle imprevisível em arremessos, saques, rebatimentos, etc; Sem perda de controle
10. How much do you feel your arm affects your current level of competition in your sport (ie, is your armholding you back from being at your full potential)? Cannot complete, had to switch sports; Desired level of competition.	V1 - O quanto você sente que o seu braço afeta o seu nível de competição no seu esporte (exemplo, seu braço está lhe impedindo de usar todo o seu potencial)? Não posso competir, tive que trocar de esporte. Nível desejado de competição V2 - Quanto você sente que seu braço afeta o seu nível atual de competição no seu esporte (isto é, seu braço tem te impedido de estar na sua capacidade máxima?) Não consigo competir, tive que mudar de esporte; Estou no meu nível de competição desejado	10. O quanto você sente que o seu braço afeta o seu nível de competição no seu esporte (ou seja, seu braço está lhe impedindo de usar todo o seu potencial)? Não consigo competir, tive que mudar de esporte; Estou no meu nível de competição desejado

V1 = Portuguese version by the first translator; V2 = Portuguese version by the second translator; and V3 = Consensus Portuguese version defined at the end of the initial translation phase.

Table 3. Comparison of back-translations

Original	Backtranslation 1 (B1) and Backtranslation 2 (B2)
Name... Age... Sex... Dominant Hand (R) (L) (Ambidextrous)... Date of Examination... Sport... Position... Years Played	B1 - Name .. Age... Sex...Dominant Hand: (R) (L) (Ambidextrous) Date of test … Sport .. Position .. Years of practice .. B2 - Name… Age… Sex…Dominant hand: (R). (L);(Ambidextrous)... Test date ... Sport... Position ... Years of practice
Please answer the following questions related to your history of injuries to YOUR ARM ONLY:	B1 - Please answer the following questions related to your history of injuries ONLY OF YOUR ARM: B2 - Please answer the following questions regarding your history of injuries TO YOUR ARM ONLY:
1. Is your arm currently injured?	B1 - Is your arm currently injured? B2 - Is your arm currently injured?
2. Are you currently active in your sport?	B1 - Are you currently active in your sport? B2 - Are you currently active in your sport?
3. Have you missed game or practice time in the last year due to an injury to your shoulder or elbow?	B1 - Did you miss any match (game) or training in the last year due to an injury to your shoulder or elbow? B2 - Have you missed any matches (games) or practices in the last year due to an injury to your shoulder or elbow?
4. Have you been diagnosed with an injury to your shoulder or elbow other than a strain or sprain? If yes, what was the diagnosis?	B1 - Have you ever been diagnosed with any shoulder or elbow injury besides strain or sprain? If so, what was the diagnosis? B2 - Have you ever been diagnosed with any shoulder or elbow injuries other than a strain or sprain? If yes, what was the diagnosis?
5. Have you received treatment for an injury to your shoulder or elbow? If yes, what was the treatment? (Check all that apply): Rest... Therapy... Surgery (please describe)	B1 - Have you ever received any treatment for injuries to your shoulder or elbow? If so, what was the treatment? (Check all that apply) Rest; Therapy; Surgery (specify) B2 - Have you ever received any treatment for injuries to your shoulder or elbow? If yes, what was the treatment? (Check all that apply) Rest; Therapy; Surgery (specify)

It continues...

Table 3. Continuation

Original	Backtranslation 1 (B1) and Backtranslation 2 (B2)
Please describe your level of competition in your current sport: (Use Professional Major League, Professional Minor League, Intercollegiate, High School as the choices)	B1 - Please, describe your level of competition in your current sport: (Use as options: Professional of Big Leagues, Second-division Professional, Intercollegiate, School) B2 - Please describe your level of competition in your current sport: (Use as options: Major League Pro, Division Two Pro, Intercollegiate, Intramural)
6. What is the highest level of competition you've participated at?	B1 - What is the highest level of competition in which you have ever participated? B2 - What is the highest level of competition you have ever participated in?
7. What is your current level of competition?	B1 - At what level are you currently competing? B2 - What level are you currently competing at?
8. If your current level of competition is not the same as your highest, do you feel it is due to an injury to your arm?	B1 - If your current level of competition is not the same as the highest at which you have ever competed, do you feel that it is due to the injury to your arm? B2 - If your current level of competition is not the same as the highest you have ever competed in, do you feel it is due to your arm injury?
Please check the ONE category only that best describes your current status: Playing without any arm trouble... Playing, but with arm trouble... Not playing due to arm trouble	B1 - Please check only ONE option that best describes your current situation: Playing with no problem in the arm; Playing, but with a problem in the arm; Not playing because of a problem in the arm; B2 - Please check only ONE option that best describes your current situation: Playing without any arm problem; Playing but with an arm problem; Not playing because of an arm problem;
Instructions to athletes: The following questions concern your physical functioning during game and practice conditions. Unless otherwise specified, all questions relate to your shoulder or elbow. Please answer with an X along the horizontal line that corresponds to your current level.	B1 - Instructions for athletes: The following questions refer to your physical functioning during games and training. All questions are related to your shoulder or elbow unless it is otherwise specified. Please, answer with an X on the space of the horizontal line that best corresponds to your current level. B2 - Instructions for athletes: The following questions refer to your physical functioning during games and practices. All questions relate to your shoulder or elbow unless otherwise specified. Please answer with an X over the space on the horizontal line that best corresponds to your current level.
1. How difficult is it for you to get loose or warm prior to competition or practice? Never feel loose during games or practice; Normal warm-up time	B1 - How difficult is it for you to warm up or get loose (relax) before a competition or training? Never feel loose (relaxed) during games or training Normal training time B2 - How difficult is it for you to warm up or loosen up (relax) before a competition or practice? Never feel loose (relaxed) during games or practice Normal Warm-up time
2. How much pain do you experience in your shoulder or elbow? Pain at rest; No pain with competition	B1 - How much pain do you feel in your shoulder or elbow? Pain at rest No pain in competition B2 - How much pain do you feel in your shoulder or elbow? Pain when resting No pain during the competition.
3. How much weakness and/or fatigue (ie, loss of strength) do you experience in your shoulder or elbow? Weakness or fatigue preventing any competition; No weakness, normal competition fatigue	B1 - How much weakness and/or fatigue (that is, loss of strength) do you feel in your shoulder or elbow? Weakness or fatigue impedes me from competing No weakness, I feel a normal fatigue of competition B2 - How much weakness and/or fatigue (loss of strength) do you feel in your shoulder or elbow? Weakness or fatigue that prevents me from competing No weakness, I feel normal competition fatigue.
4. How unstable does your shoulder or elbow feel during competition? "Popping out" routinely No instability	B1 - How unstable does your shoulder or elbow get during competitions? Dislocates (unstable) routinely; No instability B2 - How unstable is your shoulder or elbow during competitions? It is displaced (unstable); No instability
5. How much have arm problems affected your relationship with your coaches, management, and agents? Left team, traded or waived, lost contract or scholarship; Not at all.	B1 - How much have the problems in your arm affected your relationship with trainers, managers, and agents? I left the team, I was traded or let go; I lost a contract or scholarship. Not at all B2 - How much have your arm problems affected your relationships with your coaches, managers, and agents? I left the team; I was traded or fired; I lost a contract or scholarship. Not at all.
The following questions refer to your level of competition in your sport. Please answer with an X along the horizontal line that corresponds to your current level.	B1 - The following questions are referent to your competition category in your sport. Please, answer with an X on the horizontal line in the way that you think best corresponds to your current level. B2 - The following questions refer to your competition category in your sport. Please answer with an X over the horizontal line, the way you think best corresponds to your current level.
6. How much have you had to change your throwing motion, serve, stroke, etc, due to your arm? Completely changed, don't perform motion anymore; No change in motion.	B1 - How much did you have to change your throwing (pitching), serving, batting, etc. because of your arm? Changed completely, I no longer do the movement. No change in the movement. B2 - How much did you have to change your throwing, serving, batting, etc movements because of your arm? Completely changed, I don't make the move anymore No change in the movement.
7. How much has your velocity and/or power suffered due to your arm? Lost all power, became finesse or distance athlete; No change in velocity/power.	B1 - How much has your speed and/or strength diminished due to your arm? I lost all strength, I changed my throwing technique or I quit being a fastball athlete and became a long-distance thrower No changes in speed/strength B2 - How much has your speed and/or strength decreased because of your arm? I lost all power, I changed my throwing technique or went from being a fast-ball athlete to a long-distance thrower. No changes in speed/strength.

It continues...

Table 3. Continuation

Original	Backtranslation 1 (B1) and Backtranslation 2 (B2)
8. What limitation do you have in endurance in competition due to your arm? Significant limitation (became relief pitcher, switched to short races for example); No endurance limitation in competition.	B1 - What is the limitation of your endurance during competitions because of your arm? Significant limitation (I became a reserve pitcher, I switched to short-distance running, for example). No limitation of endurance in competitions B2 - What is the limitation of your endurance in competitions because of your arm? Significant limitation (I became a backup pitcher, and switched to short races, for example). No endurance limitation in competitions.
9. How much has your control (of pitches, serves, strokes, etc.) suffered due to your arm? Unpredictable control on all pitches, serves, strokes, etc; No loss of control	B1 - How much has your control (of throws (pitches), serves, batting, etc.) suffered because of your arm? Unpredictable control of throws, serves, bats, etc. No loss of control B2 - How much has your control (of throwing, serving, hitting, etc.) suffered because of your arm? Unpredictable control on throws, serves batting, etc. No loss of control.
10. How much do you feel your arm affects your current level of competition in your sport (ie, is your arm holding you back from being at your full potential)? Cannot complete, had to switch sports; Desired level of competition.	B1 - How much do you feel that your arm affects your level of competition in your sport (that is, is your arm impeding you from using your full potential)? I am not able to compete, I had to change sports I am at my desired level of competition B2 - How much do you feel that your arm affects your level of competition in your sport (is your arm preventing you from using your full potential)? I'm not able to compete, I had to change sports. I am at my desired competition level.

B1 = version from the first back translator; B2 = English version from the second back translator.

ensure that the questionnaire was understood by more than 90% of the participants. Some suggestions from the athletes improved its readability, thereby enabling the questionnaire to be culturally adapted appropriately for the Brazilian population.[30]

Similar to other translations and cultural adaptations of the KJOC questionnaire,[14,17] no difficulties were encountered in applying the Brazilian version. Athletes identified the questionnaire as easy to understand and respond to, with no need for further modifications. Previous studies have reported that athletes respond to the KJOC questionnaire in approximately 10 minutes.[16,18] Unfortunately, we did not measure the duration that athletes took to respond to the Brazilian version of the KJOC questionnaire. Despite guidelines recommending that reliability and validation analysis of a measurement instrument necessarily occur after translation and cultural adaptation,[32] studies have been conducted and published only with the translation and cultural adaptation process.[21,40–42] This is done to avoid multiple translations and versions of the same instrument, thus preventing unnecessary work.[38] Test-retest reliability of other versions of the KJOC questionnaire has been investigated and demonstrated excellent results, showing good internal consistency and the ability to detect clinically significant improvements in patients.[16,17,25] Thus, the psychometric properties of the Brazilian Portuguese version are being evaluated, and it is expected that the results will contribute to its application in Brazil.

The clinical and research relevance of this study lies in its contribution to providing another assessment tool for shoulder and elbow function in overhead athletes. This questionnaire offers valuable insights for both therapists and researchers, aiding in the collection of information necessary for rehabilitation practices by identifying specific functional impairments and tracking rehabilitation progress over time.

CONCLUSION

The translation and cultural adaptation of the KJOC shoulder and elbow questionnaire into Portuguese were completed, and a Brazilian version was obtained. Future studies are needed to verify the measurement properties of the Brazilian version of the questionnaire.

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Prevalence of Temporomandibular Disorder and its association with anxiety in academics: a cross-sectional study

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ABSTRACT

BACKGROUND: Temporomandibular disorders (TMD) are a major cause of non-dental pain in the oral and facial regions.

OBJECTIVE: This study aimed to determine the prevalence and severity of TMD and anxiety among academics and to investigate the relationship between TMD and its associated factors.

DESIGN AND SETTING: This cross-sectional study included a sample of 295 academics undertaking health courses at a university in Brazil.

METHODS: The Simplified Anamnesis Index and Beck Anxiety Inventory were used to evaluate TMD and assess anxiety, respectively. Data were statistically analyzed using relative and absolute frequencies of variables. In the bivariate analysis, Pearson's chi-square test was used, and in the multivariate analysis, raw and adjusted binary logistic regressions were used to obtain the odds ratio (OR) and respective 95% confidence intervals. Statistical significance was set at $P < 0.05$.

RESULTS: The average age of academics was 22.95 (standard deviation ± 6.14) years, predominantly comprising women (82.7%), whites (90.8%), and singles (86.6%). The findings revealed that 81.2% of academics had TMD and 50.5% exhibited symptoms of anxiety. Academics with anxiety were three times more likely to have TMD (OR = 3.6) than those without anxiety.

CONCLUSION: A significant association between anxiety and TMD was observed in academics. The prevalence of TMD was high, with academics with anxiety having a high likely to develop TMD. These findings highlight the importance of addressing mental health concerns in addition to physical health, as they are often related.

INTRODUCTION

Temporomandibular disorders (TMDs) are a class of musculoskeletal and neuromuscular conditions related to the masticatory muscles, temporomandibular joint (TMJ) complex, and attached bone structures. It results from a combination of factors with varying degrees of psychogenic influence, impairing an individual's quality of life. Several etiological agents were credited with the cause of this dysfunction, such as occlusal problems, trauma, and emotional stress.[1] TMDs are highly prevalent, affecting 25% of the population, with a peak incidence from 20 to 40 years of age, and affect women more than men.[2] The higher prevalence of TMDs among women may be attributed to the fact that women are more likely to seek treatment, indicating a greater tendency for care and attention to health compared to men.[3]

TMDs are the major cause of non-dental pain in the oral and facial regions. The pain can be manifested in the temporomandibular region, face, head, neck, and ears.[4] The development of pain due to prolonged muscle hyperactivity is mainly related to tissues tension resulting from psychological discomfort, anxiety, or stress. Specifically, the masseter, temporalis, sternocleidomastoid, and trapezius are frequently affected. These muscles react to changes in an individual's mental state, causing pain associated with psychological disorders and chronic stress.[5]

TMD encompasses conditions affecting the orofacial region, which can be divided into those affecting the masticatory muscles and those affecting the TMJ. The typical features include pain in TMJ, restriction of mandibular movement, and TMJ sounds.[6]

Anxiety is a state of apprehension and anticipation of dangers or unfavorable future events, accompanied by feelings of discomfort, worry, and tension. It is considered pathological when it causes significant suffering or functional impairment.[7] It involves physiological, mental, and emotional aspects and arises from specific personal traits combined with genetic and social

factors, characterized by hypersensitivity to stress and a tendency to experience strong negative emotions such as nervousness, anger, and sadness.[8]

University academics, especially those in their last year of college, are at a higher risk of developing TMDs due to the combined pressures of academic qualification and the uncertainty of future professional activities. The uncertainty of what the next year will be like and where one should settle for their professional development aggravates stress and anxiety levels.[9] This group was also considered for the study mainly because of high demand for performance during the academic phase, which is a fundamental requirements for becoming future professionals.[10]

OBJECTIVE

This study aimed to evaluate the prevalence and severity of TMD in academics undertaking health courses (Nursing, Medicine, Dentistry, and Psychology) at a university in southern Brazil. It sought to investigate the association between the presence of TMD and sociodemographic characteristics of the academics (sex, age, and race); days of the week with classes, courses, and the time of the day of the courses; alcohol and coffee consumption; duration of sleep on weekdays and weekends; and use of continuous medication and anxiety.

METHODS

The Ethics Committee of Research with Human Beings submitted and approved on April 12, 2017 this research under opinion numbers 2,014,448, and CAAE 66373317,6,0000.5319.

Study design and sample

This study employed a cross-sectional quantitative approach. It included academics who enrolled in health courses (Nursing Medicine, Dentistry, and Psychology) at a university located in a southern Brazilian municipality, were ≥ 17 years of age, met the inclusion criteria, and were eligible to participate in the research. The total number of academics was 1,139, including 113 nursing academics, 335 medical academics, 209 dentists, and 482 psychology academics. Using a 5% margin of error, 90% confidence level, and 50% prevalence of the outcome and adding 15% for potential losses, the calculated sample would comprise 252 academics. However, the final sample size in the present study consisted of 295 academics, which was 43 (17%) academics more than the calculated sample size.

Procedures for data collection

Data were collected online between March 2021, and September 2021 through a questionnaire available on the Google Forms platform. An invitation with a brief explanation of the research and a link to the online questionnaire was sent to the heads of the nursing, medical, dental, and psychology departments, who then distributed it to the academics via e-mail or WhatsApp, ensuring a broader coverage of participating academics. The study utilized validated scales; anxiety symptoms were evaluated using the Beck Anxiety Inventory questionnaire[11] and TMD was assessed using the Fonseca Anamnestic Index.[12] In addition, specific questions were formulated to determine the sociodemographic profile and behavioral characteristics of the academics.

Variables under study

Outcome Variable

TMD

The outcome variable of this study was the presence of TMD, evaluated according to the Anamnesis Questionnaire,[12] which is based on the Helkimo Anamnesis Index.[13] This is one of the few instruments available in Portuguese that assesses the severity of TMD symptoms. The Simplified Anamnesis Index, developed and validated by Fonseca et al.[12] consists of 10 questions covering common symptoms, including 1- difficulty opening the mouth; 2- difficulty moving the mandible sideways; 3- muscle pain or tiredness when chewing; 4- frequent headaches; 5- pain at the nape or torticollis; 6- Earaches or joint pain 7- noticeable sounds in the TMJ when chewing or opening the mouth; 8- noticeable habit of teeth clenching or grinding; 9- inability to properly articulate the teeth; 10- considering oneself as a tense or nervous person. Each question has three possible answers with corresponding scores—yes (10), no (0), and sometimes (5). Immediate diagnosis was determined from the total score, which was used for categorizing the severity of TMD as follows: no TMD (0–15 points), mild TMD (20–40 points), moderate TMD (45–65 points), and severe TMD (70–100 points).[14]

The responses were categorized as follows: 1) absence of TMD or without TMD or 2) presence of TMD (mild, moderate, or severe).

Exposure variables

Anxiety

Anxiety was assessed using the Beck Anxiety Inventory, originally developed by Beck et al.[11] in 1988 and adapted by Cunha.[15] The inventory consists of 21 items related to the presence of anxiety symptoms, including 1- numbness or tingling; 2- heat sensation; 3- trembling legs; 4- inability to relax; 5- fear that the worst will happen; 6- being stunned or dizzy; 7- heart racing; 8- no balance; 9- feeling terrified; 10- feeling nervous; 11- feeling suffocated; 12- trembling hands; 13- overall trembling; 14- fear of losing control; 15- difficulty breathe; 16- fear of dying; 17- feeling frightened; 18- indigestion or abdominal discomfort; 19- lightheadedness; 20- blushing; and 21- sweating (not due to heat). Items were evaluated on a 4-point scale, with scores ranging from 0 (no symptoms) to 3

(severe symptoms). The total score ranged from 0 to 63. The scores indicate the level of anxiety as follows:[11,15] 0–10 (no anxiety), 11–19 (mild to moderate anxiety), 20–30 (moderate anxiety), and 31–63 (severe anxiety). The inventory was adapted into Portuguese, with data on its accuracy and validity,[15] maintaining the same scoring system and classifying the intensity levels of anxiety symptoms similar to those of the original version.

Subsequently, for statistical analysis, the answers were categorized as follows: 1) no anxiety (without or with a minimum degree of anxiety) or 2) anxiety (mild, moderate, and severe).

Sociodemographic and behavioral characteristics

We assessed age (17–20 years or 21–57 years), marital status (married or civil union/single), sex (male or female), race (white or non-white), degree (nursing, medicine, dentistry, psychology), number of class days (1–4 days or 5–7 days), class shifts (morning, afternoon, night or two shifts or three shifts), alcohol consumption (never or a few times a month, 2–4 times a week, or unanswered), coffee consumption (never, one cup a day, or more than three cups a day), and use of continuous medications (yes or no).

Sleep duration on weekdays and on weekends

Sleep duration on weekdays was determined by asking the academics the following question: "On days you have lectures, what time are you ready to sleep?," "How many minutes does it take you to fall asleep on school days?," and "What time do you wake up on school days?." The duration of sleep on rest days was calculated similarly, only replacing "lecture days" with "rest days." The number of hours of sleep was calculated by subtracting the time taken to fall asleep (latency time) from the difference between the wake-up time and sleep time. Sleep duration was classified as insufficient if it was < 6 h/day for adults aged 18–64 years.

Subsequently, the answers were categorized as follows: 1) insufficient duration (≤ 6 h) or 2) sufficient duration (> 6 h).

Sleep duration was assessed using a section of the validated Munich Chronotype Questionnaire (MCTQ^{PT}),[16] which has been adapted and validated for the Portuguese language. The MCTQ^{PT} is a complete instrument, which has illustrations that help the respondent to clearly identify the meaning of the questions and make the questionnaire visually attractive.[16] The questionnaire instructs the interviewee that answers must refer to the past 4 weeks, and although it can be used to define chronotype (biological clock about the light-dark cycle), the questions were only used to characterize the duration and time of sleep latency.

Data analysis

Data were computed in a Microsoft Office Excel 2016 software database and later exported to the SPSS statistical software (version 20.0; IBM, Armonk, New York) for analysis.

Relative and absolute frequencies of the variables were calculated. Pearson's chi-square test was used in the bivariate analysis. For multivariate analysis, crude and adjusted binary logistic regressions were used to obtain the odds ratios (OR) and respective 95% confidence intervals (95%CI). All exploratory variables with a P value < 0.20 were included in the crude model, and only those with a P value < 0.05 remained in the adjusted model.

RESULTS

The average age of the 295 included academics was 22.95 (± 6.14) years, with a sociodemographic profile comprising predominantly women, whites, and singles (82.7%, 90.8%, and 86.6%, respectively). Among the academics, 72.9% attended school 5–7 days per week and 33.9% had three class shifts. Additionally, 15.3% of the academics had insufficient sleep duration on weekdays (< 6 h/day) (**Table 1**).

Table 1. Analysis of the variables among academics in a university in Brazil in 2021 (n = 295)

Variables	n	%
Age (age group)		
17–20 years	119	40.3
21–57 years old	176	59.7
Marital status		
Married/Civil union	39	13.2
Single	256	86.8
Race		
White	268	90.8
Non-white	27	9.2
Number of class days		
1–4 days	80	27.1
5–7 days	215	72.9
Class shifts		
Morning, afternoon, night, or two shifts	195	66.1
Morning, afternoon, or night	100	33.9
Consumption of alcoholic beverages		
Never or a few times a month	209	70.8
2–4 times a week	57	19.3
No answer	29	9.8
Coffee consumption		
Never or one cup per day	176	59.7
More than three cups per day	119	40.3
Presence of TMD		
Neither TMD	53	18
Mild. moderate, or severe	242	82
Sex		
Female	244	82.7
Male	51	17.3
Duration of sleep on weekdays		
Up to 6h	45	15.3
More than 6 hours	250	84.7
Sleep duration on rest days		
Up to 6h	3	1.0
More than 6 hours	292	99.0

TMD = temporomandibular disorder.

Data from academics with TMD are presented in **Table 2.** Among the academics, 43.4% had mild TMD, 27.5% had moderate TMD, and 11.2% had severe TMD. The academics' data on anxiety are presented in **Table 2.** Notably, 25.8% of the academics had mild to moderate anxiety, 15.3% had moderate anxiety, and 9.5% had severe anxiety. The overall prevalence of anxiety was 50.5% (n = 149).

Bivariate analysis using Pearson's chi-square test was performed to examine the association between the presence of TMD and marital status; age; race or ethnicity; alcohol consumption; sex; course; number of class shifts; frequency of coffee consumption per day; use of continuous medication for anxiety, stress, or sleep; sleep duration on working days; and sleep duration on weekends and anxiety. Variables with P values < 0.20 were included in the multivariate model, which included race or ethnicity; sex; age; number of class shifts; continuous medication for anxiety, stress, or sleep; sleep duration on working days; and anxiety. After adjusting for confounding factors in the regression analysis, some variables lost the association with the outcome variable (TMD), which included race or ethnicity; sex; age; number of class shifts; continuous medication for anxiety, stress, or sleep; and sleep duration on working days. Therefore, these variables were excluded from the final model (P > 0.05). In the final adjusted model, the results indicated that academics with anxiety are three times more likely to have TMD (OR = 3.60; 95%CI = 1.79–7.24) compared to those without anxiety (**Table 3**).

Table 2. Prevalence of temporomandibular disorder and anxiety levels, according to Fonseca's Anamnesis Index and the Beck Anxiety Inventory, among academics in a university in Brazil in 2021 (n = 295)

	n	%
TMD		
Neither TMD	53	18.0
Mild TMD	128	43.4
Moderate TMD	81	27.5
Severe TMD	33	11.2
Anxiety		
Absence of symptoms	146	49.5
Mild anxiety	76	25.8
Moderate anxiety	45	15.3
Severe anxiety	28	9.5

TMD = temporomandibular disorder.

DISCUSSION

The present study demonstrated an association between TMD and anxiety, revealing a high prevalence of TMD (81.2%) and anxiety (50.5%) observed among university academics.

Table 3. Odds ratio (OR) and confidence intervals (95%CI) between the independent variables and temporomandibular disorder outcome calculated using the binary logistic regression analysis

Variables	Presence of TMD Crude OR (95%CI)	P*	Presence of TMD Adjusted OR (95%CI)	P*
Sleep duration/working days				
Enough	1	**0.041***	1	0.099
Insufficient	2.11(1.03–4.41)		2.01(0.87–4.64)	
Number of class shifts				
One or two shifts	1	0.190	1	0.342
Morning, afternoon, or night	1.53(0.79–2.98)		1.41(0.69–2.87)	
Race				
White	1	0.100	1	0.359
Non-white	2.08(0.86–5.06)		1.59(0.58–4.32)	
Sex				
Female	1	0.056	1	0.158
Male	1.98(0.98–4.02)		1.73(0.80–3.71)	
Age group				
17–20 years	1	**0.025***	1	0.054
21–57 years	2.13(1.10–4.13)		1.99(0.98–4.03)	
Anxiety				
No	1	**< 0.001***	1	**< 0.001***
Yes	3.94(2.00–7.7)		3.60(1.79–7.24)	
Use of sleep medication/stress/anxiety				
No	1	**0.025***	1	0.077
Yes	2.26(1.10–4.61)		1.99(0.92–4.27)	

*Wald test – P < 0.05, statistically significant.

OR = odds ratio; CI = confidence interval; TMD = temporomandibular disorder.

Adjusted for race or ethnicity; sex; age; number of class shifts; continuous medication for anxiety, stress, or sleep; duration of sleep; duration of sleep on working days; and anxiety

The Fonseca Anamnestic Questionnaire was chosen to assess TMD due to its availability in Portuguese, simplicity, and ease of application.[12] In the literature, various instruments have been investigated for evaluating TMD, including questionnaires, anamnestic and clinical indexes, and diagnostic criteria. The Research Diagnostic Criteria for TMD has been used by several authors.[17-23] The Uto-explanatory Screening Questionnaire recommended by the American Academy of Orofacial Pain was used by Manfredi et al.[24] for clinical examination of TMD. The Craniomandibular Clinical Dysfunction Index, developed by Helkimo[13] in 1974, is one of the pioneering tools for TMD evaluation. It aims to classify volunteers based on the severity of their TMD clinical signs. The Fonseca Anamnestic Questionnaire, developed in 1994 based on Helkimo's Anamnestic Index, is one of the few Portuguese instruments used to determine the severity of TMD symptoms. This questionnaire has been tested in patients with TMD and demonstrated a 95% correspondence with the Helkimo Anamnesis Questionnaire.[13] Researchers evaluating the Fonseca questionnaire, translated into Turkish and Arabic, provide strong evidence of its reliability as a screening tool for TMD.[25,26] Studies suggested that adapting the questionnaire to include only some of the original questions could potentially increase its reliability. However, the authors emphasized the importance of validation studies to ensure that the new version of the instrument maintains adequate psychometric characteristics.[27] While the Fonseca Questionnaire is a validated tool widely used for screening TMD, it cannot provide a definitive diagnosis and may not account for all factors that can influence the condition, such as psychosocial or behavioral factors. Therefore, clinical evaluation by a qualified healthcare professional is necessary for a comprehensive and accurate diagnosis of TMD.

The prevalence of TMD in our study was as follows: 18% of the academics did not have TMD, 43.4% had mild TMD, 27.5% had moderate TMD, and 11.2% had severe TMD. The results vary depending on the instruments used. In the present study, 38.7% of the academics required treatment. Among the 295 academics evaluated, 81.2% reported having some degree of TMD. This prevalence was similar to that reported by Garcia et al.,[28] which was 83.3% among dental academics. Using the same questionnaire, Minghelli et al.[29] found that 42.4% of university academics from various courses had some degree of TMD. Alamri et al.[30] reported that 54.2% of academics who studied health courses had TMD. Srivastava et al.[31] found a 36.9% prevalence among dental academics in Saudi Arabia, similar to the 31.7% prevalence reported in a study including Chinese medical academics. Based on these findings, it can be inferred that academics are likely to feel tense or nervous about various factors such as test evaluations and oral presentations, which may contribute to the development of TMD.

In our study, anxiety was evaluated according to the Beck Anxiety Inventory,[11] revealing that 50.6% of the academics experienced anxiety, with 15.3% experiencing moderate anxiety and 9.5% experiencing severe anxiety. These findings are consistent with those of Santos et al.,[32] who reported a 47.4% prevalence of anxiety among academics pursuing health courses, using the same instrument.

A statistically significant association was observed between the presence of TMD and anxiety, with academics experiencing anxiety having three and a half times the likelihood of developing TMD compared to individuals without anxiety. Some studies have reported a significant association between anxiety and TMD with a higher probability of dysfunction occurring in individuals who had anxiety.[33-35] However, a different result was observed in a study including dentistry academics, which showed no significant association between TMD and anxiety levels.[9] In another study, the prevalence of TMD was higher in women than in men.[30] Bezerra et al.[10] when conducting a study involving university academics found a higher frequency of TMD in single female individuals, aged 18–22 years. According to Yadav et al.,[36] the prevalence of TMD was higher in female individuals, accounting for 73% of all cases, and no significant association was found between TMD and sex or age.

Social isolation, changes in routine, and fear of COVID-19 caused an increase in the levels of anxiety, stress, and depression in the general population.[37] A study conducted by Medeiros et al.[23] to assess the influence of COVID-19 on TMD symptoms and their consequences reported that during the period of social isolation due to the pandemic, there was an increase in the prevalence of TMD symptoms, depression, and anxiety.

Our study did not find an association between TMD and sleep disorders. However, a previous study evaluated the association between TMD, anxiety (measured using the Beck Anxiety Inventory), and sleep disturbances in dental academics, considering enrollment periods. This study reported a relationship between TMD, sleep disturbance, and enrollment period, revealing that first-year academics had a higher prevalence of moderate to severe anxiety.[38] In another study, half of the academics exhibited moderate to severe anxiety symptoms, making them more susceptible to poor sleep quality compared to those with lower levels of anxiety.[39]

Studies have evaluated the association between bruxism, TMD, and anxiety. Daytime clenching or grinding has been identified as a significant risk factor for myofascial pain in patients with TMD (OR = 4.9).[40] Another study explored the association between self-reported sleep bruxism and factors such as age, sex, clinical subtypes of TMD, pain intensity, and degree of chronic pain in patients with TMD. The study found a significant correlation between the presence of sleep bruxism and age < 60 years, female sex, pain intensity, pain interference in their daily activities, and muscle and joint pathology.[41] Patients with self-reported awake bruxism undergoing orthodontic treatment did

not develop TMJ or masticatory muscle pain. However, self-reported awake bruxism was associated with higher levels of anxiety, depression, and a worse quality of life in patients undergoing orthodontic treatment.[38]

The limitations of this study include the online application of the research instrument, which prevented clinical examination to confirm TMD diagnoses. Another limitation was the sampling choice; including academics from other courses beyond the health care area might have yielded different results or variations between undergraduate courses.

The clinical significance of this study lies in identifying parafunctional habits, as the high prevalence indicates that the academic environment can become exhaustive, making academics anxious and influencing the emergence of these habits. Thus, it is necessary to create interventions to address emotional problems affecting academics to prevent the onset of TMD.

However, further studies are required to evaluate their association with other variables.

CONCLUSION

The results of this study revealed a high prevalence of TMD among academics undertaking health courses at a university in southern Brazil, with the highest prevalence of mild TMD.

Additionally, academics with anxiety were more likely to have TMD compared to those without anxiety.

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Intensity-modulated radiation therapy for early-stage breast cancer: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Radiation therapy (RT) is a standard treatment for non-metastatic breast cancer and is associated with acute and late toxicities. Intensity-modulated RT (IMRT) may decrease toxicity and is convenient for patients.

OBJECTIVES: To assess the efficacy and safety of IMRT in women with early stage breast cancer.

DESIGN AND SETTING: Systematic review study; Multi-institutional centers.

METHODS: Seven databases were searched. Randomized controlled trials (RCT) comparing IMRT with any "non-IMRT" strategies were included. Primary outcomes were local control and acute toxicity. Cochrane Handbook was use to plan and conduct the review, and PRISMA 2020 was used to report results.

RESULTS: Five RCT involving 2,556 women (n = 1,283 IMRT; n = 1,274 control arm) were included. Baseline characteristics were similar between trials and arms. Local relapse-free survival rates were not different (hazard-ratio [HR] 0.62; 95%confidence interval [CI] -0.38 to 1.62; P > 0.05); however, IMRT reduced the overall acute toxicity (RR 0.69, 95%CI 0.58 to 0.82; P < 0.00001) and acute moist desquamation (risk-ratio [RR] 0.71, 95%CI 0.60 to 0.82; P < 0.00001). Lymphedema and pneumonitis rates, and survival outcomes were not affected by IMRT. The 2-year telangiectasia rate was decreased with IMRT (RR 0.66, 95%CI 0.47 to 0.93; P = 0.02); however, edema, pain, pigmentation, or fibrosis remained unaffected. IMRT did not improve cosmesis.

CONCLUSIONS: IMRT improved acute toxicity and lowered telangiectasia rates, without affecting oncological and aesthetic outcomes.

SYSTEMATIC REVIEW REGISTRATION: This review was registered at Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD010420. https://doi.org/10.1002/14651858.CD010420.

INTRODUCTION

Breast-conserving surgery (BCS) followed by radiation therapy (RT),[1,2] with or without systemic therapy, is the standard treatment for early-stage breast cancer. RT has been used in patients with breast cancer who have undergone radical mastectomy or breast-conserving treatments.[3,4]

After RT, approximately 30% of women develop high-grade acute skin toxicity, which significantly affects their quality of life.[5] The primary risk factors for acute radiation-induced toxicity include large breast size and variations in radiation doses within tissues.[6] However, most studies have not mentioned quality assurance standards. Given that women with breast cancer often have good prognoses and long life expectancies, reducing both acute and late toxicities while maintaining the effectiveness of RT is an important strategy.

Conventional RT involves dose distribution calculations based on a single patient outline, potentially contributing to both acute and late toxicities. Advancements in radiation oncology, including three-dimensional conformal RT and intensity-modulated RT (IMRT), have improved dose distribution homogeneity. IMRT enables the modulation of radiation beam intensities in two ways:[7,8] the field-in-field technique, and inverse planning.

IMRT in breast cancer reduces radiodermatitis[9] and improves breast cosmesis. However, clinicians do not routinely use it due to increased costs and associated complexity.[10,11]

OBJECTIVE

This systematic review aimed to assess the effectiveness and safety of IMRT in women with early stage breast cancer.

METHODS

Design and setting

This is a systematic review of randomized controlled trials (RCTs) with a protocol previously registered in the Cochrane Database.[12] The review was conducted according to the Cochrane Handbook for Reviews of Interventions[13] and reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2020) statement.[14]

Criteria for including studies

Study design: Only RCTs were considered.

Participants: Women with pathologically confirmed ductal carcinoma in situ or nonmetastatic invasive breast cancer (stages I, II, and III) who underwent conservative treatment, including breast surgery, axillary management, and RT of the whole breast, with or without nodal chain inclusion. Systemic therapies were allowed.

Intervention: An experimental intervention was defined as any type of IMRT, including inverse-planning IMRT using linear accelerators and field-in-field techniques and other methods.

The control group received external-beam RT without IMRT. Hypofractionated RT was included.[15,16] Treatments using integrated or sequential boost (electron beam, brachytherapy, or photon beam delivery) were included. Partial breast RT was excluded. **Supplementary Material** (https://t.ly/noSz6) provides information about RT treatment planning volumes.

Outcomes

Primary outcomes:

1) Local control, defined as recurrence in the ipsilateral breast, from randomization to the development of any local recurrence during follow-up (time-to-event outcome).
2) Acute toxicity related (breast, skin, lungand heart) was considered within 3 months of RT completion. It was classified according to the scales used by the authors of each study, otherwise, we classified them according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[17]

Secondary outcomes:

3) Overall survival, defined as the time from randomization to any-cause death during follow-up.
4) Disease-free survival, defined as the time from randomization to relapse during follow-up.
5) Late toxicity, was considered after > 6 months of RT completion. It classified according to the scales used by the authors; otherwise, we classified them as grade 3 or 4 toxic events according to the NCI-CTC.
6) Cosmesis was classified according to the scales used by authors; otherwise, we used scores from the Harvard/Radiation Therapy Oncology Group (RTOG)/National Surgical Adjuvant Breast and Bowel Project criteria.[18]
7) Quality of life was classified according to the scales used by authors or current scores (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire C30 and BR-23, Global Health Score, and Arm Symptoms Score).

Search Methods and Analyses

Details of search sources and strategies are provided in **Supplementary Material** (https://t.ly/noSz6).

The risk of bias assessment was performed independently by two authors using the Cochrane Collaboration's risk of bias tool.[19] A third author resolved disagreements. **Appendix 1** summarizes the risk of bias and the reasons for each judgment (https://t.ly/noSz6).

The unit of analysis was the individual participant. For bilateral synchronous tumors, each treatment was individually analyzed.

The methodological and clinical heterogeneities of the included RCTs were evaluated. Statistical heterogeneity was assessed using the chi-square test ($P < 0.1$ indicating significance) and I^2 test ($I^2 > 50\%$ indicating high inconsistency among RCTs).

Risk ratios (RR), hazard ratios (HR), and mean differences were used to estimate effects for dichotomous, time-to-event, and continuous variables, respectively, with a 95% confidence interval (95%CI).[20] Meta-analysis was conducted using random-effects models due to expected diversity among RCTs. Review Manager 5.4 software was used for analysis.[17]

Publication bias was investigated by visually inspecting funnel plots if at least ten studies were included in a single meta-analysis.

Authors of the included studies were contacted for missing data. Missing standard deviations were calculated using reported 95%CIs and/or standard mean errors.

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations approach.[21] Justifications for all judgments were presented and incorporated in the summary of findings tables.

RESULTS

After searching major databases and trial registries, 1,593 records were retrieved. After removing 380 duplicate records, 1,195 records were screened based on titles and abstracts and 1,180 were excluded. Fifteen full-text records were evaluated, resulting in the inclusion of five RCTs reported in 13 records.[22-34]

A flowchart of the included studies is shown in **Figure 1**. Patient characteristics are summarized in **Table 1**.

Among five RCTs, three compared IMRT with conventional RT (2D)[20,21,22] and two[23,24] compared IMRT with 3D-conformal RT. The following trials were included in this study.

1) Cambridge Trial (five articles):[20,26-29] This RCT included 815 patients with, which were treated with standard RT, or re-treated with simple IMRT. Breast tissue toxicities were assessed at 5 years using photographic and clinical assessments. The groups were compared using logistic regression.

2) Royal Marsden Trial:[21] This RCT included 306 women with early stage breast cancer treated with conventional fractionation. The primary outcome was a change in breast appearance, and the secondary outcomes were patient's self-assessment of breast discomfort, breast hardness, quality of life and physician's assessment of breast induration.
3) Sunnybrook Trial:[22,32] In this RCT, the authors from two Canadian institutions included 358 women. The primary outcomes were rates of acute skin reactions and late breast pain. Secondary endpoints included breast cosmetics; quality of life; and local recurrence-free, disease-free, and overall survivals. Patients were analyzed each week during treatment and for up to 6 weeks thereafter.
4) KROG 15-03 trial:[24] This RCT included patients from six tertiary South Korean institutions. The primary endpoint was local recurrence-free survival at 3 years. The secondary endpoints were overall, recurrence-free, and distant metastasis-free survivals; treatment-related toxicity; and dosimetric issues.
5) MC2 Trial:[23,30,31] This German single-site RCT included 502 patients from two institutions. The primary endpoints were local control and cosmesis. The secondary endpoints were quality of life, overall survival, and disease-free survival.

Across all five studies, 2,556 women who fulfilled the inclusion criteria were included in the IMRT arm (n = 1,283) and control group (n = 1,274). Baseline characteristics were similar between trials and radiotherapy arms. Medium-sized breasts (595 mL) were most common among the breast with known size. Smoking rate was approximately 10%. The mean volume of breast tissue receiving 107% and 105% of the prescribed dose (V107% and

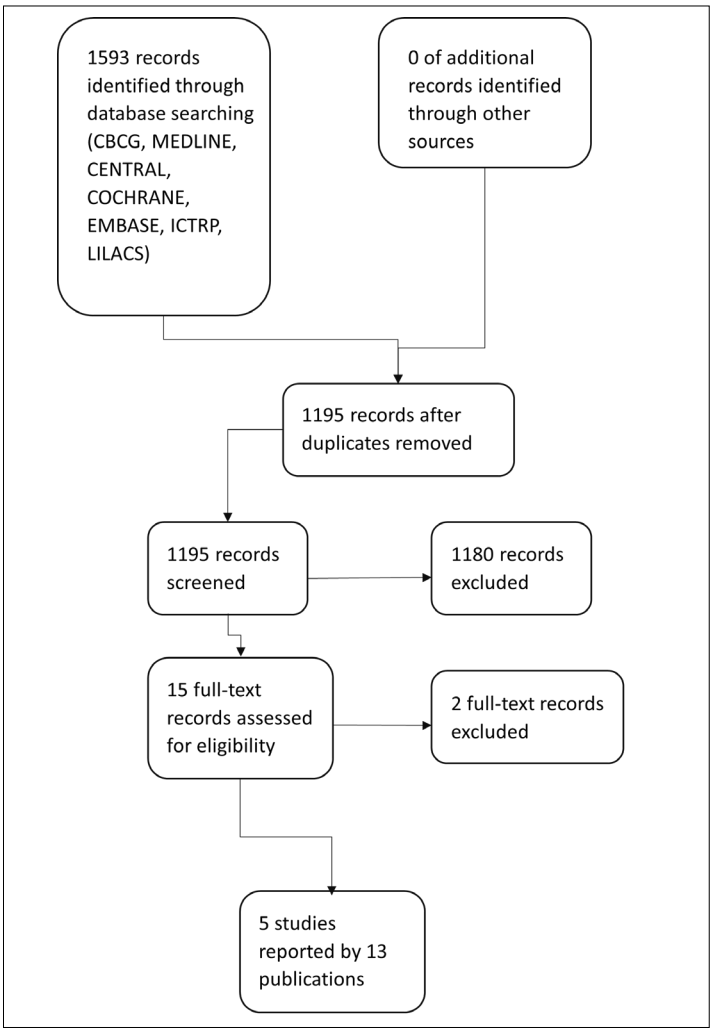

Figure 1. Flowchart of the Included Studies.

Table 1. Summary of Patient Characteristics in the Included Studies

Included Study	Sunnybrook Trial	Cambridge Trial	Royal Marsden Trial	MC2 Trial	KROG 15-03 Trial
RT Schedule	50Gy/25fx	40Gy/15fx	50Gy/25fx	50.4Gy/28fx + 16Gy/8fx (sequential) 50.4Gy/28fx + 64.4Gy/28fx (integrated)	50.4Gy/28fx + 9Gy/5fx (sequential) 50.4Gy/28fx + 57.4Gy/28fx (integrated)
Age (years, mean, SD/range)	57.1 (SD 10.7)	58 (34-78)	31.2 (SD 22.7)	56 (27–76)	52 (SD 9)
Smoking (n, %)	19 (11.2%)	22 (10%)	-	-	-
Chemotherapy (n, %)	52 (30.8%)	46 (20%)	63 (42%)	219 (43.6%)	442 (64%)
Hormone therapy (n, %)	67 (39.9%)	158 (73%)	126 (85%)	351 (69.9%)	505 (73%)
DM (n, %)	8 (4.7%)	9 (4%)	-	-	51 (7.5%)
Arterial hypertension (n, %)	42 (24.7%)	5 (2%)	-	-	143 (42%)
Breast size (ml, mean, SD)	585 (SD 133.8)	1,260 (285–3,436)	-	-	-
Boost (n, %)	51 (30%)	141 (62%)	150 (100%)	251 (99.2%) – IMRT arm 236 (94.7%) – 3D arm	100%
Photon energy	6 MV in 137 (80.6%)	-	6 MV/10MV	6 MV (100%)	6 MV (100%)
Mean volume V107% or V105%	V107 = 2.6%	V107 = 9.6 (0–369)	V105 = 5–10% in 6.2%	-	-
Axillary RT (n, %)	-	0	17 (11%)	72 (14.3%)	-
Supraclavicular fossa RT (n, %)	-	4 (2%)	42 (29%)	-	-

Fx = fractions; RT = radiotherapy; SD = standard deviation; DM = diabetes mellitus; MV = megavolt.

V105%, respectively) was low in the IMRT arm, as expected. RT to the axilla or supraclavicular fossa and boosts were included in the analysis (**Table 1**). We assessed performance and detection bias of each outcome of interest (**Supplementary Material** https://t.ly/noSz6). **Figure 2** summarizes the risk of bias after pooling the included studies.

Primary outcomes

Table 2 illustrates the results of the primary outcomes.

Local control

Four out of five studies reported information regarding local recurrence-free survival.[20,22-24] Recurrence events from studies comparing IMRT with 3D and conventional RT were grouped. No difference were observed among the groups (RR 1.43; 95%CI 0.71 to 2.87; I^2 = 0%; P = 0.61; n = 2,247; 4 studies; low certainty evidence) (**Supplementary Material** https://t.ly/nUr8Z).

Acute toxicity

All studies addressed this outcome considering the incidence of any acute toxic events (within 3 months) only in the irradiated breast, instead of the lung, heart, and other organs at risk. We grouped patients using the NCI-CTC into four categories—those with at least grade 2 skin reactions; those with moist desquamation, those with lymphedema, and those with pneumonitis.

Three RCTs[20,22,24] reported skin reaction, two[20,22] reported moist desquamation, two[23,24] reported lymphedema, and one[24] reported pneumonitis. Postoperative toxicities (wound complications, hematoma, and local infection) were not considered in these studies. The following results were obtained:

- Overall acute toxicity: lower risk with IMRT than with conventional RT (RR 0.69, 95%CI 0.58 to 0.82; I^2 = 0%; P = 0 < 0.0001; n = 1,836; 3 studies; Low evidence certainty; **Figure 3**).
- Moist desquamation: lower risk with IMRT than with conventional RT (RR 0.71, 95%CI 0.60 to 0.83; I^2 = 0%; P = 0 < 0.0001; n = 1,824; 3 studies; very low evidence certainty; **Figure 4**).
- Lymphedema: no difference between IMRT and conventional RT (RR 0.62, 95%CI 0.36 to 1.05, P = 0.07; I^2 = 0%; n = 1,051; 2 studies; very low evidence certainty).
- Pneumonitis: no difference between IMRT and conventional RT (RR 0.65, 95%CI 0.25 to 1.65, P = 0.36; n = 690; 1 study; very low evidence certainty).

Secondary outcomes

Overall survival

Four of the five studies reported this outcome.[20,22-24] The HR obtained from three studies[20,23,24] was 0.32 (95%CI -0.66 to 1.30; n = 2006; I^2 = 0%; P = 0.52; moderate certainty of evidence).

Disease-free survival

Three of the five studies reported disease-free survival.[22-24] The HR was obtained from two studies.[23,24] Data from the Sunnybrook Trial[22] could not be obtained because of the impossibility of calculating HRs using Parmar's method.

The HR from two studies[23,24] showed no significant differences in disease-free survival (HR 0.7; 95%CI -0.14 to 1.54; n = 1,192; I^2 = 0%; P = 0.1; moderate certainty of evidence).

In the Sunnybrook Trial,[22] no differences were observed between the groups. At 9 years, the disease-free survival rate was 82.4% for IMRT and 82% for conventional RT (P = 0.90).

Late toxicity

Late toxicity was evaluated in four studies[20-22,24] as skin toxicity (telangiectasia, pigmentation changes, and breast seroma), breast pain, breast induration, or fibrosis. Toxicity to the lungs, heart, and other at-risk organs was not analyzed because of the lack of such information in the included studies.

Late skin toxicity (telangiectasia, edema, pigmentation change)

Three RCT assessed this outcome[20,22,24] and the following results were found at 2 years (**Supplementary Material** https://t.ly/nUr8Z):

- Telangiectasia: lower risk with IMRT than with conventional RT (RR 0.66; 95%CI 0.47 to 0.93; n = 1,374; 3 studies; I^2 = 0%; P = 0.02; very low certainty evidence);
- Breast edema: no difference between IMRT and conventional RT (RR 0.76, 95%CI 0.43 to 1.35; n = 1,437; 2 studies; I^2 = 56%; P = 0.34; very low certainty evidence);
- Breast skin pigmentation: no difference between IMRT and conventional RT (RR 0.75, 95%CI 0.55 to 1.03; n = 760; 1 study; P = 0.07; very low certainty evidence).

Breast pain

Four RCT assessed this outcome.[20,21,24] The Royal Marsden Trial reported no difference between the groups but did not provide the numeric data necessary to perform a meta-analysis. We performed a meta-analysis of two RCTs[20,22] that used a four-point scale to rank outcomes.

No difference in breast pain was observed between the groups at 24 months (RR 0.94, 95%CI 0.83 to 1.07; n = 1,496; 3 studies; I^2 = 0%; P = 0.37; very low certainty evidence) (**Supplementary Material** https://t.ly/nUr8Z).

Assessment of breast induration or fibrosis

Clinical breast induration was assessed in some studies.[20-22,24] However, a pooled analysis including all studies of breast induration data could not be performed because the outcome was assessed differently in the Royal Marsden Trial.

Figure 2. Risk of Bias Summary.

Table 2. Main Findings

Outcomes	Anticipated absolute effects* (95%CI)		Relative effect (95%CI)	Nº of patients (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Non-IMRT	Risk with IMRT				
Local control assessed with: Risk Ratio follow-up: mean 5 years	Low 0 per 1000	**0 per 1000** (0 to 0)	**RR 2.03** (0.85 to 4.85) [Local Control]	2249 (3 RCTs)	⨁⨁⊖⊖ Low[a,b]	
Acute toxicity - overall (grades 3 and 4) - 2D control group assessed with: frequency of patients who experienced at least one acute toxicity	18 per 100	**11 per 100** (8 to 14)	**RR 0.61** (0.46 to 0.81)	1146 (2 RCTs)	⨁⨁⊖⊖ Low[a]	
Acute toxicity - moist desquamation assessed with: frequency of patients who experienced the event	24 per 100	**17 per 100** (14 to 20)	**RR 0.71** (0.60 to 0.83)	1824 (3 RCTs)	⨁⊖⊖⊖ Very low[a,c]	
Acute toxicity - lymphedema assessed with: frequency of patients who experienced the event	6 per 100	**4 per 100** (2 to 6)	**RR 0.62** (0.36 to 1.05)	1151 (2 RCTs)	⨁⊖⊖⊖ Very low[a,c]	
Acute toxicity - pneumonitis assessed with: frequency of patients who experienced the event	3 per 100	**2 per 100** (1 to 5)	**RR 0.65** (0.25 to 1.65)	690 (1 RCT)	⨁⊖⊖⊖ Very low[b,d]	
Overall survival follow-up: median 5 years	Low 0 per 1000	**0 per 1000** (0 to 0)	**RR 0.32** (-0.66 to 1.30) [Death]	2006 (3 RCTs)	⨁⨁⊖⊖ Low[b,e]	
Late toxicity - skin - Telangiectasia assessed with: frequency of patients who experienced the event follow-up: 24 months	11 per 100	**7 per 100** (5 to 10)	**RR 0.66** (0.47 to 0.93)	1374 (3 RCTs)	⨁⊖⊖⊖ Very low[a,d,e]	
Late toxicity - skin - Pigmentation assessed with: frequency of patients who experienced the event follow-up: 24 months	23 per 100	**17 per 100** (13 to 24)	**RR 0.75** (0.55 to 1.03)	633 (1 RCT)	⨁⊖⊖⊖ Very low[a,c]	
Late toxicity - skin, edema assessed with: frequency of patients who experienced the event	35 per 100	**27 per 100** (15 to 48)	**RR 0.76** (0.43 to 1.35)	1083 (2 RCTs)	⨁⊖⊖⊖ Very low[a,d,e]	
Late toxicity - breast pain assessed with: frequency of patients who experienced the event follow-up: 24 months	38 per 10	**36 per 100** (32 to 41)	**RR 0.94** (0.83 to 1.07)	1496 (3 RCTs)	⨁⊖⊖⊖ Very low[a,c]	
Late toxicity - breast induration or fibrosis assessed with: frequency of patients who experienced the event follow-up: 24 months	55 per 100	**52 per 100** (43 to 64)	**RR 0.96** (0.78 to 1.18)	1324 (3 RCTs)	⨁⊖⊖⊖ Very low[a,c,e]	
Overall cosmesis assessed with: frequency of patients with excellent or good evaluation follow-up: 24 months	86 per 100	**85 per 100** (79 to 91)	**RR 0.99** (0.92 to 1.06)	495 (1 RCT)	⨁⨁⊖⊖ Low[a]	

It continues...

Table 2. Continuation

Outcomes	Anticipated absolute effects* (95%CI)		Relative effect (95%CI)	Nº of patients (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Non-IMRT	Risk with IMRT				
Quality of life follow-up: mean 5 years	The mean quality of life was 0	mean **1.45 more** (0.1 fewer to 0.12 more)		2.96 (1 RCT)	⨁⊖⊖⊖ Very low[a]	The Cambridge Trial used the EORTC QLQ BR-23 and C30 at 6, 24, and 60 months and they reported results at 2 and 5 years showing no significant differences between groups at 24 and 60 months. The Royal Marsden Trial reported no significant differences between groups at 24 and 60 months (EORTC QLQ C-30 and BR-23). The Sunnybrook Trial reported no significant differences between groups at 1 month (EORTC QLQ C-30 and BR-23). No numeric data was provided for meta-analysis.
Overall cosmesis - excellent or good evaluation - At least 5-year of follow up assessed with: frequency of patients with excellent or good evaluation follow-up: 60 months	59 per 100	**61 per 100** (56 to 66)	**RR 1.03** (0.95 to 1.11)	964 (3 RCTs)		
Overall cosmesis - excellent or good evaluation - At up to 1-year of follow-up	784 per 1000	**800 per 1000** (706 to 909)	**RR 1.02** (0.90 to 1.16)	753 (2 studies)		
Quality of life - Baseline	The mean quality of Life - Baseline was 0	MD **0.01 higher** (0.08 lower to 0.1 higher)	-	764 (1 study)	-	
Quality of life - 6 months	The mean quality of Life - 6 months was 0	MD **0.02 lower** (0.12 lower to 0.08 higher)	-	705 (1 study)	-	
Quality of life - 2 years	The mean quality of Life - 2 years was 0	MD **0.04 higher** (0.06 lower to 0.14 higher)	-	669 (1 study)	-	
Quality of life - 5 years	The mean quality of Life - 5 years was 0	MD **0.01 higher** (0.1 lower to 0.12 higher)	-	504 (1 study)	-	
Quality of life - total	The mean quality of Life - total was 0	MD **0.01 higher** (0.04 lower to 0.06 higher)	-	2642 (4 studies)	-	

*The risk in the intervention group (95% confidence interval) was based on the assumed risk in the comparison group and the relative effect of the intervention (95%CI). CI = confidence interval; MD = mean difference; RR = risk ratio; a) Unblinded patients We downgraded two levels (-2) for study limitations: b) We were not certain about patients/personnel blinding. Therefore, we downgraded CI by one level (-1): c) Wide CI, including both significant benefits and significant harm. We downgraded the CI one level (-1): d) Wide CI, including both significant benefits and harm. Low rate of events. We downgraded two levels: (-2) and e) high inconsistencies among the studies. We downgraded one level (-1).

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to differ substantially from the effect estimate.

In the Royal Marsden Trial, clinical breast induration was assessed by clinicians at different locations in the breast, and induration was observed in significantly fewer patients in the IMRT group (**Supplementary Material** https://t.ly/nUr8Z). When the author compared changes in breast appearance with clinician-reported induration, 37% of the patients who reported any change in breast appearance at 2 years also had clinician-reported induration assessed at 24 months. A similar pattern emerged at 60 months.

The meta-analysis from three studies[20,22,24] revealed no difference in fibrosis between the groups at 24 months (RR 0.96; 95%CI 0.78 to 1.18; n = 1324; 3 studies; I^2 = 49%; P = 0.67; very low certainty evidence).

Cosmesis

Four of the five clinical trials evaluated cosmesis. One study[24] described the results using the Harvard scale[35] and a three-point

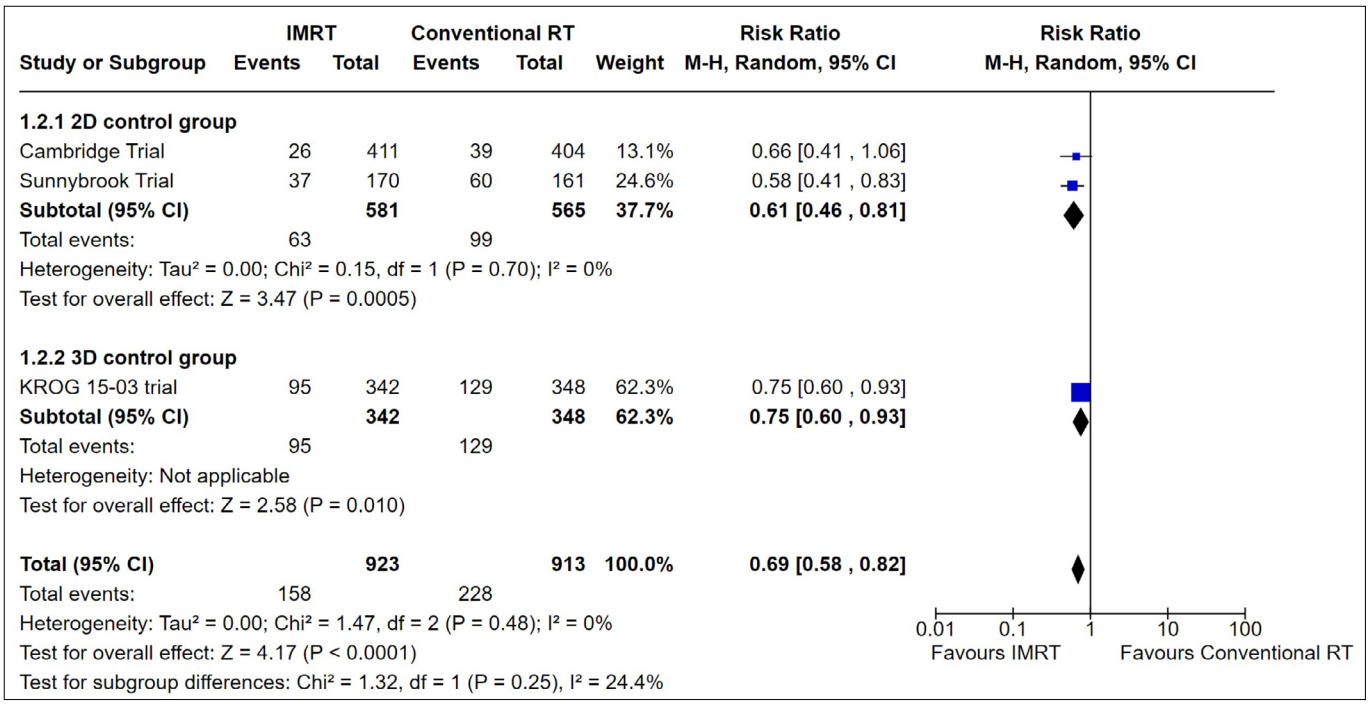

Figure 3. Forest Plot for Acute Overall Toxicity.

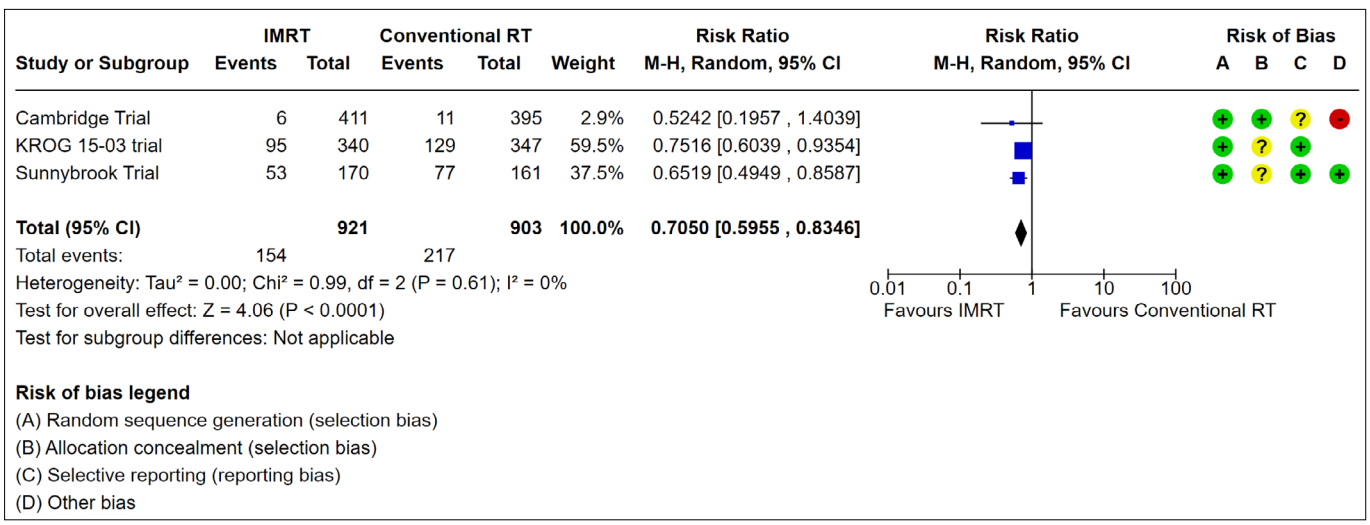

Figure 4. Forest Plot for Moist Desquamation.

scale, two[20,21] used a three-point scale, and one[22] used the EORTC cosmetic breast cancer rating system.

The Cambridge Trial evaluated the photographic assessment of breast shrinkage as the primary endpoint. Frontal photographs of both breasts were taken at baseline and at 5 years post-RT. Breast cosmesis was scored on a validated three-point scale (good, moderate, or poor) by seven observers.

The MC2 Trial evaluated breast photographs as the primary endpoint. A blinded physician evaluated the photographs using a quantitative digitizer scoring system to calculate the breast retraction assessment (BRA) scores. Photographs of both breasts were taken before RT (baseline) and at 6 weeks and 2 years post-treatment. Additionally, cosmesis was assessed by treating physician and patients using the RTOG/Harvard Scale and was independently scored as excellent, good, fair, or poor. At 2-year follow-up, 378 of 502 patients (75.3%) underwent planned photographic assessments. The baseline (range) breast retraction assessment (pBRA) was 8.9% (0.5%–47.5%) for IMRT and 8.7% (0.2%–53.1%) for 3D imaging. Six weeks post-RT, cosmesis was not inferior in the IMRT group than in the control group (median [range] pBRA of 9.1% [0.7%–43.9%] vs. 9.1% [0.2%-51.2%], respectively). Non-inferiority was also detected for cosmetic outcomes 2 years post-treatment, with a median (range) pBRA of 10.4% (2.2%–32.6%) and 9.8% (0.4%–63.2%) in the intervention and control groups, respectively (95%CI 0.317% to 0.107%; P = 0.332). Cosmetic assessment according to the Harvard criteria by treating physician and patients was available 6 weeks, and 2 years post-treatment. No significant cosmetic differences were detected using these criteria between the two treatment arms at both time points of assessment

The Royal Marsden Trial evaluated breast photographs as a cosmetic outcome. Frontal images of both breasts were collected at baseline and 1, 2, and 5 years after treatment. Three observers provided scores using a 3-point graded scale (none/minimal = 0, mild = 1, marked = 2) based on the changes in breast size and shape.

The Sunnybrook Trial provided cosmetic outcomes in its second publication, with scoring based on the EORTC cosmetic breast cancer rating system during a median of 9.8 years of follow-up. The proportion of good-to-excellent cosmetic outcomes was similar between the groups (82.0% vs. 82.7% for IMRT and conventional RT, respectively). They also reported self-reported cosmesis rates in patients using the Breast Cancer Treatment Outcome Scale questionnaire.[36]

The pooled analysis from four studies[20-22,24] revealed no difference in fibrosis between the groups at 24 months (RR 1.01, 95%CI 0.98 to 1.05; 2930 patients; 4 studies; I^2 = 0%; P = 0.54; very low certainty evidence) (**Supplementary Material** https://t.ly/nUr8Z).

Quality of life

Three of the five studies described this outcome.[20,21,22] Detailed information is available in **Supplementary Material** (https://t.ly/nUr8Z).

DISCUSSION

This systematic review included five RCTs suggesting the benefit of reduced dose inhomogeneity for acute skin toxicity, with a 31% reduction in corresponding rates. Moreover, fewer patients presented grades ≥ 2 acute skin toxicities in the IMRT group, representing a 24% reduction. The rates of acute toxicity and local control did not differ between the groups. The overall and disease-free survival rates were similar between IMRT and conventional RT. The telangiectasia rate exhibited a 34% reduction in the IMRT group; no differences were observed in the remaining late toxicities such as breast fibrosis, breast induration, and breast pain.

This review suggests that IMRT is as effective as a non-IMRT modality concerning local control, overall survival, and disease-free survival and is less toxic to patients, regardless of other clinical features. We suppose that the reduction in acute and late toxicity outcomes has generated therapeutic benefits.

The increase in radiodermatitis rates may generate increased medical and multidisciplinary team consultations during treatment,[37] RT interruptions owing to pain,[38] and treatment dropout rate and reduced effectiveness. The use of hypofractionation would decrease the chance of patient withdrawal from treatment. Pertinently, the Cambridge Trial adopted moderate hypofractionation in both arms, which supports the use of IMRT even in the hypofractionation setting.

Three studies evaluated aesthetic outcomes. Our review revealed no differences between the groups.

The improvements in aesthetic outcomes observed in individual studies did not translate into significant benefits when patients were grouped for this specific endpoint, probably due to the difference in assessment, methods and timing across the studies. Furthermore, some late toxicity events (telangiectasia) may be accounted as either late toxicity or aesthetic dissatisfaction. Interpreting these data is challenging.

Regarding quality of life, pooling the data was not possible due to the lack of available data at fixed time points during follow-up. No difference was observed between the groups concerning this endpoint analyzed individually.

Cost has been analyzed in other studies besides the RCTs included in this review; however, it has not been shown to correlate with clinical endpoints. Additionally, our study group included all IMRT modalities, including simple planning with field-in-field techniques, inverse planning with IMRT of static beams and arc beams, and even concomitant boost with IMRT arm. This inclusion allowed us to conduct the proposed analyses, but the cost and complexity of simple planning are undoubtedly lower than those of inverse planning, as exemplified by a publication form the group in Louisiana.[39] Considering this, we might infer that the use of simpler IMRT techniques would generate benefits as observed in

our study. Acute toxicity is directly linked to the risk of treatment interruption,[40] which can cause a greater demand for health services, leading to indirect effects on cost-effectiveness.

The risk of late toxicities is robustly related to the dose received by a specific tissue or organ.[40] The radiation dose inhomogeneity within the breast has been studied as an independent predictor of acute and late toxicities, including radiodermatitis and fibrosis or breast induration. The prescribed radiation dose can vary by up to 40% within the irradiated volume. IMRT is beneficial in in (a) improving dose homogeneity, (b) sparing the contralateral breast and the lungs or heart[11] (reducing late cardiac effects due to radiation),[41-43] and (c) diminishing the likelihood of toxicities and secondary malignancies over time.

Radio induced cardiac and lung toxicity can manifest decades after treatment. Thus, patients with breast cancer who benefit from cancer treatment experience or even die from late toxicities, especially cardiac and pulmonary toxicities. The studies included in this review did not have sufficiently long follow-up periods to analyze the impact of IMRT on cardiac toxicity. However, previous evidence, has shown a decline in the average doses received by such organs with the use of advanced technology.[24] The authors found a strong direct relationship between the rates of second primary cancers and cause-specific mortality and the mean doses to the lungs and heart.[44]

This review showed low overall quality of the evidence, due to the methodological quality of the RCTs. Although being randomized, most studies lacked generation of allocation sequences; allocation concealment; and blinding of participants, personnel, or outcome assessors or involved attrition bias.

The quality of evidence for the primary and secondary outcomes was considered low.

We observed some difficulty in examining late skin toxicities because many skin features occur late after treatment, and what may be considered indicators of late toxicity were often included in cosmetic analysis. Thus, we attempted to separate cosmetic analyses from toxicity itself, although this may introduce an interpretation bias.

Study Limitations:

1. Heterogeneity in treatment protocols and endpoints across included studies;
2. Low or very low certainty of evidence for most outcomes;
3. Limited follow-up duration in some studies;
4. Limited data on quality of life.

In our review, we grouped all types of IMRT. Thus, even in centers where IMRT alone is not available, a combination of field-in-field or "modulated" tangent fields with the classical opposed tangents technique may provide the same benefits we observed.

Well-planned and well-designed studies are necessary to provide evidence about the long-term effects of IMRT and assess patient-oriented outcomes that have been poorly addressed by available studies. Further studies are needed to identify and compare all techniques, modalities, and schemes of IMRT available to date to determine the optimal option among them. Technologies are evolving and, therefore, will likely offer less toxic treatments. Finally, a prespecified subgroup analysis, including biomarkers among other variables such as baseline and dosimetric issues of patients, is desirable.

CONCLUSIONS

In women with early stage breast cancer treated with surgery and postoperative RT, IMRT potentially reduces the risk of acute skin toxicity, specifically moist desquamation. However, no evidence suggests that IMRT improves local control, overall survival, disease-free survival, late toxicity, cosmesis, or quality of life better than conventional RT. The choice between IMRT and conventional RT should be individualized based on patient characteristics and treatment goals. Further research is needed to assess the long-term outcomes and quality of life in this population.

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Prevalence and quality of life associated with erectile dysfunction and lower urinary tract symptoms: a cross-sectional study

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ABSTRACT

BACKGROUND: Genitourinary health significantly affects the quality of life of men, particularly those in middle age. Recent studies have shown that more than half of the men aged over 40 years experience some degree of low urinary tract symptoms (LUTS) or erectile dysfunction (ED).

OBJECTIVE: To assess the prevalence of ED and LUTS in middle-aged men and correlate this with quality of life data.

DESIGN AND SETTING: A cross-sectional study was conducted in a municipality in the countryside of São Paulo.

METHODS: A trained team collected data between July 2021 and August 2022 through face-to-face interviews using a characterization instrument, International Prostate Symptom Score (IPSS), International Index of Erectile Function-6 (IIEF-6), and World Health Organization Quality-of-Life Scale.

RESULTS: The study included 375 male participants with a median age of 53 years (interquartile range [IQR] 38.5-66). The IIEF-6 showed the presence of some degree of ED in 51.1% (n = 188) of patients, with a median score of 25 (IQR 21-29). The IPSS revealed that 35.2% (n = 132) of the patients had some degree of LUTS, with a median score of 5 (IQR 2-11). The urological questionnaires had a direct proportional correlation with age ($P < 0.001$) and significant differences between the medians of different marital statuses ($P < 0.001$). The presence or severity of these disorders was inversely correlated with the individuals' quality of life ($P < 0.001$).

CONCLUSIONS: ED and LUTS significantly correlated with the quality of life, marital status, and age in men.

INTRODUCTION

The registration rates for men in primary healthcare services are low within the Brazilian National Health System (SUS), suggesting that fewer men utilize these services and, as a result, participate in fewer preventive and health-promoting initiatives.[1] Consequently, the disparity in healthcare engagement contributes to the life expectancy of men, which is 7.1 years shorter than that of women. This also correlates with a higher incidence of illness among men and elevated financial burden on the healthcare system, thereby constituting a significant public health concern.[2,3]

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) have been recognized and treated since ancient times, with records of early interventions found in Egyptian and Greco-Roman texts.[4,5] These conditions are critically important for men's health because of their high prevalence and significant impact on their quality of life. The Brazil LUTS study reported that 75% of men over 40 years of age experienced some degree of LUTS.[6] Similarly, an American study found that the combined prevalence of minimum, moderate, and complete erectile dysfunction was 52%.[7]

The pathophysiology of these conditions often involves overlapping mechanisms of endothelial and nerve dysfunctions and impaired blood flow, causing symptoms that affect daily life chronically, such as pollakiuria, nocturia, urinary urgency, voiding (obstructive) symptoms (straining, weak stream, intermittent stream, and incomplete emptying), or post-micturition symptoms (post-micturition dribbling).[8] Despite their prevalence and impact, social taboos and

a cultural tendency among men to perceive themselves as invulnerable contribute to a reluctance to seek medical help.[6] This reticence exacerbates health disparities and challenges faced by men, underscoring the need for targeted public health strategies to address these critical issues.

Genitourinary health is a primary health concern in men. Despite its significance, there remains a reticence to openly address this issue because of persistent taboos. This is compounded by the prevalent attitude among men who often perceive themselves as impervious and indestructible. Thus, they tend to dismiss or ignore conditions that could cause discomfort.[9] As a result, men shy away from discussing these issues, significantly impacting their quality of life and placing additional strain on the healthcare system.

Understanding the prevalence of genitourinary health problems in the population is necessary to efficiently tackle this problem.

OBJECTIVE

This study aimed to assess the prevalence of ED and LUTS in middle-aged men and correlate these with quality of life data and sociocultural characterization.

METHODS

This study is an observational, cross-sectional, and analytical investigation carried out between July 2021 and August 2022, following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10] The research was conducted in Bauru, São Paulo, a city situated in the central-western region of the state. Bauru has an estimated population of 380,000 residents and a Human Development Index of 0.801. To ensure the representativeness of Bauru's diverse population, a specific urban area was selected based on data provided by the municipal health department. This selected region has a population of 20,266 as estimated by the Brazilian Institute of Geography and Statistics (IBGE).[11,12]

The sample comprised middle-aged men residing in the selected neighborhood who completed all the questionnaires. Individuals under 18 years of age, middle-aged but not residing in the designated area, or who did not complete the questionnaires were excluded from the study.

Sample size was computed using confidence intervals. The confidence level was set at 95% and the margin of error was 5%. The estimated proportion of the population was calculated based on the prevalence of LUTS (69.0%) and ED (39.5%).[6,13] The minimum calculated sample size was 368 individuals.

The sampling was conducted in two stages. First, the territory was divided into two large areas based on the service territory of the local health center. Next, a street at the study site was chosen as the starting point (Street 1) for each large area, and, from there, interviews were conducted sequentially on both sides of the road. The interviewers started with the streets in the vertical direction and then followed the streets in the horizontal direction. Data collection ended when all streets in the area were covered.

To ensure consistency in data collection, the study utilized Google Forms® to standardize the instruments used. Additionally, interviewers were trained and calibrated through a meeting before data collection, explaining the details of our study, how to approach the interviewees, and addressing any potential uncertainties that may arise during the interview. Using smartphones, data were collected between July 2021 and August 2022 in men's homes. The interview began after approaching the homes, identifying the participant, and the participants agreeing to participate by signing the informed consent form.

Instruments used for data collection were internationally validated questionnaires. In this study, the transcripts were converted to digital format according to the original layout in the following sequence:

1. Instrument for the sociocultural characterization of the participants: A questionnaire was prepared by the authors themselves with the aim of characterizing the individuals through variables such as age, self-declared color (white, black, yellow, brown, and indigenous), religion (Catholic, Evangelical, other, none), and marital status (single, married, stable union, widowed, separated, other).
2. 'World Health Organization Quality-of-Life Scale (WHOQOL-BREF)': A 5-point Likert scale developed by the WHO, in which quality of life is assessed through two questions on perception and satisfaction, as well as 24 other questions divided into four domains (physical, psychological, social relations, and environment), which, in the end, give a score of 0-100 for each domain.[14,15]
3. 'International Prostate Symptom Score (IPSS)': A scale widely used in the assessment of LUTS and voiding dysfunction and validated for the Portuguese language.[16] The definition used to confirm the presence of LUTS was a score between 2 and 5 for any IPSS question (symptoms occurring less than half the time or more; or nocturia ≥ 2).[6,17]
4. 'International Index of Erectile Function-6 (IIEF-6)': A validated score for the assessment of sexual function that aids in the diagnosis and classification of ED.[18] It has shown to be as effective as the IIEF-5 and IIEF-15 variants of the score.[19,20]

After data collection, the data was transported and analyzed using Google Spreadsheets® and Jamovi® software (Jamovi OpenStats, Sidney, Australia). Descriptive statistics were performed by age group (≤ 39 years; 40-59 years; ≥ 60 years). Spearman and Kruskal-Wallis correlation tests were used to analyze the sample and associations between the variables, given their assumptions. The significance level adopted for statistical

analysis was 5%. In addition, the data are presented as median and interquartile range (IQR) based on the distribution pattern of the results.

This study was approved by the Research Ethics Committee (CEP), under protocol number 44434820.2.0000.5441, on June 30, 2023. The participants' consent was obtained by signing the informed consent form.

RESULTS

A total of 375 men with a median age of 53.0 years (IQR = 38.5 – 66.0) participated in this study. Of those interviewed, 225 (60.0%) were white, 203 (54.1%) were Catholic, and 212 (56.6%) were married. Demographic data are shown in **Figure 1**.

In the IPSS questionnaire,[16] the median score was 5 (IQR = 2–11), and the presence of LUTS, according to the criteria used in the study, was 257 (68.5%). In the IIEF-6 questionnaire,[18] the median was 25.0 (IQR = 21–29) and 188 (50.1%) patients had some degree of ED. Data on the IPSS and IIEF-6 scores are presented in **Table 1**.

Based on the first two questions of the WHOQOL-BREF questionnaire,[14] health perception and satisfaction were assessed. Regarding perception, 279 (74.4%) participants considered it GOOD or VERY GOOD, and regarding satisfaction, 267 (71.2%) reported being SATISFIED or VERY SATISFIED (**Table 2**).

Regarding the WHOQOL-BREF questionnaire,[14] **Table 3** shows the four domains (physical, psychological, social relationships, and environment) that were converted into a scale of zero to 100 points according to the syntax recommended by the score.

IPSS questionnaires[16] and IIEF-6[18] showed an inversely proportional correlation between their scores ($P < 0.001$). Furthermore, the presence and severity of the disorders measured by both questionnaires were inversely proportional to the final score of the quality of life domains measured by the WHOQOL-BREF.[14] Finally, age had a significant correlation, directly proportional to the presence and severity of symptoms in the IIEF-6 and IPSS questionnaires.[16-18] All data related to the urological questionnaires are shown in **Table 4**.

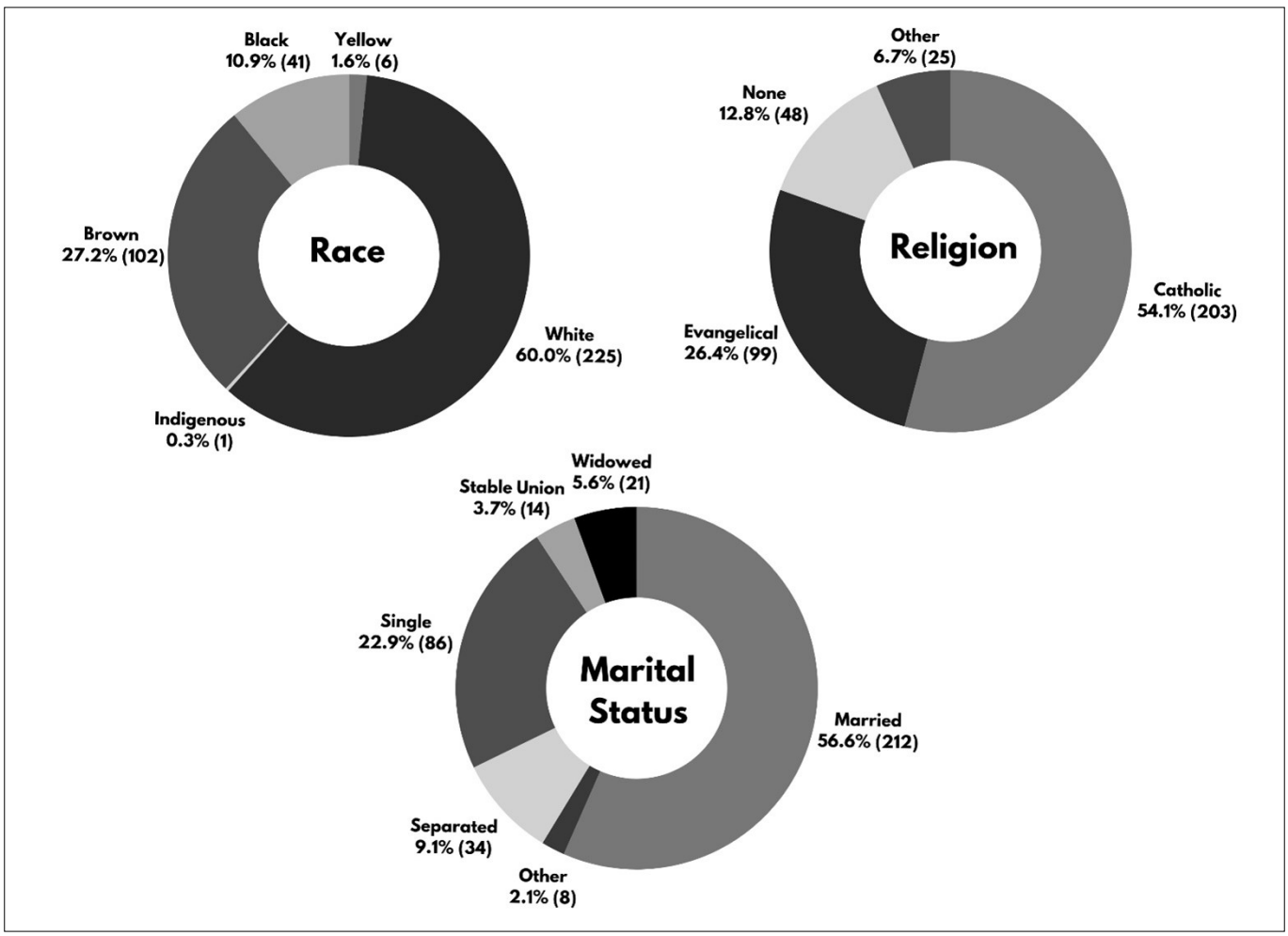

Figure 1. Sample characterization data.

Among the characterization data, only marital status showed a significant correlation with the data collection instruments, as shown in **Table 5**.

DISCUSSION

Men's health, constrained by the scope of promoting and preventing health issues, requires targeted attention. Nonetheless, men frequently seek professional healthcare only upon encountering health problems, often due to a confluence of factors, including sex and cultural, personal, physical, and historical influences.[21-23]

This cross-sectional study, conducted in a municipality in the countryside of the state of São Paulo, is the first population-based epidemiological study on LUTS and ED in middle-aged men related to the quality of life in the region. By implementing epidemiological surveys that utilize efficacious instruments, researchers can elucidate the dynamics of diseases and health. When integrated with

Table 1. Results of urological questionnaires divided by age

Questionnaire		≤ 39 years	40-59 years	≥ 60 years	Total
IPSS	Asymptomatic or mildly symptomatic (0-7)	84 (84.0%)	91 (70.0%)	68 (46.9%)	243 (64.8%)
	Moderately symptomatic (8-19)	14 (14.0%)	28 (21.5%)	56 (38.6%)	98 (26.1%)
	Severely symptomatic (20-35)	2 (2.0%)	11 (8.5%)	21 (14.5%)	34 (9.1%)
IIEF-6	Normal (26-30)	68 (68.0%)	81 (62.3%)	38 (26.2%)	187 (49.9%)
	Light (22-25)	19 (19.0%)	28 (21.5%)	36 (24.8%)	83 (22.1%)
	Mild to moderate (17-21)	10 (10.0%)	14 (10.8%)	29 (20.0%)	53 (14.1%)
	Moderate (11-16)	1 (1.0%)	7 (5.4%)	13 (9.0%)	21 (5.6%)
	Severe (1-10)	2 (2.0%)	0 (0.0%)	29 (20.0%)	31 (8.3%)

IPSS = International Prostate Symptom Score; IIEF-6 = International Index of Erectile Function-6.

Table 2. Health perception and satisfaction measured by the World Health Organization Quality-of-Life Scale questionnaire

Question	Answers	≤ 39 years	40-59 years	≥ 60 years	Total
1 - How would you rate your quality of life?	Very bad	0 (0.0%)	1 (0.8%)	1 (0.7%)	2 (0.5%)
	Bad	4 (4.0%)	1 (0.8%)	5 (3.5%)	10 (2.7%)
	Neither bad nor good	18 (18.0%)	26 (20.0%)	40 (27.6%)	84 (22.4%)
	Good	48 (48.0%)	62 (47.7%)	63 (43.4%)	173 (46.1%)
	Very good	30 (30.0%)	40 (30.7%)	36 (24.8%)	106 (28.3%)
2 - How satisfied are you with your health?	Very dissatisfied	0 (0.0%)	3 (2.3%)	4 (2.8%)	7 (1.8%)
	Dissatisfied	4 (4.0%)	5 (3.9%)	19 (13.1%)	28 (7.5%)
	Neither satisfied nor dissatisfied	22 (22.0%)	29 (22.3%)	22 (15.1%)	73 (19.5%)
	Satisfied	44 (44.0%)	54 (41.5%)	66 (45.6%)	164 (43.7%)
	Very satisfied	30 (30.0%)	39 (30.0%)	34 (23.4%)	103 (27.5%)

Table 3. Median and quartiles of the quality of life domains measured by the World Health Organization Quality-of-Life Scale questionnaire

Domain	≤ 39 years	40-59 years	≥ 60 years	Total
Physical	83.3 (75.0-91.7)	79.2 (66.7-91.7)	70.8 (58.3-83.3)	75.0 (62.5-87.5)
Psychological	79.2 (70.8-87.5)	83.3 (75.0-91.7)	79.2 (66.7-83.3)	79.2 (70.8-87.5)
Social Relations	79.2 (66.7-93.8)	83.3 (75.0-97.9)	75.0 (58.3-83.3)	75.0 (66.7-91.7)
Environment	70.3 (62.5-81.3)	71.9 (59.4-84.4)	68.8 (59.4-78.1)	71.9 (59.4-81.3)

Table 4. Urological questionnaires correlated with quality of life and characterization data

	WHOQOL-BREF	Age	Other characterization data
IPSS	Physical (sp = -0.355; P < 0.001) Psychological (sp = -0.237; P < 0.001) Social relations (sp = -0.242; P < 0.001) Environment (sp = -0.230; P < 0.001)	sp = 0.383 P < 0.001	Color (Kw = 2.64; P = 0.619) Religion (Kw = 3.95; P = 0.267) Marital status (Kw = 25.5; P < 0.001)
IIEF-6	Physical (sp = 0.390; P < 0.001) Psychological (sp = 0.269; P < 0.001) Social relations (sp = 0.363; P < 0.001) Environment (sp = 0.248; P < 0.001)	sp = -0.460 P < 0.001	Color (Kw = 5.98; P = 0.201) Religion (Kw = 8.03; P = 0.045) Marital status (Kw = 23.4; P < 0.001)

WHOQOL-BREF = World Health Organization Quality-of-Life Scale; sp = Spearman's test; Kw = Kruskal–Wallis test; IPSS = International Prostate Symptom Score; IIEF-6 = International Index of Erectile Function-6.

Table 5. Data from urological questionnaires and median age divided by marital status

	Age Median (IQR)	IPSS Median (IQR)	IIEF-6 Median (IQR)
Single	30.5 (23.2-42.8)	3.0 (1.0-6.0)	27.0 (23.0-29.0)
Married	55.5 (44.0-68.0)	4.5 (1.0-11.0)	25.0 (21.0-29.0)
Other	48.5 (33.2-62.2)	7.5 (3.8-11.8)	23.0 (20.8-28.2)
Widowed	74.0 (69.0-77.0)	10.0 (6.0-15.0)	17.0 (10.0-24.0)
Separate	60.5 (53.8-66.0)	8.0 (4.2-18.0)	23.0 (18.2-28.0)
Stable Union	46.5 (34.2-61.8)	8.5 (4.5-18.0)	27.0 (24.5-28.8)

IPSS = International Prostate Symptom Score; IIEF-6 = International Index of Erectile Function-6; IQR = interquartile range.

local political and social frameworks, these insights contribute to the formulation of public policies with the potential to significantly alter health practices at the population level.[24,25]

In the present study, it was noted that the demographic profile of the men surveyed reflects sociocultural characteristics that align with the contemporary historical context of Brazil's southeast region: predominantly white, Catholic, and married (**Figure 1**).[11,26-29] This finding is essential for analyzing the extent of disparity across diverse ethnic, social, and cultural groups, considering that these disparities are frequently rooted in historical determinants with direct repercussions on overall health outcomes.[30]

The survey findings indicated a significant prevalence of LUTS and ED (**Table 1**). Moreover, these conditions were directly associated with quality of life assessments, as gauged by the WHOQOL-BREF instrument.[14] Additionally, a correlation existed between these disorders and various demographic factors, including marital status and age.

Regarding LUTS, studies have estimated a 45.0% to 62.5% prevalence in middle-aged men over 18 years old, adhering to the International Continence Society criteria.[6,17] However, this study revealed a greater prevalence of 68.5% in middle-aged men, signifying a higher incidence of LUTS in the surveyed group compared to other national and international data, highlighting its diverse impact in Brazil.

The observed prevalence of ED in this sample was 50.1%, aligning closely with national research findings, such as 45.9% in a Santos study and 46.2% across various Brazilian regions.[31,32] These figures are also consistent with international research, such as the Massachusetts Male Aging Study that identified a 52% prevalence; a survey in Boston, Massachusetts that noted 40%-70% prevalence;[7] a French study that reported 39% prevalence among men aged 18-70 years;[33] and recent UK research that observed a 41.5% prevalence in men aged > 18 years.[34] Additionally, this study corroborates earlier research indicating an age-related increase in ED prevalence.

There is an evident analytical deficiency in examining the intersection of quality of life with urological assessments. Limited research correlating conditions such as LUTS and ED demonstrates congruence with the present study, affirming the profound effect on individual quality of life.[35-37] Quality of life in this study was interpreted through individual self-assessment of life circumstances, cultural contexts, and value systems against their aspirations and concerns. From the perspective of healthcare professionals, quality of life may signify enhanced health outcomes within individual, societal, and cultural frameworks.[14,38] This align with the intricate nature of men's perceptions of their health, masculinity, and general well-being. The highlighted prevalence of these disorders in this study, coupled with their considerable impact on the quality of life, underscores the urgency for further investigation in this field and heightens the necessity for health services at all levels to prioritize these health issues, recognizing their potential widespread influence on individuals' lives.

Finally, previous studies have rarely explored the relationship between marital status and urological health. Nonetheless, this research discovered that, particularly among widowers and separated men, there was a higher incidence and more severe symptoms reported in the IIEF-6 and IPSS assessments.[16-18] This evidence supports the theory that the presence of a partner may increase the likelihood of men seeking medical attention, thus potentially improving their self-care practices.[39] These insights should be approached with prudence and further investigated, as the older age of widowed and separated male participants could represent a confounding factor in this analysis due to the presence of age-related senility, which can contribute to higher rates of ED and LUTS. Therefore, it has not been conclusively determined whether advancing age or marital status is the primary factor influencing the prevalence of genitourinary issues.

Merits and limitations

Elucidating the health profile of men is imperative for the development of public health policies and informed distribution of resources based on the collected data. This study provides novel insights into the prevalence of specific health conditions among middle-aged men, predominantly those aged 18 to 39 years, a demographic often underrepresented in existing research despite a growing incidence of such concerns among younger individuals.[17,40-42] It has been determined that the presence of ED and LUTS in men aged ≥ 18 years is intricately associated with the deterioration of the participants' quality of life, given the substantial prevalence and direct correlation to various facets of an individual's well-being. This study is unprecedented in examining the prevalence of these conditions within the local context of a municipality. These findings underscore the necessity for an integrated approach to health interventions, recognizing that these issues substantially influence a broader spectrum of men's health.

Concerning the limitations of this study, there are issues related to the generalizability of the results. The main limitation is the inability to confirm causal relationships inherent in cross-sectional studies, followed by the inability to perform a multivariate analysis to assess the extent to which the quality of life is affected by LUTS or ED, considering the simultaneous effect of age. Our sample contained several cells with zero or very few observations (< 5), which could have significantly reduced the statistical power of the multivariate tests. Another limitation was the use of self-reported measures for ED and LUTS. This study did not include the levels of education and occupation; therefore, these may be relevant variables for future research. Finally, it was not feasible to include other regions of the municipality during the data collection period because the COVID-19 pandemic was advancing during the data collection period. Future studies with larger sample sizes are required to explore the potential correlation between age and quality of life in relation to LUTS and ED.

CONCLUSION

The prevalence of ED and LUTS in middle-aged men is high. Additionally, age and marital status were significantly correlated with these disorders. Finally, the presence or severity of these disorders is inversely correlated with the individual's quality of life.

This high prevalence highlights the urgent need for targeted public health interventions. Health professionals should consider these findings when developing health promotion and disease prevention strategies such as educational campaigns to reduce the stigma associated with discussing genitourinary health in men. This could encourage men to seek timely medical advice and guide them toward a better quality of life.

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Analyzing the effectivity of evidence-based practice in health science higher education: a narrative review

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ABSTRACT

BACKGROUND: Although multiple strategies have been suggested for evidence-based practice educational interventions, few studies have focused on the development of abilities for evidence-based practice implementation.

OBJECTIVE: To explore the effectiveness of evidence-based practice in higher education and understand its teaching methods.

DESIGN AND SETTING: Narrative review was conducted at the Universidade Municipal de São Caetano do Sul, Brazil.

METHODS: Narrative review included research studies that measured any type of evidence-based practice teaching method and its effectiveness. Searches included publications from inception to June 2022, conducted on MEDLINE, EMBASE, CINAHL, CENTRAL, ERIC, and the Cochrane Library. Two independent authors descriptively extracted and analyzed the data. The methodological quality of the studies was also analyzed.

RESULTS: The results determined that 79.2% of the studies proved their effectiveness. Teaching methods varied according to the time period, format, and types of questionnaire.

CONCLUSIONS: Most studies demonstrated the effectiveness of the chosen teaching methods. This study shows the importance of health professionals using evidence-based practice to ensure effective patient treatment.

INTRODUCTION

Evidence-based practice (EBP) consists of the best available scientific evidence, previous professional clinical experience, and patients' preferences.[1] EBP use seeks to improve the efficiency and quality of healthcare services, besides saving costs and expenses with inefficient treatments.[2] In recent years, EBP implementation has proven great advances in improving healthcare quality and prognosis of various health conditions.[1]

However, some obstacles may interfere with EBP, such as limited resources, the ability to apply adequate intervention, cultural and socioeconomic factors, issues related to valid health policies, clinical practice complexity, access to full texts of scientific articles, and continuing education programs.[3,4] In addition to those barriers, it is evident that during the entire learning trajectory, students are not taught and stimulated to have critical appraisal.[5] Many times, students assume a passive posture in the learning process and end up losing the possibility to practice and absorb didactical content without depending on a tutor to graduate.[5]

In the teaching context for healthcare professionals graduation courses, EBP must follow five basic steps to reach success on its principle application: 1) formulation of clinical question; 2) broad and efficient search in health databases; 3) critical appraisal of evidence validity; 4) application of evidence results in clinical practice; and 5) assessment of treatment effects in your own clinical practice.[6] Higher education courses have been seeking the most efficient approach to teach the necessary abilities of EBP; therefore, students turn into confident professionals when taking their clinical decisions.[7] The most efficient approach is quite challenging,[8,9] as one of the greater challenges is to adequate the theoretical structure to support and develop EBP requirements.[7]

Furthermore, a systematic review[10] of 20 articles reporting the application of EBP educational interventions in healthcare suggested that multiple strategies, such as technology and/or simulation techniques, may influence the abilities, knowledge, and attitudes regarding EBP use. The results describe strategies focused mainly on teaching critical appraisal of information; however, only a few studies have focused on the development of abilities for EBP implementation.

OBJECTIVE

Therefore, the primary objective of this study is to explore the effectiveness of EBP in higher education. The secondary objective is to understand the methods used to teach EPB in higher education.

METHODS

Inclusion and exclusion criteria

This narrative review included all original research studies that measured any type of EBP teaching method and their effectiveness. The question based on Population, Intervention, Comparison, and Outcome was as follows: Is EBP effective in higher education? Letters to the editor, editorials, and conference abstracts were excluded. Studies that included health professionals as the study population rather than students were also excluded.

Search strategy for identification of studies

We searched publications published from the inception to June 9, 2022, with no language restrictions. We conducted our search on MEDLINE, EMBASE, CINAHL, CENTRAL, ERIC, and Cochrane Library, with two key search terms: "evidence-based practice" and "graduate education" or "higher education" (**Table 1**).

Data collection

Two independent authors (PR and VS) screened all studies for eligibility. Disagreements were resolved through discussion or arbitration with a third author (AA). The screening process of the studies included (1) screening titles and abstracts and (2) screening full-text articles.

Table 1. Details of the search strategy

Database	Search strategies	Papers found
Medline (via Pubmed)	("evidence-based practice") AND ("graduate education") OR ("higher education")	2,974
ERIC	("evidence-based practice") AND ("graduate education") OR ("higher education")	1,000
CINAHL	("evidence-based practice") AND ("graduate education") OR ("higher education")	306
CENTRAL	("evidence-based practice") AND ("graduate education") OR ("higher education")	70
EMBASE	("evidence-based practice") AND ("graduate education") OR ("higher education")	26
Cochrane Library	("evidence-based practice") AND ("graduate education") OR ("higher education")	0

Medline = Medical Literature Analysis and Retrieval System Online;
ERIC = Education Resources Information Center;
CINAHL = Cumulative Index to Nursing and Allied Health Literature;
CENTRAL = Cochrane Central Register of Controlled Trials;
EMBASE = Excerpta Medica Database.

Data extraction

Two independent authors (AP and KO) extracted the following data: (1) first author, (2) year of publication, (3) research field, (4) study objectives, (5) year of search, (6) sample size, (7) EBP teaching method, (8) how data were extracted, and (9) conclusions based on the study results regarding the effectiveness of the chosen method. If required, we contacted the authors via email to request any information that was not reported in the original manuscript.

Data analysis and methodological quality of studies

The results are reported descriptively. Two independent authors (AA and VS) assessed the methodological quality of the studies using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[11] which was developed to assess the methodological quality of quasi- or non-randomized experimental studies using seven items. Each item was rated as "Yes," "Probably yes," "Probably no," "No," or "No information" and the categories for risk of bias judgments were "Low risk," "Moderate risk," "Serious risk," and "Critical risk" of bias. Both authors rated the risk of bias of studies on the number of "Yes" items, none as "Low," one or two as "Moderate," three as "Serious," and more than three as "Critical." During judgment, authors considered items rated "Probably yes," "Probably no," and "No information" as "Yes."[11]

Ethics and registration

Ethics approval was not required for this study. This review has not been registered as it does not have any health-related outcomes.[12]

RESULTS

Search results

The initial search yielded 4,376 potentially eligible studies. After screening the title and abstract, we removed duplicates, considered 34 potentially eligible studies for inclusion, and retrieved the full-text articles. Twenty-four published studies[13-36] met the inclusion criteria and were included in this review. A review flow diagram is presented in **Figure 1**.

Methodological quality of studies

The design of most of the studies was quasi-experimental, which is why the authors chose the ROBINS-I tool for methodological quality assessment. Most studies presented a moderate risk of bias (n = 14; 58.3%), followed by low (n = 4; 16.7%), serious, and critical (n = 3; 12.5% each). The methodological quality of each study is demonstrated in **Table 2**.

Characteristics of included studies

The 24 eligible studies were published between 1997 and 2019. Study designs varied among included studies: 16 quasi-experimental

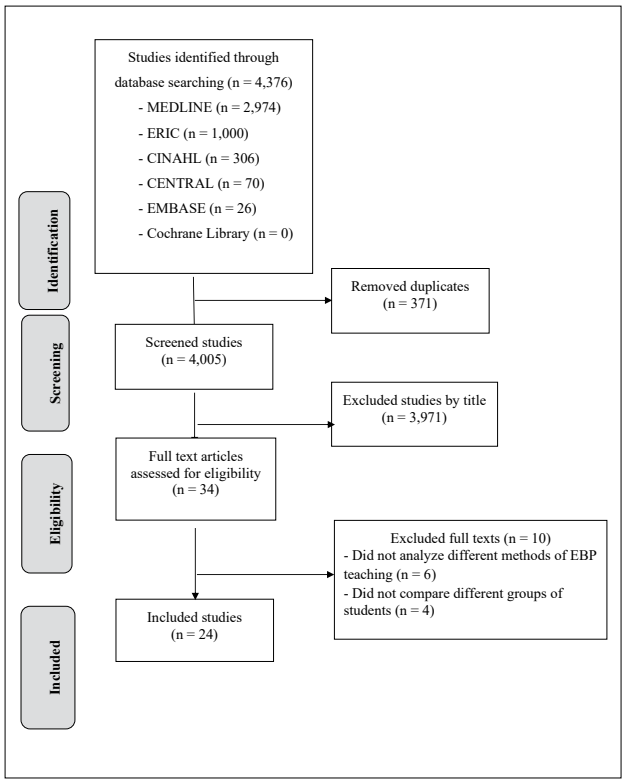

Figure 1. Review flow diagram.

studies,[13-15,17,18,21,22,24,25,27,28,31-35] 4 randomized controlled trials,[16,19,23,36] 1 mixed method,[29] 1 cross sectional study,[26] 1 prospective controlled assessment,[20] and 1 cohort study.[30] Research fields from the included studies were as follows: medicine[16-20,22-24,26,30-33,35] (58.3%), occupational therapy[14,25,29] (12.5%), physical therapy[14,28,29] (12.5%), dentistry[13,34] (8.3%), nursing[21,27] (8.3%), speech therapy[15] (4.2%), and athlete training[36] (4.2%). The main objective of the included studies was to analyze the effectiveness of EBP taught to students in the health area. EBP teaching methods varied among studies as follows: time period varied from 4 hours workshop to 6 months period course; and format varied among seminars, workshops, courses, lectures, web-based learning modules, and conferences. Data were extracted through different types of pre- and post-intervention questionnaires or only post-intervention questionnaires. The majority of studies (n = 19, 79.2%), except for five,[16,19,21,23,26] proved that teaching EBP was effective. A summary of the objectives, EBP teaching methods, how data were extracted, and conclusions based on the studies' results is presented in **Table 3**. Due to the large heterogeneity, a meta-analysis of the results was not possible.

DISCUSSION

This systematic review aimed to explore the effectiveness of EBP in higher education. The results showed that 79.2% of the studies

Table 2. Methodological quality assessment of the included studies, using the ROBINS-I tool[11]

Author, year of publication	Pre-Intervention		At Intervention		Post-Intervention			Risk of bias
Arias, Peters, Broyles, 2017[13]	Y	N	Y	Y	N	Y	Y	Critical
Bennett, Hoffmann, & Arkins, 2011[14]	Y	Y	N	N	N	N	N	Moderate
Durieux, Maillart, Donneau, Pasleau, 2018[15]	N	PN	N	N	Y	N	N	Moderate
Feldstein, Maenner, Srisurichan, Roach, Vogelman, 2010[16]	N	N	N	N	N	N	N	Low
George, Reis, Nothnagle, 2012[17]	N	N	N	N	N	N	Y	Moderate
Green Ellis, 1997[18]	N	N	N	N	N	N	N	Low
Hadley et al., 2010[19]	N	PN	N	Y	Y	N	PN	Serious
Harewood Hendrick, 2010[20]	N	N	N	N	N	N	N	Low
Jackson, 2016[21]	N	N	N	Y	Y	N	Y	Serious
Kenefick, Boykan, Chitkara, 2013[22]	N	N	N	N	N	Y	Y	Moderate
Kortekaas et al., 2016[23]	N	N	N	N	Y	N	N	Moderate
Ma, Chang, Krupat, 2021[24]	N	N	N	PY	Y	N	N	Moderate
McCluskey Lovarini, 2005[25]	N	N	N	N	N	N	N	Low
Mlika, Ben Hassine, Charfi, Mezni, Jouini, 2019[26]	N	N	N	N	N	Y	Y	Moderate
Moore, Watters, Wallston, 2019[27]	N	N	N	N	Y	Y	Y	Serious
Perraton et al., 2017[28]	N	N	N	N	N	N	Y	Moderate
Schweikhard, Hoberecht, Peterson, Randall, 2018[29]	N	N	N	N	N	N	PY	Moderate
Soma, Homme, Jacobson, 2013[30]	N	N	N	N	N	N	Y	Moderate
Tavarez, Kenkre, Zuckerbraun, 2020[31]	N	N	N	N	N	N	PY	Moderate
Thom, Haugen, Sommers, Lovett, 2004[32]	N	N	N	Y	PY	Y	Y	Critical
Thomas et al., 2005[33]	Y	Y	Y	N	N	Y	Y	Critical
Wadgave, Khairnar, Kadu, Chadha, Wadgave, 2020[34]	N	N	N	N	N	N	PN	Moderate
Wang et al., 2017[35]	N	N	N	N	NI	N	Y	Moderate
Welch, Van Lunen, Hankemeier, 2014[36]	N	N	N	Y	N	Y	N	Moderate

Y = yes; N = no; PY = probably yes; PN = probably no; NI = no information.

Table 3. Summary of objectives, EBP teaching method, how data was extracted, and conclusions based on studies' results of all 24 included studies

Nº	(Author, year of publication) Research field	Objectives Sample Size (year of search)	EBP teaching method	How data was extracted	Conclusions based on studies' results
1	(Arias, Peters, Broyles, 2017[13]) Dentistry	To develop a curriculum in biostatistics with various educational strategies to be applied in clinical practice. n = 3 (2016)	Needs assessment survey; curriculum design and implementation, with a series of 10 1-hour seminar sessions on specific learning outcomes; and curriculum evaluation, with knowledge tests and satisfaction survey.	28-item selected response extending matching and multiple choice knowledge test, focusing on improving their knowledge, high-order cognition, attitudes, and skills to develop their critical thinking when deciding the treatment.	The correct answer rate changed from 36.9% in the pretest to 79.8% in the post-test. Students showed high knowledge improvement in questions related to the identification of variable types and statistical test selection. They also benefited from the knowledge acquired in the didactic seminars and clinical learning activities allowing further critical analysis and discussions.
2	(Bennett, Hoffmann, Arkins, 2011[14]) Occupational therapy and Physical therapy	To investigate the improvement of health students' attitudes, confidence and knowledge regarding EBP. n = 59 (2010)	Course of 13-week period, with 2 hours per week, using didactic lectures, tutorial and workshop formats, and a hands-on database searching session.	Pre- and post-course adapted questionnaire of the perceptions of occupational therapists toward EBP, and another regarding general practitioners' self-rating of EBP skills.	The health students' confidence regarding EBP skills, as well as their perceived and actual knowledge regarding EBP concepts were statistically significant after the course.
3	(Durieux, Maillart, Donneau, Pasleau, 2018[15]) Speech therapy	To evaluate the improvement of EBP competencies regards skills and knowledge. n = 104 (2018)	An educational and interactive module on EBP over 2 months.	Pre- and post-adapted Fresno test and a computer-based searching task requiring a search in PsycINFO.	The mean total score of the trained group was statistically significant in the pre and post-test, who made more progress in terms of EBP knowledge and skills.
4	(Feldstein, Maenner, Srisurichan, Roach, Vogelman, 2010[16]) Medicine	To analyze the improvement of residents' EBP knowledge and better prepare them for effective clinical decision-making. n = 48 (2003 and 2004)	4-hour interactive EBP workshop for the treatment group (n = 23), as well as a journal club.	EBP knowledge and skills test were applied 6 and 18 months later on, with 25 multiple-choice questions.	There were no significant differences between treatment groups at either time point. No differences were detected in EBP knowledge between residents who did and did not participate in the workshop.
5	(George, Reis, Nothnagle, 2012[17]) Medicine	To describe the design, implementation, and evaluation of a curricular intervention tailored to individual residents. n = 26 (2008 to 2010)	A learning coach to develop EBP skills, with monthly half hour meetings devoted to EBP training.	Pre and post quantitative and qualitative methods, using a 10-item survey and 6 questions adapted from the Fresno Test of Competence in EBP.	The variable attitude was statistically significant in 4 of 10 items in the pre and post-test. The competence questionnaire was statistically significant in all items. Residents demonstrated improved knowledge and skills of EBP through the intervention.
6	(Green Ellis, 1997[18]) Medicine	To develop and implement an EBP curriculum and determine its effectiveness in improving residents' EBP behaviors and skills. n = 34 (1995 to 1996)	7-week EBP curriculum based on adult learning theory, the educational strategy with resident directed tutorial format, use of real clinical encounters and specific EBP facilitating techniques for faculty (n = 19).	Pre and post questionnaires, with a survey of EBP behaviors, a survey of self-assessed EBP competence and an EBP skills test.	The case subjects significantly improved their scores on the EBP skills test. EBP curriculum improved residents' EBM skills and certain EBM behaviors.
7	(Hadley et al., 2010[19]) Medicine	To evaluate the educational effectiveness of a clinically integrated EBP e-learning course among postgraduate medical trainees compared to a lecture-based course. n = 160 (2007)	One group received the e-learning EBM teaching program (n = 88) and the other received standard classroom-based standalone EBM teaching sessions of equivalent content (n = 72). The e-learning group were granted unlimited access for a period of 6 weeks to the e-learning materials via a project specific website.	Validated multiple-choice questions to assess EBM knowledge before accessing the e-learning materials and prior to the start of the teaching sessions. After completion of each module, the participants completed the same questions relevant to that module again.	There was no difference in the amount of improvement of knowledge between the two groups. The benefits should be considered a potentially cost-effective alternative to standard lecture-based sessions.

It continues...

Table 3. Continuation

Nº	(Author, year of publication) Research field	Objectives Sample Size (year of search)	EBP teaching method	How data was extracted	Conclusions based on studies' results
8	(Harewood Hendrick, 2010[20]) Medicine	To evaluate the impact of a workshop on the critical appraisal skills of medical trainees. n = 19 (2009)	6 hours EBP workshop, with three sessions of 2 hours each.	Nine research papers were emailed before the first lecture. Pre and post grading of the quality of these studies on a 3-point scale.	Total correct grading went from 39% before the course to 74% post course. There was an improvement in the participants' knowledge of EBP skills and an improvement in their ability to critically assess published literature.
9	(Jackson, 2016[21]) Nursing	To determine the effectiveness of an EBP learning module within a nursing residency program. n = 29 (2014)	Learning module activities over 4 months.	Pre and post module EBP questionnaire, which consisted of 24 items with 7-point rating scales.	The variable practice was statistically significant in one of six items in the pre- and post-test. The variable attitude did not statistically differ in any item. The variable knowledge/skills was statistically significant in 4 of 14 items in the pre and post-test. Therefore, most items did not show statistical differences between the pre and post-test.
10	(Kenefick, Boykan, Chitkara, 2013[22]) Medicine	To evaluate the effectiveness of partnership between librarians trained with EBP and residents' process of learning. n = 4 (2010)	Partnership between librarians trained with EBP and residents' process of learning.	Pre and post-tests on how to form a clinical question, how to conduct searches and four cases to evaluate the residents' baseline skills and efficiency.	After the alliance between the librarians and the residents, test scores went from 46.0% to 99.0%. Librarians and residents must be taught how to use available resources, especially the residents. Partnering with residents for the long term made toward better physician decision-making rewards the librarian, the physician, and ultimately the patient.
11	(Kortekaas et al., 2016[23]) Medicine	To report the results of a cluster randomized controlled trial among third year trainees comparing the effects of the integrated EBP training program with a stand-alone EBP training program. n = 79 (2011 to 2013)	EBP training in accordance with the five steps of the Sicily Statement. Main difference between the stand-alone (n = 40) and integrated EBP training program (n = 39) was the focus on the last two steps, which was adapted to emphasis the practical implication of research and to stress its clinical relevance.	EBP behavior, measured as guideline adherence and information-seeking behavior, as well as EBP attitude and knowledge.	Information-seeking behavior, guideline adherence, EBM attitude, and knowledge did not significantly differ between both groups.
12	(Ma, Chang, Krupat, 2021[24]) Medicine	To evaluate and quantify the benefits of an educational module on EBP. n = 111 (2021)	16 EBP 2 hours' sessions on a weekly basis, with a computer laboratory and audiovisual aids.	Oral presentation on the standardized cases during the first two sessions and the last three sessions, with the utilization of EBP relevant electronic medical databases for selecting and organizing references of high-level evidence. Pre- and post-intervention questionnaires on EBP behavior or practice of applying relevant resources, as well as cognition or awareness of relevant resources.	The clinical scenario presentation had a statistically significant improvement comparing pre and post intervention. Self-reported changes on behavior and awareness presented statistically significant differences for post intervention.

It continues...

Table 3. Continuation

Nº	(Author, year of publication) Research field	Objectives Sample Size (year of search)	EBP teaching method	How data was extracted	Conclusions based on studies' results
13	(McCluskey Lovarini, 2005[25]) Occupational therapy	To measure the effect of a multifaceted intervention on EBP, on knowledge, skills, behaviors, and attitudes. n = 114 (2001 to 2003)	2-day workshop on EBP, with lectures, practical sessions and small group discussions.	Pre, post, and after 8 months written questionnaires of the adapted Fresno test of competence in EBP, divided into three sections.	Tests were statistically significant pre and post workshop, with 19.0% of participants scoring at least 50.0% of correct answers before the workshop, and after that 77.0%. However, changes in behavior were not maintained after 8 months, based on the frequency of searching and appraisal activities.
14	(Mlika, Ben Hassine, Charfi, Mezni, Jouini, 2019[26]) Medicine	To assess the acceptability of learning EBP by family doctors. n = 17 (2019)	Associated lecture sessions and teamwork participative methods.	A website was created for pre- and post-test.	There was no statistical difference in pre and post-tests.
15	(Moore, Watters, Wallston, 2019[27]) Nursing	To evaluate the impact of EBP courses on nursing students' attitudes. n = 227 (2014)	6 months EBP course. An adapted EBP research instrument of the theory of planned behavior, including an EBP knowledge test.	An adapted EBP research instrument of the theory of planned behavior, including an EBP knowledge test.	The variables attitudes, self-efficacy, and behavior were statistically significant pre- and post-test for both groups (masters of science in nursing and doctorate of nursing practice). Advanced practice nurses are better prepared as leaders to implement EBP in the clinical setting, resulting in high quality of care and improved health outcomes.
16	(Perraton et al., 2017[28]) Physical therapy	To measure if there is a change in confidence and anxiety in knowledge of statistical terminology and concepts related to research design and EBP. n = 236 (2007 to 2014)	An intensive 3-week post-graduate course, which taught health research methods, biostatistics and EBP.	Pre and post questionnaires regarding confidence in methods and understanding of EBP.	The variables knowledge of statistical terminology and concepts related to research design and EBP were statistically significant pre- and post-tests. An intensive teaching program in health research methods and biostatistics and EBP was effective immediately post-course.
17	(Schweikhard, Hoberecht, Peterson, Randall, 2018[29]) Occupational therapy and Physical therapy	To evaluate the impact of the library tutorials on the information literacy skills of students in the EBP course. n = 449 (2012 to 2016)	The authors analyzed the impact of online library tutorials in association with the EBP course. Focuses were on students' search strategies and cited sources pre and post the implementation of the tutorials.	Students wrote a "Step 5 Paper", which was to synthesize each of the steps and reflect on the entire process.	When comparing the total number of studies cited in the pre- and post-tutorial Step 5 Paper, there was an improvement on the choice of papers' quality. Before the tutorials, 73.0% of studies were of higher quality, after the tutorials that number increased to 81.0%.
18	(Soma, Homme, Jacobson, 2013[30]) Medicine	To analyze if tablet computers would improve EBP knowledge, skills, and behavior. n = 38 (2011 and 2012)	Two introductory sessions, review of EBM curriculum, team assignments for learning exercises, and orientation to tablet computers. A series of 45-minute laboratory sessions twice monthly, focused on speed and efficiency for real-time, clinical use of EBM.	Pre and post intervention tests: a written test of knowledge and an online survey of skills and behaviors, an adapted Pediatric based instrument for assessing resident education in EBP.	Pre-intervention test score showed median of 32.5 of 60 points, in contrast with 53.0 points post intervention. The survey revealed statistically significant improvement in four of seven EBP skills. EBP improved knowledge, skills, and behavior through the introduction of a tablet computer and laboratory sessions.

It continues...

Table 3. Continuation

Nº	(Author, year of publication) Research field	Objectives Sample Size (year of search)	EBP teaching method	How data was extracted	Conclusions based on studies' results
19	(Tavarez, Kenkre, Zuckerbraun, 2020[31]) Medicine	To determine if implementation of EBP curriculum has an effect on pediatric emergency medicine fellows' scores on the relevant section of the in-training examination. n = 22 (2001 to 2017)	Two online, self-directed modules for fellows to access and review 3 to 4 weeks before their assigned session. Approximately 2 to 3 weeks before the fellows' scheduled session, they also had 1 hour session coaching and feedback. Monthly EBP sessions, with critical appraisal and discussion of 1 article.	Post sessions, an EBM worksheet was distributed to all fellows, with three to five questions about the chosen article. They obtained raw sub-scores on the scholarly activities section and raw sub-scores for the Emergencies Treated Medically section of the in-training examination questions.	The multivariate modeling demonstrated a higher performance of the students after the implementation of the EBP curriculum. Pediatric emergency medicine educators could consider using fellows' scores on this section of the in-training examination to assess the effect of their EBP curriculum.
20	(Thom, Haugen, Sommers, Lovett, 2004[32]) Medicine	To evaluate the EBP curriculum based on an individual block rotation and the EBP skills throughout the residency program. n = 13 (2001 to 2003)	2-week EBP rotation.	A written test of their EBP skills and knowledge before and immediately following the rotation.	The use of PubMed/Medline, other Web-based EBP resources, EBP tools and principles (critical appraisal), as well as their confidence over the course of the rotation statistically increased. Residents and faculty felt that the answers provided by the EBP intern provided useful information and led to changes in patient care within the residency program.
21	(Thomas et al., 2005[33]) Medicine	To determine if an EBP conference program would enhance resident competency at EBP or if resource intensive, small group discussions would be required. n = 46 (1997 to 1999)	EBP conferences and small-group discussions were integrated into an internal medicine curriculum to compare the efficacy of EBP competency. The students were divided into two groups and they were compared with one another.	Written examination comparing both groups.	Small-group discussion participants scored higher when compared with conference participants, also with increased confidence and high satisfaction. Therefore, small-group discussions resulted in increased EBP knowledge, increased confidence with critical appraisal skills, and high satisfaction compared with a conference-based format.
22	(Wadgave, Khairnar, Kadu, Chadha, Wadgave, 2020[34]) Dentistry	To determine the effectiveness of a formal education workshop on EBP to undergraduate dental students. n = 50 (2019)	Four interactive seminars, practical sessions, and home assignments held for 2 days at the EBP workshop.	EBP knowledge, attitudes, access and confidence questionnaire before and after the course.	EBP knowledge was statistically significant in 6 of 10 items in the pre- and post-test. Skills in accessing evidence were statistically significant in four of nine items in the pre- and post-test. A significant improvement was noted in positive attitudes of students toward EBP. Participants gained moderate confidence in critical appraisal skills.
23	(Wang et al., 2017[35]) Medicine	To assess the effectiveness of an EBP course on the Chinese medical students' critical thinking skills and dispositions. n = 158 (2017)	EBP course with 32 hours of Clinical Epidemiology and 24 hours of EBP Approaches, each taught for 8 consecutive weeks in a sequence.	A survey based on the Chinese version of the Critical Thinking Disposition Inventory before and after the course.	The results showed a significant improvement in confidence and progress in inquisitiveness after they completed an EBP course.
24	(Welch, Van Lunen, Hankemeier, 2014[36]) Athlete training	To assess whether an EBP educational intervention enhanced knowledge of EBP concepts among athletic trainers. n = 175 (2011)	10 web-based learning modules, where the experimental group had access to the web-based modules for 4 weeks, whereas the control group had no direct responsibilities for the investigation.	Knowledge assessment consisted of 60 multiple-choice questions pertaining to concepts presented in the 10 modules.	The experimental group obtained higher scores on the post-assessment than the pre-assessment. No differences were identified among time instances within the control group. Therefore, the educational intervention web-based modules was an effective mechanism to increase knowledge of foundational EBP concepts.

EBP = evidence-based practice; EBM = evidence-based medicine.

proved EBP effectiveness.[13-15,17,18,20,22,24,25,27-36] This study's secondary objective was to understand the methods used to teach EPB, which varied over time (from 4 hours to 6 months), format (seminars, workshops, courses, lectures, web-based learning modules, and conferences), and types of pre-and/or post-questionnaires.

A systematic review published in 2016[10] suggested that technology focused mainly on teaching the critical appraisal of information could influence abilities, knowledge, and attitudes regarding the use of EBP. Our results determined that the development of such abilities for EBP implementation depended on the construction and revision of EBP curriculum, through working on the teaching/learning time period, effective from at least 6 hours workshop, once Feldstein[16] did not show effectiveness with their 4 hour EBP workshop; format of EBP teaching, which could vary a lot, as long as it had enough time to cover main EBP points; and type of evaluation to check if students were really able to implement EBP, once assessment strategies were also essential.[37] The majority of higher education universities offers biostatistics discipline in their curriculum; however, such discipline rarely involves EBP in its practice components.[13,28] Our recommendation is focused on the development of a new EBP curriculum or even a restructuration of the biostatistics curriculum. The main proposal is to encourage students to engage in reflective thinking, with active methods of searching for knowledge, critical appraisal skills, behavior, and attitudes toward reading scientific articles.[16-18,20] Other suggestions for the development of the EBP curriculum have been listed elsewhere.[38]

This study has some limitations in terms of our descriptive results, as it was not possible to center the data in a meta-analysis to obtain more accurate results. Further research could analyze the association of EBP teaching effectiveness with different variables, such as teaching period and format. The strength of this review lies in the methodological analysis of the included studies.

CONCLUSION

In conclusion, most of the studies included in the present review demonstrated the effectiveness of the chosen EBP teaching method; however, future research should explore the factors that could be associated with the improvement of such effectiveness. This study used educational tools through EBP teaching methods. Additionally, it is important for health professionals to use EBPs to ensure more effective treatment of patients.

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

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

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

Covering letter

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

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

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

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

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

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

Sample size

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

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

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

Abbreviations, acronyms and products

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

Interventions

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

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

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

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

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

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

Figures and tables

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

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

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

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

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

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

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