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Databases, big data and artificial intelligence: what healthcare professionals need to know about them

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"Information is the oil of the 21st century, and analytics is the combustion engine" said Peter Sondergaard, senior vice president of Gartner Research. The more information we have, the more likely we are to find correlations that are not obvious to the eye and that can completely change the way we think or act. We are living in a reality where tons of data from several different sources are routinely collected, often without we realizing it. Every aspect of our lives, such as social activities, consumption patterns, Internet searches, geographic movements on global positioning systems, and health issues, are somehow being transformed in data. The large volume of new data being generated is straining the capacity of institutions to manage and of researchers to make use of them, a situation has been termed the "Data Deluge".[1]

One of the most notable areas where data analytics is causing makeovers is in healthcare. Apart from traditional medical research, there are numerous other sources with the potential to contribute to big data. Some examples include hospital records, patient's medical records, results of medical examinations, and lots of new computing devices (known as the "internet of things"), which are embedded in everyday objects and can collect real-time body-signals ubiquitously. Through the analysis of large amounts of data, diseases can be diagnosed earlier, thus improving the prognosis of serious diseases. Medical costs can be reduced, epidemics can be predicted, diseases can be prevented and quality of life can be improved. At the individual level, we are increasingly moving into the era of personalized medicine, where the information of a given patient, especially his/her genetic data, will be analyzed and processed for the establishment of a specific and personalized treatment.

Since the early 2000s, when the term *big data* came into use, the way data are collected and analyzed has completely changed. The famous 3 "Vs" of big data refers to volume, velocity and variety.[2] Although, other people have added several other Vs to this definition such as veracity, value, visualization, and variability, in the end, we are talking about data with sizes that exceed the capacity of traditional software to process within an acceptable time and *value*. Another good explanation for big data is that it "involves all the data collections endowed with a sufficient "size" and lack of definition (having been assembled with no *a priori* hypothesis or specific research task) to be considered as still largely unspoiled territories from where to derive new insights in the form of unforeseen regularities".[3]

The European Commission developed the following definition for "big data in Health": it refers to large routinely or automatically collected datasets, which are electronically captured and stored. It is reusable in the sense of multipurpose data and comprises the fusion and connection of existing databases for the purpose of improving health and health system performance. It does not refer to data collected for a specific study." [4]

In the medical field, with the advancements of radiomics for example, a method that extracts a large number of features from medical images using data-characterization algorithms, millions of data can be extracted automatically through software developed for this purpose, feeding large data repositories that will be used to predict outcomes, dispense new tests or optimize diagnostic investigation, reducing costs and improving the treatment of numerous diseases. [5]

Imagine the following situation: you, as a healthcare professional, have a patient with a lung nodule found in a thorax computed tomography scan. With a single chest tomography, through the analysis of radiomics and artificial intelligence, you can determine if the nodule is malignant and what the anatomopathological subtype is, sparing the patient from the risks of a biopsy. The analysis of lung

parenchyma, heart area, coronary calcifications, muscle mass and subcutaneous tissue will provide information about lung and cardiac function, sarcopenia and malnutrition, allowing a precise prediction of postoperative complications and again saving the patient from being submitted to numerous preoperative examinations. Additionally, a detailed analysis of the anatomical structures of this lung, with the recognition of possible anatomical variations, will allow a better surgical planning, in such a way that the surgeon will know in advance the difficulties he will encounter during the surgery.

Therefore, this is the future and it will probably be a reality in approximately 10 years. However, to get there we need large amounts of data; not only data automatically extracted from imaging examinations or medical devices, but also clinical data. Because that is how systems learn, that is how artificial intelligence and machine learning work. It means that constructing and feeding clinical databases are an essential step to get to the future of big data.

However, building and maintaining a clinical database is not an easy task. Using the example of lung cancer again, there are large international multicentric databases [6,7,8] that still rely on the human effort for data imputation, despite the fact that technology already exists for extracting information directly from electronic health records (EHRs). This fact is a major constraint for large-scale quality data collection, especially in countries like Brazil where there are no national or governmental initiatives for the development of medical registries, and the vast majority of health professionals are not familiar with data collection outside clinical research.

There are many challenges associated with big data in healthcare. Even in the United States, where the adoption of federally tested and certified EHR programs in the healthcare sector is nearly complete, the existence of different programs, with different clinical terminologies, technical specifications, and functional capabilities has led to difficulties in the interoperability and sharing of data.[2] Furthermore, most EHR systems contain lots of unstructured data, making it more complex to extract useful information for big data. Drawing a parallel between the United States and Brazil, Brazil are a long way from this problem yet, as many health services are either still implementing their EHR systems or simply still rely on manual health records.

Furthermore, having an EHR system available in a given health service does not mean that data will actually be extracted to contribute to a clinical database. It probably will not be because, in addition to all the technological difficulties listed above, there are other barriers related to regulatory laws on accessing and sharing personal information, such as *the General Data Protection Law ("LGPD"*) in Brazil, the *General Data Protection Regulation* ("GDPR") in Europe, and the *Health Insurance Portability and Accountability Act* (HIPAA) in United States. To buttress this point, solutions still need to be found or agreed for many issues, especially in Brazil, where the LGPD is relatively recent. First of all, who owns patients' information - hospitals, researchers, or patients themselves? Assuming that the information belongs to the patient, how can this contribute to the development of big data and ultimately to the improvement of the patient's own health? How can sensitive data related to health issues be collected in large volumes with patients' consent and privacy protection?

Owing to all this, despite all the advances in technology, a lot of health data are still being "lost" daily, even in large referral services, simply because there is no initiative for the prospective collection of such data. Addressing this problem requires, first of all, recognizing the importance of data collection for the development of science on a national scale. We urgently need initiatives for the development of national medical specialties databases and cancer registries. We need to know the dimensions of our own data to compare our numbers to international benchmarks instead of just consuming international data and trying extrapolate them to our locality.

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Trajectory of NAFLD characteristics after Roux-en-Y gastric bypass: a five-year historical cohort study

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AUTHORS' KEY WORDS:
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Hepatic steatosis.

ABSTRACT

BACKGROUND: The long-term effects of bariatric surgery on the course of non-alcoholic fatty hepatopathy (NAFLD) are not fully understood.

OBJECTIVE: To analyze the evolution of NAFLD characteristics through noninvasive markers after Roux-en-Y gastric bypass (RYGB) over a five-year period.

DESIGN AND SETTING: Historical cohort study; tertiary-level university hospital.

METHODS: The evolution of NAFLD-related characteristics was evaluated among 49 individuals who underwent RYGB, with a five-year follow-up. Steatosis was evaluated through the hepatic steatosis index (HSI), steatohepatitis through the clinical score for non-alcoholic steatohepatitis (C-NASH) and fibrosis through the NAFLD fibrosis score (NFS).

RESULTS: 91.8% of the individuals were female. The mean age was 38.3 ± 10 years and average body mass index (BMI), 37.4 ± 2.3 kg/m^2. HSI significantly decreased from 47.15 ± 4.27 to 36.03 ± 3.72 at 12 months ($P < 0.01$), without other significant changes up to 60 months. C-NASH significantly decreased from 0.75 ± 1.25 to 0.29 ± 0.7 at 12 months ($P < 0.01$), without other significant changes up to 60 months. NFS decreased from 1.14 ± 1.23 to 0.27 ± 0.99 at 12 months ($P < 0.01$), and then followed a slightly ascending course, with a marked increase by 60 months (0.82 ± 0.89), but still lower than at baseline ($P < 0.05$). HSI variation strongly correlated with the five-year percentage total weight loss ($R = 0.8$; $P < 0.0001$).

CONCLUSION: RYGB led to significant improvement of steatosis, steatohepatitis and fibrosis after five years. Fibrosis was the most refractory abnormality, with a slightly ascending trend after two years. Steatosis improvement directly correlated with weight loss.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and is expected to be the most frequent indication for liver transplantation by 2030. NAFLD is closely related to obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM). In this setting, its prevalence ranges from about 50% to up to 90%, which has made NAFLD a challenging public health concern, as the prevalence of obesity and overweight has increased to epidemic levels over the last few decades.[1,2]

NAFLD encompasses a spectrum of histopathological abnormalities ranging from simple steatosis to cirrhosis, end-stage liver failure and even liver cancer. Its diagnosis is based on the presence of abnormal fat accumulation in more than 5% of hepatocytes on liver biopsy, excluding other causes such as alcohol abuse, viral infection, autoimmune disease or drug-induced liver disease.[3] Although liver biopsy is the gold standard for diagnosing NAFLD, it is an invasive test and not free from complications.

In this context, noninvasive markers have been developed. These are mostly calculated through routine laboratory tests and clinical and anthropometric assessments. They help to identify patients at higher risk of presenting the severe forms of the disease, and to monitor disease progression.[4]

Bariatric surgery is an effective treatment for severe and refractory obesity and leads to sustained weight loss with potential reductions in liver fat, inflammation and fibrosis. Significant evidence of the beneficial effects of Roux-en-Y gastric bypass (RYGB) on NAFLD has been demonstrated through studies with follow-ups of up to two years, but evidence based on lengthier follow-up times is scarcer. Considering that weight regain, obesity recidivism and re-emergence of insulin

resistance and T2DM may occur after this two-year "honeymoon" period, a longer-term analysis of the effect of surgery on the trajectory of aspects of the NAFLD spectrum is of great importance.[5-7]

OBJECTIVE

The aim of this study was to analyze the evolution of different NAFLD characteristics through noninvasive markers among patients who underwent Roux-en-Y gastric bypass, over a five-year period.

METHODS

Study design

This was an observational historical cohort study based on a prospectively collected database. It evaluated the clinical and laboratory characteristics of individuals who underwent open RYGB, with a five-year follow-up, at a tertiary-level university hospital from July 2014 to March 2015. The research project was evaluated and approved by our institutional ethics review board on September 24, 2020 (CAAE: 37900820.8.0000.540).

Comparisons were made between the period immediately before surgery and the times of 12, 24, 36, 48 and 60 months afterwards, to measure the impact of the procedure on NAFLD, through the evolution of noninvasive markers. An analysis of the diagnostic accuracy of each score at the time of surgery was carried out using liver biopsies collected systematically during surgery.

Study population

Individuals of both genders, aged between 18 and 70 years, who had undergone RYGB were included. Patients with the following characteristics were excluded: a history of alcohol or hepatotoxic drug use; chronic viral hepatitis or serological abnormalities; a diagnosis of current or past biliary obstruction; belonging to vulnerable groups (mental patients, institutionalized or under 18 years old); incomplete medical records; and follow-up of less than five years. Out of the 90 individuals who underwent a bypass within the period considered, 49 fulfilled the criteria and were assessed in this study.

All patients who undergo bariatric surgery in our institution take part in a preoperative weight loss program that lasts from 4 to 12 weeks, consisting of weekly consultations carried out by a multidisciplinary team. Individuals undergo surgery when they reach a minimum preoperative weight loss of 10%, and provided that they have a minimum body mass index (BMI) of 35 kg/m^2 with obesity-related morbidities, or 40 kg/m^2. All procedures were performed by the same surgical team and followed the same technique.

Liver biopsy

A wedge liver biopsy is performed during surgery immediately after the main procedure. A fragment of length 2 cm is extracted using blunt scissors, usually from segment III or IV of the liver, and hemostasis is subsequently performed.

Variables

Histopathological analysis

Changes relating to NAFLD were classified into categories, according to the classification system of the Brazilian Society of Hepatology: 1) steatosis (absent, mild, moderate or intense); 2) fibrosis (according to the Kleiner-Brunt classification: 0 - absent; 1 - isolated perisinusoidal or periportal; 2 - periportal and perisinusoidal; 3 - presence of fibrous septa ("bridging fibrosis"); or 4 - cirrhosis); and 3) steatohepatitis (classified in degrees: 0, 1+, 2+ or 3+). Kleiner-Brunt grades 3 and 4 are considered to represent advanced fibrosis.[8,9]

Noninvasive markers

The results observed from liver biopsies were correlated with the results obtained using the noninvasive markers, i.e. the hepatic steatosis index (HSI), NAFLD fibrosis score (NFS) and clinical score for non-alcoholic steatohepatitis (C-NASH), at the baseline. Each marker was calculated throughout the five-year follow-up: at baseline, 12, 24, 36, 48 and 60 months. **Table 1** shows how each of them was calculated, its rationale and the respective cut-off values adopted.

Anthropometric and biochemical characteristics

The anthropometric characteristics evaluated were weight, BMI and percentage total weight loss (%TWL). The laboratory tests evaluated included fasting glucose (FG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglycerides, serum albumin and platelet count.

Statistical analysis

Descriptive analysis was performed, with presentation of frequency tables for categorical variables and position and dispersion measurements for numerical variables. To compare proportions, the chi-square test was used, or Fisher's exact test when necessary. To compare continuous measurements between two evaluation times, the Mann-Whitney test was used. For comparison between three or more evaluation times, the Kruskal-Wallis test was used, with Tukey's post-test analysis when significant. For analysis of correlations between continuous variables, linear regression models were used. To assess the reliability of each score at baseline, diagnostic accuracy measurements (sensitivity, specificity, positive and negative predictive values and overall accuracy) were calculated considering histopathological examination as the gold-standard diagnostic method. The significance level adopted for the statistical tests was 5% ($P < 0.05$). The SAS

Table 1. Main characteristics of each noninvasive score assessed

Score	Rationale	Calculation method	Cutoff values and interpretation
HSI	Designed by Lee et al.[28] in 2010 to predict occurrence of steatosis in the general population.	HSI = 8 * ALT/AST + BMI (+ 2 if T2DM and + 2 if female)	A score > 36 indicates the presence of steatosis, while a score < 30 indicates absence of steatosis
NFS	Developed by Angulo et al.[29] in 2007 to predict advanced fibrosis in NAFLD patients.	NFS = -1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m^2) * IGT/T2DM (yes = 1 or no = 0) + 0.99 * AST/ALT – 0.013 * platelet count (* 10^9/l) – 0.66 * albumin (g/dl)	A score > 0.676 indicates advanced fibrosis, while a score < -1.455 excludes advanced fibrosis
C-NASH	Created by Tai et al.[30] in 2017 to predict occurrence of NASH based on clinical characteristics.	Clinical aspect / Points BMI (kg/m^2) 40–45 / 1 > 45 / 2 AST > 40 IU/l / 2 Triglycerides > 140 mg/dl / 1	A sum of points ≥ 3 indicates the presence of steatohepatitis

* = multiplication sign; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic fatty liver steatohepatitis; HSI = hepatic steatosis index; NFS = non-alcoholic fatty liver disease fibrosis score; C-NASH = clinical score for non-alcoholic steatohepatitis; BMI = body mass index; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T2DM = type 2 diabetes mellitus; IGT = impaired glucose tolerance.

System for Windows software (Statistical Analysis System), version 9.2, was used (SAS Institute Inc., 2002-2008; Cary, North Carolina, United States).

RESULTS

Out of the 49 patients selected for this study, 45 (91.8%) were female. The patients' mean age was 38.3 ± 10 years, and their BMI was 37.4 ± 2.3 kg/m^2. Regarding comorbidities, 28 (57.1%) had hypertension, 13 (26.5%) presented T2DM and 29 (59.2%) had some form of dyslipidemia. In the histopathological analysis at the time of surgery, 41 patients (83.7%) presented steatosis and 23 (46.9%) had steatohepatitis. Fibrosis was present in 33 patients (67.3%).

With regard to weight loss during follow-up, the minimum weight was achieved after one to two years, followed by a slight increase up to five years, which was not statistically significant (**Table 2**). **Figure 1** presents a graphical representation of the %TWL over the course of the follow-up.

Analysis on the diagnostic accuracy of the tests in comparison with surgical biopsy showed that the overall accuracies of the tests were as follows: 83.7% for HSI to detect steatosis, 67.7% for NFS to detect advanced fibrosis and 73.5% for C-NASH to detect steatohepatitis. In **Table 3**, the detailed results from this analysis are presented.

There was a marked and statistically significant reduction in noninvasive NAFLD scores in the first year, such that HSI decreased from 47.15 ± 4.27 preoperatively to 36.03 ± 3.72 at 12 months ($P < 0.01$), without any further significant change from then until 60 months. C-NASH significantly decreased from 0.75 ± 1.25 preoperatively to 0.29 ± 0.7 at 12 months ($P < 0.01$); thereafter, there were no further significant changes in its values up to 60 months. NFS decreased from 1.14 ± 1.23 preoperatively to 0.27 ± 0.99 at 12 months ($P < 0.01$); from then onwards, it entered a slightly ascending trajectory, yielding a marked increase at 60 months (0.82 ± 0.89), which was significantly higher than the levels observed at 12 months ($P < 0.01$) and 24 months ($P < 0.05$), but still significantly lower than what had been seen preoperatively ($P < 0.05$). In **Figure 2**, graphical representations of the evolution of the three markers over the follow-up are presented. **Table 2** presents the detailed evolution of each marker over the follow-up, along with the prevalence of each aspect of NAFLD, according to the cutoff values of the noninvasive markers.

With regard to possible correlations between the variation in NAFLD scores and weight loss over the total follow-up period, there was a strong positive correlation between the variation in the HSI and the five-year %TWL ($R = 0.8$; $P < 0.0001$). On the other hand, there were no significant correlations between the five-year %TWL and variations in C-NASH ($R = 0.1$; $P = 0.7$) and NFS ($R = 0.1$; $P = 0.7$).

DISCUSSION

NAFLD, one of the most common causes of chronic liver disease, leads to increased long-term morbidity and mortality. The current evidence suggests that bariatric surgery reduces the degree of fat deposition, liver inflammation and fibrosis, in agreement with the findings from the present study, which revealed a marked reduction in NAFLD marker scores in the first two years after surgery.[10] With regard to weight loss, the findings were also comparable to the literature, demonstrating maximum weight loss between one and two years postoperatively, followed by mild to moderate weight recovery. Despite this recovery, there was no significant difference in mean BMI and %TWL between

Table 2. Evolution of body mass index, percentage of total weight loss, prevalence of non-alcoholic fatty hepatopathy (NAFLD) features and values of NAFLD markers over the five-year follow-up

	Baseline	1 year	2 years	3 years	4 years	5 years	P value
BMI (kg/m^2)	37.4 ± 2.3	26 ± 2.7	26.1 ± 2.9	26.7 ± 2.7	27.2 ± 2.8	27.7 ± 3.2	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.01; BL vs. 5 y: P < 0.01)
%TWL (%)	Not applicable	26.3 ± 8.3	26 ± 8.7	24.4 ± 8.1	22.9 ± 8.9	21.7 ± 9.7	< 0.0001 (1 y vs. 4 y: P < 0.01; 1 y vs. 4 y: P < 0.01; 2 y vs. 4 y: P < 0.01; 2 y vs. 5 y: P < 0.01; 3 y vs. 5 y: P < 0.01)
HSI	47.14 ± 4.27	36.03 ± 3.72	35.9 ± 4.29	35.63 ± 3.98	35.86 ± 3.6	36.3 ± 4.38	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.01; BL vs. 5 y: P < 0.01)
C-NASH	0.76 ± 1.25	0.29 ± 0.71	0.12 ± 0.48	0.06 ± 0.32	0.06 ± 0.32	0.14 ± 0.46	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.01; BL vs. 5 y: P < 0.01)
NFS	1.137 ± 1.228	0.269 ± 0.996	0.476 ± 1.043	0.640 ± 1.031	0.786 ± 1.016	0.821 ± 0.889	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.05; BL vs. 5 y: P < 0.05; 1 y vs. 3 y: P < 0.05; 1 y vs. 4 y: P < 0.01; 1 y vs. 5 y: P < 0.01; 2 y vs. 5 y: P < 0.05)
Steatosis according to HSI – n (%)	49 (100%)	21 (42.9%)	20 (40.8%)	20 (40.8%)	19 (38.8%)	19 (38.8%)	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.01; BL vs. 5 y: P < 0.01)
Steatohepatitis according to C-NASH – n (%)	10 (20.4%)	0	0	0	0	0	< 0.0001 (BL vs. 1 y: P < 0.01; BL vs. 2 y: P < 0.01; BL vs. 3 y: P < 0.01; BL vs. 4 y: P < 0.01; BL vs. 5 y: P < 0.01)
Fibrosis according to NFS – n (%)	33 (67.3%)	16 (32.7%)	16 (32.7%)	24 (49%)	26 (53.1%)	29 (59.2%)	0.001 (BL vs. 1 y: P < 0.01 BL vs. 2 y: P < 0.01)

BMI = body mass index; %TWL = percentage total weight loss; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic fatty liver steatohepatitis; HSI = hepatic steatosis index; NFS = non-alcoholic fatty liver disease fibrosis score; C-NASH = clinical score for non-alcoholic steatohepatitis; vs. = versus; N = number of individuals; BL = baseline; y = year.

the second and fifth years of follow-up, which emphasizes that the satisfactory results obtained through RYGB were maintained over this follow-up period.[11,12]

Uehara et al. conducted a prospective study with a five-year follow-up among 102 patients in Japan in which the evolution of NAFLD was analyzed through liver enzymes. They demonstrated that the reduction in enzymes was sustained over the follow-up, with a slight tendency to increase seen at five years.[13] In a prospective cohort study, Mathurin et al. evaluated 211 patients who underwent various bariatric surgery techniques and who had a paired biopsy available from a fifth-year follow-up. They found improvement in steatosis, ballooning and inflammation, with a significant reduction in the percentage of patients with NASH, compared with the preoperative assessment.[14]

One important finding from the present study was a strong correlation between %TWL and the variation in the HSI, such

that the greater the weight loss was, the greater the drop in this score also was. The absence of this same correlation between %TWL and the variation in the other scores (C-NASH and NFS) seems to relate to their dependence on factors other than weight loss. Histological studies would be more indicated for confirming these findings, but they are invasive and with a potential risk of complications.

This directly proportional relationship between steatosis and weight trajectory was also demonstrated by Yoshioka et al., in a five-year cohort study that observed improvement or worsening of NAFLD over time after weight loss or gain exclusively through changes of lifestyle, respectively.[15] Van-Wagner et al., in a large cohort study that followed 4,423 individuals over 25 years, had also suggested that the trajectory of BMI over the course of life was a reliable predictor of the risk of development and worsening of hepatic steatosis, especially when an ascending path was manifested at an early age.[16] Bariatric surgery studies based on paired biopsies during and after the procedure showed results comparable to those of the current study.[17] The improvement in steatohepatitis, although not proportional to the volume of weight loss, was also significant and was maintained over the follow-up. Lassailly et al. previously demonstrated in a paired biopsy study that improvement in steatohepatitis was consistent over a five-year follow-up in a group of 64 patients undergoing various procedures.[18]

The current study also showed that fibrosis is the most refractory abnormality among the long-term effects of bariatric surgery. While steatosis and steatohepatitis markers show an initial drop that remains constant, the NFS score shows a sharp drop in the first postoperative year, followed by subsequent slightly progressive increases in its values; nonetheless, at the end of the follow-up, the NFS values are still significantly better than at the baseline. A study carried out in 2019 by Yeo et al. demonstrated similar short-term results, showing that the correlation between weight loss and significant improvement in the NFS score only occurred in the first postoperative year.[19] Fakhry et al., in a meta-analysis of prospective studies that enrolled 2,374 patients, observed virtually universal findings pointing to almost complete reversal or improvement of steatosis and steatohepatitis after bariatric surgery, while fibrosis progressed with improvement or reversal in only 30% of the individuals.[20]

A previous study by our group revealed comparable results over a short-term one-year follow-up, with fibrosis reversal in 55%; an expansion of this same study with a three-year follow-up showed that weight regain was associated with worse results, although the benefits in relation to the baseline were still clear.[21,22] Considering the variables that make up the NFS calculation (age, BMI, glucose intolerance and/or diabetes, liver enzymes, platelet count and albumin), it can be postulated that individuals' aging and possible recovery

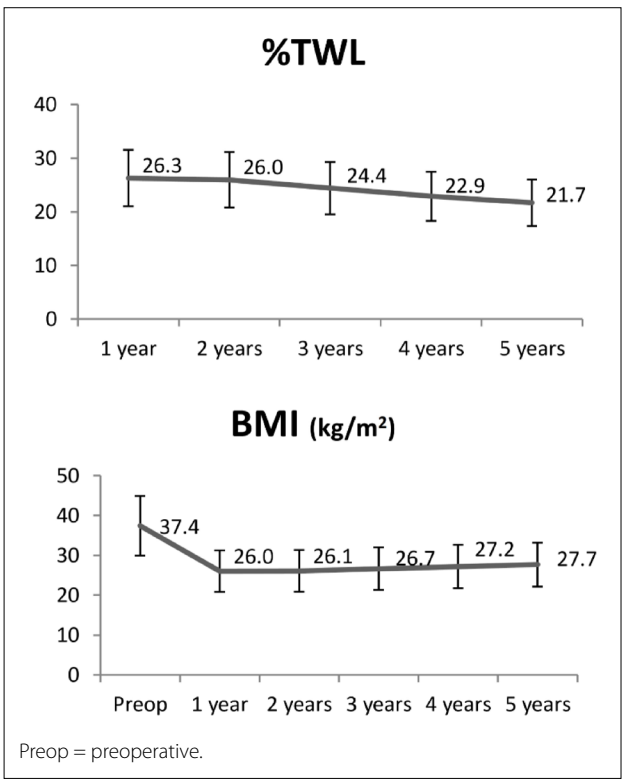

Figure 1. Evolution of percentage total weight loss (%TWL) and body mass index (BMI) over time.

Table 3. Diagnostic accuracy of noninvasive markers for aspects of non-alcoholic fatty liver disease

		Value	95% confidence interval
HSI	Sensitivity	100%	91.4%–100%
	Specificity	0	0%–36.9%
	Positive likelihood ratio	1	Not applicable
	Negative likelihood ratio	Not applicable	Not applicable
	Positive predictive value	83.7%	83.7%–83.7%
	Negative predictive value	Not applicable	Not applicable
	Overall accuracy	83.7%	70.3%–92.7%
C-NASH	Sensitivity	43.5%	23.2%–65.5%
	Specificity	100%	86.8%–100%
	Positive likelihood ratio	Not applicable	Not applicable
	Negative likelihood ratio	0.6	0.4–0.8
	Positive predictive value	100%	Not applicable
	Negative predictive value	66.7%	58.3%–74.1%
	Overall accuracy	73.5%	58.9%–85.1%
NFS	Sensitivity	100%	84.6%–100%
	Specificity	8.3%	0.2%–38.5%
	Positive likelihood ratio	1.1	0.9–1.3
	Negative likelihood ratio	0	Not applicable
	Positive predictive value	66.7%	62.8%–70.3%
	Negative predictive value	100%	Not applicable
	Overall accuracy	67.7%	49.5%–82.6%

HSI = hepatic steatosis index; NFS = non-alcoholic fatty liver disease fibrosis score; C-NASH = clinical score for non-alcoholic steatohepatitis.

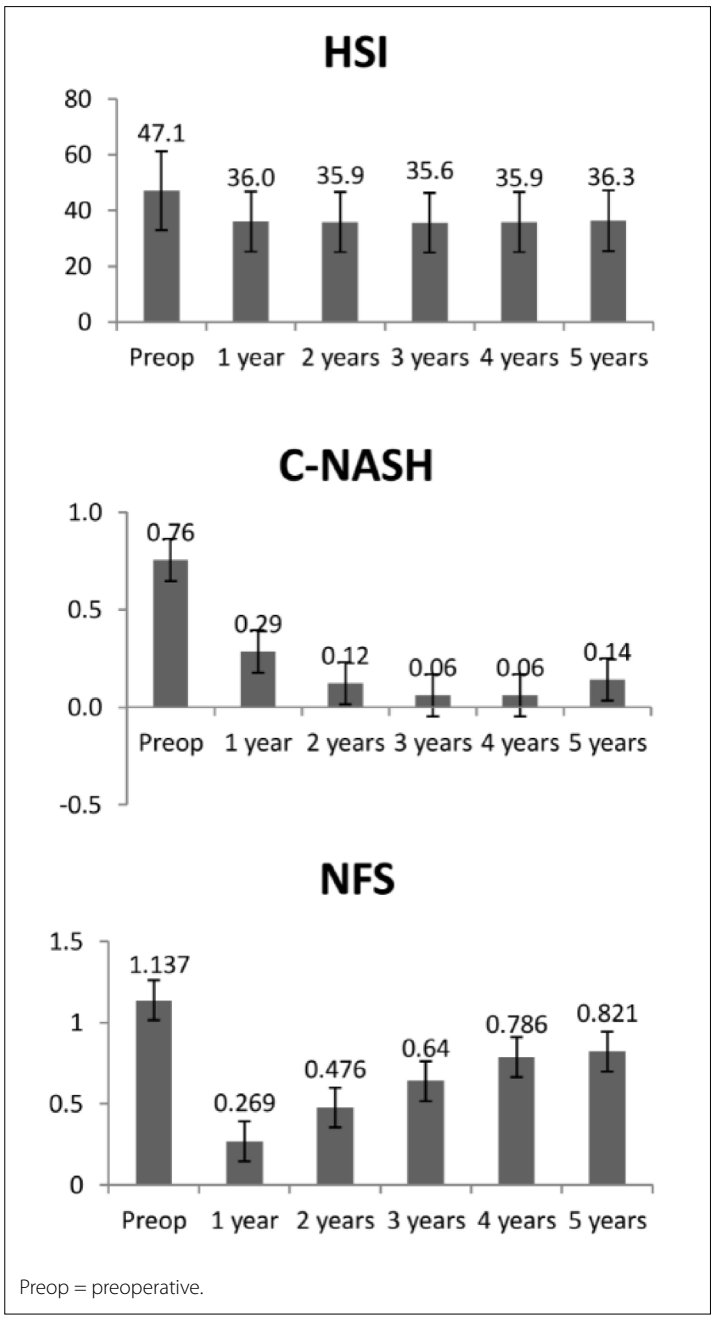

Figure 2. Evolution of hepatic steatosis index (HSI), clinical score for non-alcoholic steatohepatitis (C-NASH) and non-alcoholic fatty liver disease fibrosis score (NFS) over time.

of weight after 24 months, and the possible re-emergence of glucose metabolism disorders after this period play significant roles in mitigation of previous beneficial effects. However, it should be considered that, despite this not so marked improvement, the surgery still proved to be beneficial, since the mean score remained significantly lower than that observed in the preoperative period.

Despite this relative refractoriness of liver fibrosis to the effects of the surgical procedure, largely due to its inherently poorly reversible scarring characteristic, it is possible to speculate that, even in these cases where the outcomes were not so favorable, there was at least a tendency towards stability of this abnormality. Sanyal et al. demonstrated in a landmark study that about 20% of individuals with NAFLD-related F3 liver fibrosis progress to cirrhosis over 96 months if the disease follows its natural path.[23] Given this natural history of fibrosis, the simple absence of progression of the same degree of fibrosis should be considered to be a significant benefit for this group of individuals.

As shown in systematic reviews over the years, the effects of bariatric surgery and weight loss on NAFLD improvement are significant, thus constituting a factor that directly impacts the long-term survival of these patients.[24,25] Use of noninvasive markers has become an important tool in the long-term follow-up of these patients, as it is an easily applicable and risk-free method that allows assessment of the evolution of several NAFLD-related features and helps in understanding the effects of the surgical procedure. Furthermore, in individuals with suggestive clinical and/or imaging findings, the scores can help to define the cases for which a liver biopsy will be necessary and the ideal timing for it to be carried out.[26]

The current study had some limitations that must be considered. The retrospective design used in this study usually reduces the quality of the data considered, even if they were prospectively collected. Loss to follow-up led to a relatively small sample. Use of noninvasive markers instead of histopathological examination is not the ideal method for evaluating NAFLD, but the costs, risks and ethical issues associated with performing serial biopsies make the methods used here more practical and appropriate.[27] Hence, considering the length of follow-up adopted for our study and the availability of all tests and indexes in the entire study population at all the time points considered, the study design was adequate and was able to provide an accurate representation of NAFLD-related features over time after RYGB.

CONCLUSION

RYGB led to significant improvement of steatosis, steatohepatitis and fibrosis after five years. Fibrosis was the most refractory abnormality and presented a slightly ascending trend after two years. The improvement of steatosis directly correlated with weight loss.

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Occupational stress and work engagement among primary healthcare physicians: a cross-sectional study

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KEY WORDS (MeSH terms):
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Work engagement.
Occupational health.

AUTHORS' KEY WORDS:
Family health strategy.
Work environment.
Unified health system.

ABSTRACT

BACKGROUND: Brazil's Family Health Strategy is based on a primary healthcare model, which is considered to have case resolution capacity, with physicians at its center.

OBJECTIVES: To evaluate the levels of occupational stress and work engagement among primary healthcare physicians.

DESIGN AND SETTING: Cross-sectional study conducted in 2017, in São José do Rio Preto, São Paulo, Brazil.

METHODS: A non-probability sample including 32 physicians from family health teams was used. Three self-applied instruments were used: a scale developed by the researchers seeking sociodemographic and professional variables, the Work Stress Scale and the Utrecht Work Engagement Scale.

RESULTS: Female professionals (59.4%), permanent employees (56.3%), workload of 40 hours per week (59.4%) and 3-10 years of acting in primary care (68.8%) were more prevalent. Six professionals (19.4%) exhibited significant stress (score ≥ 2.5). The main stressors were lack of prospects for career growth (2.9 ± 1.3), form of task distribution (2.7 ± 1.0), poor training (2.7 ± 1.2) and insufficient time to perform the job (2.6 ± 1.2). Levels of work engagement ranged from 4.3 to 4.6 and were rated as high in all dimensions. Physicians with occupational stress had average levels of work engagement, whereas those without occupational stress had high levels of work commitment.

CONCLUSIONS: A notable percentage of the physicians were experiencing occupational stress. The physicians had high levels of work engagement. Occupational stress was negatively correlated with work engagement, and it significantly compromised physicians' levels of work engagement and interfered with their positive relationship with the work environment.

INTRODUCTION

Despite recent advances in primary healthcare in Brazil, numerous difficulties arising from the new National Primary Healthcare Policy continue to permeate the system, thus especially weakening management of workers. The process of recomposition of teams and reorganization of the work process has made it even more difficult to acquire aptly qualified professionals for family healthcare teams, implement more democratic and participatory work processes and regularize contractual bonds. These roadblocks impact employee satisfaction with the work environment and process, and often lead to psychological distress, which then leads to turnover of medical professionals especially.[1-4]

Therefore, it is important to know the level of work engagement among primary healthcare professionals, especially physicians, whose high turnover compromises consolidation of teams and the case resolution capacity of primary healthcare services.[1-4] Work engagement is considered essential for a good relationship between workers and their company. Engagement is conceptualized as a positive mental state that allows workers to connect deeply with the work activity, and it acts as an indicator of worker health, defined in terms of motivation and professional commitment.[2,5-6]

Engagement involves commitment to the activity and to the work environment and is characterized by three attributes: dedication, absorption and vigor. Dedication comprises the worker's level of involvement and enthusiasm, manifested as feeling proud and inspired to perform the work. Absorption relates to focus and concentration on the work, which is seen as highly pleasurable. Vigor refers to the level of energy and resilience in the face of adversity.[7-9]

Studies conducted in Brazil and elsewhere have indicated that primary healthcare professionals, especially physicians and nurses,[7,10-12] generally have good levels of engagement at work. A study carried out in two Brazilian cities showed that professionals working in cities with 100%

coverage by the Family Health Strategy presented significantly higher levels of engagement than those working in cities with only partial coverage.[10] These results emphasize the importance of assessing worker engagement as a workforce indicator within primary healthcare.

Likewise, it is important to identify the levels of occupational stress and the stressors related to the working process, in order to obtain the requisite information for reorganizing services and improving working conditions. Such endeavors can contribute towards the productivity and case resolution capacity of workers in the primary healthcare sector and can help retain doctors as well.[1,3-4]

Occupational stress results from conflict between psychological needs and levels of control over the work process. It may arise when the worker, due to lack of training, excessive demand, work overload or precarious safety conditions at work, faces difficulty in coping with challenging situations.[13]

Though at varying degrees, psychological distress is present across all categories of primary healthcare professions. However, there is evidence that physicians are more susceptible to stress due to the high physical and emotional demands that their practice imposes, especially in some specialties such as family and community medicine. Among the factors that cause mental illness among these workers, the most important are those associated with work, such as overload, precarious work conditions, lack of autonomy and pressure to meet targets.[14-15]

Some studies on occupational stress among primary healthcare professionals have highlighted the following as the main stressors: lack of training, type of control in the work environment, lack of prospects for professional growth and lack of autonomy, appreciation and time to perform the work.[7,16-17] However, there is a lack of information about occupational stress among primary healthcare physicians and the stressors relating to the work processes of these professionals.

Therefore, knowing the levels of work engagement and occupational stress among physicians can generate support for reorganizing the work process and reducing weaknesses that can cause emotional distress. In this manner, positive relationships between workers and their work activities can be strengthened and the productivity and case resolution capacity of primary healthcare services can be improved.

OBJECTIVE

To evaluate the levels of occupational stress and work engagement among primary healthcare physicians.

METHODS

Ethical considerations

Ethical approval regarding this study was obtained from our institutional ethics committee (decision: 1,776,737; date: October 17, 2016). All the participants in this study were only included after written informed consent had been obtained from them. All procedures performed in this study were compatible with the ethical standards of the institutional research committee and with those of the Declaration of Helsinki and its comparable ethical standards.

Type of study

A quantitative and observational cross-sectional study was conducted in 2017, using a non-probability convenience sample that included 32 physicians from family health teams in São José do Rio Preto, São Paulo, Brazil.

Sample participants

São José do Rio Preto is a large municipality located in the northwest of the state of São Paulo, 452 km from the state capital. It is the headquarters of the 15th Regional Health Department, the largest in the state, and forms a reference point for healthcare. At the time of this study, the estimated population of this municipality was 446,649 inhabitants and, organizationally, it was divided into five healthcare districts. It had 27 primary care units, consisting of 10 basic health units and 17 basic family health units, with 40 family health teams and 30.9% coverage of the population.

Setting

The study population comprised all physicians in the family health teams, totaling an estimated 40 professionals. Professionals who were on vacation and/or away from their professional activities during the data collection period were excluded. The sample was defined according to convenience and was composed of 32 physicians (80.0%) who provided responses in the instruments.

Procedures, measurements, variables and outcome

For data collection, the researchers used a self-administered instrument that investigated sociodemographic and professional variables, and two scales: the Work Stress Scale, validated for use in Brazil by Tamayo and Paschoal;[18] and the Utrecht Work Engagement Scale, validated for use in Brazil by Vazques et al.[19]

The Work Stress Scale is composed of 23 negative statements to which responses are given using a five-point Likert scale format, ranging from "strongly disagree" to "strongly agree;" the higher the score is, the higher the stress also is. Its indicators were developed from an analysis of the literature on organizational stressors of psychosocial nature and on psychological reactions to occupational stress. The scale has satisfactory psychometric characteristics and can contribute to investigating and diagnosing the organizational environment. It is a tool for organizational diagnosis that has undergone psychometric testing and requirements.[18]

The Utrecht Work Engagement Scale contains 17 self-assessment items grouped into three categories (dedication, absorption and vigor) and an overall score.[19] These categories are measured as follows:

- Dedication is measured through the average of five items that refer to a sense of meaning, enthusiasm, pride and inspiration for one's work: 1. I find the work that I do to be full of meaning and purpose; 2. I am enthusiastic about my work; 3. My work inspires me; 4. I am proud of the work I do; and 5. I find my work challenging.[19]
- Absorption is measured through six items that relate to immersion and attachment to work: 1. "Time flies" when I am working; 2. When I am working, I forget everything around me; 3. I feel happy when I work intensely; 4. I feel involved in the work I do; 5. I "get carried away" with my work; and 6. It is difficult to disconnect from work.[19]
- Vigor is measured through six items that relate to energy, resilience, effort and persistence with work: 1. At my work, I feel full of energy; 2. At work, I feel strong and vigorous (vitality); 3. When I get up in the morning, I feel like going to work; 4. I can continue working for long periods of time; 5. I am a mentally resilient person; and 6. At work, I am persistent, even when things are not going well.[19]

Data collection was scheduled by unit managers and was carried out during team meetings. The researchers presented the study objectives, collected the signatures on the informed consent form and handed out the questionnaires. After completion, the questionnaires were deposited in a brown envelope without identification, in order to preserve the participants' anonymity.

The data were analyzed using the SPSS software, version 23.0, developed by the International Business Machines Corporation (IBM) (New York, United States). Sociodemographic and professional variables were used to describe the physicians' profiles.

Sample size and statistical analysis

To analyze occupational stress, a general average score and an average score for each item of the scale were calculated in order to identify the most recent stressors, according to the physicians. The scores could range from one to five, and the higher the average value was, the higher the level of stress was. Mean values greater than or equal to 2.5 indicated higher levels of stress.[18]

The statistical model proposed in the preliminary manual of the Utrecht Work Engagement Scale was used to analyze the levels of engagement at work. The means and standard deviations of the dimensions of the Utrecht Work Engagement Scale were presented.[20] These dimensions were obtained as follows: Dedication - arithmetic mean of the responses to questions 2, 5, 7, 10 and 13; Absorption - arithmetic mean of the responses to questions 3, 6, 9, 11, 14 and 16; and Vigor - arithmetic mean of the responses to questions 1, 4, 8, 12, 15 and 17. The overall score was obtained through the arithmetic mean of the answers to all questions in the scale.

After the scores had been calculated, the values obtained were interpreted as prescribed in the preliminary manual of the Utrecht Work Engagement Scale: 0 to 0.99 = very low; 1 to 1.99 = low; 2 to 3.99 = medium; 4 to 4.99 = high; and 5 to 6 = very high.[20]

The internal consistency indicator Cronbach's alpha was used to ascertain the reliability of the measurements of the constructs of the Utrecht Work Engagement Scale. Comparison of the mean scores of the scales was performed using the t test for two means or using analysis of variance, with a significance level of 95% ($P \leq 0.05$).

The correlation between occupational stress and work engagement was assessed using Pearson's correlation test. In this, r up to 0.30 was taken to represent a weak correlation; r between 0.40 and 0.60, moderate correlation; and r greater than 0.70, strong correlation.

RESULTS

Thirty-two physicians working at primary healthcare units participated in this study; 19 (59.4%) were female and 20 (62.5%) were married. Their ages ranged from 27 to 75 years, with a mean age of 45.2 years and standard deviation (SD) of 11.7 years.

As shown in **Table 1**, 15 (46.9%) of these professionals had undergone specialized training, 17 (53.2%) were overweight or obese, 18 (56.3%) were permanent employees, 19 (59.4%) worked at the primary care unit for 40 hours a week, 16 (50.0%) were involved in another paid activity, 16 (50.0%) practiced physical activity, 25 (78.1%) reported engaging in leisure activities, 17 (53.1%) practiced religious observance and 23 (71.9%) had six to eight hours of sleep per night. The monthly family income reported by 22 physicians (68.8%) was higher than 10 minimum monthly wages (the current minimum monthly wage value is R$ 937.00, i.e. approximately US$ 284.00). The length of employment of these professionals working in primary healthcare ranged from six months to 30 years, with a median of seven years.

In the occupational stress analysis, one professional was excluded because of not having answered the questions of this instrument. The general average obtained among the 31 physicians evaluated was 2.1, with a SD of 1.1. It was observed that eight (25.0%) of the professionals presented scores that corresponded to major stress (≥ 2.5).

As can be seen in **Table 2**, the major stressors were lack of prospects for career growth (2.9; SD = 1.3), the way in which tasks were distributed (2.7; SD = 1.0), deficiencies in professional training (2.7; SD = 1.2), insufficient time to perform the job (2.6; SD = 1.2), the type of control imposed (2.5; SD = 1.0) and lack of autonomy in executing the job (2.5; SD = 1.2).

The levels of physicians' work engagement are presented in **Table 3**. In the reliability analysis, Cronbach's alpha coefficient values ranged from 0.833 to 0.950, thus indicating that the results showed good reliability. The means of the dimensions ranged from 4.3 (SD = 1.2) to 4.6 (SD = 1.3). Both dimensions presented engagement levels classified as high (**Table 3**).

Table 1. Sociodemographic characteristics of primary healthcare physicians

Variables	n	%
Gender		
Male	13	40.6
Female	19	59.4
Age group		
Up to 30 years old	3	12.5
From 31 to 49 years old	16	50.0
50 years old or over	12	37.5
Marital status		
Married	20	62.5
Single	9	28.1
Divorced	2	6.3
Widowed	1	3.1
Education level		
Bachelor's degree	11	34.4
Specialist degree	15	46.9
Master's degree	5	15.6
Doctoral degree	1	3.1
Body mass index		
Normal	11	34.4
Overweight	14	43.8
Obesity grade I	2	6.3
Obesity grade III	1	3.1
No information	4	12.5
Type of contract		
Permanent (statutory regime)	18	56.3
Contracted (consolidation of Brazilian labor laws)	14	43.8
Weekly workload		
20 hours	9	28.1
30 hours	4	12.5
40 hours	19	59.4
Family income (minimum wages)*		
From 6 to 10 minimum wages	9	28.1
More than 10 minimum wages	22	68.8
No information	1	3.1
Other remunerated activity		
Yes	16	50.0
No	16	50.0
Practice of physical activity		
Yes	16	50.0
No	16	50.0
Recreational activity		
Yes	25	78.1
No	7	21.9
Frequent religious observance		
Yes	17	53.1
No	15	46.9
Daily hours of sleep		
Less than 6 hours	9	28.1
From 6 to 8 hours	23	71.9

*Minimum monthly wage value: R$ 937.00 (US$ 284.00).

Occupational stress and work engagement correlated negatively (**Table 4**). We observed that the correlation between occupational stress and the attributes of dedication (r: -0.357; P = 0.049) and absorption (r: -0.369; P = 0.041) was weak, while it was moderate between occupational stress and vigor (r: -0.444; P = 0.012) and overall (r: -0.519; P = 0.003).

From analysis on the levels of engagement, according to the presence or absence of occupational stress (**Table 5**), we observed that physicians demonstrating occupational stress showed average levels of engagement in relation to all the parameters of the Utrecht Work Engagement Scale. On the other hand, physicians who did not demonstrate any occupational stress showed high levels of engagement in relation to all the parameters. This analysis confirmed that occupational stress compromised the positive relationship of these professionals with their work environment.

DISCUSSION

The sociodemographic profile of the physicians in this study corroborates the findings from other studies conducted in Brazil and elsewhere.[7,15,21-24] Currently, in the field of medicine, there is a predominance of women working in various positions, including under precarious working conditions, thus leading to high occupational stress.[25]

The percentage of these physicians presenting significant occupational stress corroborated data in the literature on this topic published in Brazil and elsewhere.[7,26,27] This showed that organizational stressors interfered with practice among the physicians evaluated. These stressors may have arisen through the structure and political-administrative organization of primary healthcare within the municipality. At the time of this study, the Family Health Strategy covered 30.9% of this city's primary care. Large cities have generally implemented the Family Health Strategy in poorer regions that present greater demands for healthcare and generate greater challenges and workload for the professionals, thereby increasing their risk of developing occupational stress.[10]

As shown in this study, the most stressful factor in the physicians' perception was lack of career growth prospects. This was a major obstacle in retaining physicians within primary healthcare services, especially in remote areas.[3,4] Moreover, lack of career advancement opportunities may play an important role in occurrences of exhaustion among primary healthcare providers.[28] This result highlights the need for creation and implementation of a medical career path within Brazilian primary healthcare services, at both the state and the federal level.

Another stressor was deficiency of professional training. This compromises job satisfaction and has a high correlation with professional turnover within primary healthcare.[3] A study among primary healthcare teams in a small city in the interior of the state of São Paulo that has 100% coverage by the Family Health Strategy

indicated that lack of training was the main cause of occupational stress, thus corroborating the results from the present study.[7]

Moreover, task distribution, insufficient time to perform the work, type of control and lack of autonomy in performing the work were found to be associated with decreased levels of job satisfaction and increased stress. These factors can culminate in development of burnout syndrome among physicians and other professionals within primary healthcare services.[26,29,30]

The presence of occupational stress among physicians who did not practice any religious observance that was found in the present study corroborated the findings of a previous study.[27] However, it is noteworthy that family physicians have a higher risk of developing stress and emotional distress, regardless of sociodemographic factors, compared with other specialties.[26] In this context, it is essential that municipal managers are aware of the aspects of the work process within primary healthcare that can cause occupational stress, given that protection and development of family physicians' health will have a positive impact on the health of all professionals and on the quality of care provided for users.[31]

Furthermore, identification and correction of the causal factors behind occupational stress among physicians can reduce burnout and favor work involvement.[28] This will promote compliance

Table 4. Correlations between the Work Stress Scale and the Utrecht Work Engagement Scale

Work Engagement Scale dimensions	Work Stress Scale	P value*
Dedication	-0.357**	**0.049**
Absorption	-0.369**	**0.041**
Vigor	-0.519***	**0.003**
General score	-0.444**	**0.012**

*t test; **P < 0.05; ***P < 0.01.

Table 2. Rating of the items of the Work Stress Scale, according to the perceptions of the primary healthcare physicians

Items	Mean (± standard deviation)
Q1 - The way tasks are distributed in my area makes me irritated	**2.7 (1.0)**
Q2 - The kind of control that exists in my work annoys me	**2.5 (1.0)**
Q3 - The lack of autonomy in implementing my work is exhausting	**2.5 (1.2)**
Q4 - I am uncomfortable with my superior's lack of confidence in my work	1.8 (1.0)
Q5 - I am irritated by the lack of disclosure of information about organizational decisions	2.4 (1.2)
Q6 - I feel uncomfortable with the lack of information about my tasks at work	2.1 (1.0)
Q7 - Lack of communication between my coworkers and me makes me angry	2.1 (0.9)
Q8 - I feel annoyed that my superior mistreats me in front of coworkers	1.5 (0.7)
Q9 - I feel uncomfortable having to perform tasks that exceed my capacity	2.0 (1.1)
Q10 - I get in a bad mood through having to work for many hours at a time	2.4 (1.2)
Q11 - I feel uncomfortable with the communication between my superior and me	1.8 (1.1)
Q12 - I get irritated with discrimination/favoritism in my work environment	1.9 (1.0)
Q13 - I am uncomfortable with the deficient professional training	**2.7 (1.2)**
Q14 - I get in a bad mood because I feel isolated in the organization	2.1 (1.0)
Q15 - I get annoyed at being undervalued by my superiors	2.1 (1.3)
Q16 - The few prospects for career growth make me distressed	**2.9 (1.3)**
Q17 - I am uncomfortable about working on tasks below my skill level	2.4 (1.3)
Q18 - The competition in my work environment puts me in a bad mood	1.5 (0.6)
Q19 - Lack of understanding of what my responsibilities are in this work annoys me	2.0 (1.0)
Q20 - I get irritated about my superior giving me contradictory orders	1.6 (0.8)
Q21 - I feel annoyed that my superior is covering up my well-done job in front of other people	1.6 (0.8)
Q22 - Insufficient time to carry out my workload makes me irritated	**2.6 (1.2)**
Q23 - I am annoyed that my superior prevents me from taking on significant responsibilities	1.7 (0.8)

Values in bold indicate items of the Work Stress Scale with scores compatible with a significant level of occupational stress.

Table 3. Levels of engagement shown in the Utrecht Work Engagement Scale among the primary healthcare physicians

Dimensions	Cronbach's alpha	Minimum	Maximum	Median	Mean (± SD)	95% CI	Interpretation of level of engagement
Dedication	0.922	0.6	6.0	4.7	4.6 (1.3)	4.1–5.0	High
Absorption	0.833	1.5	6.0	4.5	4.3 (1.2)	3.9–4.7	High
Vigor	0.884	1.8	6.0	4.9	4.5 (1.1)	4.1–4.9	High
General score	0.950	2.0	6.0	4.7	4.5 (1.1)	4.1–4.9	High

SD = standard deviation; CI = confidence interval.

Table 5. Analysis on the levels of work engagement among the primary healthcare physicians, according to the presence or absence of occupational stress

Work engagement	Occupational stress	Mean score	Standard deviation	Interpretation of levels of engagement	P value*
Dedication	Yes	3.71	0.94	Medium	**0.010**
	No	4.90	1.30	High	
Absorption	Yes	3.46	1.12	Medium	**0.006**
	No	4.66	1.00	High	
Vigor	Yes	3.37	1.07	Medium	**< 0.001**
	No	4.97	0.74	High	
General score	Yes	3.50	0.99	Medium	**0.001**
	No	4.84	0.94	High	

*t test.

with the guidelines of the new National Primary Care Policy,[32] especially with regard to continuity of care, retention of physicians, establishment of bonds and appropriate accountability of professionals and users.[14] Through this, primary healthcare services can be strengthened.

The primary healthcare physicians in the present study showed higher levels of work engagement than those reported in previous Brazilian studies on healthcare professionals undergoing training,[33] professionals within multiprofessional residency programs[9] and military police officers.[34] However, these results corroborated the findings of Brazilian studies on other primary healthcare professionals[7,11,16] and those of studies conducted in other countries among dentists,[35] primary healthcare nurses[36] and hospital care nurses,[37] thus indicating that physicians present high levels of work engagement in the primary healthcare sector.

High levels of work engagement among physicians are important for the healthcare system, since these indicate that these professionals can contribute very positively towards meeting the needs of the enrolled population. High levels of energy and connection with their work allow them to cope better with the demands of their practice.[9,38]

However, it has been observed that occupational stress significantly compromises the levels of engagement with work among primary healthcare physicians, which can negatively affect the work performance of these professionals.[7] Moreover, this stress is detrimental to these professionals' willingness to continue working in primary healthcare teams.[4]

Since work engagement is related to workers' involvement with the work activity and professional effectiveness, occupational stress will also compromise the level of physicians' wellbeing, thus leading to demotivation and dissatisfaction with the work.[39] Therefore, implementation of positive managerial policies that promote recognition and appreciation can stimulate these professionals' engagement. Above all, this improves their resilience to work adversities and avoids the negative impact of stressors on their engagement levels.[7,40] It is noteworthy, however, that the responses to positive or negative stimuli may vary between different regions and healthcare units because engagement is a phenomenon that is associated with the team in which the physician is placed, as shown in a study among Portuguese nurses, whose levels of engagement varied between different regions, hospitals and care units.[41]

It is noteworthy that shared management can favor increased engagement among primary healthcare professionals through enabling participation in decision-making, thereby supporting the work process and strengthening team relationships. Likewise, allowing involvement of all workers can facilitate overcoming individual and collective difficulties, thus reducing occupational stress.[42,43]

The main limitations of this study were its cross-sectional design, which made it impossible to establish cause-and-effect relationships; and its inclusion of professionals from a single municipality, with a limited sample that does not allow generalization of the results. However, this study has provided an important diagnosis for the relationship between the work process and emotional health of physicians who work in primary healthcare services in a large city, thus contributing useful information for improvement of the work process in municipal primary healthcare services.

CONCLUSION

A notable percentage of the primary healthcare physicians surveyed presented occupational stress. The major stressors, in these professionals' perception, were lack of prospects for career growth, the way in which tasks were distributed, deficiencies in professional training, insufficient time to perform the work, the type of control imposed and lack of autonomy in performing the work.

The physicians showed high levels of work engagement, which showed that they had energy and willingness to work; they were proud, enthusiastic, focused and persistent in the face of adversity in the work environment. Occupational stress and work engagement were negatively correlated, and occupational stress significantly compromised the physicians' levels of work engagement.

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Prevalence of chondromalacia patella according to patella type and patellofemoral geometry: a retrospective study

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ABSTRACT

BACKGROUND: The relationships between the morphometric structure of the patellofemoral joint, patella type and chondromalacia patella are still a matter of debate.

OBJECTIVE: To identify the prevalence of chondromalacia patella by determining the patella type and making patellofemoral morphometric measurements.

DESIGN AND SETTING: Retrospective cohort study in an orthopedics and traumatology clinic in Turkey, conducted between June 2017 and November 2019.

METHODS: This study involved 562 knees of 522 patients with anterior knee pain (246 males and 316 females; mean age 46.59 years). The patients were grouped according to presence of chondromalacia patella (group I) or absence of chondromalacia patella (group II). The patella type, lateral trochlear inclination, medial trochlear inclination, trochlear angle, sulcus angle, patellar tilt and Insall-Salvati index were assessed. Group comparisons were made using chi-square tests or Student t tests. The r value was used to determine the magnitude of relationships between pairs of variables.

RESULTS: Among the 562 knees evaluated, 265 (50.71%) presented type I patella, 195 (36.7%) type II, 100 (12.3%) type III and 2 (0.3%) type IV. Group I consisted of 448 knees and group II consisted of 114 knees. Significant differences were found between the groups in terms of age, gender, patella type and lateral inclination angles ($P < 0.05$).

CONCLUSION: Detecting the patella type and making lateral inclination measurements in patients with anterior knee pain are of great importance for diagnosing suspected chondromalacia patella, particularly in the early degenerative period.

INTRODUCTION

Among all the joints in the human body, the knee undergoes the earliest degeneration in all age groups. Pathological conditions of the retropatellar joint cartilage are an important reason for anterior knee pain.[1,2] Chondromalacia patella (CP), one of the most common reasons for anterior knee pain, is a progressive disorder that includes softening of the articular cartilage, fibrillation, thinning, focal swelling, ulcerous formations, chondral defects and subchondral erosive changes. This condition does not entail any complaint specific to cartilage diseases or physical examination. In a study evaluating clinical diagnoses in knee-joint pathological conditions, it was reported that among inner-knee conditions, cartilage diseases were the most difficult to diagnose.

None of the imaging methods available, except specific magnetic resonance imaging (MRI) techniques, are known to help in making the diagnosis, since basic imaging methods of the skeletal system are insufficient for monitoring joint cartilage degeneration.[3] The purpose of cartilage imaging is to evaluate the integrity of the cartilage surface and the thickness and volume of the cartilage matrix and its relationship with the subchondral bone. Although arthroscopic evaluation is a standard criterion for diagnosing CP, it is not preferred, given that this is an interventional procedure.[4] Therefore, because MRI provides superior resolution in multiplanar imaging between tissues, it is currently the primary diagnostic method in evaluating joint diseases.[3]

Cartilage quality and degeneration are paramount indicators for diagnosing CP on MRI scans. Moreover, trochlear morphology and patella type play crucial roles in CP. The sulcus angle is used for primary assessment of the morphological structure of the trochlea. However, although the sulcus angle can act as a guide for evaluating the geometry of the femoral trochlea, it represents the trochlear surface geometry and this is insufficient for assessing the medial and lateral trochlear anatomy.

Recent studies have reported that the lateral trochlear inclination (LTI) and trochlear angle measurements are alternatives for evaluating the trochlear geometry. Nonetheless, the results from these studies have varied and the relationship is not yet well documented.[4-9]

OBJECTIVE

The purpose of the current study was to evaluate the prevalence of CP and the relationship between the patella type and patellofemoral morphometric measurements. To evaluate patellofemoral morphology, the patella type, LTI, medial trochlear inclination, trochlear angle, sulcus angle, patellar tilt and Insall-Salvati index were assessed.

METHODS

All the procedures performed in the current study involving human participants were undertaken in accordance with the ethical standards of the institutional and national research committee as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study. The study was approved by the local ethics committee of the same hospital (decision no. 352b; dated March 13, 2019). No approval from the National Ethics Committee was necessary, as this was a non-interventional observational study.

In the current study, 882 knees of 800 consecutive patients with anterior knee pain who came for consultations at a single institution between June 2017 and November 2019 were evaluated retrospectively. The inclusion criteria for the study were as follows: the patients needed to be older than 18 years of age and appropriate imaging needed to be available via our institution's picture archiving system (PACS). Patients with histories of inflammatory arthritis or knee surgery, anterior knee pain complaints that began more than six months earlier and body mass index higher than 35 kg/m^2 were excluded from the study. The final study cohort consisted of 562 knees of 522 patients (246 males and 316 females). The patients were divided into two groups according to whether chondromalacia patella was present: patients with CP (CP group; n = 448 knees) and without CP (nonCP group; n = 114).

The patella type, LTI, medial trochlear inclination, trochlear angle, sulcus angle and patellar tilt were assessed from fat-suppressed proton-density axial and sagittal-fraction MRI scans on all the patients. For the axial fraction measurements, the posteriormost and widest fractions of the medial and lateral posterior condyles were used. Measurements were made as follows: a) with the LTI as the angle between lines passing tangentially to the posterior aspect of the posterior condyles and tangentially to the lateral trochlear facet;[10] b) with the medial trochlear inclination as the angle between lines passing through the posterior aspect of the posterior condyles and the medial joint surface;[10] c) with the trochlear angle as the angle between lines passing through the posterior aspect of the posterior condyles and the medial/lateral condyles;[11] d) with the sulcus angle as the angle between lines passing tangentially to the ventral surfaces of the medial and lateral condyles;[12] and e) with the patellar tilt angle as the angle between a line passing through the posterior aspect of the posterior condyles and a line joining the lateral and medial edges of the patella[13] (**Figure 1**).

The Insall-Salvati index was measured using sagittal-fraction MRI to evaluate the location of the patella in the sagittal plane. In areas of the sagittal plane where the Insall-Salvati index was observed to be the highest, the ratio between the longest axis of the patellar tendon and the longest axis of the patella was calculated (**Figure 2**).[14] Measurements obtained by two separate specialists were subjected to interobserver testing. The data were distributed and the average of the measurements obtained by these two specialists was used.

The types of patella and CP were evaluated in accordance with Baumgartl's classification and the Modified International Cartilage Repair Society (ICRS) classification, respectively.[15,16]

Baumgartl's classification was graded as follows: type I patella has medial and lateral facets that are both concave and of equal

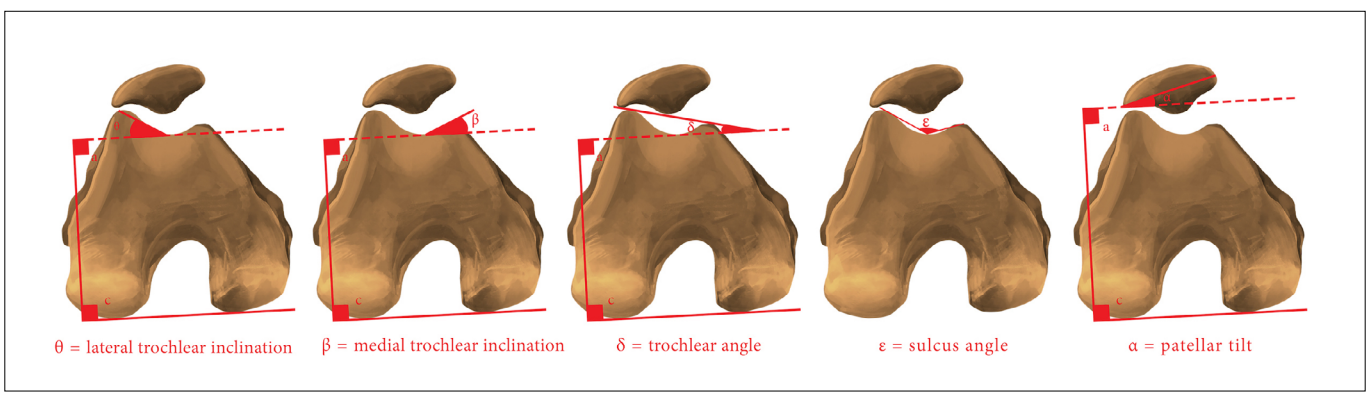

Figure 1. Measurement techniques for patellofemoral joint morphometry values.

length; type II patella has a lateral facet that is more prominent than the medial facet, while the medial facet is plane or concave; type III patella has a smaller and convex medial facet; and type IV patella has no medial facet or central rim and is also referred to as the "jockey cap" (**Figure 3**).

According to the Modified International Cartilage Repair Society (ICRS) classification, grade 0 indicates normal cartilage; grade 1 indicates superficial fissuring and softening; grade 2 indicates < 50% depth to the subchondral plate; grade 3 indicates > 50% depth to the subchondral plate; and grade 4 indicates penetration into the subchondral plate.

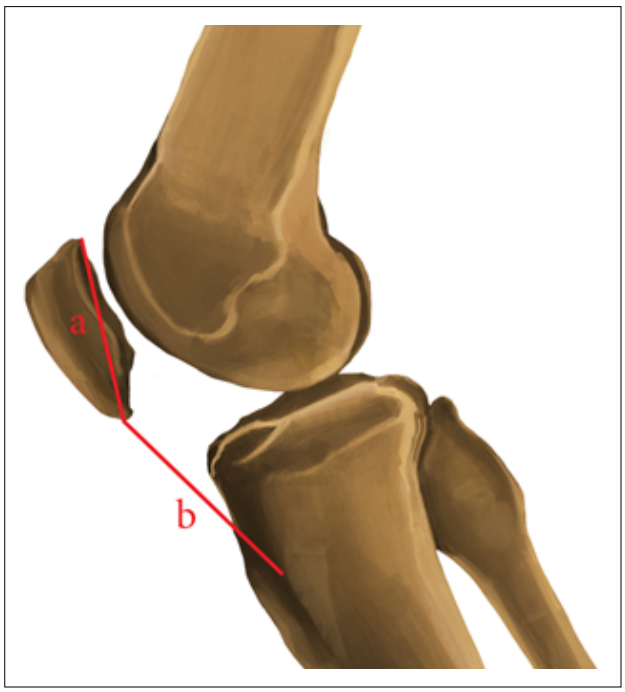

Figure 2. Insall-Salvati index (a/b) measurement method on lateral knee image. a: greatest diagonal length of the patella; b: the length of the patellar tendon (LT) is measured from the patellar apex to the tibial tuberosity.

Knees were evaluated using a GE Signa Excite 1.5-Tesla MR scanner with a superficial knee Q-coil (General Electric, Milwaukee, Wisconsin, United States). The following parameters were used in the axial fat-saturation (sat) suppressed proton sequence: fraction of repetition time (TR)/fraction of time to echo (TE): 2860/48.1 ms; fraction thickness 4 mm; field of view (FOV) 16 x 16 cm; slice thickness gap: 4/1 mm and matrix 192 x 256 pixels.

Statistical analysis

Statistical analyses were performed using the IBM SPSS version 21.0 software (IBM Corporation, Armonk, New York, United States). Descriptive statistics are presented as means, standard deviations, numbers or proportions. Comparisons of categorical variables were made using the chi-square test, while comparisons of numerical values between groups were made using the Student t test. P values less than 0.05 were considered statistically significant. The r value was used to determine the magnitude of the relationship between pairs of variables. The inter-rater reliability between the two examiners was determined using the intraclass correlation coefficient (ICC). Values greater than 0.90 indicated excellent reliability.

RESULTS

The intraclass correlation coefficient between the two examiners was found to be 0.91, thus indicating excellent interclass reliability of the measurements. Chondromalacia was present in 448 knees (79.5%) out of the total of 562 knees (246 males and 316 females). In the CP group, 241 were right knees and 207 were left knees; and there were 40 bilateral cases. The MRI findings of the patients were grouped according to the patella types. Out of the 562 knees, 265 (50.71%) were type I patella, 195 (36.7%) were type II, 100 (12.3%) were type III and 2 (0.3%) were type IV. **Table 1** summarizes the clinical and demographic findings of the two groups.

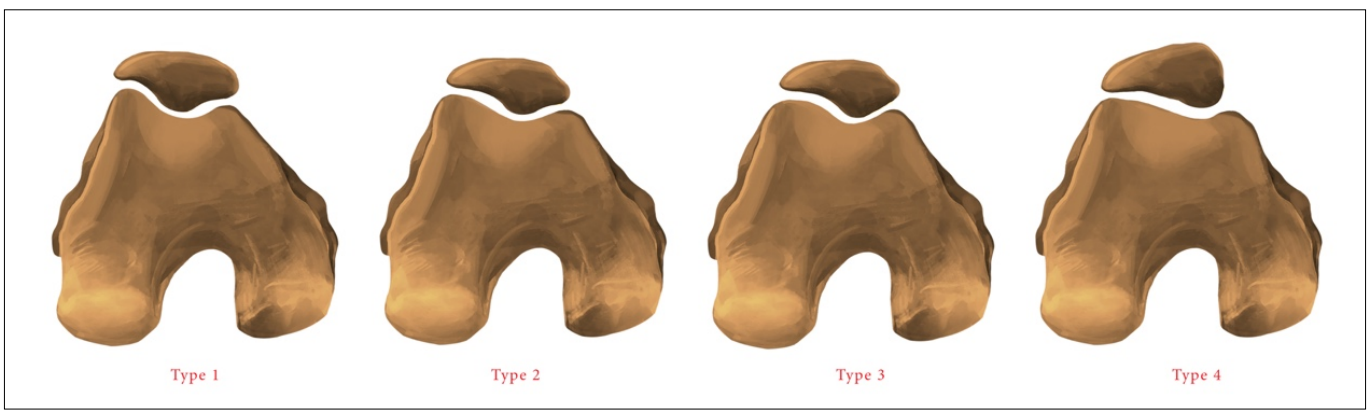

Figure 3. Patella types according to Baumgartl classification: type 1, both facets are equal and concave; type 2, lateral facet is more prominent and medial facet is planar; type 3, medial facet is convex; and type 4. there is no medial facet ("jockey cap").

Table 1. Clinical and demographical features of the groups with and without chondromalacia

Gender	Variables	CP group	nonCP group	P value
Male (n = 246)	**Age (years)**	43.16 ± 13.65	50.40 ± 16.20	**0.004**
	Patella type			
	1	82 (41.6)	33 (67.3)	**0.009**
	2	75 (38.1)	13 (26.5)	
	3	38 (19.3)	3 (6.2)	
	4	2 (1.0)	-	
	Lateral trochlear inclination	26.70 ± 2.1	27.21 ± 2.0	0.071
	Medial trochlear inclination	19.99 ± 2.7	20.21 ± 2.4	0.675
	Trochlear angle	12.73 ± 1.5	12.82 ± 1.4	0.630
	Sulcus angle	133.18 ± 5.1	134.88 ± 5.6	0.157
	Patellar tilt	11.26 ± 1.6	10.96 ± 1.3	0.318
	Patella angle	143.16 ± 4.2	141.85 ± 4.6	0.113
	Insall-Salvati index	1.09 ± 0.7	1.02 ± 0.2	0.136
Female (n = 316)	**Age (years)**	46.78 ± 13.17	52.38 ± 12.81	**0.001**
	Patella type			
	1	114 (45.4)	36 (55.4)	0.223
	2	86 (34.3)	21 (32.3)	
	3	51 (20.3)	8 (12.3)	
	4	-	-	
	Lateral trochlear inclination	26.89 ± 2.1	27.13 ± 2.2	0.274
	Medial trochlear inclination	19.80 ± 2.4	19.55 ± 2.4	0.355
	Trochlear angle	12.88 ± 1.4	12.90 ± 1.8	0.749
	Sulcus angle	131.83 ± 5.6	133.62 ± 5.6	0.127
	Patellar tilt	11.53 ± 1.4	11.10 ± 1.4	0.131
	Patella angle	142.85 ± 4.2	142.18 ± 4.8	0.079
	Insall-Salvati index	1.08 ± 0.6	1.04 ± 0.1	0.563
Total (n = 562)	**Age (years)**	51.42 ± 10.9	27.62 ± 4.8	**< 0.001**
	Gender			
	Male	177 (39.5)	69 (60.5)	**< 0.001**
	Female	271 (60.5)	45 (39.5)	
	Patella type			
	1	196 (42.8)	69 (60.5)	**0.005**
	2	161 (35.9)	34 (29.8)	
	3	89 (19.9)	11 (9.6)	
	4	2 (0.4)	0 (0)	
	Lateral trochlear inclination	23.49 ±2.3	27.00 ± 1.9	**0.018**
	Medial trochlear inclination	19.95 ± 2.5	19.66 ± 2.4	0.282
	Trochlear angle	12.80 ± 1.3	12.81 ± 1.4	0.743
	Sulcus angle	132.51 ± 5.4	132.84 ± 5.4	0.521
	Patellar tilt	11.28 ± 1.4	11.58 ± 5.0	0.522
	Patella angle	142.66 ± 4.2	143.35 ± 4.3	0.127
	Insall-Salvati index	1.07 ± 0.6	1.06 ± 0.1	0.791

CP = chondromalacia patella. The data are shown as mean ± standard deviation or n (%).

Statistically significant differences in patella type and LTI angles were found between the groups (P < 0.05). The prevalences of the different patella types in the CP group (n = 448) were type I (n = 196), type II (n = 161) and type III (n = 89) (**Table 2**). In the male population, the presence of CP showed a significant correlation with patella type (P < 0.05), particularly type II patella (38.1%) and type III patella (19.3%). In the female population, there was no significant correlation between patella type and presence/absence of CP. Overall, presence of CP showed a significant correlation with patella type (P < 0.05), particularly type II patella (35.9%) and type III patella (19.9%) (n = 562) (**Table 2**).

The LTI was significantly lower in the CP group than in the nonCP group (P < 0.05). It was 23.49° ± 2.3° in the CP group and 27.00° ± 1.9° in the nonCP group.

There was a moderate positive correlation between the severity of chondromalacia and age (r = 0.402; P < 0.001). A very weak correlation between the severity of chondromalacia and weight was also detected (r = 0.125; P = 0.03). No significant correlation was observed between the grade of chondromalacia and anatomical measurements. The correlation analyses are presented in **Table 3**.

DISCUSSION

The main finding from this study was that in patients with anterior knee pain, the patellar morphology and lateral trochlear inclination angle may act as predictors for diagnosing CP, particularly in the early degeneration period.

CP is a condition that is characterized by softening, fraying or ulceration of the cartilage at the posterior patella, accompanied by anterior knee pain. For almost half of healthy individuals over 20 years of age and nearly every individual over 50 years of age, experience of softening of the patellar cartilage has been reported.[17,18] The primary etiology of CP includes trauma in the knee area, repeated microtraumas, sports wounds, osteochondritis dissecans caused by vascular disorders and inflammatory diseases. CP is also frequently characterized by morphological complications of the patellofemoral joint.[17-19]

Although MRI plus clinical examination is the most appropriate approach for patients with suspected CP, studies have shown that MRI is insufficient for detecting early degenerative changes in the joint cartilage.[20-22] None of the currently available imaging methods have adequate sensitivity and specificity for making an early diagnosis of CP.[20-22] Arthroscopy is considered to be the gold standard for early detection of CP; however, it is not used in daily practice as it is an interventional procedure.[4,23]

In the current study, we observed that the incidence of CP depended on the patella type. CP was seen more commonly in patients with type II and type III patella, particularly in the male population. This finding is supported by data from previous studies.[24-26] Arslan et al. evaluated 1,804 patients with regard to the

Table 2. Incidence of chondromalacia patella among the patients, according to patella type and gender

	Variables	Type 1	Type 2*	Type 3*	Type 4	P value
Male	CP	82 (71.3)	75 (85.2)	38 (92.7)	2 (100.0)	**0.009***
(n = 246)	nonCP	33 (28.7)	13 (14.8)	3 (7.3)	-	
Female	CP	114 (76.0)	86 (80.4)	51 (86.4)	-	0.223
(n = 316)	nonCP	36 (34.0)	21 (19.6)	8 (13.6)	-	
Total	CP	196 (74.0)	161 (82.6)	89 (89.0)	2 (100)	**0.005***
(n = 562)	nonCP	69 (26.0)	34 (17.4)	11 (11.0)	0 (0)	

CP = chondromalacia patella. The data are shown as n (%). *Presence of CP and patella type showed a significant correlation

Table 3. Correlation analyses on patients' demographic features and morphometric measurements

Variables		Chondromalacia grade
Age	r	0.402*
	P	**0.000**
Weight	r	0.125*
	P	**0.003**
Lateral trochlear inclination	r	-0.026
	P	0.540
Medial trochlear inclination	r	-0.039
	P	0.362
Trochlear angle	r	-0.081
	P	0.054
Sulcus angle	r	0.052
	P	0.219
Patellar tilt	r	0.004
	P	0.925
Patella angle	r	0.004
	P	0.923
Insall-Salvati index	r	-0.077
	P	0.068

*Correlation analyses denote significance.

relationship between patella type and chondromalacia. They reported that a statistically significant relationship was detected between type III patella and CP.[24] Hayirlioglu et al. also reported that type III patella and chondromalacia were found to be statistically significantly associated.[26]

Carrillon et al. previously described a threshold LTI value for patients with patellar instability. According to their study, LTI < 11° is an excellent diagnostic test demonstrating patellar instability, with sensitivity of 0.93 and accuracy of 0.90.[10] In our study, comparison of the relationship between the measurement methods for patellofemoral morphology showed that LTI had a significant relationship with chondromalacia (27.00° ± 1.9° in the nonCP group; 23.49° ± 2.3° in the CP group; P < 0.05). However, contrary to the findings of the current study, lack of a significant relationship between morphological measurements of the patellofemoral joint and chondromalacia has also been reported.[4,25,26]

Nonetheless, several studies support the current findings. Tuŕkmen et al. reported that among 104 patients, the average LTI value was 21.4° ± 4.0° in chondromalacia patients and 23.2° ± 4.5° in controls.[27] In an evaluation of trochlear morphology in a cohort of 115 patients, Duran et al. reported that the LTI value was 19.5° ± 3° in chondromalacia patients and 26.3° ± 3.1° in the controls.[4] However, the patient group was smaller than in our study and also no significant relationship between other morphometric measurements and chondromalacia was identified in that study. Mehl et al. compared the geometry of the patellofemoral joint in 43 patients with an arthroscopically verified patellar cartilage defect and a control group of patients without this defect. Compared with the control group, the patients in the defect group had lower LTI, but without statistical significance. They reported that the LTI value was 19.1° ± 6.4° in the defect group and 20.6° ± 5.6° in the non-defect group. In that study too, the patient group was smaller than in our study.[5]

In the present study, an analysis on patients who underwent knee MRI for nontraumatic anterior knee pain showed that there was a statistically significant relationship between the patient's age and the presence of chondromalacia (P < 0.05). In the light of the published data available, an increase in the risk of chondromalacia with increasing age is an expected finding.

The data from the current study had certain limitations. First, although the number of patients was statistically sufficient, the study group only comprised anterior knee pain patients and so the statistical values lack a control group comparison. Second, the measurements were evaluated through MRI scans alone; computed tomography scans may be more accurate for measuring the values. However, it should also be kept in mind that MRI is the gold-standard noninvasive method for evaluating chondral surfaces such as the patella. On the other hand, despite these limitations, the large sample size of our study group and the multiple comparisons among the parameters analyzed formed a strong point in our study.

CONCLUSION

CP is highly prevalent within society and none of the imaging methods currently available can be used for making an early diagnosis of this condition. Identification of the patella type, especially in the early degenerative period, and making LTI measurements in patients with anterior knee pain and suspected CP are of great importance for correct diagnosis. The basic differential of the results from the present study was that we showed

that lower LTI may be an indicator for CP in patients without complaints and may be used as an early diagnostic parameter in individuals with type II and type III patella. We recommend that detection of patella type and measurement of lateral trochlear inclination should form part of the routine work-up in assessing patients with anterior knee pain. Randomized large-scale studies including patients with no clinical complaints should be carried out to firmly establish this recommendation in the future.

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Heart rate turbulence assessed through ergometry after myocardial infarction: a feasibility study

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ABSTRACT

BACKGROUND: Coronary artery disease is an important cause of morbidity and mortality. The impact of ventricular arrhythmias with impaired cardiac vagal activity is one of the most recently studied prognostic factors. However, there are no studies evaluating the phenomenon of heart rate turbulence (HRT) during physical exertion.

OBJECTIVE: To study the behavior of HRT during exercise testing, among individuals after myocardial infarction.

DESIGN AND SETTING: Feasibility study conducted in a university hospital among individuals 4-6 weeks after myocardial infarction.

METHODS: All subjects underwent 24-hour Holter monitoring and ergometric stress testing. We considered that abnormal HRT was present if the turbulence onset was ≥ 0% or turbulence slope was ≤ 2.5 mm/relative risk interval.

RESULTS: All 32 subjects were asymptomatic. Their median age was 58 years (interquartile range 12.8) and 70% were male. Abnormal HRT was associated with ventricular dysfunction in this population. We found no differences regarding the behavior of HRT, in relation to age, gender, smoking, systemic arterial hypertension, diabetes mellitus or dyslipidemia. Ergometric stress testing detected premature ventricular beats (PVB) in approximately 44% of the examinations, and these occurred both during the active phase of effort and in the recovery period. The low occurrence of several isolated PVB in beta-blocked subjects made it difficult to perform statistical analysis to correlate HRT between ergometric and Holter testing.

CONCLUSION: The data obtained in this study do not support performing HRT through ergometric stress testing among patients who remain on beta-blockers post-myocardial infarction, for the purpose of assessing cardiac vagal activity.

INTRODUCTION

Coronary artery disease is a condition characterized by increased atherosclerotic plaque in the epicardial arteries and is associated with high morbidity and mortality. Coronary artery disease accounts for nearly 360,000 events per year[1] in the United States, among which most occur in the hospital setting, and many events evolve to death before the patients are transported to the emergency room.[1] In the first six months of 2019, 137,713 hospitalizations due to coronary artery disease were recorded in Brazil, and 5.8% culminated in in-hospital death.[2]

Some clinical factors and complementary test markers help in the prognostic evaluation of coronary artery disease. Among these, the following can be highlighted: advanced age, male gender, systemic arterial hypertension, diabetes mellitus, dyslipidemia, smoking and myocardial dysfunction.[3,4] However, the impairment of cardiac vagal activity over the first year after a diagnosis of myocardial infarction has been made is also a good indicator for identifying the development of heart disease and sudden death over the short and medium term.[5-7]

Analysis on the behavior of heart rate turbulence (HRT), obtained through 24-hour Holter monitoring, is one of the easiest and most efficient means for assessing cardiac autonomic dysfunction.[8] Sade et al.[8] found that HRT was similar to the ejection fraction in an assessment of the prognosis of 128 individuals post-infarction. On the other hand, the Innovative Stratification of Arrythmic Risk - Heart Rate Turbulence (ISAR-HRT)[9] study showed that altered HRT parameters increased the risk of death almost sixfold, in a prospective analysis on 1,500 survivors of myocardial infarction analyzed over a 22-month period. This risk exceeded the risks attributed to severe ventricular dysfunction, diabetes mellitus and age over 65 years.

The low clinical use of HRT as a risk predictor, which was first put forward by Schmidt et al.,[5] may be related to the low sensitivity that it has been perceived to have in some studies.[8] It may also be because 24-hour Holter monitoring is not routinely indicated after myocardial infarction, considering that HRT is determined and analyzed in Holter monitoring.[10]

Ergometric stress testing assists in risk assessments on coronary events through analysis on clinical, electrocardiographic and hemodynamic parameters. Modulation of autonomous tonus takes place during physical exertion, which gives rise to increased sympathetic activity during the active phase of effort, while cardiac vagal activity increases in the recovery period.[11] Thus, vagal activity may increase during physical exercise. Hence, ergometric stress testing is already incorporated in regular monitoring for patients with coronary artery disease.

OBJECTIVE

The aim of our study was to evaluate the behavior of post-myocardial infarction HRT during ergometric stress testing.

METHODS

This was an observational, prospective study using primary data to estimate changes in HRT during ergometric stress testing among individuals who had recently had a myocardial infarction episode. The study was conducted in the "Professor Luiz Tavares" Cardiological Emergency Service (Pronto Socorro Cardiológico Universitário de Pernambuco Professor Luiz Tavares), which is affiliated with the University of Pernambuco, between 2018 and 2019. All the patients met the criteria for myocardial infarction, in accordance with the fourth universal definition of myocardial infarction.[12] We excluded individuals with a history of previous events relating to coronary disease, those who could not undergo the ergometric stress testing (due to orthopedic/neurological problems, balance deficits or peripheral vascular alterations) and those who presented factors that precluded the possibility of HRT (atrial fibrillation, cardiac pacemaker and artifacts in the examination recordings).

All of the individuals included in this study had become asymptomatic by the time that they reached four to eight weeks after the ischemic event and they were continuing to use of beta-blockers regularly. All of them underwent 24-hour Holter monitoring (CardioLight 3-channel recorder; Cardios, São Paulo, Brazil) and ergometric stress testing using the Naughton protocol (KT 10200 AT multi-programmable treadmill; Inbramed, Porto Alegre, Brazil). Turbulence onset (TO) ≥ 0% or turbulence slope (TS) ≤ 2.5 mm/relative risk interval in 24-hour Holter monitoring was considered to be the gold standard for abnormal HRT.

The analysis on the HRT parameters was standardized in accordance with the study by Bauer et al.[11] In order to eliminate errors in the analysis, we excluded the following: interpolated premature ventricular beats (PVBs); PVB with prematurity less than 20%; PVB with compensation pause below 120% of the average of the last five previous relative risk (RR) or PVB values; and very short (< 300 ms) or very long (> 2000 ms) PVB tachograms.

TO was calculated based on the last two sinus RR intervals immediately before the PVB-coupling interval, and the two sinus RR intervals immediately after the compensatory pause. TO (as a percentage) has negative values for patients with low cardiovascular risk since there is an immediate heart rate acceleration after PVB.

$$Turbulence\ onset = \frac{(RR_1 + RR_2) - (RR_{-1} + RR_{-2})}{(RR_2 + RR_1)} \times 100\ (\%)$$

Where RR = R-to-R wave interval in electrocardiogram

On the other hand, TS was calculated using the slope of the line formed by five RR intervals after the PVB, which were obtained from among the first 15 sinus RR intervals that followed the PVB. TS is expressed in milliseconds per RR interval, and the heart rate of patients with a low cardiovascular risk is decreased by up to 8 beats/min following the initial acceleration caused by the PVB. Thus, the reference value is > 2.5 ms/RR, which translates as the maximum variation in sinus RR intervals (ms) among the five sinus RR intervals to be analyzed.

$$Turbulence\ slope = \frac{Y5 - Y1}{X5 - X1}$$

Where Y = maximum positive regression slope assessed after the PVB; and X = five consecutive sinus rhythm R-R intervals after PVB.

The choice between parametric and nonparametric tests was made according to the presence or absence of normal distribution of the data, as shown in the Kolmogorov-Smirnov test. Parametric continuous variables were expressed as the mean ± standard deviation, and nonparametric variables as the median and interquartile range. The Mann-Whitney or Student t test was used, as indicated. Strategic variables were calculated as relative and absolute frequencies. A significance level of $P < 0.05$ and a statistical power of 80% were adopted for all tests. The IBM SPSS version 21.0 software (IBM, Chicago, Illinois, United States) was used for the statistical analysis.

This study was approved by the Research Ethics Committee of the Hospital Universitário Oswaldo Cruz - Pronto-Socorro Cardiológico Universitário de Pernambuco (HUOC-PROCAPE), under registration number 2.681.495 of May 29, 2018.

RESULTS

The population had a median age of 58 years (interquartile range, IQR 12.8) and about two-thirds were male. Among the 32 individuals evaluated for the presence of HRT, 24 presented normal

TO and TS parameters and eight individuals presented abnormal TO and/or TS. We did not find any differences between the normal and abnormal HRT groups regarding cardiovascular risk factors (presence of hypertension, diabetes mellitus, dyslipidemia or smoking), ischemic presentation (ST-segment-elevation or non-ST-segment-elevation infarction), infarct wall affected (anterior or inferior) or ventricular depolarization (QRS) complex duration. The parameters of heart rate variability were similar in the groups that presented normal HRT and abnormal HRT.

The individuals with abnormal HRT showed an association with lower left ventricular ejection fraction, compared with those with normal HRT (46.6% versus 58.6%; P = 0.004). The demographic and baseline characteristics of the patients are summarized in **Table 1**.

All ergometric stress testing was stopped when fatigue was reached or upon reaching the submaximal heart rate. The mean baseline heart rate was 66.5 ± 13.2 beats per minute (bpm) and the mean peak heart rate was 123.2 ± 21.2 bpm. The patients achieved an estimated metabolic equivalent performance of 5.94 ± 2.27 metabolic equivalents (MET). The hemodynamic changes in pressure levels were compatible with the degree of exertion performed. Ventricular extrasystoles were detected in approximately 44% of the examinations and occurred both during the active phase of effort and in the recovery period (**Table 2**).

Only three individuals had more than five isolated PVBs during the ergometric stress testing (minimum number required to perform the HRT parameter calculations, according to Bauer et al.).[11] This extremely low number did not allow us to undertake any statistical treatment of associations of HRT parameters between the ergometric test and 24-hour Holter test.

DISCUSSION

In our study, it was not possible to adequately perform analysis on HRT using ergometric stress testing due to the low density of ventricular arrhythmia. All the individuals analyzed were making

Table 1. Demographic and cardiovascular profile of the study population

Variable	Total (n = 32)	Normal HRT (n = 24)	Abnormal HRT (n = 8)	P
Age, median (IQR), years	58.0 (12.8)	58.0 (11.5)	59.0 (20.5)	0.535
Gender				
Male, n (%)	22 (68.8%)	15 (68.2%)	7 (31.8%)	0.186
Female, n (%)	10 (31.2%)	9 (90%)	1 (10%)	
Smoking				
Yes, n (%)	3 (9.4%)	2 (66.7%)	1 (33.3%)	0.726
No, n (%)	29 (90.6%)	22 (75.9%)	7 (24.1%)	
Systemic arterial hypertension				
Yes, n (%)	22 (68.8%)	18 (81.8%)	4 (18.2%)	0.186
No, n (%)	10 (31.2%)	6 (60%)	4 (40%)	
Diabetes mellitus				
Yes, n (%)	9 (28.1%)	8 (88.9%)	1 (11.1%)	0.256
No, n (%)	23 (71.9%)	16 (69.6%)	7 (30.4%)	
Dyslipidemia				
Yes, n (%)	15 (46.9%)	11 (73.3%)	4 (26.7%)	0.838
No, n (%)	17 (53.1%)	13 (76.5%)	4 (23.5%)	
LVEF	55.7 ± 11.1	58.6 ± 9.03	46.6 ± 10.6	0.004
QRS complex length (ms)	89.5 ± 16.8	89.0 ± 13.6	96.0 ± 31.7	0.448
Heart rate variability				
SDNN (ms), mean ± SD%	119.7 ± 40.7	118.5 ± 39.1	107.3 ± 39.2	0.491
RMSSD (ms), mean ± SD	39.3 ± 35.1	41.4 ± 36.4	25.7 ± 12.9	0.247
pNN50 (%), mean ± SD	7.8 ± 7.0	7.6 ± 7.2	5.0 ± 5.2	0.363
Myocardial infarction type				
STEMI (%), mean ± SD	26 (81.3%)	20 (76.9%)	6 (23.1%)	0.601
NSTEMI (%), mean ± SD	6 (18.8%)	4 (66.7%)	2 (33.3%)	
Damaged myocardial wall				
Previous (%), mean ± SD	14 (53.8%)	9 (64.3%)	5 (35.7%)	0.240
Inferior (%), mean ± SD	12 (46.2%)	11 (91.7%)	1 (8.3%)	

IQR = interquartile range; LVEF = left ventricle ejection fraction; QRS = ventricular depolarization; SDNN = mean of the standard deviations of all normal sinus RR intervals for all 5-min segments; RMSSD = root mean square of successive differences between normal heartbeats; pNN50 = proportion of NN50 divided by the total number of NN (R-R) intervals.; STEMI = ST-segment-elevation myocardial infarction; NSTEMI = non-ST-segment-elevation myocardial infarction; SD = standard deviation; HRT = heart rate turbulence.

Table 2. Ergometric parameters of the study population

Variable	Total (n = 32)	Normal HRT (n =24)	Abnormal HRT (n = 8)	P
Baseline HR (bpm), mean ± SD, %	66.51 ± 13.2	65.47 ± 14.4	77.0 ± 13.2	0.064
Peak HR (bpm), mean ± SD, %	123.2 ± 21.2	120.3 ± 22.3	129.7 ± 20.7	0.319
HR recovery after 1 min (bpm), mean ± SD, %	16.7 ± 9.8	15.8 ± 9.9	16.6 ± 11.7	0.870
MET, mean ± SD	5.94 ± 2.27	6.01 ± 2.51	5.21 ± 1.91	0.427
PVB, n (%)	14 (43.8%)	11 (78.6%)	3 (21.4%)	0.681

HR = heart rate; SD = standard deviation; min = minute; MET = metabolic equivalent; PVB = premature ventricular beat; bpm = beats per minute; HRT = heart rate turbulence.

regular use of beta-blockers, and this medication is known to significantly decrease the occurrence of PVBs.

The physiological mechanism of HRT involves patency of baroreceptors and the autonomic nervous system. Thus, a PVB is expected to promote a transient hemodynamic change, initially manifested as a decrease in the systolic volume perceived in the baroreceptors. Since blood pressure is the product of ejected systolic volume, heart rate and peripheral vascular resistance, the immediate response is inhibition of vagal stimuli with a consequent increase in blood pressure levels. Therefore, there should be an accelerated heart rate and increased peripheral vascular resistance after a PVB[10] in individuals without cardiac dysautonomia.

This first response is usually ephemeral, since baroreceptors will also detect an elevation in blood pressure and consequently recruit the vagal stimulus that is responsible for heart rate deceleration.[10] Later on, they will return to the hemodynamic situation prior to PVBs.

Several studies have demonstrated the prognostic importance of HRT, post-myocardial infarction. Hoshida et al. analyzed 313 patients after myocardial infarction, over a mean follow-up of three years, and showed that HRT parameters were strong predictors of cardiac mortality (heart rate, HR 5.7; 95% confidence interval, CI 2.1-15.9; P = 0.0008).[13] Huikuri et al. followed up 310 patients who had suffered myocardial infarction two years earlier and found that TS was associated with ventricular arrhythmia (HR 2.8; 95% CI 1.1-7.2; P = 0.038).[14]

In the ISAR-HRT study, 1,500 survivors of acute myocardial infarction were assessed. It was found that combination of abnormal TO and TS was the strongest predictor of mortality (odds ratio 5.9; 95% CI 2.9-12.2). Another important finding of that study was that HRT was able to provide information on mortality risk in a more relevant way than that obtained using the left ventricle ejection fraction (LVEF).[9]

In the REFINE study, on 320 patients with acute myocardial infarction and LVEF of < 40%, HRT proved to be a good predictor of cardiac death or resuscitated cardiac arrest (HR 2.91; 95% CI 1.13-7.48; P = 0.026) when at least one of the HRT parameters was altered.[15]

The few studies[16,17] that have attempted to analyze the behavior of HRT over short periods failed to show good accuracy because they were conducted at rest and expected the individuals to spontaneously present an isolated PVB. For example, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) study evaluated the behavior of HRT among approximately 900 patients after recent myocardial infarction and found that there was no statistically significant association between HRT parameters and mortality, from at-rest records over 10 minutes of recording.

Some efforts have been made to spread the concept of the prognostic value of HRT through faster recordings. Thus, physical exertion could be used as an alternative for obtaining this parameter by inducing ventricular arrhythmia in the active phase and increasing cardiac vagal activity in recovery. Ergometric stress testing is already envisaged in the follow-up of coronary artery disease patients and, thus, if it is possible to analyze the parameters of HRT during ergometric stress testing, this might form a valuable piece of information for these individuals.

In our study, heart rate variability parameters were unchanged in both the normal and the abnormal HRT groups. Suspension of the patients' use of beta-blockers could have sensitized the examination, thereby providing an increase in the occurrence of ventricular arrhythmia and enabling detection of changes in cardiac vagal tone. However, for ethical reasons, suspension of this medication was not authorized, even if it would have only been temporary.

The major limitation of our study was the fact that the small sample size precluded observation of any statistical difference regarding the behavior of HRT involving demographic data and cardiovascular risk factors. Likewise, this did not enable assessment of the possible association of the HRT parameters obtained through ergometry with the gold standard obtained through the 24-hour Holter monitoring.

CONCLUSION

The data obtained in this study do not support assessment of HRT through ergometric stress testing in patients who remain on beta-blockers post-myocardial infarction, for the purpose of assessing cardiac vagal activity, as a replacement for 24-hour Holter monitoring.

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Association between glycemic control and albuminuria among Peruvian adults with diabetes mellitus 2: a cross-sectional analytical study

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ABSTRACT

BACKGROUND: Albuminuria is a risk factor for microvascular and macrovascular complications in the diabetic population. However, few studies have correlated poor glycemic control and albuminuria prevalence in Hispanic populations.

OBJECTIVE: To evaluate the association between glycemic control and albuminuria among Peruvian adults with type 2 diabetes mellitus (T2DM).

DESIGN AND SETTING: Cross-sectional analytical study among adults with T2DM in Lima, Peru.

METHODS: We included adults over 18 years old who were in a clinical follow-up program at a private clinic in Lima in 2018. Poor glycemic control was defined as a serum value of glycosylated hemoglobin A1C (HbA1C) ≥ 7%. Albuminuria was defined as albumin values > 30 mg/dl in the first morning urine. We generated generalized linear regression models from the Poisson family with robust variance. We calculated the crude and adjusted prevalence ratios (PRs) with their 95% confidence interval (CI).

RESULTS: We analyzed 907 participants of median age 58 years (interquartile range, IQR 49 to 66), and 62.8% were males. The prevalence of poor glycemic control was 39.8%, and the prevalence of albuminuria was 22.7%. The prevalences of albuminuria in groups with poor glycemic control and adequate glycemic control were 32.7% and 16.1%, respectively. In the adjusted regression analysis, we found a statistically significant association between poor glycemic control and albuminuria (annual percentage rate, aPR = 1.70; 95% CI: 1.28-2.27).

CONCLUSIONS: The prevalence of poor glycemic control and albuminuria was high in our study population. Moreover, Peruvian T2DM adults with poor glycemic control were more likely to have albuminuria.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide public health problem.[1] The prevalence of T2DM in 2017 was 451 million cases worldwide, and according to the estimate of the International Diabetes Federation for the year 2045, this figure will rise to 693 million people.[2] Around the world, almost 50% of T2DM cases have not yet been diagnosed.[2]

In Peru, diabetes treatment and control are poor. Regarding management, a study on rural, rural-to-urban migrant and urban participants showed that the proportions of diabetes awareness, treatment and control were 71.1%, 40.6% and 7.7%, respectively.[3] In another study on ambulatory T2DM patients at a public hospital in Lima, almost seven out of ten patients had abnormal glycemic control.[4] At the primary care level, one study found that 20 to 30% of diabetic patients who knew about their disease were not following any type of treatment and had had a late diagnosis, given that 68% of the cases knew that their diagnosis had only been made because of the complications of T2DM.[5]

In this context, complications relating to T2DM among Peruvian adults, such as retinopathy, cardiovascular disease, neuropathy and kidney disease, are an important target for public health strategies.[6] However, there are structural problems in the Peruvian healthcare system that limit adequate care for diabetes patients.[7] In addition to the poor quality of clinical practice guidelines for diabetes, there is also a lack of diagnostic methods and medications in primary care centers for managing these patients.[8,9]

Albuminuria, along with a decreased glomerular filtration rate, is a component of diabetic kidney disease and is a risk factor for mortality and cardiac and ocular complications among diabetic people.[10-12] There are several risk factors for albuminuria, such as duration of diabetes, male gender, creatinine levels and poor glycemic control, among other variables.[13] Glycosylated hemoglobin A1C (HbA1c) is a glycemic control marker. This marker has a positive correlation with blood glucose levels

during the previous six to ten weeks. Higher levels are associated with an increased risk of developing microangiopathy among diabetics.[14]

In Peru, the prevalence of albuminuria is high in the population at risk. A study in a screening campaign in 23 nephrology centers nationwide found that the frequency of microalbuminuria was 53.45%, and that 8.96% of the patients had microalbuminuria > 100 mg/dl.[15] In another study in a primary care center, the prevalence of albuminuria was 17.9% among diabetes patients and 10.8% among hypertension patients.[16]

Poor glycemic control has been correlated with albuminuria in various studies using HbA1C,[17-21] while intensive glucose control reduces the risk of albuminuria.[21] However, although studies have been conducted in different ethnic groups, few studies have included any significant proportion of Hispanic patients, despite the evidence that there are ethnic variations in albuminuria prevalence among diabetic patients.[22,23] Some studies have found that Hispanic patients have greater probability of albuminuria or the initial stages of diabetic kidney disease than other ethnic groups.[24,25] Considering the burden of diabetic kidney disease in the Hispanic population, and that studies that have included the Hispanic population have been conducted in the United States and not in Latin America, under the conditions of a different healthcare system that could condition different health outcomes,[26] studies on this disease in this ethnic group are needed.[27]

OBJECTIVE

Thus, we aimed to evaluate the association between glycemic control and albuminuria among Peruvian adults with T2DM.

METHODS

Study design and population

We conducted a study with an analytical cross-sectional design. We included adults over 18 years of age with T2DM who attended a healthcare program called "Take Care" at a private clinic in Lima, Peru, in 2018.

"Take Care" is a healthcare program among chronic patients previously diagnosed with T2DM, arterial hypertension, dyslipidemia or asthma, with comprehensive monthly follow-up controls. The program offered by each patient's insurance policy covers laboratory tests, procedures and medical consultations, according to that patient's comorbidities. In addition, the clinical staff register all the patient's information in the database of the program in order to carry out personalized follow-up and provide adequate treatment.

We excluded patients whose data were incomplete or poorly recorded in the database and patients with a history of arterial hypertension and chronic kidney disease.

Sampling and calculation of sample size

To calculate the sample size, we used a study in which albuminuria and HbA1C among type 2 diabetic patients was evaluated. This showed that the prevalence of poor glycemic control was 70%.[20] In addition, in that study, the prevalence of microalbuminuria among participants with poor glycemic control was 57%, while the prevalence of microalbuminuria was 28% among participants with adequate glycemic control. With these values and using a 95% confidence level and statistical power of 80%, we calculated a sample size of 110 patients. However, because we had access to the "Take Care" program database, we decided to analyze all participants who met our eligibility criteria during 2018.

Main variables

Our exposure variable was glycemic control. A serum value for glycosylated HbA1C ≥ 7% was defined as indicative of poor glycemic control. Our outcome variable was the presence of albuminuria, defined as its presence in the first morning urine, considering values > 30 mg/dl as positive results.[28] We considered the following as potential confounding variables: age, sex, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg), fasting glucose (mg/dl), uric acid (mg/dl), creatinine (mg/dl), waist circumference (cm) and body mass index (BMI) (kg/m^2).

Data collection procedure

In the "Take care" healthcare program, the anamnesis and physical examination were carried out and recorded in the electronic medical record during the consultation with the physician. Subsequently, the clinical staff grouped the electronic medical records and laboratory tests in the healthcare program database.

We requested the database of the patients with T2DM who had undergone a check-up within the "Take care" healthcare program in 2018. These patients had attended at least one annual check-up; for this purpose, laboratory tests were performed two days before they saw the physician.

We reviewed the database and eliminated patients whose data were incomplete. We considered the HbA1C data that coincided with the date on which the participants underwent the albuminuria test. Moreover, we considered only the first annual measurement of both of these variables. In the same way, other laboratory tests were conducted on the same date on which the participants underwent an albuminuria test. The laboratory method for measuring glycosylated hemoglobin consisted of high-resolution chromatography, and the immunoturbidimetric method was used for albuminuria.

Ethical considerations

The Institutional Review Board of the Universidad Peruana de Ciencias Aplicadas approved the research protocol on March 31, 2020 (PI 113-18). This study did not have identification codes for the participants, which thus maintained the confidentiality of patient information. The information used in this study was handled solely and exclusively by the authors of this study. Similarly, permission for collection of information from the database of the

private clinic was obtained from the ethics committee of the private clinic, which approved the handling of data and its publication (letter no. 006-TI-UDID-CI-2019).

Statistical analysis

We used the mean and standard deviation to describe the numerical variables with normal distribution. For variables with skewed distribution, we used the median and interquartile range (IQR). We used absolute and relative frequencies for categorical variables.

We used Student's t test to compare numerical variables with normal distribution, and for numerical variables with skewed distribution, we performed the Mann-Whitney U test. We used the chi-square test to compare categorical variables and correlated numerical variables using the Pearson coefficient.

We generated crude and adjusted generalized linear models from the Poisson family with robust variance to assess the association between poor glycemic control and albuminuria. We reported the prevalence ratio (PR) as an association measurement, with the respective 95% confidence interval (CI). As described in the literature, we entered potential confounding variables into the multivariable model using an epidemiological approach.[29] Additionally, we evaluated collinearity between the variables before entering them into the multivariable model.

We carried out all analyses in the STATA statistical package (Statacorp, College Station, Texas, United States), version 14.0.

RESULTS

In total, we analyzed 907 participants; the majority of the sample was male (62.8%). The participants' median age was 58 years (IQR 49 to 66) and their median BMI was 29.05 kg/m^2 (IQR 26.6 to 32.3). The median HbA1C was 6.6% (IQR 6 to 7.9) and the median albuminuria was 12.9 mg/dl (IQR 6.02 to 26.1). The prevalence of poor glycemic control was 39.8% (n = 361) (**Table 1**).

The median albuminuria was higher among individuals with poor glycemic control (17.2 mg/dl; IQR 7.32 to 43.6) than among those with adequate glycemic control (10.7 mg/dl; IQR 5.55 to 20.1), and this difference was statistically significant (P < 0.01). The logarithms of the albuminuria and glycosylated hemoglobin levels showed a positive and statistically significant correlation (r = 0.25; P < 0.01) (**Figure 1**). Also, we found higher medians of fasting glucose, creatinine, waist circumference, SBP and DBP in the group with poor glycemic control than in the group with adequate glycemic control (P < 0.05). The demographic, laboratory and clinical variables referring to the population are described in **Table 1**.

The prevalence of albuminuria was 22.7% and was higher among men (25.6% versus 17.8%, P < 0.01). In addition, there was higher median fasting glucose, abdominal circumference and SBP in the group with albuminuria than in the group without albuminuria (P < 0.01). The prevalences of albuminuria in the groups with poor glycemic control and adequate glycemic control were 32.7%

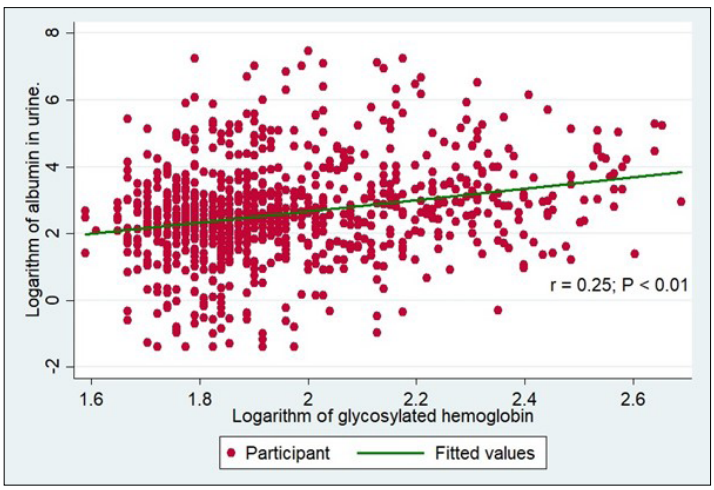

Figure 1. Scatter plot between the logarithms of glycosylated hemoglobin and serum albumin.

Table 1. Clinical and demographic characteristics of the study population according to glycemic control

Variable	Whole sample (n = 907)	Poor glycemic control (n = 361)	Good glycemic control (n = 546)	P-value
Albuminuria (mg/dl)	12.9 (6.02-26.1)	17.2 (7.32-43.6)	10.7 (5.55-20.1)	< 0.01
Age (years)	58 (49-66)	56 (47-64)	58 (49-67)	< 0.01
Gender				0.01
Female	337 (37.2)	116 (32.1)	221 (40.5)	
Male	570 (62.8)	245 (67.9)	325 (59.5)	
Fasting glucose (mg/dl)	122 (106-150)	157 (125-200)	114 (101-126)	< 0.01
BMI (kg/cm^2)	29.1 (26.6-32.3)	29 (26.8-32.5)	29.1 (26.2-32.1)	0.36
Uric acid (mg/dl)	5.2 (4.2-6.1)	4.7 (3.8-5.6)	5.4 (4.6-6.2)	< 0.01
Creatinine (mg/dl)	0.79 (0.67-0.94)	0.78 (0.66-0.91)	0.8 (0.68-0.95)	0.07
WC (cm)	101 (10.7)	102 (10.2)	100 (11.0)	0.02
SBP (mmHg)	117 (10.5)	119 (9.9)	116 (10.7)	< 0.01
DBP (mmHg)	72 (7.7)	73 (7.9)	71 (7.5)	< 0.01

Values are presented as mean (standard deviation), median (interquartile range) or number (percentage).
BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; WC = waist circumference.

and 18.1% (P < 0.01), respectively. **Table 2** shows the differences in the study population according to albuminuria.

The crude regression analysis showed an association between poor glycemic control and albuminuria (PR = 2.03; 95% CI: 1.59-2.58). After adjusting for age, sex, SBP, DBP, fasting glucose, uric acid, BMI and creatinine in the multivariable analysis, the association with poor glycemic control remained statistically significant (PR = 1.48; 95% CI: 1.19 -1.85) (**Table 3**).

Table 2. Clinical and demographic characteristics of the study population according to albuminuria status

Variable	Albuminuria (n = 206)	No albuminuria (n = 701)	P-value
Poor glycemic control	118 (32.7)	243 (67.3)	< 0.01
Adequate glycemic control	88 (16.1)	458 (83.9)	
Age (years)	57 (48-65)	58 (49-66)	0.43
Gender			< 0.01
Female	60 (17.8)	277 (82.2)	
Male	146 (25.6)	424 (74.4)	
Fasting glucose (mg/dl)	133 (109-181)	120 (106-144)	< 0.01
BMI (kg/cm^2)	29.3 (27.1-32.7)	28.9 (26.3-32.2)	0.09
Uric acid (mg/dl)	5.1 (4.2-6.1)	5.2 (4.3-6.0)	0.72
Creatinine (mg/dl)	0.8 (0.7-1.0)	0.8 (0.7-0.9)	0.11
WC (cm)	103 (9.6)	100 (11.0)	< 0.01
SBP (mmHg)	120 (10.2)	116 (10.5)	< 0.01
DBP (mmHg)	73 (8.1)	71 (7.6)	0.05

Values are presented as mean (standard deviation), median (interquartile range) or number (percentage).
BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure; WC = waist circumference.

Table 3. Crude and adjusted regression models for the association between glycemic control and albuminuria

Variable	Crude PR (95% CI)	P-value	Adjusted PR (95% CI)	P-value
Glycemic control				
Adequate glycemic control	Reference	--	Reference	--
Poor glycemic control	2.03 (1.59-2.58)	< 0.01	1.70 (1.28-2.27)	< 0.01
Age (years)	0.99 (0.98-1.01)	0.52	1.00 (0.99-1.01)	0.89
Gender				
Female	Reference	--	Reference	--
Male	1.44 (1.10-1.88)	< 0.01	1.31 (0.99-1.75)	0.06
Fasting glucose (mg/dl)*	1.04 (1.03-1.06)	< 0.01	1.02 (1.01-1.04)	0.02
BMI (kg/cm^2)	1.02 (0.99-1.04)	0.07	1.01 (0.99-1.04)	0.21
Uric acid (mg/dl)	0.99 (0.91-1.07)	0.83	1.02 (0.95-1.10)	0.60
Creatinine (mg/dl)	1.15 (1.10-1.21)	< 0.01	1.11 (1.04-1.18)	0.01
WC (cm)**	1.02 (1.01-1.03)	< 0.01	-	
SBP (mmHg)	1.01 (1.01-1.03)	< 0.01	1.02 (1.01-1.03)	< 0.01
DBP (mmHg)	1.02 (0.99-1.03)	0.05	0.99 (0.98-1.01)	0.62

*Scaled variable for an increase of 10 mg/dl; **Variable not entered into the adjusted regression model due to collinearity with BMI.
BMI = body mass index; DBP = diastolic blood pressure; PR = prevalence ratio; SBP = systolic blood pressure; WC = waist circumference; CI = confidence interval.

DISCUSSION

The main finding from our study was an association between poor glycemic control and albuminuria in our population. Additionally, almost one third of the sample studied had poor glycemic control or albuminuria.

Two out of every ten patients with DM had albuminuria. In a previous study in Peru, the prevalence of albuminuria was 13.4%, in hospitals in Arequipa.[30] In a multicenter study on diabetic patients who attended their first nephrological consultation in four hospitals in Lima, 69.3% of them had albuminuria greater than 30 mg/24 hours.[31] The prevalence of albuminuria in our study was higher than in high-income countries, probably because fewer T2DM patients achieve control over their disease through healthcare services.[32,33]

The prevalence of albuminuria has been found to vary significantly in other countries. Rates of 19.8% to 36.3% were found in southern India and 25.5% in northern India.[34-36] Also, the prevalence of albuminuria was found to be 13.4% in China,[37] 16.8% in Saudi Arabia[38] and 24.9% in the United Kingdom.[39] The differences found are likely to have been due to the sample size, sampling and sample characteristics or, especially, the albuminuria measurement method. For example, while albuminuria was measured with using the first morning urine in our study, the study by Herrera et al., also conducted in Lima, used 24-hour urine. Thus, our findings may have been underestimates.[31]

Our results regarding the association between poor glycemic control and albuminuria were similar to those reported in recent studies conducted in India,[20,40] Iran,[13] Nigeria[8] and Pakistan.[18] In contrast, although a cross-sectional study conducted in Nepal in 2015 showed a positive correlation between albuminuria and HbA1c, this was not statistically significant; the difference in results was likely to have been due to the limited sample size, as the authors of that study acknowledged.[41]

No specific studies have evaluated this association in the Hispanic population, to the best of our knowledge, although there is evidence suggesting ethnic variation in the prevalence of albuminuria. For example, a study using the National Health and Nutrition Examination Survey (NHANES), on 2,310 diabetic patients, found that the prevalence of early chronic kidney disease (CKD) was greater among Hispanics and African Americans than among whites, and Hispanics had higher albuminuria.[24] In another study that used NHANES, it was found that among individuals without diabetes, blacks had 2.18-fold and Mexican Americans had 1.81-fold greater odds of having albuminuria than whites, after adjustment for potential confounding factors.[25] Although the reasons for this variation are not entirely clear, they may be related to the reasons why diabetes and its complications are more frequent in the Hispanic population. These include biological factors, such as predisposition to insulin resistance, augmented insulin secretion and abdominal obesity, as well as complex socioeconomic and cultural factors.[42-45]

Among patients with poor glycemic control, hemodynamic and metabolic changes to the glomerulus occur, which damage endothelial cells and podocytes and alter the glomerular basement membrane properties, thus contributing to alteration of the physical-chemical characteristics of the glomerular filtration barrier.[46] In diabetic kidney disease, the glomerular basement membrane loses negative ionic charges and both endothelial and podocyte lesions increase the size of the pores, which thus causes loss of selectivity of glomerular filtration and produces albuminuria.[47]

Clinicians need to emphasize the importance of correct glycemic control among patients with T2DM. The Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group recommends an individualized HbA1c target ranging from < 6.5% to < 8.0% among patients with diabetic kidney disease that is not being treated with dialysis, in order to reduce the risk of microvascular and macrovascular complications.[48] Combining interventions such as medication compliance, increased physical activity and healthy nutritional habits can reduce microvascular complications and improve the quality of life of patients with T2DM.[39-41] Clinicians need to seek periodic measurement of albuminuria levels, especially among patients with poor glycemic control.[28]

Despite this recommendation, glycemic control is not always achieved. In some studies in Peru, it was found that in diabetic patients treated in city hospitals, between 40% and 70% had an HbA1C level greater than 7%.[4,31] Similar findings have been obtained in other countries such as Russia, China, Myanmar and Angola, where the diabetes control rates were 58.5%, 16.9%, 35.2% and 2.7%, respectively.[49-52]

A systematic review found two key healthcare system barriers to effective T2DM care and management: financial constraints faced by the patient and limited access to healthcare services and medication. It also found three healthcare system factors that facilitated effective T2DM care and management: use of innovative care models, increased pharmacist involvement in care delivery and education programs led by healthcare professionals.[26]

Our study had some limitations. First, it had a cross-sectional design, which therefore did not allow assessment of causal relationships between the variables. Second, information bias was possible; however, we performed rigorous quality control on the data collected. Third, we did not have any information on some other potential confounding variables, such as the number of years for which the patients had been suffering from T2DM, their physical activity levels, their dietary habits, the length of time since their inclusion in the program and whether they were previously seen at another institution. Similarly, we did not have information on patients' adherence to the program, or whether they were visiting other doctors outside the program or were hospitalized during the follow-up. Fourth, we unable to use the gold standard for measuring albuminuria (24-hour urine test), which could have caused misclassification of outcomes. However, initial screening of albuminuria using a urine sample collected early in the morning, as was done in our study, has good sensitivity compared with the 24-hour urine test.[53,54] Lastly, we could not be sure that all the conditions for adequate albuminuria measurement were observed, which might have produced false positives in our sample.

CONCLUSION

There was an association between poor glycemic control and higher prevalence of albuminuria among Peruvian patients with T2DM. Therefore, we recommend further research on cost-effective glycemic control interventions, in order to reduce the risk of microvascular and macrovascular complications in the Hispanic population.

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Population-based analysis of the epidemiology of the surgical correction of hyperhidrosis in 1,216 patients over 11 years: a cross-sectional study

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ABSTRACT

BACKGROUND: Endoscopic thoracic sympathectomy is the definitive surgical treatment for hyperhidrosis and a nationwide study has suggested that cultural and socioeconomic factors play a role in the numbers of operations performed. Thus, there is a need to evaluate local data in order to understand the local epidemiology and trends in hyperhidrosis treatment.

OBJECTIVE: To study the epidemiology of sympathectomy for treating hyperhidrosis in São Paulo, the largest city in Brazil.

DESIGN AND SETTING: Population-based retrospective cross-sectional study.

METHODS: Data on sympathectomies for treating hyperhidrosis between 2008 and 2018 were assessed from the database of the Municipal Health Department of São Paulo, Brazil.

RESULTS: 65.29% of the patients were female, 66.2% were aged between 20 and 39 years and 37.59% had registered with addresses outside São Paulo. 1,216 procedures were performed in the city of São Paulo from 2008 to 2018, and 78.45% of them were in only two public hospitals. The number of procedures significantly declined over the years (P = 0.001). 71.63% of the procedures were associated with 2-3 days of hospital stay, only 78 intensive care unit days were billed and we did not observe any intra-hospital death.

CONCLUSION: The profile of patients operated on in São Paulo (young women) is similar to that described in other populations. Sympathectomy is a very safe procedure, with no mortality in our series. There was a decreasing trend in the number of surgeries over the years.

INTRODUCTION

Sweat exceeding the needs of thermoregulation in certain body areas, due to hyperfunctioning sweat glands, characterizes hyperhidrosis (HH). This condition seems to be related to higher levels of cholinergic acetylcholine and nicotinic alpha-7 receptors in these individuals' sympathetic ganglia.[1] This disease, which affects up to 2.8%-4.8% of the population,[2,3] has a significant negative impact on patients' quality of life, and it impairs their personal and professional relationships.[4] HH commonly begins in childhood and can persist throughout adulthood if not properly treated.[2,5]

Currently, the definitive surgical treatment for HH consists of endoscopic thoracic sympathectomy (ETS), which is safe and clinically effective and results in significant improvement in quality of life.[4,6,7]

Although this treatment is covered by the Brazilian National Health System (Sistema Único de Saúde, SUS), a recent nationwide analysis reported that there was large variability in terms of regional ETS rates for treating HH that could not be fully explained by climate differences. Thus, it was suggested that cultural and socioeconomic factors have contributed to the numbers of ETS performed.[8] Hence, we hypothesized that in order to learn the local epidemiology and trends in HH treatment, it may be necessary to evaluate local data as well.

Therefore, we designed the present study to assess the epidemiology and outcomes of ETS for treating HH in the city of São Paulo, which is the largest, wealthiest and most populous city in Brazil, with an estimated population of 12 million inhabitants,[9] among whom more than 5 million are exclusively dependent on SUS.[10] Furthermore, the database of the Municipal Health Department of São Paulo provides the most detailed health data,[11] thus yielding more information than the national database.

OBJECTIVE

To study the epidemiology and outcomes of ETS for treating HH in the city of São Paulo, with evaluation of the total number of ETS performed for treating HH, hospital volumes, trends over time, costs, in-hospital mortality and lengths of hospital and intensive care unit (ICU) stay, along with the proportion of patients from other cities who came to São Paulo to undergo ETS for treating HH.

METHODS

This study involved analysis of data available on the health information (Informações em Saúde, TabNet) platform of the Information Technology Department of SUS (Departamento de Informática do Sistema Único de Saúde, DATASUS),[11] which provides open data on procedures performed in accredited public hospitals. Such accreditation is a prerequisite for government reimbursement for the surgeries performed.

Data regarding sympathectomies for treating HH (as coded in accordance with the International Classification of Diseases, 10th edition: R61) covering the years 2008 to 2018 were selected from TabNet of the Municipal Health Department of São Paulo. Among the selections, sex, municipality of residence, age group, number of surgeries performed (total and per establishment), mortality during hospitalization, length of stay in the establishment, ICU stay and amounts paid were analyzed.

Age was stratified as follows: under 14 years, between 15 and 19 years, between 20 and 39 years and over 39 years. The amounts paid in Brazilian official currency (reais, R$) were converted into United States dollars (USD) on December 31, 2012, which was the midpoint date between the first and last data analyzed, at the rate of 1.00 USD = R$ 2.04). Hospitals were numbered, in descending order, according to the total number of procedures performed.

The information was obtained from publicly accessible websites by means of computer programs for accessing content from web scraping codes. These codes were programmed in Python language, version 2.7.13 (Python, Beaverton, Oregon, United States), in the Windows 10 single-language operating system. The steps of collecting and selecting fields on the platform and later adjusting the tables were performed using the Selenium WebDriver package, version 3.1.8 (Selenium HQ, various contributors around the world); and Pandas, version 2.7.13 (Lambda Foundry, Inc., and PyData Development Team, New York, United States). We used the Mozilla Firefox browser, version 59.0.2 (Mountain, California, United States), and the Geckodriver WebDriver. version 0.18.0 (Mozilla Corporation, Bournemouth, England).

After collection and treatment, the data were organized and grouped in a spreadsheet in the Microsoft Office Excel 2016 program, version 16.0.4456.1003 (Microsoft, Redmond, Washington, United States).

For statistical analysis, linear regression analysis was performed to evaluate the trends in procedures over the years, using the SPSS version 22.0 (IBM Corp. Armonk, New York, United States). For all tests, the level of statistical significance was taken to be $\alpha = 0.05$.

This study was approved by the ethics committee of the institution where it was conducted (procedural number 3067-17; approved on July 18, 2017). Data are anonymous at DATASUS; therefore a waiver of informed consent was requested and granted by our institutional review board.

RESULTS

Most of the patients were female (65.29%), aged between 20 and 39 years (66.2%) and with a registered residential address in the city of São Paulo (62.41%). The age stratification of the operated patients is presented in **Table 1**.

In total, 1216 procedures were performed in the city of São Paulo from 2008 to 2018. Most surgeries (78.45%) were performed in only two public hospitals. The distribution of procedures in each hospital and the overall distribution of procedures over the years are shown in **Table 2** and **Figure 1**, respectively.

We observed a progressively decreasing trend in the total number of procedures over the years (P = 0.001). The first year studied, 2008, presented the largest number of cases (192 surgeries), whereas in recent years there have been fewer cases, especially in 2016 (47 surgeries).

In all the years evaluated, we did not observe any case of intra-hospital death. In other words, no patient died within the same hospital admission following sympathectomy for hyperhidrosis in the city of São Paulo during the period studied.

The number of procedures classified according to length of hospital stay is shown in **Figure 2**. We observed that procedures with a length of hospital stay of 2 to 3 days predominated (71.63%). Only 89 patients (7.31%) remained in the hospital for 4 days or more.

Regarding ICU stay, SUS reimbursed a total of 78 days of ICU stay for the entire cohort: 2 days of ICU were paid for in 2008, 24 days of ICU in 2010, 2 days of ICU in 2015 and 50 days of ICU in 2017. In all other years, no ICU stay was recorded for any patient.

The number of procedures, equivalent dollar amounts reimbursed by SUS and average amounts per procedure according to hospital establishment are presented in **Table 3**.

Table 1. Age stratification into four subgroups (< 14 years, 15–19 years, 20–39 years and > 39 years)

Age	n	%
< 14 years	75	6.16
15–19 years	251	20.64
20–39 years	805	66.2
> 39 years	85	6.99

A total of 534,916.96 USD was reimbursed by SUS for all the surgeries, corresponding to an average amount of 439.90 USD per surgery. The reimbursement per procedure ranged from 417.20 USD to a maximum of 607.46 USD over the years.

DISCUSSION

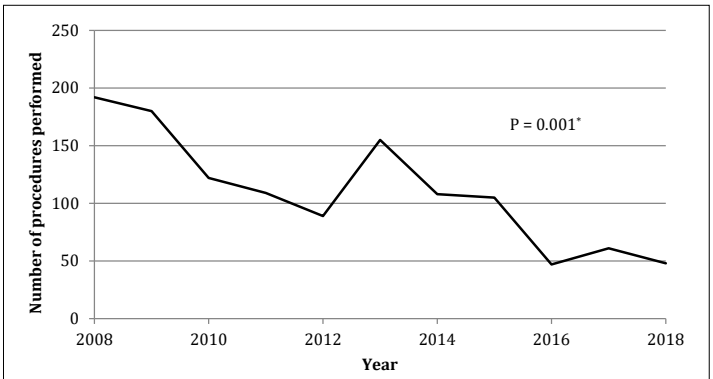
Patients' demographics

In line with previous reports, we observed a predominance of female patients.[1,8] Even though the prevalence of HH is similar between the sexes,[5] there is a greater demand for treatment among females, likely due to generally greater esthetic concern in this group.[12-15]

Regarding age, ETS for treating HH has proven to be beneficial for a wide range of age groups.[16,17] However, the demand for treatment of hyperhidrosis is estimated to be greater in young and economically active age groups,[5] which is in agreement with our findings, as most individuals in our study were aged between 20 and 39 years (66.2%).

More than one third of the patients had registered with addresses outside of the city of São Paulo (37.59%). Healthcare inequalities in Brazil and the concentration of resources in its southeastern region, and in some southeastern centers like the city of São Paulo, are well documented.[9] A similar high proportion of out-of-town patients who come to the city of São Paulo to seek treatment has been observed in other reports.[18]

The state of São Paulo comprises 645 municipalities, which are organized into 17 healthcare service reference regions (HSRR).[19] Ideally, in accordance with the principle of regionalization of the Brazilian National Health System, each HSRR should be designed to meet most of the healthcare demands of its municipalities.[20] The city of São Paulo is the only municipality included in its HSRR.[19] Hence, the patients treated by mean of sympathectomy for hyperhidrosis with a registered address outside of the city of São Paulo, belonged to other HSRRs.[19] It is likely that many of these patients went to São Paulo to seek treatment, thus practicing healthcare tourism,



*Linear regression analysis to assess the trend of reduction in the number of procedures over the years.

Figure 1. Distribution of sympathectomies for treating hyperhidrosis between 2008 and 2018, in public hospitals in São Paulo.

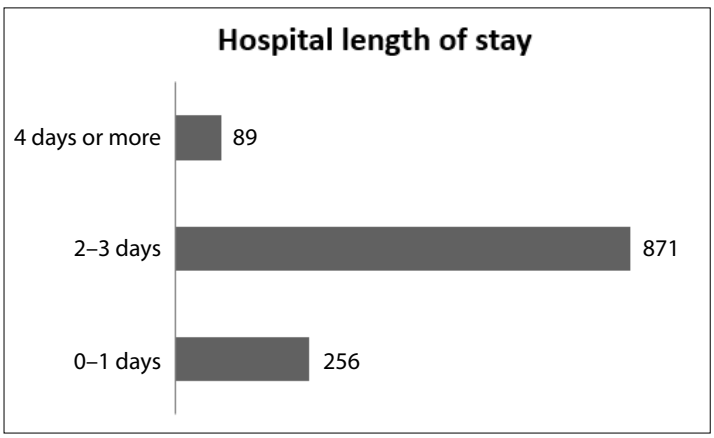


Figure 2. Distribution of patients according to length of hospital stay in days.

Table 2. Number of procedures performed in each hospital between 2008 and 2018

Hospital	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
1	153	158	81	65	32	94	45	36	34	31	24
2	3	0	17	12	20	34	42	53	3	10	7
3	28	9	13	10	3	12	0	0	0	0	1
4	2	0	0	0	11	7	9	7	3	16	11
5	2	7	3	10	18	7	5	0	3	1	0
6	3	3	2	4	1	0	1	0	0	1	1
7	3	0	0	2	0	1	1	3	0	0	1
8	0	1	1	4	1	0	3	1	0	0	0
9	0	0	0	0	0	0	0	5	3	0	1
10	0	0	0	2	2	0	1	0	0	2	2
11	3	1	4	0	0	0	0	0	0	0	0
12	2	1	0	0	1	0	0	0	1	0	0
13	0	0	0	0	0	0	1	0	0	0	0
14	0	0	1	0	0	0	0	0	0	0	0

Table 3. Number of procedures (%), amounts reimbursed by the public healthcare system and average amount per procedure, in United States dollars

Hospital	Number of procedures (%)	Total reimbursed	Average amount per procedure
1	753 (61.92)	314,153.19	417.20
2	201 (16.53)	94,278.25	469.04
3	69 (5.67)	32,493.74	470.92
4	66 (5.43)	33,052.79	500.80
5	56 (4.61)	26,898.84	480.34
6	16 (1.32)	7,610.58	475.66
7	11 (0.90)	5,411.38	491.95
8	11 (0.90)	4,607.50	418.86
9	9 (0.74)	5,467.13	607.46
10	9 (0.74)	4,209.31	467.70
11	8 (0.66)	3,293.05	411.63
12	5 (0.41)	2,336.79	467.36
13	1 (0.08)	658.72	658.72
14	1 (0.08)	445.67	445.67
Total	**1,216 (100)**	**534,916.96**	**439.90**

instead of being properly referred from their own municipality to a center in the main city of their own HSRR. Being aware of these statistics is important, from the point of view of better allocation of resources and regulation of healthcare demands, in order avoid overloading the healthcare services and incurring deficits in the revenue of the healthcare system.

Procedure rates and trends

Starting in the first year of the period studied, we observed a progressively downward trend in the number of ETS procedures for treating HH. This contrasts with national statistics showing an initial upward trend between 2008 and 2012, and a downward trend thereafter.[8] This difference may have been because the municipal center with the highest volume of ETS (hospital 1) was also the one in which an "oxybutynin first" protocol for treating HH started to be used in 2007, such that sympathectomy was then reserved for refractory cases or for patients with intolerance to oral treatment, in an attempt to reduce the incidence of compensatory hyperhidrosis, a common complication after sympathectomy.[21-24] Good results from the "oxybutynin first" strategy started to be reported from 2011 onwards,[25-31] which might well have contributed to the national decrease in use of ETS for treating HH from 2012 onwards.

Hospital and ICU length of stay and in-hospital mortality

We observed that the hospital stay was short, in line with other studies.[32,33] Most of the patients were discharged on the second or third day of hospitalization, which likely corresponded to the first and second postoperative days, respectively, given that patients are usually admitted on the day before the surgery.

Regarding ICU length of stay, due to the anonymity of the data, we only had access to the total number of ICU days paid by the government. Thus, we did not know how many patients were admitted to the ICU and for how many days, or what the indications for ICU admittance were. These therefore were limitations of our study. In total, we observed that 78 days of ICU stay were reimbursed to the hospitals, which were unevenly distributed over the years of 2008, 2010, 2015 and 2017 only. This number is small, but not negligible, especially when considering that most of the patients were young adults. Some of these days in the ICU may have related to patients with severe early postoperative complications, such as pneumothorax or hemothorax, which have been reported by other authors.[32] Nevertheless, no in-hospital death subsequent to ETS for treating HH was reported in the public hospitals of São Paulo between 2008 and 2018, as reported in other large studies,[32,33] which emphasizes the low mortality associated with this treatment.

Within the city of São Paulo, 78.45% of the procedures were performed in only two public hospitals. Considering that hyperhidrosis is a bothersome but not lethal disease, and given the underfunding of the public healthcare system,[34] there are few referral centers dedicated to this treatment. This concentration in just a few centers would tend to improve perioperative outcomes and may likely explain the absence of fatalities.

Costs

A total of 534,916.96 USD was reimbursed by the government for ETS for treating HH, with an average amount of 439.90 USD per procedure, a little less than reported by other authors.[35] One of the limitations of our cost analysis was that the reimbursement was based on a compensation table for procedures, which often does not reflect the actual amount spent on procedures by the hospitals. We may conjecture that the decrease in the number of surgeries may have led to higher public expenditure on clinical treatments. As HH is a frequent disease among young people, who may use medications over the long term, this should be considered within publicly funded healthcare, although a cost-effectiveness study would be necessary in order to evaluate it properly.

Limitations

Besides the limitations already mentioned, i.e. anonymous data precluding follow-up and adjusted analysis, along with reimbursement based on a fixed compensation table, another limitation of our study was that the database only provides data relating to selected procedures performed in accredited public hospitals. Thus, the database is susceptible to some loss of data.

On the other hand, this was a comprehensive and detailed epidemiological analysis on sympathectomy for treating HH that made use of objective data that had been compulsorily recorded in a public database. Our findings revealed the demographics of

patients who were seeking surgical treatment for hyperhidrosis and the high volume of out-of-town patients who were seeking treatment in São Paulo; and highlight the safety of this treatment.

CONCLUSIONS

Over the last 11 years, sympathectomy for treating HH has been widely performed in the city of São Paulo. The profile of patients operated on in São Paulo (young women) is similar to that described in other populations. Sympathectomy is a very safe procedure, with no mortality in our series. There was a decreasing trend in the number of surgeries over the years.

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Clinico-epidemiological profile of patients at children's psychosocial care centers in São Bernardo do Campo: a cross-sectional study

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ABSTRACT

BACKGROUND: Child and Adolescent Psychosocial Care Centers (Centros de Atenção Psicossocial, CAPSI) are dedicated centers for persistent psychiatric disorders, which provide an individualized therapeutic approach based on extra-hospital services.

OBJECTIVES: We aimed to describe the clinico-epidemiological profiles of the patients seeking interventions at the CAPSIs.

DESIGN AND SETTING: A cross-sectional study was conducted in two CAPSI in São Bernardo do Campo, SP, Brazil. One CAPSI is dedicated to the treatment of alcohol- and drug-related disorders, and the other to the treatment of other mental disorders.

METHODS: In July 2017, we reviewed all active medical records of these two CAPSI, and collected the patients information including sex, race, education, type of referral, initial complaints, psychiatric diagnoses, and medication utilization.

RESULTS: Of the 233 patients, 69.5% were male and 42.5% lived with their immediate family. Most of the patients were referred from other health services. Complaints on admission included agitation and aggressive behavior (30.9%). Autism spectrum disorder (ASD) was the most prevalent diagnosis (46.8%), followed by depressive disorder (13.8%). Of the patients, 81.5% were on regular medical follow-up and 70.3% were on a single medication only.

CONCLUSION: Aggression complaints are the most prevalent in CAPSI, and diagnoses of ASD and psychotic disorders are more common. This situation differs from most CAPSI that present school complaints as the most prevalent, in which diagnoses of attention-deficit/hyperactivity disorder and conduct disorders are likely to be more frequent. The epidemiological profile of each CAPSI should guide the implementation of human and structural resources targeting the most prevalent complaints and diagnoses.

INTRODUCTION

A child and adolescent mental health is one of the challenges of the Brazilian Psychiatric Reformation, and has become a public health issue involving the Brazilian Unified Health System (Sistema Único de Saúde, SUS).[1,2]

The Child and Adolescent Psychosocial Care Centers (Centro Estadual de Atenção Psicossocial e Infanto-Juvenil, CAPSIs) are dedicated to persistent psychiatric disorders and provide an individualized therapeutic approach based on extra-hospital services, such as therapeutic residences and outpatient clinic income-generation workshops, among others.[3,4]

In Brazil, the prevalence of mental health disorders among children and adolescents may vary from 7%–24.6%, with clinical intervention prevalence rates ranging from 4%–7.3%.[5,6] However, limited studies have described the utilization of mental health services in this population.[7]

Lauridsen-Ribeiro et al.[8] conducted a study on 141 children and adolescents (1–19 years old) and reported a 4.7% prevalence of mental disorders. Concomitantly, 74% of the affected patients did not seek for specific intervention before admission, 55.6% consulted a general hospital or service, and 12.9% consulted a psychologist.[8,9]

Mental illness among children and adolescents may be underestimated owing to a range of difficulties in discerning what is related to their development. Moreover, cultural and social

factors may influence the qualitative and quantitative analysis of behaviors and symptoms.[10] In addition, parents, teachers, and neighbors usually have distinct perceptions of the same problem, and the instruments employed for detecting early mental disorders may be poorly validated or standardized.[11]

Garcia et al.[11] characterized the distribution and user profile of CAPSIs, and reported that 29.7% of the patients were diagnosed with behavioral disorders typical during childhood and adolescence, 23.6% with psychological development disorders, and 12.5% with intellectual disabilities. Moreover, 10.4% of the cases were neurotic, stress-related, and somatoform disorders and 1.8% of the patients have mental disorders due to psychoactive substances.[12]

São Bernardo do Campo (SBC) has approximately 850,000 inhabitants and hosts two CAPSIs, one dedicated to the treatment of alcohol and drug use disorders, and the other to mental health disorders.

The analysis of CAPSIs epidemiological data may suggest better strategies to improve CAPSI activities and promote tailored therapeutic interventions to reduce the impact of early disorders in the patient life course.

OBJECTIVES

This study aimed to identify the prevalence of mental disorders of the patients in two CAPSIs in São Bernardo do Campo, Brazil, as well as describe their basic information such as sex, initial complaints, diagnoses according to the International Classification of Diseases (ICD-10), treatment adherence rates, and prescribed medications in the CAPSIs.

METHODS

Study setting

According to the Brazilian government, CAPSI is a facility for the assistance of children and adolescents who present with severe and persistent mental disorders, including substance use disorders. It serves cities and or regions with at least 70.000 inhabitants.[4] Despite this definition, some large Brazilian cities, such as SBC, divide CAPSI into two different facilities for mental disorders and substance use disorders. These two services and the basic health units (BHU) are responsible for the entire city's child and adolescent mental health care, with BHU managing mild mental disorders.

Sample

SBC is a city in the metropolitan area of São Paulo, with an estimated population of 844.483 as of 2020.[13] According to the last demographic census in 2010, 28.5% of the population aged 0–19 years.[13]

Procedures

We performed a cross-sectional study in July 2017 by reviewing the medical records of the two CAPSIs. All patients treated by multidisciplinary staff and/or medical staff between January and July 2017 were included, and patients accessing a single evaluation were not included. A single evaluation usually means that they are evaluated and referred to another service.

The first, second, and third authors independently collected the data. Disagreements were resolved by group discussion until an inter-rater agreement of 100% was achieved. Missing data were further discussed with the professional of the CAPSI team, who was in charge of the patient.

An estimation of the prevalence of mental disorders and their correlates in this specific population has been provided.[14,15]

Measures

Patient data from the medical records were obtained from a clinical protocol in place during the study period. The following information were collected for clinical reasons: Sex (male or female); race (white, black, Asian, native, or mixed); education (adequate for age, inadequate for age, school dropout, or school for special needs; type of referral (spontaneous or referred [e.g., basic health unit, school, rehabilitation centers, psychiatric emergency room, tutelary council, clinical emergency room units, private health services, technical guidance teams]); initial complaint (agitated/aggressive behavior, impairment in social interactions and neurodevelopmental delays, impairment in social interaction, neurodevelopmental delays, use of psychoactive substances, suicidal ideation, or suicide attempts; psychiatric diagnoses (autism spectrum disorder, acute psychotic disorder, depressive disorder, autism associated with intellectual disabilities, schizophrenia, intellectual disabilities, conduct disorder, attention-deficit/hyperactivity disorder, panic disorder, mental and behavioral disorders related to the use of multiple drugs, bipolar affective disorder, personality disorder, mental and behavioral disorders related to cannabis use, mental and behavioral disorders related to cocaine use, and obsessive-compulsive disorder); and medication utilization (antipsychotic monotherapy, antidepressants, psychostimulants, mood stabilizers, antihistamines, and benzodiazepines as monotherapy or in combination).

The computation and analyses of collected data were conducted using the Statistical Package for the Social Sciences (SPSS) version 15.0 (IBM Corp., Armonk, New York, United States).

Ethics statement

Informed consent was obtained from both the patient and their legal guardians. This study was approved by the Faculdade de Medicina do ABC (FMABC) Ethics Committee (CAAE 2823.5719.3.0000.0082) dated June 19, 2020.

RESULTS

We reviewed all active medical records of 233 patients (69.5% male and 30.5% female). The patient characteristics are shown in **Table 1**. Of the patients, 66.5% were white, 29.6% brown, and 2.6% black. Moreover, 43% of the patients are living with both parents, 46% with a single parent, 5.1% with other family members, 3.8% with shelters, and 2.1% with their grandparents.

Of the 233 patients, 57.1% were attending their expected school grade, 20.1% had failed at least one school year, 12.9% attended special schools, and 9.9% dropped out of school. School dropout was associated with specific ICD-10 diagnoses such as acute psychotic disorders (F23) and mental and behavioral disorders related to the use of multiple substances (F19), with a school dropout rate of 17.4%. In addition, the prevalence of drug addiction as a comorbidity among those who reported school dropout was 26.1%.

Diagnoses associated with school failures were as follows: depressive disorders (F32), 23.4% of cases; schizophrenia (F20), 12.8%; conduct disorders (F91), 8.5%; and conduct disorders associated with attention-deficit/hyperactivity disorder (F91 + F90), 8.5%. In addition, one case of attention-deficit/hyperactivity disorder (ADHD) with no associated comorbidity was the leading cause of school failure.

Notably, only a minority of patients sought medical help from the CAPSIs spontaneously, with 73.8% and 27.1% of them were referred from other services and BHU, respectively (**Table 2**).

Only 3.2% of patients reported disorders related to substance use. However, most were referred to the CAPSIs for other comorbidities, such as ADHD. We also observed that 4.2% of patients presented with substance use as an initial complaint but were not referred by the BHUs.

Common cause for referring to CAPSIs include agitated/aggressive behavior (30.9 %) and impairment in social interactions associated with neurodevelopmental delays (13.7 %) (**Table 3**). In the analysis of single symptoms as reasons for referral, we found that impairment in social interactions was the third most common cause of referral (12.4%), followed by neurodevelopmental delays (9.9%), chemical substance use (4.3%), suicidal ideation, suicide attempts (3.9%), and self-aggressiveness (3.4%). Other causes (21.5%) are presented in **Table 3**.

ICD-10- based diagnoses include autism spectrum disorder (F84) (32.6%), depressive disorder (F32) (12%), and autism associated with intellectual disabilities (F84 + F79) (7.3%) (**Table 4**). Other diagnoses include schizophrenia (F20) (4.7%), intellectual disabilities (F79), conduct disorder (F91) (3.9%), ADHD (F90) (3%), panic disorder (F41) (2.6%), mental and behavioral disorders related to the use of multiple drugs (F19) (2.6%), bipolar affective disorder (F31) (2.1%), personality disorder (F60) (1.7%), acute psychotic disorder (F23) (1.7%), mental and behavioral disorders

Table 1. Epidemiological profile of the patients in CAPSIs in São Bernardo do Campo

Epidemiological profile			
Variable	n (233) % total		
Sex			
Male	162		**69.5**
Female	71		**30.5**
Suitable school grade	**Male**	**Female**	
Yes	93	40	**57.1**
No	69	31	**42.9**
Family nucleus			
Both parents	73	26	**42.5**
One parent	72	36	**46.4**
None	17	9	**11.1**
Search for service			
Spontaneous	46	15	**26.2**
Referred	116	56	**73.8**
Medical follow-up			
Regular	131	59	**81.5**
Irregular	31	12	**18.5**

CAPSI = Centros de Atenção Psicossocial (Child and Adolescent Psychosocial Care Centers).

Table 2. Referrals from other services to the CAPSI's of São Bernardo do Campo

Referrals	**Percent**
Basic Health Units	27.1%
Not referred	24.9%
Others	12.1%
School	9.1%
Rehab Center	9.1%
Psychiatry Emergency Rooms	8.6%
Private Health Services	3.0%
Tutelary Council	2.2%
Clinical ER Units	2.0%
Technical Guidance Team	1.7%

CAPSI = Centros de Atenção Psicossocial (Child and Adolescent Psychosocial Care Centers).

Table 3. Initial complaints of the patients in CAPSIs in São Bernardo do Campo

Initial complaints	**Percent**
Impairment in social interactions	12.4%
Neurodevelopmental delays	9.9%
Impairment in social interaction and neurodevelopmental delays	13.7%
Agitated/aggressive behavior	30.9%
Suicidal ideation or suicide attempts	3.9%
Self-aggressiveness	3.4%
Use of psychoactive substances	4.3%
Others	21.5%

CAPSI = Centros de Atenção Psicossocial (Child and Adolescent Psychosocial Care Centers).

Table 4. Diagnoses of the patients in the CAPSIs in São Bernardo do Campo

Diagnoses	Percent
Autism Spectrum Disorder (F84)	32.6%
Autism Spectrum Disorder with Intellectual Disabilities (F84 + F79)	7.3%
Reactions to Severe Stress and Adaptation Disorders (F43)	0.4%
Panic Disorder (F41)	2.6%
Depressive Disorder (F32)	12.0%
Intellectual Disabilities (F79)	3.9%
Obsessive-Compulsive Disorder (F42)	0.9%
Mental and Behavioral Disorders Related to the Use of Multiple Drugs (F19)	2.6%
Attention-Deficit/Hyperactivity Disorder (F90)	3.0%
Conduct Disorder (F91)	3.9%
Attention-Deficit/Hyperactivity Disorder with Conduct Disorder (F90 + F91)	3.9%
Mental and Behavioral Disorders Related to Cannabis Use (F12)	0.9%
Autism Spectrum Disorder with Epilepsy (F84 + G40)	0.9%
Bipolar Affective Disorder (F31)	2.1%
Mental and Behavioral Disorders Related to the Use of Multiple Drugs with Intellectual Disabilities (F19 + F79)	1.3%
Autism Spectrum Disorder with Attention-Deficit/ Hyperactivity Disorder (F84 + F90)	2.6%
Mental and Behavioral Disorders Related to the Use of Multiple Drugs with Conduct Disorder (F19 + F91)	1.7%
Schizophrenia (F20)	5.2%
Schizophrenia with Intellectual Disabilities (F20 + F79)	0.9%
Phobic-Anxious Disorders (F40)	1.7%
Acute and Transient Psychotic Disorders	1.7%
Others	2.6%
Autism Spectrum Disorder with Disorders of Habits and Impulses (F84 + F63)	2.1%
Autism Spectrum Disorder with Intellectual Disabilities with Attention-Deficit/Hyperactivity Disorder (F84 + F79 + F90)	0.9%
Attention-Deficit/Hyperactivity Disorder with Intellectual Disabilities (F90 + F79)	0.4%
Depressive Disorder with Reactions to Severe Stress and Adaptation Disorders (F32 + F43)	0.9%
Autism Spectrum Disorder with Intellectual Disabilities with Epilepsy (F84 + F79 + G40)	0.4%
Mental and Behavioral Disorders Related to the Use of Multiple Drugs with Depressive Disorder (F19 + F32)	0.9%

CAPSI = Centros de Atenção Psicossocial (Child and Adolescent Psychosocial Care Centers).

related to cannabis use (F12), mental and behavioral disorders related to cocaine use (F14), and obsessive-compulsive disorder (F42) (all 0.9%). The following are the rank of comorbidities: F90+ F91(3.9%), F84 + F62 (2.6%), F84+ F90 (2.6%), F19+ F91 (2.1%), F19 + F79 (1.3%). Several other comorbidities reported similar percentages: F20+ F79 (0.9%), F19+ F32 (0.9%), F79+ F90 (0.9%), F32+ F43 (0.9%), and F84+F79+G40 (0.9%). Meanwhile, 2.6% of the sample had unspecified diagnoses.

A total of 46.8% of patients were diagnosed with autism spectrum disorder (ASD), and 32.6% reported no associated comorbidities. Of these, 78.9% were male and 21.1% were female, with 31.2% aged 1–7 years. Among comorbidities related to ASD, 15% had intellectual disability, followed by ADHD (5.5%), and trichotillomania (4.5%). In general, 20.2% of the whole sample received multidisciplinary treatment without medical follow-up, whereas 65.1% of patients with ASD were taking psychotropic medications.

In addition, 81.5% of the sample was on regular medical follow-up (**Table 1**) and 70.3% on pharmacological treatment: antipsychotic monotherapy (25.8%), antidepressants (12%), psychostimulants (4.7%), mood stabilizers (2.2%), and antihistamines and benzodiazepines (0.4%). The following are the combination therapies: antidepressants and antipsychotics (9%), antipsychotics and mood stabilizers (5.6%), mood stabilizers + antidepressants (1.3%), psychostimulants + antipsychotics (1.3%), antipsychotics + benzodiazepines (0.9%), antidepressants and psychostimulants (0.4%), antidepressants + anticholinergic (0.4%), antidepressants + benzodiazepines (0.4%), and mood stabilizers + psychostimulants (0.4%). Combinations of the three medications were rated as 5.3% (**Table 5**).

DISCUSSION

We described the clinico-epidemiological profiles of the patients attending the two CAPSIs in SBC to better understand their characteristic, as limited literature has examined this specific population to date. In this study, patients attending CAPSIs in SBC were mostly male and have attended their expected school grade. This is consistent with a previous study,[16] which reported a male rate of 66.1% based on an analysis of 248 medical records of patients in CAPSI in Rio de Janeiro state, Brazil.[16] Aggressive/agitated behavior and ASD were the most prevalent initial complaints and diagnoses, respectively.

Most of the referrals to the CAPSIs were mainly BHUs, suggesting the active involvement of these units in the public health system. São Bernardo do Campo's BHUs refer both externalizing and internalizing disorders to the CAPSI. Furthermore, most children and adolescents attended their expected school grade, indicating that patients could attend schools despite their mental health issues.

Our study found that psychomotor agitation was the main reason for referral. These externalizing behaviors are potentially urgent medical issues, which should be addressed by comprehensive child and adolescent mental health services, such as CAPSI.[17] Delfinee & Reis, Beltrame & Boarini[18], and Cunha[20] found school issues to be the most prevalent initial complaints in their CAPSIs.[19] We found that 4.3% of patients had psychoactive substance use as an initial complaint, whereas Hoffman et al.[3] reported no substance abuse cases in their CAPSI sample. This may be due to São

Table 5. Main pharmacological therapies of the patients in CAPSIs in São Bernardo do Campo's

Main pharmacological therapies	Percent
Antipsychotics	25.8%
Antidepressants	12.0%
Antipsychotics + Antidepressants	9.0%
Antipsychotics + Mood stabilizers	5.6%
Psychostimulants	4.7%
Mood stabilizers	2.2%
Others	40.7%

CAPSI = Centros de Atenção Psicossocial (Child and Adolescent Psychosocial Care Centers).

Bernardo do Campo's city hosting a specific CAPSI to treat alcohol- and drug-related issues.

The prevalence of mental disorders found in our study remarkably differs from the findings of Hoffman et al.[3] in Paraná state, Brazil. ASD was the most prevalent diagnosis in our sample, followed by depressive disorder. In contrast, Hoffman et al.[3] reported behavioral and emotional disorders with onset usually occurring in childhood and adolescence (i.e., a broad ICD-10 category, which includes ADHD and conduct disorder) as the most prevalent (44.5%) in their CAPSI, followed by anxiety, dissociative, stress-related, somatoform, and other non-psychotic mental disorders (19.8%).

Medical follow-up of patients with CAPSI was regular in most cases. A predominance of antipsychotic medication use in monotherapy was found, which could be attributed to the aim of promoting patients' adherence to treatments and reducing side effects.

This study was limited by a small sample size and short sampling period.

CONCLUSION

The characteristics of the patients in the two CAPSIs in SBC had a different epidemiological profile from the CAPSI evaluated in previous studies. In CAPSI, such as in this study, in which complaints of aggression are the most prevalent, diagnoses of ASD and depressive disorders are more common. This situation differs from most CAPSI that present school complaints as the most prevalent, in which diagnoses of ADHD and conduct disorders are likely to be more frequent. Therefore, further studies of the clinico-epidemiological profile of CAPSIs are required. The epidemiological profile of each CAPSI should guide the implementation of human and structural resources targeting the most prevalent complaints and diagnoses.

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First-line biologic therapy with tumor necrosis factor inhibitors for psoriatic arthritis: a prospective observational study

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ABSTRACT

BACKGROUND: Psoriatic arthritis (PsA) is a chronic inflammatory disease that affects multiple joints. It is associated with psoriasis and treated with synthetic and biologic drugs.

OBJECTIVE: The objective of this study was to assess the outcomes of patients who received biologic therapy with tumor necrosis factor (TNF) inhibitors in terms of effectiveness, safety, functionality, and quality of life.

DESIGN AND SETTING: A prospective observational study was performed at a single center in Belo Horizonte, Brazil.

METHODS: Patients with PsA who received their first TNF inhibitor treatment were followed up for 12 months. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Clinical Disease Activity Index (CDAI). Functionality was measured using the Health Questionnaire Assessment (HAQ), and quality of life was evaluated using the European Quality of Life Five Dimensions (EQ-5D). Multiple linear regression was used to identify predictors of the clinical response at 12 months.

RESULTS: A total of 143 patients treated with adalimumab or etanercept were evaluated. Most of the clinical measures were significantly improved at 12 months. However, 31%–51% of the patients did not achieve good clinical control. No differences were observed between adalimumab and etanercept, except for poor functionality at 12 months among patients treated with etanercept. The main predictors of a worse clinical response were female sex, etanercept use, poor functionality, or lower quality of life at baseline. The main adverse reactions were alopecia, headache, injection site reaction, sinusitis, flu, dyslipidemia, and infections.

CONCLUSION: TNF inhibitor therapy was effective and safe. However, despite improvements in clinical measures, most patients did not achieve satisfactory control of the disease.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease that is usually seronegative for rheumatoid factor and has diverse clinical manifestations.[1] The different clinical features are challenging for physicians in terms of diagnosis and treatment.[1,2] Delayed diagnosis of PsA is associated with irreversible damage, and streamlined early treatment with disease-modifying antirheumatic drugs (DMARDs) can slow disease progression and improve physical function and quality of life.[1,3]

In Brazil, the treatment of PsA is covered by the Unified Health System (Sistema Único de Saúde, SUS), a national public health system subsidized by taxes, which provides primary, outpatient, and hospital care in addition to drugs and other health technologies for comprehensive treatment.[4,5] Around 210 million people are covered, of which 75% are exclusively assisted by the SUS. PsA patients are attended to by doctors from the public and private sectors (SUS and non-SUS). Their medication is covered by the SUS, health plans, or out-of-pocket expenses. However, the supply of biologic DMARDs (bDMARDs) is almost entirely realized by SUS pharmacies because of the high cost of these drugs to PsA patients.[4,5]

The drugs available through the SUS include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and conventional synthetic, biologic, and target-specific synthetic DMARDs.[6] NSAIDs and glucocorticoids are usually used to control disease symptoms, such as pain and swelling. DMARDs are immunosuppressive and immunomodulatory agents that can modify

the natural course of the disease, including delays in clinical or radiographic progression. bDMARDs, including tumor necrosis factor-alpha inhibitors (adalimumab, etanercept, infliximab, golimumab, and certolizumab) and interleukin-17 inhibitors (secukinumab), are usually prescribed after the failure of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[6]

The advent of tumor necrosis factor inhibitors (TNFis) has resulted in a substantial improvement in the treatment of PsA refractory to csDMARDs, and the efficacy of these agents has been demonstrated in randomized controlled trials.[7] However, limited head-to-head studies have compared the clinical efficacy of these drugs.[8]

Despite the benefits observed with biologic TNFis in the last few years, approximately 40% of patients discontinued treatment in the 12 months of follow-up. In addition, the substantial economic impact of TNFi therapy on health systems was observed, accounting for 90% of the PsA treatment cost.[4] Therefore, a real-world evaluation is warranted.

Observational studies are instrumental in complementing the scientific evidence of efficacy and safety provided by randomized controlled trials.[9] Furthermore, in the absence of head-to-head randomized controlled trials comparing two or more bDMARDs, observational studies with a common drug comparator can be used to evaluate and compare these drugs in clinical practice.[10]

OBJECTIVE

The objective of this study was to evaluate the outcomes of patients diagnosed with PsA in Brazil who received TNFi therapy in terms of effectiveness, functionality, quality of life, and safety.

METHODS

Type of study, patient characteristics, and data collection

An open, prospective, observational study of patients with PsA treated through the SUS was performed at a single center in Belo Horizonte from January 2012 to July 2019. This center is responsible for supplying drugs to approximately 320 patients with PsA.

The eligibility criteria were 18 years of age or older, diagnosis of PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR), and use of TNFis.[11] Patients treated with golimumab and infliximab were excluded due to the small number of patients. Furthermore, patients who were unable to visit the pharmacy regularly to receive their medications were excluded from the study.

Follow-up started on the first dispensation of TNFis, and the patients were reassessed at approximately 6 and 12 months.

A standardized research form was used, which was developed and tested previously. Sociodemographic characteristics, such as age, sex, education, marital status, and self-declared ethnicity, were recorded. Data on disease duration, current and previous PsA drug use, comorbidities, adverse reactions, disease activity, functionality, and quality of life were also collected. Interviews were conducted face-to-face with the patients by a team of researchers comprising pharmacists and graduate and undergraduate pharmacy students. The researchers were trained in a specialized rheumatology center where it was possible to follow up on the care of patients with PsA.

The Research Ethics Committee of the Universidade Federal de Minas Gerais (UFMG) approved this study (opinion number 0069.0.203.000-11) on May 26, 2011. All of the patients signed a consent form.

Outcomes

Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Clinical Disease Activity Index (CDAI).[12-15] The BASDAI assesses axial involvement, and the CDAI evaluates peripheral involvement. Functionality was measured using the Health Questionnaire Assessment (HAQ), and quality of life was evaluated using the European Quality of Life Five Dimensions Questionnaire (EQ-5D); both have versions that have been validated for Brazil.[12,13]

A good clinical response (GCR) was defined as a BASDAI < 4 and a CDAI ≤ 10. Additionally, the outcome for a BASDAI reduction ≥ 2 points or 50% was assessed.[13,14] A minimal clinically important difference (MCID) was defined as an improvement of ≥ 0.05 for quality of life according to the EQ-5D and a reduction of ≥ 0.35 for HAQ functionality.[16,17] The GCR and MCID were defined as the proportion of clinical response. Subgroup analysis was performed to verify the effect of the main comorbidities on disease activity, functionality, and quality of life. The occurrence of drug adverse reactions was self-reported.

Statistical analysis

The sample size was estimated considering the MCID for the HAQ and EQ-5D outcomes for paired samples (baseline and end of follow-up). A difference of 0.35 ($\Delta = 0.35$), a standard deviation of 0.70, a correlation between paired samples of 0.60, a statistical significance of 5% ($\alpha = 0.05$), and a power test of 80% ($\beta = 0.80$) were used for the HAQ outcome, which indicated a minimal sample of 28 patients per group, for a total of 56 patients. A difference of 0.05 ($\Delta = 0.05$), a standard deviation of 0.15, a correlation between paired samples of 0.60, a statistical significance of 5% ($\alpha = 0.05$), and a power test of 80% ($\beta = 0.80$) were used for the EQ-5D outcome, which indicated a minimal sample of 59 patients per group, for a total of 118 patients. Therefore, a sample of 118 patients was considered for this study.

Descriptive analysis was performed using the frequency distribution, mean, and standard deviation. An independent t-test for two independent groups and a paired t-test for two paired groups

were used for continuous variables. Pearson's chi-squared test was used for categorical variables.

Multiple imputations addressed missing data. A predictive mean matching method was adopted considering the monotonic pattern observed in the missing data; missing data at 6 months were also missing at 12 months.[18,19]

Nearest neighbor matching was used to evaluate the comparative effectiveness, functionality, and quality of life between TNFis.[20] Therefore, patients were paired according to similar characteristics at baseline. A significance level of 5% was used for comparative analysis.

Multiple linear regression with a 95% confidence interval (CI) was used to identify predictive factors for clinical response according to the CDAI, BASDAI, HAQ, and EQ-5D at 12 months of follow-up. Sex, age, education, marital status, ethnicity, disease duration, comorbidity, disease activity, functionality, quality of life, bDMARD use, NSAID use, csDMARD use, and glucocorticoid use were considered independent variables. A significance level of 5% ($P < 0.05$) was used for these analyses.

Statistical analyses were performed using Stata version 16.1 (StataCorp, College Station, Texas, United States).

RESULTS

Baseline characteristics

A total of 143 PsA patients were included. Loss to follow-up (withdrawal from the study) was observed for 21 patients (14.7%) at 6 months and 92 patients (35.7%) at 12 months. Lack of effectiveness (23.1%) and adverse reactions (14.1%) were the main causes of the loss to follow-up.

The mean age was 51.13 years (standard deviation = 12.23), and the mean duration of the disease was 5.09 years (6.90). Most patients were white (53.8%), married (61.0%), and educated up to the high school level (69.5%) (**Table 1**). Of the 143 patients, 91 patients (63.6%) were treated with adalimumab, and 52 patients (36.3%) were treated with etanercept. In addition, 58 (40.6%), 34 (23.8%), and 36 (25.2%) patients concomitantly used csDMARDs, NSAIDs, and glucocorticoids, respectively. At baseline, the mean CDAI, BASDAI, HAQ, and EQ-5D scores were 22.79 (16.29), 5.38 (2.42), 1.22 (0.73), and 0.65 (0.18), respectively (**Table 1**).

The main comorbidities reported were hypertension (n = 43; 30.1%), dyslipidemia (n = 34; 23.8%), depression (n = 28; 19.6%),

Table 1. Baseline sociodemographic and clinical characteristics of psoriatic arthritis patients

Variable	Adalimumab (91)	Etanercept (52)	Total (143)	P value
Sex, n (%)				0.386
Female	51 (56.0)	33 (63.5)	84 (58.7)	
Male	40 (44.0)	19 (36.5)	59 (41.3)	
Age, mean (SD)	50.92 (11.89)	51.50 (12.90)	51.13 (12.23)	0.787
Duration of disease, mean (SD)	5.36 (7.27)	4.61 (6.25)	5.09 (6.90)	0.532
Ethnicity, n (%)				0.92
White	48 (52.8)	29 (55.8)	77 (53.8)	
Brown	31 (34.1)	16 (30.8)	47 (32.9)	
Black	12 (13.2)	7 (13.5)	19 (13.3)	
Marital status, n (%)				0.162
Single	17 (19,1)	17 (32.7)	34 (24.1)	
Married	59 (66.3)	27 (51.9)	86 (61.0)	
Other	13 (14.6)	8 (15.4)	21 (14.9)	
Education, n (%)				0.066
≤ Elementary	27 (30.3)	12 (23.1)	39 (27.7)	
> Elementary to ≤ high school	41 (46.1)	18 (34.6)	59 (41.8)	
Undergraduate	21 (23.6)	22 (42.3)	43 (30.5)	
Comorbidity, n (%)	68 (74.7)	40 (76.9)	108 (75.5)	0.769
Concomitant csDMARDs, n (%)	43 (47.2)	15 (28.9)	58 (40.6)	**0.031**
Concomitant NSAIDs, n (%)	25 (27.5)	9 (17.3)	34 (23.8)	0.170
Concomitant glucocorticoids, n (%)	27 (29.7)	9 (17.3)	36 (25.2)	0.101
CDAI, mean (SD)	23.74 (16.64)	21.13 (15.69)	22.79 (16.29)	0.357
BASDAI, mean (SD)	5.21 (2.46)	5.68 (2.39)	5.38 (2.42)	0.266
HAQ, mean (SD)	1.23 (0.74)	1.21 (0.71)	1.22 (0.73)	0.873
EQ-5D, mean (SD)	0.64 (0.18)	0.66 (0.18)	0.65 (0.18)	0.507

n = number of patients; SD = standard deviation; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal anti-inflammatory drugs; CDAI = Clinical Disease Activity Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions.

and diabetes mellitus (n = 22; 15.4%). Other reported comorbidities were gastritis (n = 11; 7.7%), hypothyroidism (n = 10; 7.0%), anxiety (n = 9; 6.3%), and fibromyalgia (n = 6; 4.2%).

Effectiveness, functionality, and quality of life

All clinical measures of disease activity, functionality, and quality of life were significantly improved at 6 and 12 months compared with the baseline among patients treated with adalimumab (P < 0.001). Most clinical measures also showed a statistically significant reduction at 6 and 12 months compared with the baseline among patients treated with etanercept, except for a borderline value in the HAQ at 12 months (**Table 2** and **Figure 1**).

Following nearest neighbor matching, no differences were observed between TNFis in a comparative effectiveness analysis, except for poor functionality according to the HAQ at 12 months among patients treated with etanercept compared with those treated with adalimumab (**Table 3**).

In terms of the proportion of GCR and MCID, minimal differences were observed between TNFis. The overall GCR was 49.0% according to the CDAI and 69.2% according to the BASDAI at 12 months. The overall MCID was 59.4% according to the HAQ and 63.6% according to the EQ-5D at 12 months. The results for each TNFi are presented in **Table 4**.

Comorbidities

The main comorbidities were hypertension (n = 62; 30.2%), dyslipidemia (n = 47; 22.9%), depression (n = 37; 18.0%), diabetes (n = 29; 14.1%), gastritis (n = 15; 7.3%), hypothyroidism (n = 13; 6.3%), fibromyalgia (n = 9; 4.4%), anxiety (n = 9; 4.4%), arthrosis (n = 7; 3.4%), obesity (n = 7; 3.4%), and herniated disc (n = 6; 2.9%). According to the CDAI, patients with arthrosis, fibromyalgia, herniated disc, and depression showed higher disease activity at baseline. Of these patients, those with fibromyalgia and depression had a significantly lower clinical response (GCR) at 12 months (P < 0.05) (**Table 5**).

According to the BASDAI, patients with herniated disc, depression, gastritis, fibromyalgia, obesity, and hypothyroidism had higher disease activity at baseline. Of these patients, those with depression, gastritis, and obesity had a significantly lower clinical response (GCR) at 12 months (P < 0.05) (**Table 5**). Furthermore, patients with arthrosis, depression, fibromyalgia, gastritis, and herniated disc had poor functionality and lower quality of life at baseline.

Predictors of clinical response

Predictors of a worse CDAI response were female sex, comorbidities, etanercept use, and poor functionality. Predictors of a

Table 2. Effectiveness, functionality, and quality of life at baseline, 6 months, and 12 months for patients who received TNFi therapy

Variable	CDAI									
TNFi	Baseline		6 months				12 months			
	mean	SD	mean	SD	Δ	P value*	mean	SD	Δ	P value**
Overall	22.79	16.29	13.29	12.94	-9.50	< 0.001	13.45	12.85	-9.35	< 0.001
Adalimumab	23.74	16.64	13.42	12.77	-10.32	< 0.001	11.73	11.00	-12.01	< 0.001
Etanercept	21.13	15.69	13.07	13.35	-8.06	< 0.001	16.44	15.24	-4.69	0.033
Variable	**BASDAI**									
TNFi	**Baseline**		**6 months**				**12 months**			
	mean	**SD**	**mean**	**SD**	**Δ**	**P value***	**mean**	**SD**	**Δ**	**P value****
Overall	5.38	2.42	3.59	2.42	-1.79	< 0.001	3.06	2.08	-2.32	< 0.001
Adalimumab	5.21	2.44	3.67	2.40	-1.54	< 0.001	2.82	2.07	-2.39	< 0.001
Etanercept	5.68	2.39	3.45	2.47	-2.23	< 0.001	3.47	2.03	-2.21	< 0.001
Variable	**Functionality (HAQ)**									
TNFi	**Baseline**		**6 months**				**12 months**			
	mean	**SD**	**mean**	**SD**	**Δ**	**P value***	**mean**	**SD**	**Δ**	**P value****
Overall	1.22	0.73	0.87	0.68	-0.35	< 0.001	0.82	0.62	-0.40	< 0.001
Adalimumab	1.23	0.74	0.79	0.63	-0.44	< 0.001	0.69	0.55	-0.54	< 0.001
Etanercept	1.21	0.71	1.01	0.73	-0.20	0.020	1.05	0.67	-0.16	0.055
Variable	**Quality of life (EQ-5D)**									
TNFi	**Baseline**		**6 months**				**12 months**			
	mean	**SD**	**mean**	**SD**	**Δ**	**P value***	**mean**	**SD**	**Δ**	**P value****
Overall	0.65	0.15	0.73	0.18	0.09	< 0.001	0.76	0.15	0.11	< 0.001
Adalimumab	0.64	0.18	0.74	0.18	0.10	< 0.001	0.77	0.15	0.13	< 0.001
Etanercept	0.66	0.18	0.73	0.18	0.07	0.003	0.73	0.17	0.07	0.004

TNFi = tumor necrosis factor inhibitor; CDAI = Clinical Disease Activity Index; SD = standard deviation; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions.

*P value based on 6 months versus baseline; **P-value based on 12 months versus baseline.

worse BASDAI response were etanercept use and poor functionality, whereas a higher quality of life was associated with a better BASDAI response. Predictors of poor functionality according to the HAQ were female sex, lower education level, and etanercept use, whereas the higher quality of life and marriage were associated with better functionality. In addition, poor functionality was a predictor of lower quality of life according to the EQ-5D (**Table 6**).

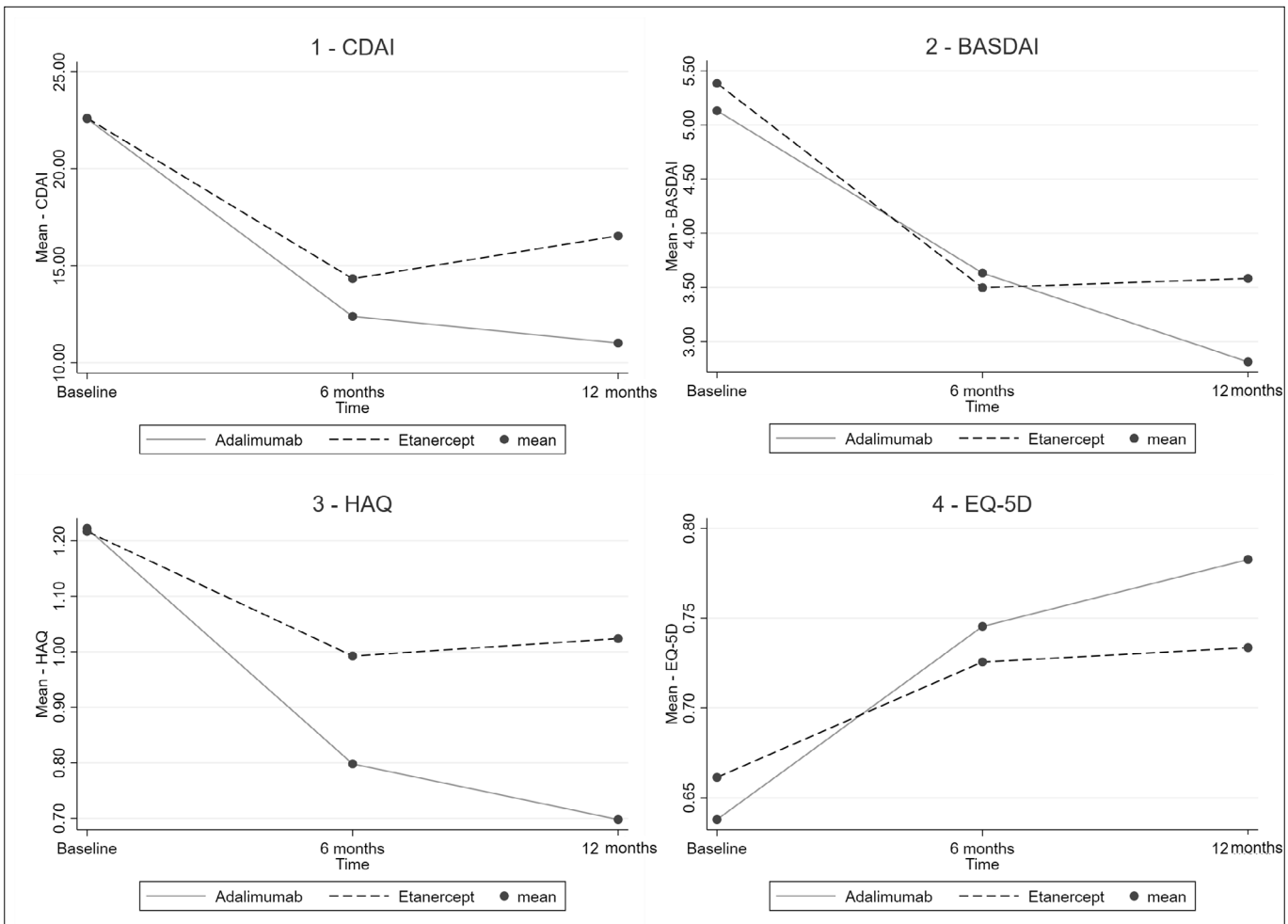
Safety

The main adverse reactions reported by the patients were alopecia, headache, injection site reaction, sinusitis, flu, dyslipidemia, and infections. No cases of tuberculosis and herpes zoster were reported (**Table 7**).

DISCUSSION

This comparative study was conducted to evaluate the outcomes of PsA patients treated with adalimumab or etanercept in a real-world setting in Brazil. Loss to follow-up was 14.7% at 6 months and 35.7% at 12 months of follow-up, similar to the rates of medication non-persistence in Brazil.[21] Lack of effectiveness and adverse reactions were the main causes of the loss to follow-up, as described in other studies.[22-24] Although adverse reactions contributed to discontinued follow-up, the use of TNFis can be considered safe with manageable adverse reactions.[25]

Most clinical measures of disease activity, functionality, and quality of life were significantly improved at 6 and 12 months. A recent network meta-analysis reported the efficacy and acceptable safety profile of bDMARDs for PsA.[26] Overall, TNFis could improve the signs and symptoms of articular and cutaneous involvement in addition to patient functionality and quality of life.[25-27] Oliveira Junior et al. reported a clinical improvement in the quality of life regardless of the biologic therapy (monotherapy or combination) of patients with rheumatic diseases, including PsA. Most of the participants showed a significant clinical improvement in quality of life after 6 and 12 months of follow-up.[28]



CDAI = Clinical Disease Activity Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions.

Figure 1. Disease activity, functionality, and quality of life at baseline, 6 months, and 12 months for patients treated with adalimumab or etanercept.

Several comparative observational studies have been conducted for PsA and reported no differences in the effectiveness of adalimumab and etanercept, except for some outcomes such as lower medication persistence with etanercept.[4,21,24,25,29] In our study, patients treated with adalimumab showed a greater improvement in functionality at 12 months. In addition, despite no significant differences in other outcomes, better results were obtained for disease activity and quality of life when adalimumab was administered.

In Brazil, etanercept was considered a cost-effective option in comparison to adalimumab in the past owing to its lower cost and effectiveness.[30] However, currently, adalimumab is more cost-effective than etanercept and continues to offer some benefits, making it a cost-effective drug.[4,31]

Table 3. Comparative effectiveness of TNFi therapy analyzed by nearest-neighbor matching

Outcome	Period	ATE (SE)	P value
CDAI	6 months	-1.69 (2.61)	0.518
CDAI	12 months	4.37 (2.61)	0.094
BASDAI	6 months	-0.53 (0.47)	0.256
BASDAI	12 months	0.72 (0.42)	0.083
HAQ	6 months	0.18 (0.14)	0.199
HAQ	12 months	0.31 (0.12)*	0.008*
EQ-5D	6 months	-0.01 (0.03)	0.855
EQ-5D	12 months	-0.04 (0.03)	0.191

TNFi = tumor necrosis factor inhibitor; ATE = average treatment effect; SE = standard error; CDAI = Clinical Disease Activity Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions.
Balance variables: conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, education, and marital status ($P < 0.20$ at baseline).
*$P < 0.05$.

Comorbidities, functional disability, and quality of life at baseline have been reported as predictive factors of the EQ-5D response at 12 months of follow-up.[28] In this study, poor functionality at baseline was predictive of worse CDAI response. Studies have reported that better functionality is associated with a lower level of pain and structural damage and better work productivity, contributing to a good clinical response according to the CDAI.[32,33] Overall, some sociodemographic and clinical factors, such as the patient's sex, marker levels, and clinical characteristics at baseline, are predictive of poor disease control over time.[34]

Despite the observed reduction in disease activity, approximately 30–50% of the patients did not achieve adequate control of PsA. A previous study reported that 45% of patients with PsA discontinued biologic therapy in the first year.[4] Similar results have also been obtained for other rheumatic diseases.[28,35-37] Subgroup analysis showed that patients with depression, fibromyalgia, and other comorbidities had higher disease activity in addition to poor functionality and lower quality of life at baseline. Moreover, patients with these conditions had more difficulty in achieving good control of PsA. A recent study showed that comorbidities, such as depression, fibromyalgia, obesity, and hypothyroidism, negatively affected the quality of life of patients with PsA, reducing the utility score up to 0.20.[38]

Some factors that could influence the treatment response include immunogenicity and patient preferences, which could result in a reduced clinical response.[39,40] Patients have been found to prefer oral over injectable administration and home over hospital administration.[40,41] These factors could affect the effectiveness of TNFis. Another factor that could influence biologic therapy is the storage of these drugs. A recent study showed that more than 80% of patients do not maintain

Table 4. Proportion of patients who achieved a good clinical response and minimal clinically important difference at 6 and 12 months for each TNFi

Variable		Adalimumab (91)	Etanercept (52)	TNFi total (143)	P value
Outcome	**Period**	**n (%)**	**n (%)**	**n (%)**	
CDAI	6 months	45 (49.4)	26 (50.0)	71 (49.6)	0.950
CDAI	12 months	47 (51.6)	23 (44.2)	70 (49.0)	0.393
BASDAI*	6 months	51 (56.0)	33 (63.5)	84 (58.8)	0.386
BASDAI*	12 months	67 (73.6)	32 (61.5)	99 (69.2)	0.132
BASDAI**	6 months	43 (47.2)	30 (57.7)	73 (51.0)	0.230
BASDAI**	12 months	53 (58.2)	30 (57.7)	83 (58.0)	0.949
HAQ	6 months	55 (60.4)	23 (44.2)	78 (54.6)	0.061
HAQ	12 months	59 (63.7)	27 (51.9)	85 (59.4)	0.166
EQ-5D	6 months	54 (59.3)	28 (53.8)	82 (57.3)	0.523
EQ-5D	12 months	62 (68.1)	29 (55.8)	91 (63.6)	0.139

TNFi = tumor necrosis factor inhibitor; CDAI = Clinical Disease Activity Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions.
*BASDAI < 4 points; **BASDAI reduction of 50% or ≥ 2 points.

Table 5. Disease activity, functionality, and quality of life according to comorbidities: subgroup analysis

Comorbidity		CDAI				BASDAI				HAQ			EQ-5D		
		Baseline Mean (SD)	12 months Mean (SD)	P value	GCR (%)	Baseline Mean (SD)	12 months Mean (SD)	P value	GCR (%)	Baseline Mean (SD)	12 months Mean (SD)	P value	Baseline Mean (SD)	12 months Mean (SD)	P value
Anxiety	no	23.20 (17.15)	13.59 (12.34)	< 0.001	48.0	5.25 (2.52)	3.28 (2.14)	< 0.001	63.3	1.23 (0.70)	0.84 (0.59)	< 0.001	0.65 (0.18)	0.75 (0.16)	< 0.001
n = 9	yes	14.64 (8.48)	16.75 (15.10)	0.729	44.4	5.36 (1.97)	3.36 (1.97)	0.015	88.9	0.97 (0.61)	0.96 (0.65)	0.947	0.68 (0.11)	0.70 (0.15)	0.722
Arthrosis	no	22.34 (16.69)	13.61 (12.56)	< 0.001	48.5	5.24 (2.53)	3.28 (2.14)	< 0.001	63.6	1.20 (0.70)	0.83 (0.60)	< 0.001	0.65 (0.18)	0.75 (0.16)	< 0.001
n = 7	yes	36.57 (19.55)	17.30 (8.77)	0.069	28.6	5.63 (1.15)	3.17 (1.79)	0.043	85.7	1.86 (0.31)	1.26 (0.34)	0.019	0.52 (0.14)	0.72 (0.14)	0.021
Depression	no	21.37 (16.46)	12.38 (11.29)	< 0.001	***53.0****	5.02 (2.44)	3.03 (2.05)	< 0.001	**69.0***	1.14 (0.69)	0.78 (0.60)	< 0.001	0.67 (0.17)	0.77 (0.15)	< 0.001
n = 37	yes	29.36 (17.76)	19.86 (15.48)	< 0.001	***24.3****	6.34 (2.48)	4.42 (2.10)	< 0.001	**43.2***	1.58 (0.64)	1.17 (0.47)	< 0.001	0.53 (0.17)	0.66 (0.16)	< 0.001
Diabetes	no	22.39 (16.58)	13.08 (11.73)	< 0.001	48.9	5.24 (2.41)	3.28 (2.15)	< 0.001	64.2	1.20 (0.68)	0.83 (0.58)	< 0.001	0.65 (0.18)	0.75 (0.16)	< 0.001
n = 29	yes	25.48 (19.10)	17.67 (15.82)	0.03	41.4	5.36 (2.98)	3.28 (1.94)	< 0.001	65.5	1.36 (0.80)	0.98 (0.68)	0.008	0.62 (0.21)	0.77 (0.15)	< 0.001
Dyslipidemia	no	21.86 (16.29)	13.26 (12.11)	< 0.001	48.1	5.24 (2.43)	3.23 (2.17)	< 0.001	63.3	1.19 (0.69)	0.81 (0.59)	< 0.001	0.66 (0.18)	0.76 (0.16)	< 0.001
n = 47	yes	26.08 (18.79)	15.32 (13.52)	< 0.001	46.8	5.32 (2.71)	3.46 (1.98)	< 0.001	68.1	1.31 (0.74)	0.99 (0.59)	0.002	0.60 (0.18)	0.73 (0.15)	< 0.001
Fibromyalgia	no	22.38 (16.85)	13.34 (12.52)	< 0.001	***50.0****	5.22 (2.49)	3.21 (2.12)	< 0.001	65.3	1.20 (0.69)	0.83 (0.60)	< 0.001	0.65 (0.18)	0.75 (0.16)	< 0.001
n = 9	yes	32.52 (16.99)	22.26 (6.53)	0.136	***0.0****	6.06 (2.63)	4.88 (1.44)	0.211	44.4	1.74 (0.69)	1.27 (0.22)	0.058	0.55 (0.18)	0.72 (0.13)	0.039
Gastritis	no	22.44 (17.02)	13.40 (12.14)	< 0.001	49.0	5.18 (2.53)	3.19 (2.11)	< 0.001	**66.3***	1.18 (0.71)	0.82 (0.59)	< 0.001	0.66 (0.18)	0.76 (0.16)	< 0.001
n = 15	yes	27.67 (15.61)	17.94 (15.73)	0.028	33.3	6.24 (1.76)	4.38 (2.05)	0.005	**40.0***	1.66 (0.44)	1.22 (0.49)	0.003	0.53 (0.12)	0.65 (0.17)	0.041
Herniated disc	no	22.62 (16.93)	13.64 (12.50)	< 0.001	48.2	5.21 (2.51)	3.22 (2.10)	< 0.001	64.8	1.21 (0.70)	0.84 (0.60)	< 0.001	0.65 (0.18)	0.76 (0.15)	< 0.001
n = 6	yes	29.68 (17.34)	16.69 (11.06)	0.099	33.3	6.75 (1.45)	5.00 (2.24)	0.022	50.0	1.56 (0.56)	1.17 (0.45)	0.056	0.55 (0.11)	0.57 (0.24)	0.766
Hypertension	no	22.28 (16.62)	13.47 (12.29)	< 0.001	48.2	5.26 (2.50)	3.35 (2.21)	< 0.001	62.9	1.19 (0.69)	0.84 (0.59)	< 0.001	0.66 (0.18)	0.74 (0.16)	< 0.001
n = 62	yes	24.09 (17.74)	14.34 (12.88)	< 0.001	46.8	5.26 (2.51)	3.12 (1.91)	< 0.001	67.7	1.29 (0.73)	0.88 (0.60)	< 0.001	0.63 (0.19)	0.77 (0.14)	< 0.001
Hypothyroidism	no	22.54 (16.84)	13.39 (12.18)	< 0.001	49.5	5.21 (2.51)	3.26 (2.51)	< 0.001	64.1	1.21 (0.71)	0.84 (0.60)	< 0.001	0.66 (0.18)	0.75 (0.16)	< 0.001
n = 13	yes	27.03 (18.65)	18.82 (15.61)	0.063	23.1	6.01 (2.12)	3.61 (1.87)	< 0.001	69.2	1.30 (0.61)	0.99 (0.59)	0.025	0.52 (0.17)	0.74 (0.13)	< 0.001
Obesity	no	22.88 (16.90)	13.44 (12.06)	< 0.001	48.5	5.23 (2.48)	3.24 (2.13)	< 0.001	**66.2***	1.21 (0.70)	0.84 (0.59)	< 0.001	0.65 (0.18)	0.75 (0.16)	< 0.001
n = 7	yes	21.41 (19.38)	21.99 (20.25)	0.903	28.6	6.05 (3.00)	4.28 (1.59)	0.096	**14.3***	1.41 (0.83)	1.19 (0.69)	0.204	0.54 (0.27)	0.74 (0.13)	0.057

CDAI = Clinical Disease Activity Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ = Health Assessment Questionnaire; EQ-5D = European Quality of Life Five Dimensions; GCR = good clinical response (CDAI ≤ 10 and BASDAI < 4).

*P < 0.05.

Table 6. Predictors of effectiveness, functionality, and quality of life at 12 months for bDMARD-naïve patients

CDAI response			
Predictor	**β coefficient**	**CI 95%**	**P value**
HAQ	5.91	3.24; 8.58	< 0.001
Sex (female)	5.39	1.55; 9.24	0.006
Comorbidity (No)	5.00	0.62; 9.37	0.026
TNFi (etanercept)	4.32	0.50; 8.15	0.027
BASDAI response			
Predictor	**β coefficient**	**CI 95%**	**P value**
HAQ	0.94	0.37; 1.50	0.001
EQ-5D	-3.33	-5.65; -1.02	0.005
TNFi (etanercept)	0.74	1.74; 5.87	0.014
HAQ response			
Predictor	**β coefficient**	**CI 95%**	**P value**
EQ-5D	-1.43	-1.88; -0.98	< 0.001
Sex (female)	0.26	0.9; 0.43	0.002
Marital status (married)	-0.22	-0.42; -0.02	0.032
Education			
High school	0.23	0.04; 0.43	0.021
Elementary	0.39	0.17; 0.61	0.001
TNFi (etanercept)	0.38	0.21; 0.56	< 0.001
EQ-5D response			
Predictor	**β coefficient**	**CI 95%**	**P value**
HAQ	-0.09	-0.11; -0.05	< 0.001

bDMARD = biologic disease-modifying antirheumatic drug; CDAI = Clinical Disease Activity Index; CI = confidence interval; HAQ = Health Assessment Questionnaire; TNFi = tumor necrosis factor inhibitor; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D = European Quality of Life Five Dimensions.

Table 7. Main adverse reactions reported at 12 months by psoriatic arthritis patients who received biologic therapy

Adverse reaction	**Adalimumab (91)**		**Etanercept (52)**		**Total (143)**	
	n	**%**	**n**	**%**	**n**	**%**
Alopecia	9	9.9%	6	11.5%	15	9.7%
Headache	6	6.6%	4	7.7%	10	6.5%
Injection site reactions	5	5.5%	4	7.7%	9	5.8%
Sinusitis	4	4.4%	2	3.8%	6	3.9%
Flu	4	4.4%	1	1.9%	5	3.2%
Dyslipidemia	3	3.3%	2	3.8%	5	3.2%
Swelling	3	3.3%	1	1.9%	4	2.6%
Urinary infection	3	3.3%	1	1.9%	4	2.6%
Fungal infection	2	2.2%	2	3.8%	4	2.6%
Nausea	2	2.2%	2	3.8%	4	2.6%
Asthenia	2	2.2%	2	3.8%	4	2.6%
Brittle nails	2	2.2%	1	1.9%	3	1.9%
Dizziness	1	1.1%	1	1.9%	2	1.3%
Rhinitis	1	1.1%	1	1.9%	2	1.3%
Hypertension	2	2.2%	0	0.0%	2	1.3%
Urticaria	2	2.2%	0	0.0%	2	1.3%
Pruritus	0	0.0%	1	1.9%	1	0.6%
Diarrhea	0	0.0%	1	1.9%	1	0.6%
Weight gain	1	1.1%	0	0.0%	1	0.6%
Fever	1	1.1%	0	0.0%	1	0.6%
Others	15	16.5%	9	17.3%	24	15.5%

adequate home storage conditions for biopharmaceuticals. The intrinsic factors of household refrigerators have been suggested to play a role in temperature deviations.[42] The difficulty in the application of biopharmaceuticals by patients should be further investigated.

An important challenge faced by rheumatologists in Brazil is patient access and follow-up, which may be associated with compromised care.[43] Furthermore, the median time to medication access through the SUS for PsA treatment following a medical prescription has been reported to be longer than 2 months.[5] Therefore, additional strategies that can help achieve good disease control should be considered, which may include: (a) improving access to rheumatologists, which reduces the time until consultation and follow-up by a rheumatologist; (b) improving access to multidisciplinary care; (c) discovery of a novel pathway or cellular subset; (d) applying stratification biomarkers to individualize therapy; (e) preclinical intervention; (f) combination therapy with conventional synthetic drugs; (g) lifestyle modification; (h) addressing chronic pain and fatigue.[44]

A strength of this study is that this is the first comparative study carried out in a Brazilian real-life setting. Multiple outcomes were evaluated for patients diagnosed with PsA, which was conducted according to performance guidelines for evaluating incorporated drugs in the SUS to validate clinical and economic outcomes in the Brazilian population. The findings of our Brazilian study could provide useful information for health technology assessment in the SUS.

This study has some limitations. Skin involvement was not evaluated because the Brazilian clinical guidelines for PsA started to consider this manifestation only after the update in 2018.[6] The BASDAI and CDAI are not specific indices for PsA. However, the BASDAI was used by the Brazilian clinical guidelines for PsA until 2018, and the CDAI has a strong correlation with a specific feature of PsA.[6,14] In addition, laboratory and radiological test results were not obtained as they are not required for drug treatment through the SUS. Finally, the method used to select patients was also a limitation as only individuals who visited the health center were eligible to participate in the study. Therefore, more severe cases of PsA may not have been included, and the results should be interpreted and generalized with caution.

CONCLUSION

The study found that TNFi therapy was effective and safe. However, despite improvements in clinical measures, most patients did not achieve adequate control of the disease, mainly those with poor functionality and lower quality of life at baseline and comorbidities, such as depression and fibromyalgia.

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Clinical and epidemiological characteristics and individual experiences of illness in men with COVID-19: mixed method study

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ABSTRACT

BACKGROUND: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, studies have shown that this disease has affected the male population on a significant scale in various parts of the world, making men one of the main risk groups.

OBJECTIVE: To analyze the clinical and epidemiological characteristics and experiences of illness in men with COVID-19.

DESIGN AND SETTING: A mixed sequential-explanatory study with cross-sectional and exploratory-descriptive approaches.

METHOD: Data was collected from a small municipality located in the central-north region of the state of Bahia, Brazil. Primary quantitative data was extracted from compulsory notification forms from 598 men. Qualitative data from individual interviews of 30 men was analyzed by the Discourse of the Collective Subject method.

RESULTS: The findings identified the characterization of reports of suspected and confirmed cases of COVID-19 in men, the organization of the healthcare system, and strategies for the control and combat of COVID-19 directed towards the men of the investigated municipality. They revealed the clinical characteristics based on the collective discourse of men with COVID-19.

CONCLUSION: In men, the individual experience of disease explicitly explains the clinical markers of COVID-19 expressed by the self-reported syndromic approach. Additionally, this understanding also explains the behaviors observed in their search for health care, as well as the adoption of prevention and control measures and therapies recommended by health professionals.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has significantly affected the male population in various parts of the world.[1-4] In countries such as Brazil, the number of cases of the disease in men varies according to municipality.[5-6]

In addition to being the most affected gender, men have the worst clinical outcomes. Among the population that progressed to a picture of severe acute respiratory syndrome (SARS) caused by COVID-19, until the epidemiological period from February 21st to 27th, 2021, 62,613 cases were registered, with 54.5% of these cases comprising men. The most affected age group from this population was between 60 and 69 years, with a total of 24,775 cases (21.6%). Regarding deaths caused by SARS due to COVID-19 in Brazil, during this period, 16,444 (54.3%) were men, with the most affected age group between 70 and 79 years old, with a total of 7,717 (25.5%).[7]

Several reasons have been suggested in the literature for the difference between sexes in the presentation of COVID-19, which indicate that being male is a risk factor for the new disease. Among these reasons, the influence of hegemonic patterns of masculinities was highlighted. This legitimizes the dominant position of men in society, which can contribute to the neglect of health care, and the disregard and disrespect for measures to prevent and control the transmission of SARS-CoV-2.[8,9]

There are also factors related to habits such as smoking, abusive consumption of alcohol and other drugs, sedentary lifestyle, and clinical conditions, such as the presence of chronic diseases which occur more often in men. Moreover, new causes have been recognized with the arrival of

the pandemic, namely hormonal factors related to testosterone[10] and generators of repercussions on sexual and reproductive health,[11] genetic factors of chromosomal origin,[12] and immunological factors[1,3].

Another relevant aspect to be considered that has also been occurring in the context of the pandemic, is that a large proportion of the male population delays searching for healthcare services.[7,9] This resistance to seeking healthcare is necessary for the early detection of COVID-19 infections and leads to increased underreporting and/or late compulsory notification. It also leads to the progression of infections into more severe and complex clinical situations. Moreover, one cannot lose sight of the aspects related to weaknesses in healthcare services and networks, limited healthcare human resources[13] and the presence of barriers to access and sensitize the male population for health promotion and prevention of diseases and avoidance of injuries.[14,15]

When considering the presence of a gap in scientific knowledge in the difference in disease presentation based on sex and gender, and given the clinical and epidemiological context of men with COVID-19, the combination of quantitative and qualitative approaches used in this study is justified. A joint study may contribute to a broader interpretation of the investigated problem, providing better evidence for best practice care for men with COVID-19.

OBJECTIVE

To analyze the clinical and epidemiological characteristics and experiences of illness in men with COVID-19.

METHODS

Research design

A mixed methods study, with sequential-explanatory type from a transverse and analytical study, and an exploratory-descriptive research with a qualitative approach. In this study design, the quantitative approach was developed first and had the greatest weight; that is, it is the priority stage of the research. Next, a qualitative approach of secondary weight and complementary character was developed. Quantitative data were extracted from COVID-19 compulsory notification forms. Individual interviews were conducted at the qualitative stage. Thus, the data collected in the quantitative stage led and directed the data collection of the qualitative stage,[15] especially regarding the details of clinical characteristics and experiences of patients such as the recognition of signs and symptoms, perception of the disease, adherence to therapies and treatment, and apprehension of senses and meanings.

Data collection period

The study population consisted of suspected cases of infection with the COVID-19 in men, notified to the municipal epidemiological surveillance, from February to December 2020.

Selection criteria

Suspected cases of COVID-19 infection were individuals with an acute respiratory condition, characterized by at least two of the following signs and symptoms: fever (even if referred), chills, sore throat, headache, cough, runny nose, olfactory disorders, or taste disturbances.

The study excluded males who passed through the city, were suspected, or were assisted/notified during the data collection period.

Sample

The quantitative sample consisted of 598 men, notified as suspected cases of SARS-CoV-2 infection from February to December 2020. The qualitative sample consisted of 30 men with a confirmed diagnosis of COVID-19 presenting with symptoms. The men included exclusively accessed the Municipal Center for Coping with COVID-19 and sought care. In addition, we sought participants who only accessed the service to ensure greater sample specificity, considering that it is a rural municipality, with habits, customs, and health behaviors that may have influenced the way they experienced the disease. The municipal health department, epidemiological surveillance sector, and participants agreed to access the data contained in the medical records.

Data collection

Data were collected in the municipality of Quixabeira, Bahia, Brazil, from October to December 2020. During this period, the municipality had 598 notified cases, diagnosed using reverse transcription polymerase chain reaction (RT-PCR) (311 cases) or rapid tests (87 cases). At the end of that period, seven cases were still under monitoring, awaiting test results. Of these, 121 cases were positive: 77 (63.6%) were women and 44 (36.4%) were men. The municipality registered three cases of clinical admissions in a reference emergency care unit, one case of hospitalization requiring assistance in the intensive care unit, and no confirmed cases of death during the investigated period.

Data collection was conducted in two stages. The first – the quantitative stage – was based on data from the Municipal Epidemiological Surveillance, obtained via access to primary data from the Ministry of Health records of "compulsory notification forms of suspicious of coronavirus disease 2019 - COVID-19 Flu-like Syndromes." The data were exported from the Google Forms application to an *Excel* spreadsheet, and manipulated for structuring the bank, checking for incompleteness and duplication. In the second stage – the qualitative stage – individual in-depth interviews were conducted with the participants.

The interviews were conducted by a single interviewer researcher and were audio-recorded in a single meeting, with an average duration of 30 minutes. They were previously scheduled under the support of the Epidemiological Surveillance service and the team of the COVID-19 Combat Center of the investigated municipality. Interviews adhered to health protocols and ensured the safety of

the participants and the research team. Additionally, patients were later re-evaluated by a medical professional and given a diagnosis and cure for the disease. Participants were intentionally selected based on the indication of professionals from the Epidemiological Surveillance Service and the municipal COVID-19 Combat Center. An unstructured script was used for the following open questions: Tell us how you experienced the impairment caused by COVID-19? How does COVID-19 manifest clinically? This management was conducted using data surveys in the quantitative stage.

Data processing and analysis

For data collection, notification forms were accessed from the health surveillance department after prior authorization. Then, data from the forms were read, organized, and encoded in a spreadsheet in Microsoft Excel application, version 16.0, developed by Microsoft (Redmond, Washington, United States), and submitted to processing in the Statistical Package for Social Sciences (SPSS) software, version 23.0, developed by the International Business Machines Corporation (IBM) (Nova York, United States).

After collecting the qualitative data, the narratives were read line by line, and the data were systematized and coded with the support of NVIVO12 software developed by QSR International (Melbourne, Australia). COREQ guidelines were followed to ensure the quality of the qualitative data. The analysis of narrative data was performed using the Discourse of the Collective Subject (DCS) technique,[16] which facilitated raising the Key Expressions (KE) and the Central Ideas (CI) of collective representation of the research group on the phenomenon of patient experience with COVID-19.

DCS is a category of exposure to the results of qualitative research, with testimonies as raw material, in the form of one or more synthesis speeches written in the first person of the singular. This method consists of pointing out, from each answer, the KEs, which are the CIs of the discursive content expressed by the interviewees.[16] The data described on the form of a Discourse-Synthesis, first person singular, represent the DCS of the men.

After the analysis of the quantitative and qualitative data, a combination of the data was conducted through the connection and integration of the results. Thus, additional information on the study objectives was identified.

Since this research was conducted in the context of the still-in-progress COVID-19 pandemic, ethical requirements in research were fulfilled, which involved biosafety to preserve the participants and researchers. The interviews were carried out with the researchers duly dressed in compliance with social distancing. The application of the Free and Informed Consent Term was associated with the dispensing of alcohol gel and disposable tissues to access the pens made available by the researchers.

The study was approved by the Research Ethics Committee (CEP) of the Universidade Federal da Bahia (UFBA) under Opinion No. 4,087,611 on June 15, 2020. Furthermore, we obtained authorization from the Municipal Health Department and Municipal Health Surveillance Department of Quixabeira to access notification forms and patient records.

RESULTS

The first part of the results, derived from notifications, describes the clinical and epidemiological characteristics of men with COVID-19. The second part presents data from patient records, relating to clinical and epidemiological features and the control and combat strategies for COVID-19. Finally, the third source of data presents the clinical characteristics from the collective discourse of participants, retrieved from interview audio.

Characterization of reports of suspected COVID-19 cases in men

This study included 515 reports of suspected COVID-19 infections in men living in the municipality. As shown in **Table 1**, most notifications were made by health services in the state itself (98.6%), predominantly men aged 25–59 years (61.9%), mixed race (57.5%), and those who did not work in healthcare (98.6%) **(Table 1).**

As shown in **Figure 1**, there was an increase in the number of notifications from April to August 2020, when the peak in the number of notified cases occurred. From then on, there was an oscillation in the number of suspected cases registered, with an increase during April to August 2020. The increase in the number of confirmed cases followed what happened with the notifications **(Figure 1)**.

Data analysis showed that 20.6% of cases were notified eight days or more after the onset of symptoms, causing delays in the

Table 1. Sociodemographic characteristics of participants suspected of having coronavirus disease 2019 (COVID-19). Brazil, 2020-2021

Variables	n	%
Notifying state		
Bahia	508	98.6
Other states	7	1.4
Age group		
< 12 years	47	9.1
12 to 18 years	25	4.9
19 to 14 years	52	10.1
25 to 59 years	319	61.9
60 years or more	72	14.0
Race/color		
Mixed	296	57.5
White	85	16.5
Black	75	14.6
Yellow	49	9.5
Ignored	10	1.9
Health professional		
Yes	7	1.4
No	508	98.6

Source: Prepared by the authors. Research data.

surveillance process and possibly in the medical care of these patients. As shown in **Figure 2**, there was a delay in notification among patients kept in home care or who died **(Figure 2).**

The results also showed that death occurred in older men (≥ 60 years). The men kept in home care, who were negative for COVID-19, had an average age of 19-24 years. Reports of young teens and adult men who had confirmed COVID-19 infections predominantly progressed to cure **(Figure 3)**.

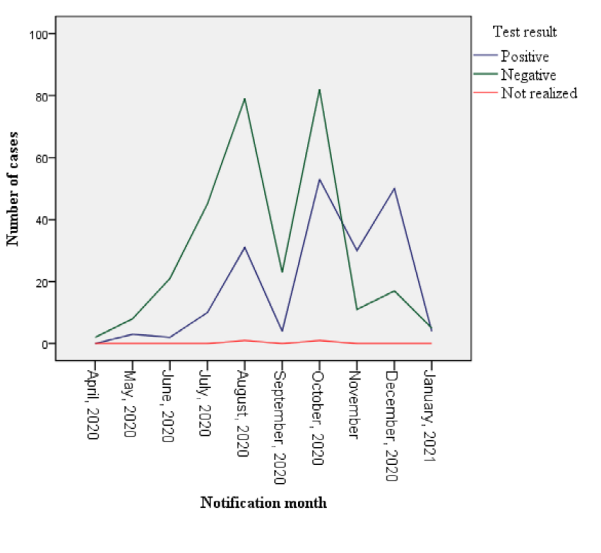
The secondary Qual stage of the study involved data from 30 interviews with participants in the first quantitative stage, which was explained in the form of discourse synthesis. Its respective CIs were framed, theoretically, from the fields/variables that make up the "compulsory notification forms of suspicious of coronavirus disease 2019 - COVID-19 Flu-like Syndromes."

Narrative qualitative data presented in the form of DCS of participants were retrieved to further investigate the clinical and epidemiological male health from the perception of users. The following illustrates a Discourse-Synthesis composed of a CI of representation of the collective as a whole regarding the clinical characteristics and experience of COVID-19.

Discourse-synthesis: Clinical characteristics, from the collective discourse of men with COVID-19

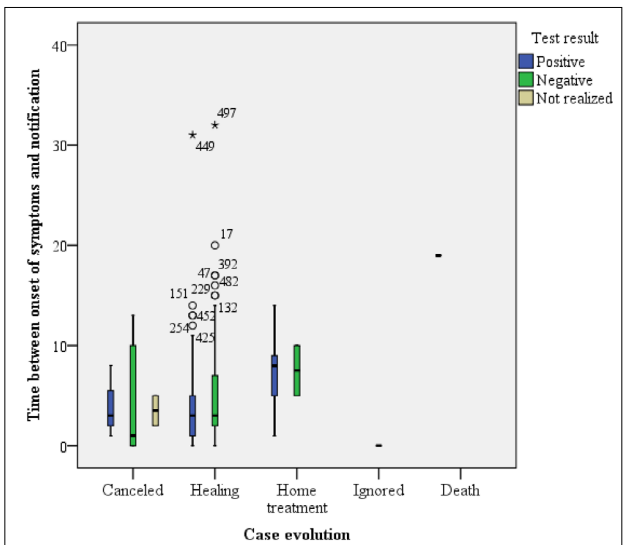
The male collective discourse revealed that the clinical characteristics of COVID-19 are demarcated by the presentation of nonspecific symptoms. However, the disease presented its course with clinical characteristics of classic symptomatologic evolution, progressiveness, and worsening of the health status and clinical picture.

The clinical trajectory of participants involved access to diagnostic and therapeutic intervening resources used by health professionals, such as nursing technicians, nurses, and doctors, of specialized units for the treatment of disease and subsequent obtention to improve and present complications and/or sequelae. To illustrate the integration of the results of the study, **Chart 1** is presented, the theoretical framework of summary statements DCS,



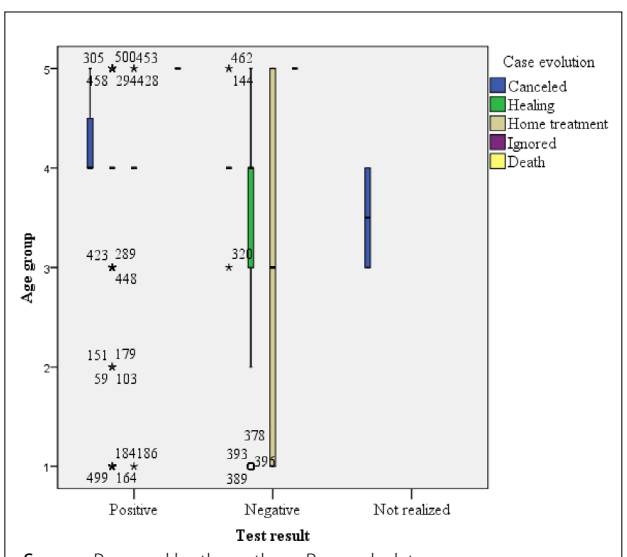
Source: Prepared by the authors. Research data.

Figure 1. Distribution of suspected cases of coronavirus disease 2019 (COVID-19) in men, according to the month of notification and the result of the diagnostic test. Brazil, 2020–2021.



Source: Prepared by the authors. Research data.

Figure 2. Distribution of suspected cases of coronavirus disease 2019 (COVID-19) in men, according to the days between symptom onset and notification, diagnostic test results and case evolution. Brazil, 2020–2021.



Source: Prepared by the authors. Research data.

Figure 3. Distribution of suspected cases of coronavirus disease 2019 (COVID-19) in men, according to age group, diagnostic test result and case evolution. Brazil, 2020–2021.

from the categories of variable of "compulsory notification forms of suspicious of coronavirus disease 2019 - COVID-19 Flu-like Syndromes seized in the first stage (quantitative)."

DISCUSSION

The analysis of clinical and epidemiological characteristics is essential for the planning and execution of strategic and programmatic actions to promote men's health and prevent diseases and conditions, especially in critical and complex contexts, such as pandemics. Although the clinical findings have indicated satisfactory clinical outcomes – reduced mortality and high cure rate, assuming mild forms of the disease in the investigated period, the data indicate a growing number of investigated cases. This represents the Brazilian and international scenario and indicates that men are more vulnerable to infection and suffering from COVID-19 and are worthy of attention from health professionals and managers.

Understanding the clinical and epidemiological characteristics of the male public in research on COVID-19 contributes to the early identification and overview of the reasons that indicate why men are getting sick. The discursive findings reported by men

Chart 1. Integration of quantitative and qualitative results. Brazil, 2020–2021

Variables of form mandatory reporting	Central Idea	Discourse of the Collective Subject (Patient experience)
Sociodemographic characteristics	From territorial description to socioeconomic and labor conditions that relate to contagion	[...] *I live in the town, but I need to work in another town. This made me more exposed to the virus. I think I got infected at work or on public transport. Due to the need to keep working to provide for my family, I had no choices. At work, colleagues didn't always wear a mask and the service didn't care much about sanitary measures.* (DCS of men who have had COVID-19).
Symptomatology	From the perception of discrete clinical manifestations to the symptomatologic intensification	*[...] I started to feel headaches that became stronger than usual. Symptoms started while I was working. I thought it was something normal, but as the days went by, it got worse. I spent an average of seven days with these pains and then I started to feel pain in my stomach. Then came the tiredness, which increased, and then came the flu-like symptoms such as a runny nose, sore throat, cough, and headaches, which lasted for approximately three days. Then I started to feel chills, fever, body aches, tiredness, lack of energy, fatigue, lack of smell and taste and shortness of breath. I had difficulty sleeping because of the change in breathing and the appearance of nausea.* (DCS of men who have had COVID-19).
Comorbidities	From the conception of good health condition to the appearance of comorbidities	[...] *I had good health; I had no disease. I didn't lose a night's sleep, either drink or smoke exaggeratedly. The only change I had was in blood pressure, which I believe is due to my diet.* (DCS of men who have had COVID-19).
Notification	From compulsory notification of the disease to case monitoring	[...] *I suspected Covid-19 and sought the health service. Upon arriving at the health unit, I was referred for an evaluation with a nurse who informed me that she would notify the case. She took me a lot of information about my health status, about the symptoms, when they started, who had contact with me in the past few days and then referred me to undergo the tests. In addition, the nurse told me that I would be monitored by the health team, and in fact this happened, because while I was sick, I received constant calls from the epidemiological surveillance to monitor my situation and to find out if I was complying with the isolation and the care recommended by the health professionals.* (DCS of men who have had COVID-19).
Testing	From initial clinical evaluation to testing for detection of SARS-CoV-2	[...] *I was evaluated by a nursing technician, then by a nurse, and then I took the exam at the COVID-19 care center. Before performing the exam, the nursing technician confirmed some personal information such as my full name, explained to me how the rapid test and the RT-PCR exam in the nasal cavity would be, identified the test with my name and soon after started the procedure, all complying with sanitary requirements.* (DCS of men who have had COVID-19).
Case confirmation	From the receipt of the positive result for COVID-19 to the search for the reasons for the contagion	[...] *I needed to go to the health service to perform the coronavirus detection test and the result was positive. It was a great tension and anguish to have to wait for the result and be stuck inside home [...] I believe I got infected at work because my colleagues didn't wear masks and I started to relax with the measures of prevention.* (DCS of men who have had COVID-19).
Case evolution	From therapeutic interventions offered by professional teams to self-care measures	[...] *after being evaluated by the nurse, I waited to be evaluated by a doctor, who prescribed me tests and medication and provided me with some information on how I should act in face of COVID-19. During this period, I completed the quarantine and remained at home and taking care so that my family would not be infected. We isolated ourselves. We separated personal belongings such as cutlery and towels and start taking care of domestic hygiene. After using the medicines and following the recommendations for other cares, I improved over the days, and on the date determined by the health service I returned to the nurse and doctor to be reassessed and released to return to normal activities and the abandonment of quarantine. I also tried to eat better, drink plenty of water, teas to improve immunity, sleep well, rest, have faith and positive thinking so as not to bring down my psychological condition.* (DCS of men who have had COVID-19).

Source: Prepared by the authors. Research data.

strengthen the understanding of health and disease, the experiences of the patient, the clinical pathways, the therapeutic itineraries, barriers and critical routes adopted by men, and weaknesses in healthcare in the pandemic context, which makes it an effective integration methodology to be employed in the production of evidence for the planning and management of healthcare.

Unlike the findings in our study, the clinical profile of the male population with COVID-19 has indicated a high number of complications resulting from impairment by severe forms of the disease, greater need and length of hospital stay, development of SARS, and death.[17-18] It is necessary to point out that the profile of men surveyed involved the residents of a small town located in the semi-arid Bahia, a region with significant rural extension, which can indicate the presence of protective factors, such as healthy lifestyle habits, reduction of urban exposure, work, and other stressors, as well as the presence of satisfactory health behavior and perception of health.

In our study, young adult men and those with self-reported mixed race/color were the most affected by COVID-19. In the investigated period, vaccination had not yet started in the city, which implies greater exposure of the target population, mainly because in Brazil, the vaccination schedule for COVID-19 includes the young adult population at non-priority levels. Regarding this difference in the clinical-epidemiological profile, epidemiological bulletins in Brazil pointed out in 2020 the impairment of older men, especially in cases of SARS.[17]

However, a focused study had already shown a growing number of severe infections in younger men with an average age of 40 years[19] in countries like India.[20] From 2021, the clinical profile in Brazil began to show a growing number of young men affected by COVID-19 and more severe forms of the disease, especially with the arrival of new variants into the country.[21]

The work environment and occupational relationship of men who were diagnosed with COVID-19 showed a significant relationship with infection. According to the qualitative findings, this may indicate weaknesses in the adoption of individual and collective protection measures, the low quality of personal protective equipment in work environments, and vulnerabilities in access to work, such as in the use of public transport, in addition to failure of institutional protocols for disease prevention and control, as indicated in the literature on the subject.[22]

Regarding compulsory notification of the disease, the full completion of notification forms is extremely useful in the assessment of groups at higher risk, which could be prioritized in actions to combat and control the epidemic in states and municipalities. Such professional action in health is legally required throughout the Brazilian territory and, through the Epidemiological Surveillance Service, allows the monitoring and follow-up of cases. In addition, it presents a panoramic status of active, suspected, under treatment, cured, and death profiles.

Many small municipalities have greater difficulty carrying out epidemiological surveillance actions because of structural limitations and the small number of professionals involved in the health surveillance system. This can compromise the quality of notifications or lead to underreporting of cases, especially in high-demand situations such as the COVID-19 pandemic.[23]

These potential failures in notification systems may occur at the local or national level, and directly impact the conduct of combating actions and delay the collection of knowledge of epidemics. Whether failures occur as a result of the government, or the management and operation of occupational health teams, they can result in episodes of severe disease proliferation, such as what was seen with the COVID-19 pandemic.[24] The integration of quantitative and qualitative findings indicated the possibility of weaknesses in the response time between the day of symptom onset and mandatory notification, which may contribute to a greater spread of the virus.

The exponential increase in new registrations observed corroborates the high number of new clinical cases, giving COVID-19 the status of high transmissibility, even if the estimates of the basic reproductive number reported in the literature vary widely.[24] Thus, the sustained advance of COVID-19 cases worldwide has been accompanied by the formulation of plans for rapid responses to the spread of the disease, conducted in large part by professional nurses, who develop actions of primary care, epidemiological surveillance in health, and assistance to hospitals, among others.[25]

The direction of COVID-19 prevention and epidemiological control strategies among the male population must consider the sociodemographic profile, such as race/color, social class, and occupation, and clinical profile related to signs and symptoms, complaints, complications and infection pattern.[26] It is necessary to direct more attention specifically to the adult male population, considering that this population is economically active and widely distributed, and, consequently, is more exposed to SARS-CoV-2. Furthermore, according to Brazilian literature, this population has adhered less to preventive health care[27,28]. Even out of the context of high risk for viral transmission, male population was more prevalent in the findings identified in this study.

The increase in the number of home deaths, especially among the elderly, as cited in this study, requires attention from health care managers. It reinforces the importance of ambulatory control of chronic diseases and the need to clarify the safety measures to be adopted by the population regarding the clinical complications unrelated to COVID-19 during the pandemic.

The use of combat strategies focused on health promotion, health education, and communication can be decisive factors in preventing and controlling the spread of SARS-CoV-2 among the male population, considering the pattern of behaviors of greater exposure to the risk of infection, for various reasons. These include construction of masculinity, kind of occupational activity, largest social life in the public environment, incorporated concepts of health and health care, beyond personal beliefs about the health and disease process, social and economic vulnerabilities, level of literacy and health literacy, and

difficulties in accessing health services.[26,27] Such actions also need to ensure awareness of the male population regarding sanitary measures and adherence to daily health care.

Government efforts must be directed towards ensuring the reach of COVID-19 epidemic control, with focal investments that reach men more precisely. For this, actions with an impact on health in the workplace are necessary, massive testing drives in places with larger male populations, expansion of opening hours of health services, and investment in social communication, with a gender focus.

Finally, with satisfactory effects of the use of these joint efforts, it is possible to reduce the economic impact on the national health system, ensuring greater sustainability of the system before a crisis context. In addition, this will guarantee increased survival and a reduction in male mortality by COVID-19 and secondary complications to the disease, reducing the burden of services and health professionals and will in turn ensure an early and safe return of non-essential daily activities and promotion of social welfare, with positive effects influencing the culture of health care.

As a limitation of the study, some of the cases had incomplete information documented in the medical records, and the clinical documentation of the patients was not homogeneous. However, this is a common limitation in analytical studies, considering that data generation is clinically oriented and not systematically oriented.

CONCLUSION

The clinical and epidemiological characteristics of men in the investigation of suspected and confirmed cases of COVID-19 were designed for adult men aged 25 to 29 years, mixed race/color, and who did not work in health care. Compulsory notifications were carried out in the municipality of their residence, with an increase in the period from April to August 2020, representing a peak in notified cases. Fatality and maintenance of home treatment were higher among elderly men, and a progression to cure predominated among adolescent, young, and adult men.

The findings in the data pointed to the causal relations of the COVID-19 infection, contagion and transmission, secondary complications generated by the disease, and combat strategies aimed at the male population in the municipal health network. The individual understanding of the disease explains the clinical markers of COVID-19 expressed by the self-reported syndromic approach as well as the search for healthcare in the public service, the adoption of measures to prevent and control illness, and adoption of the recommended therapies by health professionals.

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Comparison of ultrasonography learning between distance teaching and traditional methodology. An educational systematic review

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Ultrasonography.
Telemedicine.
Education, distance.

AUTHORS' KEYWORDS:
Ultrasound.
Distance learning.
Web-based.
M-learning.
E-learning.

ABSTRACT

BACKGROUND: Use of the web for radiological education is an obvious application. Many computer-based teaching materials have been developed over recent years, and e-learning is becoming increasingly popular in medical schools.

OBJECTIVE: To assess whether the effectiveness of distance-learning and/or e-learning, m-learning and web-based methods are equivalent to traditional methods.

DESIGN AND SETTING: Systematic review of comparative studies of teaching techniques guided by Best Evidence Medical Education.

METHODS: A search was carried out in the MEDLINE, EMBASE, Cochrane Library, Tripdatabase, CINAHL and LILACS online databases in April 2020, for original publications in all languages. The following MeSH terms were used: Ultrasonography; Teleradiology; Telemedicine; Education, Medical; Teaching; and Simulation Training; along with the terms e-learning, m-learning and web-based. All eligible studies were assessed using the Kirkpatrick model and Buckley's quality indicators.

RESULTS: The search in the databases and a manual search resulted in 4549 articles, of which 16 had sufficient methodological quality for their inclusion. From analysis of these data, it was observed that teaching of ultrasonography using telemedicine methods is similar to the traditional method, except for venous access procedures, for which the studies did not show agreement.

CONCLUSION: We found that learning via telemedicine methodologies presents great acceptance among students, besides demonstrating quality similar to the traditional method. Thus, at least at the moment, this has the capacity to serve as an important adjunct in the teaching of ultrasonography.

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INTRODUCTION

Learning is an event consisting of a goal, a training activity and an appraisal.[1] The aim is to have a total instructional experience, associated with the usual descriptors.[1] The method for acquiring further information is not merely a matter of obtaining data (surface learning); additionally, it involves the capacity to interpret it and feasibly do this.[2]

One essential feature of the learning method relates to student motivation.[3] Student motivation involves mutual communications within ambient circumstances, actions and particular aspects of these.[3] This automated manner of learning develops when learners become self-aware administrators of their own motivation and performance, in order to reach the desired goals.[3] Fun is also a meaningful part of learning events and, perhaps, can be one of the principal components, with self-determination, towards achievement of problem-based learning within health-related teaching.[4]

Undergraduate, postgraduate and continuing professional development studies compose medical education.[2] All trainees have their limitations, skills and decision-making capacity.[2] The job of mentors is to provide an atmosphere and resources within which any trainee can develop.[2]

There is a lack of formal teaching time in medical schools dedicated to interpretation of radiological images.[5] This situation is disappointing, given that imaging can be used as a dynamic teaching utility, to demonstrate anatomy, pathology and physiology.[5] Medical students develop the way they learn, but their progression does not always go from duality to multiplicity.[2]

Health-related teaching needs a diversity of elements, comprising institutional, visual, concrete and accurate knowledge.[6] Conventional health-related teaching includes use of books, speeches, pictures

and guidelines.[6] The value of lectures within teaching has been challenged historically, and investigations have revealed that they have insufficient influence on short and, notably, long-term retention, particularly with regard to expositions that last for longer than 20 minutes.[7] Just 20% to 30% of the information imparted in any given session can be put into practice by trainees immediately following the exposition. Moreover, over the subsequent two weeks, 90% of the data is wasted.[7]

Low-cost telemedicine technologies can enable doctors to access expert support, remote procedure guidance and real-time training opportunities, thereby reducing unnecessary transportation costs and improving patient outcomes.[8-11] There are studies in the medical literature that have reported that doctors who were trained remotely over the internet had a good degree of satisfaction with the quality of their training and achieved a quality level in evaluating ultrasound images that was similar to that of doctors who underwent in-person training.[5,12]

OBJECTIVE

The objective of this systematic review was to assess whether the effectiveness of distance-learning and/or e-learning, m-learning and web-based methods, for ultrasonography training, is equivalent to traditional methods.

METHODS

Study model

The reference point for this study was the education-oriented systematic review model for Best Evidence Medical Education (https://www.bemecollaboration.org/). The study was registered on the OpenScience Framework platform (https://osf.io/wn762). This study was considered exempt from formal institutional review by our institutional review board because no human or animal subjects were studied.

Modalities of distance-learning

- Electronic learning (E-learning) is an online educational assistance website that instructs and enables students to enhance specific topics.
- Mobile learning (m-Learning) can be described generically as a modality of e-Learning in which learning takes place through easy-to-handle mobile electronic devices (such as smartphones and tablets, for example).
- A video lesson is a video that presents educational material to a subject.
- A live distance class is an online class at a regularly planned time in which learners work together with their instructor and classmates at the same time on the same days. Homework tasks are then accomplished outside of this dedicated lesson period, just like in in-person lessons.

Search strategy

A systematic search of the literature was carried out on April 16, 2020, in the following online databases: Medline (PubMed); EMBASE; Cochrane Library; LILACS; Tripdatabase; CINAHL; ERIC; and SciELO. Original published articles in any language were sought using the following MeSH terms: Ultrasonography; Distance-learning; Online learning; Teleradiology, Telemedicine; Education, Medical; Medical Education Online; Simulation Training; and Teaching. In addition, the terms e-learning, m-learning and web-based were also used. The reference lists of studies that were included and those of the main reviews on this subject were also evaluated. Manual searches were also carried out in the reference lists. All of these searches are shown in **Table 1.**

The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies that compared the teaching of ultrasonography for healthcare professionals, between traditional methods and electronic means through distance-learning, e-learning, m-learning and web-based learning, were included regardless of their publication status.

There was no language restriction. There was no exclusion for population size or age. There was no funding for this study. The PICO technique (Population, Intervention, Comparison, Outcome) was used to define the question and the development of the research, as follows:

P = Undergraduate health care students; postgraduate trainees; continuous professional development training – independent of the specialties.

I = Distance-learning to teach ultrasonography.

C = Traditional methodology versus distance-learning.

O = Improved ultrasound skills, to achieve an accurate diagnosis

Selection of studies and data extraction

The study selection process was carried out by two independent reviewers and any disagreement was resolved by a third reviewer. The selection of studies was carried out in two stages. In the first stage, the titles and abstracts of the references identified through the search strategy were evaluated and the potentially eligible studies were preselected. In the second stage, a full-text evaluation of the preselected studies was carried out to confirm their eligibility. In cases of disagreement, a third author was consulted. Data extraction was performed using a standardized form. The outcomes analyzed were the score previously established for the training method and the performance of the procedure.

The selection process was carried out through the Rayyan platform (https://rayyan.qcri.org).13

Quality assessment

All eligible studies were assessed using Buckley's quality indicators[14] and the Kirkpatrick training assessment model described

Table 1. Search strategy according to the corresponding database

Database	Search strategy
Cochrane Library	#1: MeSH descriptor: [Ultrasonography] explode all trees #2: MeSH descriptor: [Education, Distance] explode all trees #3: MeSH descriptor: [Teleradiology] explode all trees #4: MeSH descriptor: [Telemedicine] explode all trees #5: MeSH descriptor: [Education, Medical] explode all trees: #6: MeSH descriptor: [Simulation Training] explode all trees #7: MeSH descriptor: [Teaching] explode all tress #8: #1 AND #2 OR #3 OR #4 AND #5 OR #6 OR #7
MEDLINE	#1: "Ultrasonography"[Mesh] OR (Echotomography) OR (Diagnostic Ultrasound) OR (Diagnostic Ultrasounds) OR (Ultrasound, Diagnostic) OR (Ultrasounds, Diagnostic) OR (Sonography, Medical) OR (Medical Sonography) OR (Ultrasound Imaging) OR (Imaging, Ultrasound) OR (Imagings, Ultrasound) OR (Ultrasound Imagings) OR (Echography) OR (Ultrasonic Imaging) OR (Imaging, Ultrasonic) OR (Echotomography, Computer) OR (Computer Echotomography) OR (Tomography, Ultrasonic) OR (Ultrasonic Tomography) OR (Diagnosis, Ultrasonic) OR (Diagnoses, Ultrasonic) OR (Ultrasonic Diagnoses) OR (Ultrasonic Diagnosis) #2: "Teleradiology"[MeSH] OR "Telemedicine"[MeSH] OR (mobile health) OR (health, mobile) OR (health) OR (telehealth) OR (ehealth) OR "m-learning" OR "e-learning" OR "web based" OR "Education, Distance"[MeSH] OR (distance education) OR (distance learning) OR (learning, distance) OR (online learning) OR (learning, online) OR (online education) OR (education, online) OR (online education) OR (correspondence courses) OR (correspondence course) OR (course, correspondence) #3: "Education, Medical"[MeSH] OR (medical education) OR "Simulation Training"[MeSH] OR (training, simulation) OR (interactive learning) OR (learning, interactive) OR "Teaching"[MeSH] OR (training techniques) OR (technique, training) OR (techniques, training) OR (training technique) OR (training technics) OR (technic, training) OR (technics, training) OR (training technic) OR (pedagogy) OR (pedagogies) OR (teaching methods) OR (method, teaching) OR (methods, teaching) OR (teaching method) OR (academic training) OR (training, academic) OR (training activities) OR (activities, training) OR (training activity) OR (techniques, educational) OR (technics, educational) OR (educational technics) OR (educational technic) OR (technic, educational) OR (educational techniques) OR (educational technique) OR (technique, educational) #4: #1 AND #2 AND #3
EMBASE	#1: Echography/exp #2: Online learning/exp OR online education/exp OR teleradiology/exp OR telemedicine/exp OR e learning OR m-learning #3: Medical education/exp OR medical education training/exp OR Simulation training/exp OR Clinical education/exp OR Teaching/exp #1 AND # 2 AND #3
LILACS	#1: mh:"Ultrassonografia"/exp OR (Ultrasonografía) OR (Ultrasonography) OR (Ecografia) OR (Ecotomografia Computador) OR (Sonografia Médica) OR (Ecografia Médica) OR (Tomografia Ultrassônica) OR (Diagnóstico Ultrassom) OR (Imagem Ultrassônica) OR (Imagem Ultrassonográfica) OR (Imagem Ultrassom) OR (Imagem Ultrassom) OR (Ecotomografia) OR (mh:E01.370.350.850$) #2: mh:" Educação a Distância"/exp OR (Educación a Distancia) OR (Education, Distance) (Correspondence Course) OR (Correspondence Courses) OR (Course, Correspondence) OR (Cyberlearning) OR (Distance Education) OR (Distance Learning) OR (Education, Online) OR (Interactive Tele-Education) OR (Learning, Distance) OR (Learning, Online) OR (Online Education) OR (Online Educations) OR (Online Learning) OR (Tele-Education) OR (Teletraining) OR (eLearning) or(mh:I02.195$) OR (mh:SP2.021.167.010.090.030$) OR (mh:SP2.021.172.010.099$) OR (mh:SP2.031.332.030$) OR (mh:SP4.017.047.599$) OR (SP4.127.428.764) OR mh:"Teleradiology"/exp OR (Telerradiología) OR (Telerradiologia) OR (mh:E05.920.700$) OR (mh:H02.010.850.700$) OR (mh:H02.403.840.700$) OR (mh:L01.178.847.652.700$) OR (mh:N04.452.515.825.500$) OR (mh:N04.590.374.800.700$) OR (mh:SP2.021.167.010.090.210$) OR (mh:SP2.031.332.210$) OR (Telemedicine) OR (Telemedicina) OR (mh:H02.403.840$) OR (mh:L01.178.847.652$) OR (mh:N04.590.374.800$) OR (mh:SP2.016.303$) OR (mh:SP2.021.167.010.090$) OR (mh:SP2.031.332$) #3: mh: "Education, Medical"/exp OR (Educación Médica) OR (Educação Médica) OR (Medical Education) OR (mh: I02.358.399$) OR #4: mh: "Simulation Training"/exp OR (Entrenamiento Simulado) OR (Treinamento por Simulação) OR (Interactive Learning) OR (Interactive Learning) OR (Training, Simulation) OR (mh: I02.903.847$) OR mh: "Ensino"/exp OR (Enseñanza) OR (Teaching) OR (Academic Training) OR (Activities, Training) OR (Educational Technic) OR (Educational Technics) OR (Educational Technique) OR (Educational Techniques) OR (Method, Teaching) OR (Methods, Teaching) OR (Pedagogies) OR (Pedagogy) OR (Teaching Method) OR (Teaching Methods) OR (Technic, Educational) OR (Technic, Training) OR (Technics, Educational) OR (Technics, Training) OR (Technique, Educational) OR (Technique, Training) OR (Techniques, Educational) OR (Techniques, Training) OR (Training Activities) OR (Training Activity) OR (Training Technic) OR (Training Technics) OR (Training Technique) OR (Training Techniques) OR (Training, Academic) OR (mh:I02.903$) #4: #1 AND #2 AND #3

Continue...

Table 1. Continuation.

Database	Search strategy
Tripdatabase	(title:Ultrasonography)(title:Teleradiology OR Telemedicine OR Education, Distance OR e-learning OR m-learning OR Online learning) (Education, Medical OR Medical Education Training OR Simulation Training OR Teaching)
CINAHL	#1: (Ultrasonography) #2: (Telemedicine & e-Health) OR (Distance Education) OR (Medical Education Online) #3: (Medical Education) #4: #1 and #2 and #3
ERIC	#1: MeSH descriptor: Ultrasonography #2: MeSH descriptor: Education, Distance #3: MeSH descriptor: Teleradiology #4: MeSH descriptor: Telemedicine #5: MeSH descriptor: Education, Medical #6: MeSH descriptor: Simulation Training #7: MeSH descriptor: Teaching #8: #1 AND #2 OR #3 OR #4 AND #5 OR #6 OR #7
SciELO	#1: MeSH descriptor: Ultrasonography #2: MeSH descriptor: Education, Distance #3: MeSH descriptor: Teleradiology #4: MeSH descriptor: Telemedicine #5: MeSH descriptor: Education, Medical #6: MeSH descriptor: Simulation Training #7: MeSH descriptor: Teaching #8: #1 AND #2 OR #3 OR #4 AND #5 OR #6 OR #7

in BEME Guide No. 8 by Steinert et al.[15] These tools are based on instruments that cover a wide range of methodological issues in studies on evaluation of teaching methodologies.

RESULTS

The search in the databases yielded 5,090 articles. Additionally, seven articles were found through a manual search. After excluding duplicates, 5,048 articles were screened, out of which 61 were evaluated in their entirety; from these, 16 presented sufficient methodological quality for their inclusion (**Figure 1**). The study by Socransky et al.[16] was excluded due to loss to follow-up of over 50% of the initial participants. Hempel et al.[17] was not included because its results from the study phase that were compatible with our inclusion criteria had already been published previously.[7]

Eleven studies evaluated teaching among doctors and/or residents and/or medical school students;[7,18-27] one study conducted in England evaluated teaching among nurses,[28] and four studies carried out in Spain evaluated physical therapy students.[4,29-31]

Regarding methodology, one study was a cross-sectional, randomized study,[28] one was a prospective pseudorandomized study,[25] one was a prospective cohort[19] and three were randomized controlled trials.[4,7,18,20-24,26,27,29-31]

In ten studies, a questionnaire was administered both before and after each teaching technique was applied.[7,18-21,23-25,27-29] In three of these,[19,20,27] a questionnaire was also administered long after the last lesson, as a late assessment of knowledge retention. In three studies, no questionnaire was used;[22,26,30] while in two studies a questionnaire was administered only after the teaching technique.[4,31] In six studies, teaching of the FAST ultrasound technique (directed ultrasound in trauma cases),[24,25] or structures included in this,[28] was evaluated; or point-of-care was evaluated.[7,21,27]

One study assessed thoracic structures,[19] and one was specifically directed to pneumothorax.[20] Three studies evaluated interventions: venous access,[18] arterial access[22] and intravenous central catheter.[26] Five studies evaluated the teaching of structures of the musculoskeletal system.[4,23,29-31] Five studies did not involve any practical evaluation, and their results were based only on questionnaires carried out after applying the teaching technique.[18,19,23-25]

Arroyo-Morales et al.[31] conducted a randomized clinical trial to evaluate the learning of knee ultrasound therapy among 44 students who were divided into two groups: traditional method and textbooks associated with e-learning. At the end of the study, they reported that the two groups obtained similar results in the theoretical evaluation; however, in the practical evaluation with ultrasound, the students in the e-learning group obtained higher-quality images despite taking longer to perform the examination. It should be noted that the students in the e-learning group showed good acceptance of distance-learning.

Bertran et al.[26] also conducted a randomized clinical trial, in which they evaluated 43 residents in anesthesiology regarding

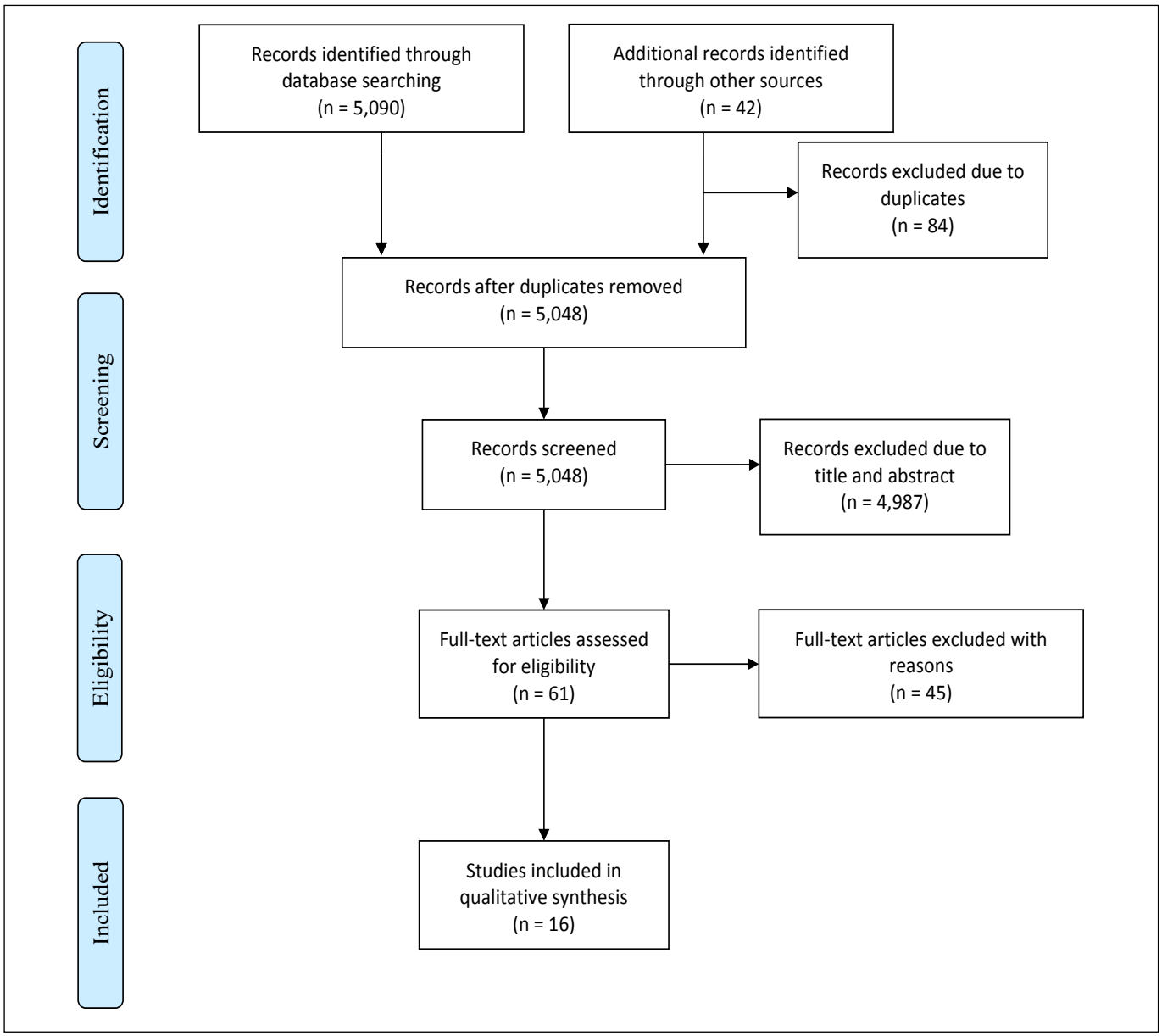

Figure 1. PRISMA flow diagram.

positioning of the central venous catheter guided by ultrasound. They concluded that the residents who had had a video lesson showed better results than those who had had a classroom lesson.

Ten nurses participated in a randomized comparative cross-sectional study by Brisson et al.[28] in which they were learning about the Morrison space. The subjects were divided into two groups: telemedicine and face-to-face group (classroom lesson). At the end of the study, teaching by means of telemedicine proved to be equivalent to classroom lessons for acquiring the practical skill of ultrasound, and this was achieved within similar times.

In a randomized clinical trial by Cantarero-Villanueva,[30] teaching of lumbopelvic ultrasonography was evaluated among 44 physiotherapy students. It was concluded that the e-learning group showed better results than the control group, which used books, and that this could be an effective adjunctive strategy for teaching.

Chenkin et al.[18] conducted a randomized clinical trial in which only theoretical ultrasonography was assessed, with no evaluation of ultrasound practice, among 21 emergency department doctors and residents. They found that the group that received an internet-based tutorial was at least as effective as the group who had attended an in-person teaching lecture on ultrasound-guided venous access.

Furthermore, in the prospective cohort study by Cuca et al.,[19] no assessment of ultrasonography practice was conducted. There were only assessments via questionnaires regarding thoracic structures in ultrasonography, including two post-tests. That study evaluated 75 doctors and medical students and it was found that teaching via e-learning showed results that were similar to those of the traditional method, including through a survey conducted two weeks after the teaching, which evaluated the retention of information.

In a randomized clinical trial by Edrich et al.,[20] 138 anesthesiologists were assessed. They were divided into three groups: a group without instruction, a group with classroom instruction and a group that received instruction through telemedicine. It was concluded that teaching via telemedicine provided results that were similar to those through the traditional methodology, including in a questionnaire administered four weeks after the teaching, to evaluate the retention of information.

Fernández-Lao et al.[29] carried out a randomized clinical trial among 49 physiotherapy students. They concluded that the group with m-learning showed better positioning and handling of the transducer, and patient positioning, than the group with traditional methodology for shoulder ultrasound assessment.

Haskins et al.[21] evaluated 18 anesthesiology residents through a randomized clinical trial. They found that there was no evidence of difference between the traditional teaching and e-learning groups regarding the learning results or satisfaction, in relation to point-of-care ultrasound. Hempel et al.[7] analyzed 60 medical students from the third year of an undergraduate course in a randomized clinical trial and, like Haskins et al.,[21] found that teaching via e-learning showed results similar to those of the traditional method, regarding point-of-care ultrasonography.

Lian et al.[22] evaluated 30 medical students in three groups: traditional method, e-learning and no previous instruction. Through this randomized clinical trial, they analyzed the teaching of ultrasound-guided vascular access and concluded that the traditional method group achieved significantly better performance than the e-learning group and the uneducated group.

Lozano-Lozano et al. conducted a randomized clinical trial[4] in which the teaching of 105 physiotherapy students for evaluating sports pathological conditions using ultrasound was evaluated. They concluded that the m-learning group achieved better patient positioning, transducer management and image adjustment than the traditional method group. However, less time was required for performing the examination through the traditional method.

In a randomized clinical trial by Maloney et al.,[23] theoretical teaching of musculoskeletal ultrasonography was evaluated among 33 radiology residents, without any practical evaluation. It was concluded that the group with the traditional teaching methodology presented a result that was slightly better than that of the e-learning group (less than 5% difference).

Platz et al. carried out two studies analyzing FAST, but without evaluation of ultrasound practice. One was a prospective pseudorandomized trial[25] among 55 doctors and residents of different specialties divided into three groups: traditional method, telemedicine method and no previous instruction. From this, it was concluded that telemedicine teaching presented results similar to those of the traditional method. The other was a randomized clinical trial[24] among 44 emergency and surgery residents, in which it was found that computer-based classes were not inferior to classroom classes among individuals without previous training, for teaching about FAST ultrasound.

Soon et al.[27] carried out a randomized clinical trial on point-of-care ultrasound for pleural effusion and pneumothorax, among 45 pediatric physicians without experience of ultrasound. These subjects were divided into two groups: web classroom and in-person classroom, followed by practice on living models. They concluded that teaching via the web was at least as effective as the usual teaching method, including with regard to evaluation of information retention, among 39 of the study participants, conducted two months later.

A summary of all the studies is presented in **Table 2**.[4,7,18-31]

DISCUSSION

Out of the 16 studies analyzed, nine[7,18-21,24,25,27,28] showed similar results between the traditional and telemedicine groups. It should be noted that in four of these studies[18,19,24,25] there was no practical evaluation; in these, assessments were only made through questionnaires that were administered before and after the teaching intervention.

In five studies,[4,26,29-31] it was demonstrated that distance-learning was superior. Moreover, among these five studies, four[4,29-31] evaluated physical therapy students; in two of these studies, m-learning technology was used,[4,29] while e-learning technology was used in the other two.[30,31] Two studies[22,23] showed that the traditional education group had slightly better results than the telemedicine group that used e-learning technology. We need to contextualize that all these studies were carried out before the COVID-19 pandemic. Although the study by Lozano-Lozano et al.[4] was published in 2020, it was carried out in 2014-2015.

In the present-day world, people acquire information daily through computers and, especially, smartphones. The current generation of students uses electronic media regularly, such that this is an essential part of their daily lives and modifies their brain structures in relation to learning. Thus, 37% of healthcare students have already used an application to develop their professional skills.[32] Therefore, there is a need to adapt teaching methods. In this regard, the use of traditional teaching tools is now out of context.[4]

A study by Gul et al. showed that medical students prefer telemedicine teaching over classroom lesson approaches, with regard

Table 2. Summary of study findings

Study/year	Country	Design	Students	Examination	Intervention	Comparator	Results	Kirkpatrick
Arroyo-Morales et al.[31]/2012	Spain	Randomized clinical trial with questionnaire only after intervention	44 second-year physiotherapy students	Knee	E-learning - ECOFISIO + books and texts	Books and texts	No difference in the theoretical part. Practice: e-learning group took longer, but the image was better. E-learning was better in the questionnaire. The students liked the site.	3
Bertran et al.[26]/2017	France	Randomized clinical trial without questionnaire	43 residents in anesthesiology and intensive care	Positioning of the central venous catheter	Video lesson	Classroom lesson	Residents who had a video lesson showed better results than those who had an in-person class.	2B
Brisson et al.[28]/2015	Canada	Comparative cross-sectional randomized study with questionnaire pre and post-intervention	10 nurses	Morrison space evaluation	Live distance class	Classroom lesson	Telemedicine teaching is equivalent to classroom lesson for the acquisition of practical ultrasound skills and in a similar time.	3
Cantarero-Villanueva et al.[30]/2012	Spain	Randomized clinical trial without questionnaire	44 physiotherapy students	Lumbopelvic region	E-learning - ECOFISIO + books and texts	Books and texts	E-learning can be an effective adjunct strategy in teaching.	3
Chenkin et al.[18]/2008	Canada	Randomized clinical trial with questionnaire before and after intervention	21 participants between staff physicians and residents of the emergency sector	Positioning of the central venous catheter	E-learning	Books and texts	Web-based tutorial was at least as effective as a teaching lecture. Did not carry out a practical evaluation.	2B
Cuca et al.[19]/2013	Germany	Prospective cohort study with a questionnaire before and after intervention, plus a post-intervention sustainability questionnaire two weeks later	75 doctors and medical students	Chest and lungs	E-learning	Classroom lesson	Teaching by e-learning showed results similar to the traditional method. Did not carry out a practical evaluation.	2B
Edrich et al.[20]/2016	United States; Germany; Austria	Randomized clinical trial with a questionnaire before and after intervention, plus a post-intervention retention questionnaire four weeks later	138 anesthesiologists	Chest and lungs	E-learning	Classroom lesson; No teaching technique	Telemedicine teaching showed results similar to the traditional method.	3
Fernández-Lao et al.[29]/2016	Spain	Randomized clinical trial with questionnaire before and after intervention	49 physiotherapy students	Shoulder	M-learning - ECOFISIO + books and texts	Books and texts	The group with m-learning showed better positioning of the patient and transducer and better handling of the probe.	3
Haskins et al.[21]/2018	United States	Randomized clinical trial with questionnaire before and after intervention	18 anesthesiology residents	Point-of-care	E-learning	Classroom lesson	There was no evidence of a difference between traditional teaching groups and e-learning in learning or satisfaction results.	3

Continue...

Ta ble 2. Continuation.

Study/year	Country	Design	Students	Examination	Intervention	Comparator	Results	Kirkpatrick
Hempel et al.[7]/2016	Germany	Randomized clinical trial with questionnaire before and after intervention	60 third-year medical students	Point-of-care	E-learning	Classroom lesson	Teaching by e-learning showed results similar to the traditional method.	3
Lian et al.[22]/2017	Australia	Randomized clinical trial without questionnaire	30 medical students	Positioning of central venous catheter	E-learning	Classroom lesson; No teaching technique	The traditional method group performed significantly better on ultrasound-guided vascular access than those who did not receive training and e-learning.	2B
Lozano-Lozano et al.[4]/2020	Spain	Randomized clinical trial with questionnaire only after intervention	105 physiotherapy students	Sports pathologies	M-learning - ECOFISIO + books and texts	Books and texts	The m-learning group had better patient positioning, transducer handling and image adjustment, but took more time than the control group. The students found it very useful.	3
Maloney et al.[23]/2016	United States	Randomized clinical trial with questionnaire before and after intervention	33 radiology residents	Musculoskeletal	E-learning	Classroom lesson	The difference in quality from traditional to e-learning was small (less than 5%). Did not carry out a practical evaluation.	2B
Platz et al.[25]/2010	Germany	Prospective pseudorandomized study with pre and post intervention questionnaire	64 doctors and residents: anesthesiologists, surgeons, internal medicine specialists and orthopedists	FAST	E-learning	Classroom lesson; No teaching technique	Telemedicine teaching showed results similar to the traditional method. Did not carry out a practical evaluation.	2B
Platz et al.[24]/2011	Germany	Randomized clinical trial with questionnaire before and after intervention	44 emergency and surgery residents	FAST	E-learning	Classroom lesson	Classes on computer are not inferior to school attendance regarding FAST ultrasound. Did not carry out a practical evaluation.	2B
Soon et al.[27]/2020	United States	Randomized clinical trial with a questionnaire before and after intervention, plus a post-intervention retention questionnaire two weeks later	45 pediatric physicians	Point-of-care	E-learning	Classroom lesson	Web-based learning is at least as effective as the usual classroom.	2B

FAST = focused assessment with sonography in trauma.

to the clarity of procedures, the ability to ask questions and the quality of time spent learning, even in relation to surgical procedures.[28,33] The most evident advantage of telemedicine teaching was the better positioning of the patient and handling of the transducer.[4,29] Weber et al.[34] also reported that there was a marked improvement in performance in the early stages of teaching; however, in their study, only the telemedicine group used augmented reality together with telementoring, which could be characterized as a form of bias.

Regarding studies on ultrasound-guided procedures, there was no agreement among the results. Bertran et al.[26] compared teaching of central venous access by video and by the traditional method and concluded that residents who took video classes obtained better results. Lian et al.[22] carried out a similar study comparing the teaching of vascular access by e-learning and the traditional method; they found that the traditional method showed significantly better results. In a randomized clinical trial by Chenkin et al.,[18] a web tutorial teaching venous access was compared with an in-person lecture and it was concluded that the methods were equivalent.

Three studies[4,30,31] from the University of Granada compared e-learning using a cell phone app versus books and texts, and another study[29] compared m-learning versus books and texts. It was concluded from these four studies that the app was at least as effective as a teaching lecture, but that sometimes more time was needed for performing the ultrasound examination. Chenkin et al.[18] reached the same outcome when teaching venous access in the University of Toronto. It needs to be noted that cell phones or tablets do not have present certain issues that relate to books, such as their weight (cell phones and tablets can store many books, independent of their volume and cost). It is also important to remember, on the other hand, that reading books on an electronic device is not always a pleasant experience for the learner and, thus, some students prefer textbooks on paper.

From gathering this data together, we can infer that ultrasound telemedicine teaching methods are similar to the traditional method, except in the case of teaching venous access procedures, for which the studies did not show agreement. The studies demonstrated that telemedicine teaching was effective in relation to teaching thoracic ultrasound, FAST ultrasound, point-of-care and musculoskeletal ultrasound. Hempel et al.[17] reported that use of social networks after the e-learning course presented superior results only when compared with classroom lessons. Student satisfaction compared between teaching methods was also similar, according to the studies evaluated.

The benefits of learning from computers are numerous and include interactivity, novelty, flexible programming, teachers' relief from the need to give repetitive lectures and greater consistency in quality.[16,35,36] The disadvantages of computer-based instruction include the lack of human interaction and guidance, the material presented in a format that is less pleasant to read than in a textbook and the possibility for a student to have unanswered questions.[7,23,35]

Use of the web for radiological education is an obvious application.[37-39] Many computer-based teaching materials have been developed over recent years. M-learning, which is defined as "the ability to access educational resources, tools and materials anywhere, using a mobile device (smartphone)",[4,29,40] along with e-learning, is becoming increasingly popular in medical schools. Guides on the implementation of e-learning have been appearing.[6,18,22,30,31,35,41-44] This method of learning has many organizational advantages over classroom lessons, as follows:[5,7,17,19,20,25,27,30,31,41]

- Environment free from stressful factors and without judgment.
- Live updates.
- Easy and uniform dissemination of teaching resources for teachers.
- Temporal and spatial flexibility for students.
- Greater accessibility.

The monetary savings that accrue through use of these new teaching methods should also be taken into account. Professionals in rural areas need to travel to major centers to receive medical education and training;[28,45] alternatively, trained professionals from the main centers need to travel to teach in remote areas.[8,28,46] Both of these situations are time-consuming and expensive.[8,28,46] Telemedicine education offers an economical alternative for teaching skills in remote environments or for situations in which resources are limited.[8,28,45,47]

One limitation of this systematic review was that it seemed that many types of ultrasound examinations have not been evaluated in primary studies on distance-learning techniques in the medical literature, such as examinations on the thyroid, neck, breasts and prostate. In addition, because of the variability of outcomes between studies, performing a meta-analysis was not possible.

Regarding the implications for research, distance-learning techniques can be expanded to other areas of healthcare, such as biomedicine and nutrition, among others. Evaluations among medical specialties that remain little explored also need to be undertaken. It should be noted that none of the studies presented level 4 of the Kirkpatrick model (changes in system/organizational practice and changes among participants, students, residents or colleagues). Studies at level 4 could confirm the good results that were shown by the studies at levels 2B and 3 that were found. Another possibility that needs to be better explored is to combine these technologies with augmented reality and virtual reality, which would facilitate teaching in relation to areas that are difficult to access. Such combinations have already been successfully demonstrated with regard to obstetric examinations, in a study published by Zimmermann et al.,[48] and this should be extended to other ultrasound examinations.

Therefore, we can state that teaching of ultrasound by means of telemedicine is a novelty that is being implemented in the 21st century. It presents possibilities such as videos and texts on computers or cell phones, with use of the internet and applications and/or programs, in addition to the possibility of augmented reality, which has already been analyzed in some studies. Thus, a new teaching technique is presented here, which is available to teachers for implementation, with the possibility of recording classes and making them available for repeated student viewing. This is something that is often impossible with classroom lessons. It should be noted that not all the studies evaluated here included practical analyses on ultrasound. However, with regard to the theoretical part of teaching, distance-learning presents results similar to traditional methods in the classroom.

CONCLUSION

In this systematic review, we found that learning by means of telemedicine methodologies is widely accepted by students. Distance-learning can have quality similar to the traditional method and, at least at present, it can serve as an important adjunct in the teaching of ultrasonography, especially in relation to places that are difficult to access, where there are no schools/universities where this teaching could take place.

However, instructors need to pay attention to each student's particularities. Some students might not adapt to or appreciate the techniques of online teaching because of low levels of interaction between people or the need to study using a textbook rather than a screen. The need for internet access in order to have live video classes may be a problem for some locations. Studies conducted using this technology during the COVID-19 pandemic will provide new data on this technology. In addition, studies are still needed to assess the practical part of teaching ultrasonography at a distance.

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Association of salivary alpha-2-macroglobulin with glycemia and glycated hemoglobin in type 2 diabetes mellitus: a systematic review and meta-analysis study

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ABSTRACT

BACKGROUND: Chronically elevated alpha-2-macroglobulin (A2MG) in the blood has been correlated with diabetes and the HbA1c profile; however, no systematic review has been conducted to evaluate the association of A2MG salivary levels and glycemia or HbA1c levels in diabetes mellitus type 2 (DM2) patients.

OBJECTIVE: To evaluate whether A2MG salivary levels are related to the glycemia or HbA1c levels in DM2 patients.

DESIGN AND SETTING: Systematic review developed at Universidade Federal de Uberlândia (UFU), Brazil.

METHODS: Eight databases were used as research sources. The eligibility criteria included studies that reported data regarding mean salivary A2MG and the correlation between glycemia and/or HbA1c levels of DM2 subjects (uncontrolled and well-controlled) and non-diabetic subjects. The risk of bias of the studies selected was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for use in JBI systematic reviews. Pooled correlation coefficients were estimated using the Hunter-Schmidt method. Study estimates were weighted according to their sample size, and heterogeneity was calculated using the chi-square statistic.

RESULTS: Four studies on DM2 patients were included in this systematic review after careful analysis of 1482 studies. Three studies compared A2MG with HbA1c and glycemia. Overall, the correlation between A2MG and HbA1c was strong (r = 0.838). In contrast, the correlation between A2MG and glycemia was low (r = 0.354).

CONCLUSION: The strong association between HbA1C and salivary A2MG suggests that this salivary protein has the potential to be a surrogate for HbA1C, if corroboratory further evidence is obtained through large-scale studies.

SYSTEMATIC REVIEW REGISTRATION: CRD42020183831.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a metabolic disorder caused by a combination of decreased insulin secretion and decreased insulin sensitivity in peripheral tissues, primarily in the liver, muscles and adipose tissue as target organs.[1] Currently, glycemia levels and glycated hemoglobin-A1c (HbA1c) are the gold-standard parameters for diagnosing and monitoring DM2. HbA1c is suitable for reflecting glycemic control from the previous 2-3 months, in accordance with the half-life of red blood cells.[2]

Different diagnostic tools, such as glycemia, HbA1C and the oral glucose tolerance test (OGTT), are used in the diagnosis of diabetes. According to the American Diabetes Association (ADA) guidelines, individuals with glycemia concentration ≥ 126 mg/dl, HbA1C level ≥ 6.5% or two-hour plasma glucose value after 75-gram OGTT ≥ 200 mg/dl are considered to be people with diabetes.[3] The blood tests are invasive and painful[4] and may lead to development of finger calluses, poor peripheral finger circulation and risk of infection.[4]

However, the classical HbA1c tests require several reagents with relatively high cost, and need some laboratory platforms.[5] This reduces the availability of HbA1c tests in low and middle-income countries, despite their well-recognized capability for diabetes surveillance.[6] Consequently, other types of biological samples for evaluating glycemic control, such as salivary biomarkers, might be an attractive alternative for early detection and monitoring of DM2.

The major salivary glands secrete saliva in response to the autonomic nervous system, which regulates the salivation process, including the flow and concentration of some salivary components such as α-amylase, which provides a reliable measurement of the sympathetic response.[7] We previously showed that diabetes promotes changes in the autonomic activity of salivary glands, affecting both acinar and ductal cells, which are reflected in salivary composition.[8,9]

Human saliva contains a wide variety of proteins, including enzymes derived from salivary glands, blood, microorganisms and gingival crevicular fluid.[10] In this context, saliva may contain potential biomarkers for DM2, which could be used as alternative non-invasive biofluids for diagnosing and monitoring DM2. Diabetes mellitus affects both salivary composition and salivary flow, due to microvascular alterations, neuropathies and hormonal imbalances.[11] In this regard, both salivary sugars and glycosylated proteins have been found to be capable of distinguishing between hyperglycemic and normoglycemic conditions.[12]

Alpha-2-macroglobulin (A2MG) is a glycoprotein produced by the liver that can be present in human blood plasma, cerebral spinal fluid and saliva fluid.[13] The molecular structure of A2MG (720 kDa) consists of an assembly of four 180 kDa subunits into two disulfide-linked dimers, which form a noncovalent association that completes the tetrameric quaternary structure of the protein.[14] A2MG is a glycoprotein capable of inhibiting a broad spectrum of proteases, and it also regulates the activity of cytokines, hormones, growth factors and other proteins.[15] It can be stimulated by several factors, including by cytokines related to activation of the NF-kB, C/EBPb and C/EBPd pathways.[16] Thus, patients with diabetes with positively regulated acute-phase proteins frequently express higher concentration of A2MG synthesis. Therefore, the clearance of tetrameric α2-macroglobulin-protease complexes is higher and, in compensation, there is enhanced synthesis of entire A2MG molecules, thus resulting in a net increase in the non-tetrameric circulating complex.[17] Furthermore, the condition of proteinuria in patients with diabetes also can induces greater protein synthesis in the liver, thereby increasing the concentration and activity of plasma A2MG.[18]

Chronically elevated A2MG in the blood has been correlated with diabetes.[19,20] Moreover, plasma A2MG levels have been correlated with the HbA1c profile.[21] High serum A2MG levels could decrease the bioavailability of insulin and lead to impairment of blood sugar control.[4,22] Salivary proteomic analysis on DM2 cases has indicated that A2MG was increased in subjects with uncontrolled diabetes, compared with prediabetic subjects.[23,24] Furthermore, Aitken et al. (2015) and Chung et al. (2016) suggested that the level of salivary A2MG could be used as a surrogate for glycemic control in diabetic patients and that this protein represents a potential non-invasive alternative method for evaluating metabolic control.[22,25] In this way, A2MG salivary levels could be useful as an alternative auxiliary tool for diagnosing DM2.

OBJECTIVE

The aim of the present systematic review was to answer the following guiding question: "Are A2MG salivary levels related to glycemia or HbA1c levels in DM2 patients?" We tested the following hypothesis: salivary A2MG concentrations are correlated with HbA1c and glycemia levels in uncontrolled DM2 patients, compared with well-controlled DM2 patients or normoglycemic subjects.

METHODS

Protocol and registration

The protocol for this study was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[26] and was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) database, under the number CRD42020183831 (registration date: July 5, 2020), available from: https://www.crd.york.ac.uk/prospero/. This systematic review was reported following the guidelines for the Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA)[27] and was conducted in accordance with the Joanna Briggs Institute (JBI) Manual.[28]

Eligibly and exclusion criteria of the study

Studies were included if they were observational studies (cross-sectional) among patients with uncontrolled type 2 diabetes mellitus and if they also assessed the correlation between salivary A2MG concentration and blood sugar level and/or serum HbA1c, compared with well-controlled DM2 patients or normoglycemic subjects. Studies were selected without restriction regarding their year and publication status (published or accepted/ahead of print articles).

The exclusion criteria consisted of the following situations: I) the study was unrelated to the objective; II) the study was a review article; III) the study was a follow-up or it assessed participants with other comorbid diseases, like patients with rheumatic diseases, terminal illnesses, chronic liver disease, chronic inflammatory processes in the oral cavity, chronic kidney disease in stages IV and V and autoimmune diseases; IV) the study did not report the procedures in accordance with the ethical standards.

Sources of information and search

We searched for studies that evaluated salivary A2MG levels and serum glycemia and glycated hemoglobin (HbA1c) in

type 2 diabetes mellitus cases. The MEDLINE (via PubMed), Scopus, LILACS, Web of Science, Embase and SciELO electronic databases were used as the primary study sources. In addition, OpenGrey and OpenThesis were used to partially capture the "gray literature". MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors) and Emtree (Embase Subject Headings) were used to search the descriptors. The Boolean operators "and" and "or" were combined with the descriptors to improve the search strategy (**Table 1**). The bibliographic search was conducted up to a cutoff point of November 2020. In addition, we also manually checked the reference sections of the eligible studies and any indications by expert researchers, for the possibility of any additional studies that might have been missed by the electronic search. E-mails were sent out to three referral specialists for articles potentially eligible for this review.

Study selection

Studies were selected in four stages. Initially, a calibration exercise was performed to fit pre-specified eligibility criteria and apply them to a small sample of the studies (20%) that had been retrieved, in order to determine inter-examiner agreement. After achieving an appropriate level of concordance (kappa ≥ 0.81), the reviewers (DCC and PRCP) performed a methodical analysis on all the study titles independently. Any disagreements between these examiners were discussed with a third reviewer (LRP), so as to reach a consensus.

In the first stage, the studies obtained from the databases were identified. The data were exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed. The remaining results were exported to Microsoft Word™ 2016 (Microsoft™, Redmond, Washington, United States), in which any remaining duplicates were manually removed.

Table 1. Strategies for database search

Database	Search strategy (November 2020)
PubMed (Best Match) http://www.ncbi.nlm.nih.gov/pubmed	(("Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM") AND ("A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG"))
SCOPUS http://www.scopus.com/	("Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM") AND ("A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG")
LILACS http://lilacs.bvsalud.org/	(("Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM") AND ("A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG"))
Web of Science http://apps.webofknowledge.com/	(("Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM") AND ("A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG"))
EMBASE https://www.embase.com	('diabetes mellitus type 2'/exp OR 'diabetes mellitus type 2' OR 'diabetes mellitus, noninsulin-dependent' OR 'diabetes mellitus, non-insulin-dependent'/exp OR 'diabetes mellitus, non-insulin-dependent' OR 'diabetes mellitus, type ii'/exp OR 'diabetes mellitus, type ii' OR 'niddm'/exp OR 'niddm' OR 'type 2 diabetes'/exp OR 'type 2 diabetes' OR 'dm2' OR 't2dm'/exp OR 't2dm') AND ('a2m protein, human' OR 'α2-macroglobulin' OR 'salivary α2-macroglobulin' OR 'α2-mg' OR 'alpha 2-macroglobulin'/exp OR 'alpha 2-macroglobulin' OR 'a2mg')
SciELO https://www.scielo.org/	(("diabetes mellitus type 2" OR "diabetes mellitus, noninsulin-dependent" OR "diabetes mellitus, non-insulin-dependent" OR "diabetes mellitus, type ii" OR "niddm" OR "type 2 diabetes" OR "dm2" OR "t2dm") AND ("a2m protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-mg" OR "alpha 2-macroglobulin" OR "a2mg"))
OpenGrey http://www.opengrey.eu/	"Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM" AND "A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG"
OpenThesis http://www.openthesis.org/	(("Diabetes Mellitus Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes" OR "DM2" OR "T2DM") AND ("A2M protein, human" OR "α2-macroglobulin" OR "salivary α2-macroglobulin" OR "α2-MG" OR "alpha 2-macroglobulin" OR "A2MG"))

In the second stage, all the titles were analyzed independently by the two reviewers, in order to determine their relevance. The reviewers were not blinded to the names of authors and journals. Titles that were not related to the topic were eliminated in this phase.

Then, in the third stage, the abstracts were reviewed in order to apply the exclusion criteria mentioned above. Titles in accordance with the aims of the present study but without abstracts available were fully analyzed in the fourth stage. In addition, expert investigators and potentially eligible studies found in the reference lists were included for subsequent analyses.

In the fourth stage, the full texts of the preliminarily eligible studies were obtained and evaluated to verify whether they did indeed fulfill the eligibility criteria, including expert investigators and potentially eligible studies found in the reference lists.

Data collection

The two reviewers (DCC and PRCP) then independently accessed full-text copies of all eligible articles and collected data from each study using a pre-prepared spreadsheet. The following data were extracted from the studies: author, year, country, DM2 population, average age, average age range, gender ratio, diagnosis and collection period. In addition, information on the characteristics, preparation and measurement of the samples in the eligible studies was collected (saliva collection, saliva collection criteria, saliva preparation, blood collection, A2MG measurement, glycemia measurement and HbA1c measurement), along with the main results from the studies included (mean glycemia, mean HbA1c, mean A2MG, correlation of salivary A2MG with glycemia and correlation of salivary A2MG with HbA1c).

In order to ensure consistency between the reviewers, a calibration exercise was performed with both reviewers (DCC and PRCP), in which information was extracted jointly from an eligible study. Any disagreement between the reviewers was resolved through discussions, and if the disagreement continued, a third reviewer (LRP) was consulted to make a final decision.

Risk of individual bias of the studies

The Joanna Briggs Institute Critical Appraisal Tools for use in JBI systematic reviews on observational (cross-sectional) studies[28] were used to assess the risk of bias and the individual quality of the studies selected. Two authors (DCC and RSS) independently assessed each domain regarding its potential risk of bias, as recommended in the PRISMA statement.[27]

Each study was categorized according to the percentage of positive responses to the questions of the assessment tool. The risk of bias was considered high when 49% of the responses relating to the study in question were "yes" answers, moderate when 50% to 69% of the responses were "yes" and low when more than 70% of the responses were "yes".[29]

Statistical analyses

The correlations between the A2MG and DM2 biomarkers (glycemia or HbA1c) were considered in the meta-analysis. Correlation coefficients were pooled using the Hunter-Schmidt method[30,31] and stratified according to the DM2 biomarker, for comparison with A2MG. Estimates using this method are weighted according to the sample size of each study. The correlation was considered perfect if the coefficients were equal to 1 or -1; strong if the coefficients ranged between |0.7| and |0.9|; moderate if the coefficients ranged between |0.4| and |0.6|; weak if the coefficients ranged between |0.1| and |0.3|; and zero if the coefficients were 0.[32]

The presence or absence of between-study heterogeneity was also assessed through the Hunter-Schmidt method using the chi-square statistic.[30,31] The significance level was taken to be 5% in all analyses, which were all conducted using the Stata 16.1 software (StataCorp LLC, College Station, Texas, United States).

Certainty of evidence

Quality of evidence and strength of recommendation were assessed using the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) tool. The GRADE pro GDT software (http://gdt.guidelinedevelopment.org) was used for summarizing the results. This assessment was based on study design, methodological limitations, inconsistencies, indirect evidence, imprecision and other considerations. The quality of evidence was characterized as high, moderate, low or very low.[33]

RESULTS

Study selection

During the first phase of study selection, 1,581 results were found distributed in eight electronic databases, including the "gray literature". After removing duplicate results, 1,482 articles remained for analysis of titles and abstracts.

In this phase, after a detailed analysis of titles and abstracts, only seven studies were found to be eligible for full-text analysis. The references of these seven potentially eligible studies were also carefully evaluated and one additional article was selected. Besides that, one article was indicated by an expert investigator, thus resulting in nine studies for full-text reading.

After reading the full text, five studies were found not to fulfil the inclusion criteria and were eliminated. Among these excluded studies, one[34] was not related to the objective of this systematic review, two[23,24] were proteomic analysis studies, one[35] was a review study and another one[25] was a follow-up study. Therefore, for these reasons, they were removed from further consideration.

Thus, four studies[22,36-38] were selected for qualitative evaluation and meta-analysis. **Figure 1** depicts the search, identification, inclusion and exclusion process for article selection.

Study characteristics of eligible studies

The studies selected were published between 2015 and 2019 and were performed in Chile,[22] China,[36] Egypt[37] and India.[38] All studies[22,36-38] had been approved by the ethics committee of their respective institution or hospital and also reported that informed consent had been obtained from the subjects prior to the start of the study. None of the articles used the STROBE checklist for cross-sectional studies.

Three studies included the sources of funding: Fondo Investigación Facultad de Odontología, Universidad de Chile (FIOUCH 13-002),[22] ICMR Short Term Studentship Funding[38] and nil (no funding).[37] Other information regarding demographics and characteristics of the populations are presented in **Table 2**.

Risk of bias within studies

All the studies presented a low risk of bias or high methodological quality. However, one study[38] did not describe any specific information about the population and the parameters that assisted in making the diagnosis of diabetes. Therefore, this was indicated as unclear in the risk-of-bias table (**Table 3**).

Summary measurements and synthesis of results

Table 4 describes the correlation of salivary A2MG with glycemia and/or HbA1c and the respective means/standard deviations for glycemia, HbA1c and A2MG in the selected studies that were included in the quantitative analysis. All of these four studies were also included in the meta-analysis. However, only three studies compared A2MG with HbA1c,[22,36,37] and only three studies compared A2MG with glycemia.[36-38]

The correlation between A2MG and HbA1c ranged from 0.722 to 0.977 in the three studies analyzed. Overall, the pooled correlation between these biomarkers was strong (r = 0.838; 95% confidence interval, CI: 0.719 to 0.956; P < 0.001) (**Figure 2**). In contrast, the pooled correlation between A2MG and glycemia was low (r = 0.354; 95% CI: 0.077 to 0.630; P = 0.006). Both meta-analyses presented significant heterogeneity between study results (P < 0.001); however, the heterogeneity levels were higher for glycemia analysis than for the HbA1c analysis.

Certainty of evidence

The GRADE tool[33] assessed two outcomes. Both outcomes (correlation between A2MG and HbA1c and correlation between A2MG and glycemia) were categorized as very low level of certainty, which means that the true effect is likely to be substantially different from the estimated effect. **Table 5** shows more details regarding each outcome.

DISCUSSION

We conducted a systematic review to evaluate whether the increase in salivary A2MG concentration was correlated with HbA1c and glycemia levels in blood, in DM2 patients. We showed that there was a strong correlation between salivary

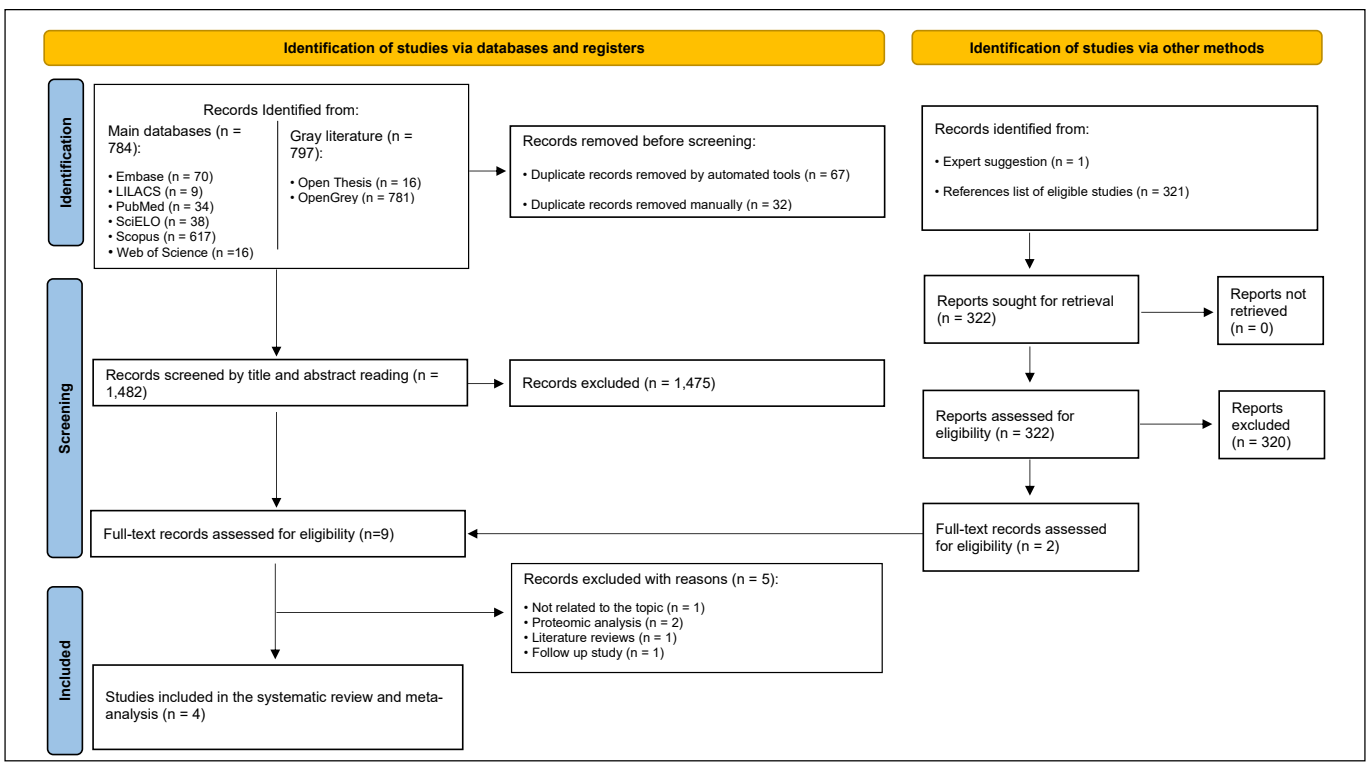

Figure 1. Flow-chart showing the search strategy, identification and inclusion/exclusion criteria used in the systematic review and meta-analysis.

Table 2. Characteristics of the populations of the eligible studies included

Study	Country	Type of DM2 population	Control population	Average age (years)	Average age range (years)	Sex ratios	Diagnosis	Data collection period
Aitken et al.[22]	Chile	120 patients (75 patients with uncontrolled glycemia and 45 patients with well-controlled glycemia)	NA	61.6 ± 10.1	31-79	32.5% ♂, 67.5% ♀	Patients with HbA1c levels < 7% were classified as having adequate glycemic control and those with levels > 7% were classified as having inadequate glycemic control	July 2013 to December 2013
Feng et al.[34]	China	116 patients with DM2 and 60 patients with IFG (impaired fasting glucose)	60 healthy volunteers	DM2 (57 ± 12.3); IFG (55 ± 14.3); Control (51 ± 11.3)	Not reported	DM2 (54♂/62♀); IFG (27♂/33♀); Control (22♂/38♀)	American Diabetes Association in 2010 for DM2; IFG ≥ 7.0 mM (pre-diabetic); fasting blood glucose ranged from 5.6-6.9 mM (control)	February 2011 to March 2012
Nsr-Allah et al.[35]	Egypt	40 patients: 20 patients with uncontrolled glycemia (group 1) and 20 patients with well-controlled glycemia (group 2)	20 healthy volunteers (group 3)	Group 1 (49.75 ± 10.74); Group 2 (50.90 ± 10.54); Group 3 (48.9 ± 11.47)	23-65	Group 1 (7♂/13♀); Group 2 (9♂/11♀); Group 3 (13♂/7♀)	Patients with HbA1c levels < 7% were classified as having adequate glycemic control and those with levels ≥ 7% were classified as having inadequate glycemic control. Group 3 included with fasting plasma glucose less than 100 mg/dl and HbA1c less than 5.7%.	April 2016 and June 2017
Rastogi et al.[36]	India	87 patients: 53 patients with uncontrolled glycemia and 34 patients with well-controlled glycemia	NA	52.4 ± 8.1	35-65	43♂, 44♀	Not reported	August 2018 to October 2018

NA = not applicable; ♀ = women; ♂ = men; DM2 = type 2 diabetes mellitus; HbA1c = hemoglobin-A1c.

A2MG and HbA1c, but with a low level of certainty. Hence, further studies are needed in order to determine the potential for application of A2MG in salivary platforms. However, the low association between A2MG and glycemia levels suggests that A2MG is not an accurate salivary protein that can act as a surrogate in glycemia tests.

Considering that glycemia reflects the blood glucose levels at the moment of the analysis, this test presents limitations with regard to reflecting glucose control over prolonged periods.[38] The HbA1c test has been recommended as a means for assessing variations in glucose tolerance in type 2 diabetic patients, for long-term monitoring of diabetes.[6] In addition, HbA1c tests can be performed at any time of the day without concerns about the fasting and it can indicate the average plasma glucose concentration over two to three months.[40,41]

However, the classical HbA1c test is performed in laboratory settings and only have limited use in point-of-care (POC) devices.[5] This reduces the availability of HbA1c tests in low and

Table 3. Risk of bias assessed using the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies[28]

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	% Yes	Risk
Aitken et al.[22]	√	√	√	√	√	√	√	√	100	Low
Feng et al.[34]	√	√	√	√	√	√	√	√	100	Low
Nsr-Allah et al.[35]	√	√	√	√	√	√	√	√	100	Low
Rastogi et al.[36]	√	U	√	U	√	√	√	√	75	Low

Q1. Were the criteria for inclusion in the sample clearly defined?; Q2. Were the study subjects and the setting described in detail?; Q3. Was the exposure measured in a valid and reliable way?; Q4. Were objective, standard criteria used for measurement of the condition?; Q5. Were confounding factors identified?; Q6. Were strategies to deal with confounding factors stated?; Q7. Were the outcomes measured in a valid and reliable way? Q8. Was appropriate statistical analysis used? √ = yes; -- = no; NA = not applicable; U = unclear.

Table 4. Summary of the main results from the studies included in the quantitative analysis.

Study	Mean glycemia	Mean HbA1c	Mean A2MG	Correlation of salivary A2MG with glycemia	Correlation of salivary A2MG with HbA1c
Aitken et al.[22]	NA	HbA1c > 7% (62.5%); HbA1c < 7% (37.5%)	Not reported	NA	r = 0.7748; P < 0.0001
Feng et al.[34]	DM2 (10.08 ± 2.44 mM); IFG (6.58 ± 0.24 mM); Control (5.01 ± 0.41 mM)	DM2 (8.7 ± 1.7%); IFG (5.8 ± 1.1%); Control (5.7 ± 0.7%)	Salivary A2MG (ng/ml): DM2 (192.6 ± 65.3); IFG (158.1 ± 60.1); Control (134.8 ± 63.2). Plasmatic A2MG (g/l): DM2 (1.70 ± 0.55); IFG (1.57 ± 0.36); Control (1.54 ± 0.38)	DM2 (r = 0.12, P = 0.199)	NA
Nsr-Allah et al.[35]	Group 1 (172.20 ± 26.52 mg/dl); Group 2 (100.65 ± 21.30 mg/dl); Group 3 (90.95 ± 8.66 mg/dl)	Group 1 (9.02 ± 1.38%); Group 2 (6.20 ± 0.61%); Group 3 (5.35 ± 0.44%)	Salivary A2MG (ng/ml): Group 1 (820.65 ± 190.17); Group 2 (331 ± 98.01); Group 3 (146.90 ± 42.01)	Group 1 (r = 0.586, P < 0.05); Group 2 (r = 0.146, P = 0.539); Group 3 (r = 0.650 ,P < 0.05); All subjects (r = 0.788, P < 0.001)	Group 1 (r = 0.778, P < 0.001); Group 2 (r = 0.666, P < 0.05); Group 3 (r = 0.474, P < 0.05); All subjects (r = 0.927, P < 0.001)
Rastogi, et al.[36]	Uncontrolled glycemia (290.58 ± 96.126 mg/dl); Well-controlled glycemia (172.83 ± 39.955 mg/dl)	HbA1c > 7% (60.9%); HbA1c < 7% (39%)	Salivary A2MG (ng/mL): Uncontrolled glycemia (2017.42 ± 575.133); Well-controlled glycemia (772.54 ± 118.324)	r = 0.660, P < 0.001	r = 0.977, P < 0.001

NA = not applicable; DM2 = type 2 diabetes mellitus; HbA1c = hemoglobin-A1c. A2MG = alpha 2-macroglobulin; IFG = impaired fasting glucose.

middle-income countries.[6] Moreover, several biological factors such as clinical conditions that alter erythropoiesis, glycation rate and erythrocyte destruction, and analytical interferences such as hyperbilirubinemia, carbamylated hemoglobin, certain medications and hemoglobin variants, affect the alteration cutoff values of the HbA1C test.[42] Our findings from this meta-analysis confirm the hypothesis that A2MG presents a strong correlation with HbA1c test.

In this context, the higher correlation between salivary A2MG and HbA1C levels indicates that saliva is a promising alternative biofluid for diagnosing and monitoring diabetes. Among the advantages, saliva is simple and non-invasive to collect; it is convenient to store; and, compared with blood, it requires less handling during clinical procedures. Hence, further studies should be carried out in order to investigate the clinical applicability of salivary A2MG as a surrogate for HbA1C in diagnosing and monitoring DM2.

This systematic review had some limitations. The absence of a control group in some studies included[22,38] could be considered a limitation, but their analysis on uncontrolled hyperglycemic subjects and subjects with type 2 diabetes presenting

Table 5. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of findings table for the outcomes of the systematic review and meta-analysis

Quality assessment							Summary of results		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication biases	Number of participants	Effect r (95% CI)	General quality
Outcome 1: Correlation between A2MG and HbA1c									
3	Cross-sectional studies	Not serious	Serious[1]	Not serious	Serious[2]	Not serious	247	0.838 (0.719- 0.956)	⊕ VERY LOW
Outcome 2: Reduction of salivary creatinine after dialysis									
3	Cross-sectional studies	Not serious	Not serious	Not serious	Serious[2]	Not serious	243	0.354 (0.077- 0.630)	⊕ VERY LOW

CI = confidence interval, A2MG = alpha-2-macroglobulin; HbA1c = hemoglobin-A1c.

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 be substantially different from the estimate of effect

[1]The heterogeneity (I^2) among the studies was high (> 75%); [2]The number of participants included in the meta-analysis was too low.

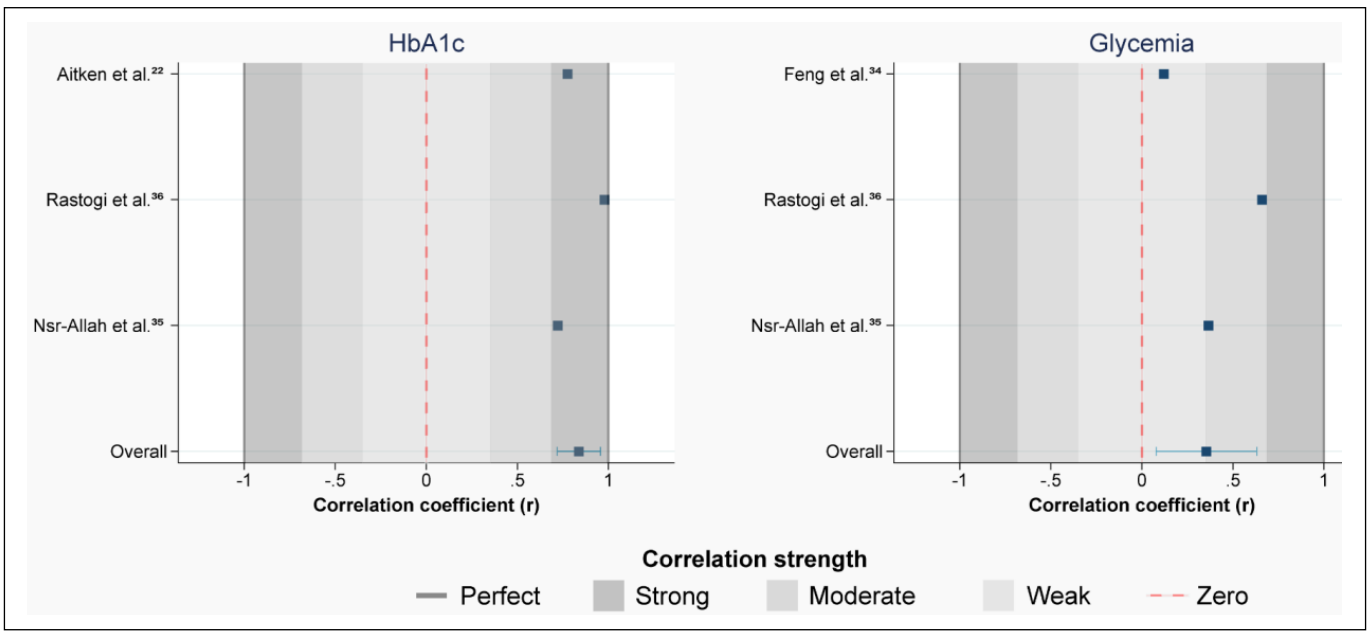

Figure 2. Correlations of salivary alpha 2-macroglobulin (A2MG) with hemoglobin-A1c (HbA1c) and glycemia.

suboptimal control is also clinically relevant. In addition, the GRADE evaluation found that there were high levels of inconsistency and imprecision in the results obtained through the meta-analysis, which means that the evidence obtained was of very low level and that, possibly, the effect estimate found may differ from the real effect. Further studies with larger populations should be carried out in order to minimize imprecisions: these should include normoglycemic subjects, uncontrolled diabetic subjects and well-controlled diabetic subjects. Although HbA1c levels reflect the average blood glucose levels during approximately the previous 75 days, the mean duration of diabetes was not included in these studies.

On the other hand, lastly, the absence of systematic reviews and meta-analyses in this field gives added importance and timeliness to the meta-analysis of the present study. In the future, it will be important to define the predictive power of salivary A2MG for estimating HbA1c levels.

CONCLUSION

The present study described a strong association between HbA1C and A2MG levels in saliva, in uncontrolled DM2 subjects, compared with well-controlled DM2 patients or normoglycemic subjects. On the other hand, the meta-analysis suggests that there was a very low correlation between glycemia and salivary A2MG. Further large-scale studies are needed in order to be able to recommend salivary A2MG levels as alternative surrogate for HbA1c. Nonetheless, the present study suggests that this has a potential role in providing a clinically valuable advance towards salivary monitoring of diabetes.

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Assessment of the strength of recommendation and quality of evidence: GRADE checklist. A descriptive study

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ABSTRACT

BACKGROUND: Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a tool for assessing evidence produced in synthesis reports.

OBJECTIVES: To present the translation into Portuguese of the GRADE checklist, whose original version is in English, and to describe and explain each topic, in order to provide examples to researchers and professionals who will use the tool.

DESIGN AND SETTING: Descriptive study developed at Centro Universitário Tiradentes, Maceió, Alagoas, Brazil.

METHODS: This was a translation of the GRADE checklist, with the addition of the Risk Of Bias In Systematic Reviews (ROBIS) tool in the checklist, with examples of its use.

RESULTS: Situations of practical use of the tool were presented in order to facilitate and expand the use of assessment of the quality and strength of evidence among Portuguese speakers.

CONCLUSIONS: The GRADE checklist is valuable in helping to assess the strength and quality of evidence for synthesis reports for healthcare decision-making.

INTRODUCTION

Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a tool for evidence quality assessment and strength-of-evidence recommendation. This system was developed to provide transparency and to structure the evidence synthesis development process, such as through guidelines, systematic reviews, economic analysis, etc.[1]

According to the tool, the process of evaluating the quality of evidence is separate from the process of formulating recommendations. In the case of a systematic review, the quality of the evidence will reflect the confidence that the effect estimates are correct. Regarding the strength of the recommendation, the quality reflects the confidence that the effect estimates are adequate for supporting a specific recommendation, thus helping the decision-making process.[2]

Thus, when using GRADE approach in a synthesis of the quality of evidence from experimental and observational studies, the levels of evidence are classified (for each outcome studied) on a four-level scale: very low, low, moderate or high.[3]

As established by the tool, the set of available evidence from randomized clinical trials has an initial quality-of-evidence rating of "high", given that these are experimental studies. If the evidence comes from observational studies, it start with a low quality-of-evidence level.[3]

Furthermore, the quality of evidence can become compromised by factors within five domains, with the consequence of lowering its initial classification. These domains are the following: risk of bias, imprecision, inconsistency, indirect evidence of study results and publication bias. Particularly for observational studies, the GRADE system establishes three criteria that can raise the level of evidence: large magnitude of effect, residual effect of confounding variables and dose-response gradient.[2]

From a practical perspective, correct use of the tool allows healthcare decision-making to be informed by the best evidence, with a lower degree of uncertainty and, consequently, less likelihood of error for patients, the healthcare system and decision-makers.

From a theoretical perspective and to improve the use of the tool, a checklist of questions was developed in 2014 to guide researchers and healthcare professionals in extracting the information that is necessary to conduct an evaluation: a GRADE checklist.[4]

For people who have never done a systematic review, or who have no experience in critically evaluating scientific literature, using the GRADE tool can be a challenge. Professionals

who are in healthcare services making decisions on a daily basis need mechanisms that contribute to their understanding of how the evidence was evaluated, or if necessary, need to learn how to evaluate the evidence studied.[5]

The GRADE checklist is an important tool for researchers and other professionals that helps them in the process of evaluating the quality and strength of evidence through a systematic approach. This is because it provides a structure of questions for each of the five domains responsible for downgrading the evidence, which helps raters to detail each item critically and reproducibly, for analysis through GRADE.[4]

OBJECTIVE

The purpose of this article was to present the translation of the GRADE checklist and to describe and explain each topic, with the aim of reaching out to researchers and professionals who will use the tool.

METHODS

Given the need to facilitate and expand the use of the GRADE system, a checklist of questions was developed in 2014 to guide researchers and healthcare professionals in extracting the information needed to conduct an assessment using GRADE.[4]

The aim of this checklist was to assist in enhancing the reproducibility of GRADE assessments, given that this system can present a certain degree of complexity. Use of this checklist would be very helpful for assessors with regard to transparently identifying and extracting information that is needed. Through this approach, the items used are clearly identified, in a perfectly reproducible manner, which allows repetition to confirm the results found.[4]

Two medical students translated the checklist into Portuguese under the supervision of a senior researcher.

RESULTS

A free translation is presented in **Table 1**, along with analysis of methodological quality and the degree of evidence for systematic reviews of randomized clinical trials.

Box 1[2-4,6-13] presents the factors responsible for lowering the quality of the evidence, together with the three factors responsible for upgrading the quality of the evidence, which are particularly applicable to observational studies.

The GRADE system is a comprehensive and transparent tool for evaluating the evidence and strength of recommendations, and therefore it is very useful in analyzing systematic reviews and developing healthcare guidelines.[3]

Table 1. Meader checklist for assessing methodological quality and the degree of evidence for randomized clinical trials[4]

Study limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)? Was allocation concealment used (i.e. no potential for selection bias)? Was there blinding of participants and practitioners (i.e. no potential for performance bias)? Was there blinding of the outcome assessment (i.e. no potential for detection bias)? Were objective outcomes used? Were more than 80% of the participants enrolled in the trial included in the analysis (i.e. no potential reporting bias)? Was the data reported consistently for the outcome of interest (i.e. no potential selective reporting)? Did the tests finish as scheduled (i.e. they did not stop early)? Was random sequence generation used (i.e. no potential for selection bias)?
Inconsistency[b]	Does the estimated point not vary widely? How much do the confidence intervals overlap? All: confidence intervals overlap in at least one of the estimated points of the studies included; Some: confidence intervals overlap, but not all overlap, at least at one of the estimated points; None: There is at least one outlier; the confidence intervals of several studies included do not overlap at most of the estimated points. Is the direction of effect consistent? What is the magnitude of the heterogeneity estimated through the I^2 statistic? Low: $I^2 < 40\%$; Moderate: $I^2 = 40\%$-60%; High: $I^2 > 60\%$. Was the test for heterogeneity not statistically significant ($P > 0.1$)?
Indirect evidence[c]	Does the population included in the study have applicability in the context of decision-making? Do the interventions in the studies included have applicability in the context of decision-making? Is the outcome included not a surrogate outcome? Was the outcome assessment time sufficient? Were the conclusions based on direct comparisons?

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Imprecision[d]	Is the confidence interval for the pooled estimate (meta-analysis) consistent with benefit or risk? What is the magnitude of the median sample size (high: > 300 participants; intermediate: 100-300 participants; low: < 100 participants)? What is the magnitude of the number of studies included (large: > 10 studies; moderate: 5-10 studies; small: < 5 studies)?[e] Is the outcome a common event (e.g. more than 1/100 occurrences)?
Publication bias[e]	Was a broad search performed? Was gray literature sought after? Were there no restrictions on study selection based on language? Is there no industry influence on the studies included in the review? Is there evidence of asymmetry in the funnel plot? Are there no discrepancies between the published and unpublished findings of the studies?

[a]Risk-of-bias questions are answered in relation to most evidence pooled in the meta-analysis, rather than in individual trials; [b]Questions about inconsistency are mainly based on visual assessment of forest plots and on statistical quantification of heterogeneity based on I^2; [c]In judging the width of the confidence interval, it is recommended that a clinical decision threshold is used to assess whether the imprecision is clinically significant; [d]The questions address search strategy breadth, industry influence, funnel plot asymmetry and discrepancies between published and unpublished studies; [e]Depends on the context of the systematic review area; N/A = not applicable. Judgments: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; NA2 = not applicable.

Box 1. Explanation for using each domain of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

A – Study limitations

Among the factors that can reduce the quality of evidence pointed out by GRADE, there are study limitations or risk-of-study bias. Bias can be defined as a systematic error, or deviation from the truth, in the results.[7] Assessing the risk of bias of the studies included in the systematic review is important because it is a way of verifying whether the effects of the analyzed interventions were overestimated or even underestimated.[2]

It is, therefore, an evaluation of the methodological quality of the primary studies analyzed in the systematic review, verifying possible limitations to their designs or executions that, through influencing the estimates of the treatment effect, can lead to inadequate conclusions, thereby affecting the estimate of the effect (systematic reviews) and the recommendation to follow (strength of recommendation). Thus, based on the analysis of these studies, the more serious the limitations are, the more the level of evidence may be lowered.[3]

Today, there are already several tools available to researchers that allow them to assess the risk of bias in scientific research. However, the Guidelines for the Systematic Review of Randomized Clinical Trials[6] recommend to researchers that the risk-of-bias assessment should be carried out using the new version of the Cochrane risk-of-bias tool (RoB 2),[8] which is composed of a fixed set of five domains, with a series of "signaling questions" that focus on different aspects of the study design, conduct and reporting, in order to obtain the main information for the analysis of the risk of bias. It is, therefore, a very useful tool for assessing methodological quality.

It is also important to note that biases can have a different impact on each outcome. For example, suppose that, in evaluating the effect of a given surgery among patients with chronic kidney problems, a systematic review identified four eligible studies. All were randomized clinical trials, but without adequate blinding of outcome assessors, thus showing a risk of bias due to lack of allocation concealment. However, this risk of bias can vary between the results, depending on the outcome analyzed: the absence of blinding certainly impacts on outcomes such as quality of life, as this is more prone to subjectivity, so it is necessary to downgrade the level of evidence in this case. But if the outcome is overall mortality, masking can already be considered irrelevant, as the outcome of death does not depend on whether the researcher knows which patient underwent the intervention or not, and therefore is not a reason to downgrade the level of evidence for this outcome. All this needs to be taken into account by the evaluator, to ensure correct judgment of this domain.[9]

The questions about the domain of limitations of the checklist study were prepared based on the items of the Cochrane risk-of-bias tool, in order to establish the main points of analysis for the domain, thus facilitating the subsequent analysis in the GRADE system.[4] Hence, the following points of analysis need to be answered for each outcome:

1. Was random sequence generation used (i.e. no potential for selection bias)?
2. Was allocation concealment used (i.e. no potential for selection bias)?
3. Was there blinding of participants and practitioners (i.e. no potential for performance bias)?
4. Was the outcome evaluation blinded (i.e. no potential for detection bias)?
6. Were objective outcomes used?
7. Were more than 80% of the participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?
8. Was data reported consistently for the outcome of interest (i.e. no potential selective reporting)?
9. Did tests end as scheduled (i.e. they did not stop early)?
10. Was random sequence generation used (i.e. no potential for selection bias)?

The answers to these questions should vary between the following: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; and NA2 = not applicable. The questions should be answered taking into account most of the evidence aggregated in the meta-analysis, and not the individual trials. Thus, by

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carefully analyzing each of these points in the available body of evidence, it will be possible to make a more accurate judgment about the risk of bias of the GRADE tool.[4]

B - Inconsistency

According to the GRADE system, the criteria for judging the extent of heterogeneity are based on the similarity of point estimates, the extent of overlapping confidence intervals and statistical criteria (including tests of heterogeneity and I^2). If the study methods applied provide a convincing explanation for differences in results between studies, the evaluator can maintain the assessment of the quality of the evidence. However, when the variability in the magnitude of the effect is large and remains unexplained, it is appropriate to downgrade the quality of the evidence due to inconsistency. A strong indication of heterogeneity in a group of randomized clinical trials analyzed in a systematic review, is presented when, for example, some of these studies point to a substantial benefit from a particular drug for a certain health problem, while others do not point to any effect. or damage; rather than finding large versus small effects.[10]

Importantly, for GRADE, if the effect size differs between studies, the inconsistencies may be due to differences in four possible variables: populations (for example, a drug may have greater relative effects in populations with health problems that are treated using this drug); interventions (e.g. a drug may have better effects at higher doses); results (e.g. the effectiveness of a treatment with a particular drug may be better with a longer duration of treatment); and study methods (e.g. experimental studies with higher and lower risk of bias).[3]

Hence, when heterogeneity exists and the evaluator does not attribute the difference to any of these four variables, thus making it difficult to interpret the results such that they cannot be explained, the quality of the evidence is affected. In such cases, therefore, the level of evidence should be downgraded because of inconsistency, by one or even two levels.[2]

In this manner, in short, inconsistency consists of an unexplained heterogeneity of results and gives rise to downgrading of the level of evidence by one or two notches, depending on the magnitude of the inconsistency in the results. In the checklist, the analysis on inconsistency takes place through questions based mainly on visual evaluation of forest plots and on statistical quantification of heterogeneity based on I^2 and Q statistics, following the directions given by GRADE, including evaluation of subgroups that can explain the inconsistency.[4]

The tool therefore proposes a reflection on clinical and methodological differences between studies in which the outcome was analyzed, through presenting four questions to help in this evaluation, which can have any of the following answers: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; or NA2 = not applicable:[4]

1. Does the estimated point not vary widely?
2. How much do the confidence intervals overlap?

   All: confidence intervals overlap in at least one of the estimated points of the studies included;
   Some: confidence intervals overlap, but not all overlap, at least at one of the estimated points;
   None: There is at least one outlier; the confidence intervals of several studies included do not overlap at most of the estimated points.

1. Is the direction of effect consistent?
2. What is the magnitude of the heterogeneity estimated through the I^2 statistic?
   Low: $I^2 < 40\%$;
   Moderate: $I^2 = 40\%$-60%;
   High: $I^2 > 60\%$."
3. Was the test for heterogeneity not statistically significant ($P > 0.1$)?

C – Indirect evidence

It is a fact that confidence in the results of a study that presents direct evidence is greater. Evidence is direct when a study directly compares interventions of interest to the researchers that are delivered to the populations of interest and in which results important to the researchers and patients are measured.[3]

However, this relationship will not always be available. Thus, the quality of the evidence may decrease when this occurs, given that in these cases it is necessary to resort to indirect evidence. In such cases, inferences are made about the relative effects of two interventions: not based on comparison between them, but rather, through comparison of a third control condition.[11]

Therefore, in analyses on indirect evidence, the evaluator is faced with the lack of a direct answer to the question addressed in the studies available, due to four possibilities: differences in populations, interventions, comparators or outcomes, taking into account the acronym PICO that was previously explained.[2]

As an example, imagine that a systematic review aimed to analyze the effect of a drug for treating morbid obesity, and that studies in which this evaluation was carried out in groups of people in countries in the Americas were selected. It would not be expected that the effect of this drug in European countries would be different, and therefore it would not be necessary to downgrade the level of evidence. However, if these studies analyzed the effectiveness of this drug in adults, generalizing these results to children would constitute a situation of indirect evidence, which would therefore generate less confidence in these results. For this reason, in this case, the level of evidence would need to be downgraded because of the use of indirect population-based evidence.[6]

In the checklist, to analyze indirect evidence, questions about population applicability, interventions, comparators and outcomes are included. In short, in this domain, it is necessary to analyze whether the study met its objectives, i.e. whether what it set out to research was found, or whether there was any deviation of interest in relation to the PICO research question. Five questions guide the classification of evidence in this domain:[4]

1. Does the population included in the study have applicability in the context of decision-making?

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2. Do the interventions in the studies included have applicability in the context of decision-making?
3. Is the outcome included not a surrogate outcome?
4. Was the outcome assessment time sufficient?
5. Were the conclusions based on direct comparisons?

As in the previous items, the answers to these questions can vary between the following: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; or NA2 = not applicable. Thus, this analysis will make it possible to arrive at the best possible judgment of the indirect evidence, in the GRADE tool.[4]

D - Imprecision

The GRADE system considers that the 95% confidence interval is the main criterion for decisions about imprecision around differences in effect between the intervention and the control for each outcome analyzed. The confidence interval reflects the impact of random error on the quality of evidence. However, it is important to point out that there are limitations to this reliability, so that even if the confidence interval seems satisfactory, when the effects reported in the study are large and the sample size or the number of events are modest, the evaluator must downgrade the quality of evidence because of imprecision.[12]

Thus, for example, when a researcher seeks to assess the effectiveness of a treatment, but the study includes relatively few patients and few events, with a wide confidence interval, the quality of the evidence must be downgraded due to the imprecision of the results found.[2]

In accordance with the GRADE predictions, imprecision was addressed in the checklist through items relating to the width of the confidence interval, the sample size, the magnitude of the effect between the studies under analysis and whether the outcome occurs commonly. Four questions help in reflecting on this domain, and should be answered as follows: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; or NA2 = not applicable. These questions are the following:[4]

1. Is the confidence interval for the pooled estimate (meta-analysis) not consistent with benefit or risk?
2. What is the magnitude of the median sample size?
3. What is the magnitude of the number of studies included (large: > 10 studies; moderate: 5-10 studies; small: < 5 studies)?
4. Is the outcome a common event (e.g. occurs in more than 1/100)?

E -Publications bias

Publication bias occurs when a reported effect is underestimated or overestimated due to selective publication of studies. Thus, the risk of publication bias may be greater for systematic reviews of observational studies than for reviews of randomized controlled trials.[3]

From this perspective, publication bias occurs when entire studies are not reported. For example, systematic reviews that fail to identify unpublished studies, consisting of studies that were published in a non-indexed journal or in the gray literature, present publication bias. It is common to see that when studies report statistically significant findings they are more likely to be accepted for publication than those that report statistically insignificant findings. For this reason, it is necessary to use rigorous research techniques to identify all possible studies, so as not to fall into the problem of publication bias.[13]

Small studies that present conflicts of interest due to commercial funding, as in the case of studies sponsored by the pharmaceutical industry, may be suspected of publication bias. This is because it is a common practice for studies that reveal negative results for the industry to be withheld from publication. In addition, evaluators should also be suspicious of studies with small sample sizes that show uniformly positive results. These are just some of the indications of possible publication bias.[13]

Thus, when publication bias is suspected, the quality of the evidence should be downgraded by one level, or by two levels when the suspicion is robust. However, when the possibility of publication bias is unlikely, as in the case of funnel plot symmetry, or when the evaluator perceives that the systematic review involved an extensive search of the literature for unpublished studies, there is no need to downgrade the quality of the evidence.[3]

As an example, imagine a systematic review composed of 60 randomized clinical trials seeking to estimate the effects of a new insulin for treating diabetes. Among the studies included, 32 showed a positive effect estimate and all were published. Among the other 28 studies, which were seen as "negative", only 10 were published. A publication bias of this magnitude can significantly compromise estimates of the effect of bias, which is why the quality of evidence should be downgraded.[3]

The checklist's analysis of publication bias addresses questions about the breadth of the search strategy and the databases used, about language restrictions, about investigating whether the studies included were influenced by the industry, about funnel plot asymmetry and also about the possibility of discrepancies between published and unpublished trials.[4]

Thus, the objective is to investigate possible factors that could generate some type of publication bias. To assist in this analysis, the GRADE checklist proposes analysis on six questions:

1. Has a broad search been performed?
2. Was the gray literature sought out?
3. Were restrictions on study selection applied, based on language?
4. Was there any industry influence on the studies included in the review?
5. Is there any evidence of asymmetry in funnel plots?
6. Are there any discrepancies between published and unpublished findings among the studies?

The answers to these questions can also vary between the following: 1 = yes; 0 = uncertain; -1 = no; NA1 = not evaluated; or NA2 = not applicable. Through this, upon completion of the review, the assessor will be able to arrive at a transparent judgment of the risk of publication bias through the GRADE tool.[4]

Continue...

Although not included in the checklist, it is important to mention that another three factors are present in the GRADE system. These need to be evaluated with regard to the possibility of upgrading the level of evidence in observational studies. They comprise large magnitude of effect, presence of a dose-response gradient and residual confounders that increase confidence in the estimate. These factors were not analyzed through the tool, as it was designed specifically for systematic reviews of randomized clinical trials, and these three domains are recommended only in the context of systematic reviews of observational studies.[4]

Next, the factors that increase the quality of evidence in observational studies will be briefly analyzed since, as previously explained, the quality of evidence in these studies starts as low.

F – Magnitude of effect

It is important to emphasize that a decision to upgrade the quality of evidence should only rarely be taken if serious limitations are present in any of the five domains previously analyzed.[3]

That said, the next issue to be analyzed is situations of a large magnitude of effect. This may be responsible for raising the level of evidence by one or even two levels, whenever the magnitude of the effect identified in observational studies is large, especially if this effect is observed over a short period.[3]

This is because some interventions made by healthcare professionals present significant reliability, such as antihypertensive drugs for treating high blood pressure, with great confidence in their effectiveness. Thus, in cases in which there is a drastic reduction in the incidence of an outcome after the intervention, the level of evidence should be considered high, even if the evidence comes from observational studies.[6]

From this perspective, when the evidence from observational studies is not downgraded by any of the five domains described above and, in addition, the estimated magnitude of the intervention effect is large or very large, confidence in these results is considerable, thus raising the quality of the evidence. Therefore, it is important to note whether the effect is rapid and consistent, whether the previous disease course is actually reversed by the intervention, and whether the large magnitude of an effect is supported by indirect evidence. Given these analyses, it is possible to make an accurate judgment about this domain.[3]

G – Dose-response gradient

The presence of a dose-response gradient is a factor that indicates the occurrence of a cause-effect relationship, which is why it is considered to be another domain that increases the quality of evidence in observational studies.[3]

Thus, if the evaluator identifies a consistent increase in effect from increased exposure, such as the observation that patients receiving anticoagulant treatment with warfarin have a high dose-response gradient due to an increased risk of bleeding, it becomes possible to upgrade the quality of evidence attributable through the presence of a dose-response gradient.[3]

H – Residual confounders that increase confidence in the estimate

In observational studies, the quality of evidence starts as low. This is because in these studies there is a high possibility that unmeasured or unknown factors are not adequately balanced between the different groups evaluated, unlike when randomization is used in randomized clinical trials. This is characterized as residual confounding, with overestimation of the effect estimate.[3]

Consequently, in observational studies that have strong methodological rigor, factors associated with the outcomes of interest will be accurately account for, and analyses adjusting for differences in these factors between the intervention and control groups will be conducted. In such cases, the quality can be upgraded, given the evidence for the existence of residual confounders, thereby increasing the level of confidence in the estimate.[6]

As an example, imagine that a rigorous systematic review of observational studies was designed to assess the recovery rate among 30 million sick patients and that the number of patients in non-profit private hospitals was found to be greater than the number in for-profit private hospitals. The factors associated with the outcomes of interest were carefully analyzed and biases relating to the severity of diseases in patients in both types of hospitals were considered. From this, it was possible to upgrade the quality of the initially graded evidence, in view of the quality of the results found.[2]

DISCUSSION

The concept of evidence-based healthcare has been used by many professionals. Over the years, numerous systems have emerged as alternatives for classifying and grading the quality of published evidence. The GRADE Working Group is a collaborative working group that aims to minimize the deficiencies of existing classification systems within healthcare, and thus to develop a standardized system for classifying evidence in a transparent and sensible way.[5]

GRADE is already used in more than 110 organizations in 19 countries. Among these, the World Health Organization and the Cochrane Collaboration can be mentioned.[1] The strength of the study recommendation refers to the possibility that the object of analysis might be adopted or rejected, and this is normally carried out in the analysis of clinical guidelines and technical documents.[3]

It can be seen, then, that judgments about the strength of a recommendation go beyond the analysis of the quality of the evidence. Recommendations can be classified as strong or weak, and this is determined by weighing up the relationship between the advantages (such as improvement in quality of life or increased survival) and the disadvantages (including adverse effects, psychological burden or increased costs).[3]

CONCLUSION

The translation of this checklist into Portuguese, as reported in this article, provides another tool for assisting in understanding

and making better use of the GRADE system. It therefore provides an additional resource for evaluators who do not have much experience with the tool, or who have insufficient time or limited resources to carry out the assessment.

Lastly, it should be noted that GRADE is constantly evolving, due to advances in and development of its approach, with the aim of expanding its use in other areas, such as diagnostic accuracy, economic evaluation and prognosis. These expansions in its use certainly shows that GRADE has fundamental importance and, furthermore, extend assessment of healthcare technologies.[3]

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Use of artificial intelligence in ophthalmology: a narrative review

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ABSTRACT

BACKGROUND: Artificial intelligence (AI) deals with development of algorithms that seek to perceive one's environment and perform actions that maximize one's chance of successfully reaching one's predetermined goals.

OBJECTIVE: To provide an overview of the basic principles of AI and its main studies in the fields of glaucoma, retinopathy of prematurity, age-related macular degeneration and diabetic retinopathy. From this perspective, the limitations and potential challenges that have accompanied the implementation and development of this new technology within ophthalmology are presented.

DESIGN AND SETTING: Narrative review developed by a research group at the Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.

METHODS: We searched the literature on the main applications of AI within ophthalmology, using the keywords "artificial intelligence", "diabetic retinopathy", "macular degeneration age-related", "glaucoma" and "retinopathy of prematurity," covering the period from January 1, 2007, to May 3, 2021. We used the MEDLINE database (via PubMed) and the LILACS database (via Virtual Health Library) to identify relevant articles.

RESULTS: We retrieved 457 references, of which 47 were considered eligible for intensive review and critical analysis.

CONCLUSION: Use of technology, as embodied in AI algorithms, is a way of providing an increasingly accurate service and enhancing scientific research. This forms a source of complement and innovation in relation to the daily skills of ophthalmologists. Thus, AI adds technology to human expertise.

INTRODUCTION

Early diagnosis of eye diseases is of great importance for preventing loss of vision and thereby improving the quality of life. However, the teaching of ophthalmology has declined in medical schools, thus leaving general practitioners with the task and difficulty of identifying ocular pathological conditions.

In addition, there is irregular distribution of ophthalmology specialists in many countries, which makes it difficult for the population to access adequate eye care.[1] Within this scenario, artificial intelligence (AI) may offer an alternative that could increase the population's access to eye care.[2,3]

Formation of a convolutional layer is the basis of an algorithm. This transforms the input data through application of a set of filters to produce a final response (such as the output). Neural networks set weights on their own for the filters used during the training process. The filters are defined before the training phase but can be optimized during the learning process.

During the learning phase, algorithm performance can be improved. This phase can be supervised when data is assigned during training. It can also be unsupervised and, in this case, the device creates its own input sample.

The training and development phase of an algorithm is generally divided into training, validation and test data sets. These data sets should not be repeated: hence, an image that is in one of the data sets (for example, training) should not be used in any of the other data sets (for example, validation). The data set used during the training phase can be made as subsets and can be optimized through retro-propagation of the information collected.

The data set used in validation is used for selection of parameters and adjustments, and for implementation of training conditions. After the training phase, independent test data is used, captured using different devices, from different populations under different clinical contexts.

When examining the performance results from an algorithm, it is important to evaluate the methodology and the way in which it was developed. For example, an algorithm developed for analysis of fundus retinography may perform poorly if applied to a retinal photograph with a larger field.[4-9]

OBJECTIVE

The purpose of this article was to provide an overview of the basic principles of AI and its main studies in the fields of glaucoma, retinopathy of prematurity, age-related macular degeneration and diabetic retinopathy. From this perspective, the limitations and potential challenges that have accompanied implementation and development of this new technology within ophthalmology are presented.

METHODS

We searched the literature on the main applications of artificial intelligence within ophthalmology, using the keywords "artificial intelligence", "diabetic retinopathy", "macular degeneration age-related", "glaucoma" and "retinopathy of prematurity", covering the period from January 1, 2007, to May 3, 2021. We used the Medical Literature Analysis and Retrieval System Online (MEDLINE) database (via PubMed) and the Latin American and Caribbean Literature in Health Sciences (Literatura Latino-Americana e do Caribe em Ciências da Saúde, LILACS) database (via Virtual Health Library) to identify relevant articles.

Through this search, we selected and reviewed articles on the potential automated clinical applications of artificial intelligence technologies and big data analysis. A summary of the articles selected is provided below. The details of the search strategy are shown in **Table 1.**

RESULTS

From the search in the databases, one clinical trial, four meta-analyses, four randomized controlled trials, 47 reviews and four systematic reviews were identified. After screening the titles and abstracts, removing duplicates and screening the citations, 47 studies were considered eligible for critical analysis. The article selection process is detailed in **Figure 1**.

Diabetic retinopathy

Diabetes is the leading cause of blindness in adulthood, affecting more than 415 million people worldwide.[10,11] Recent studies on the use of AI for monitoring diabetic retinopathy have demonstrated that it has high precision for detecting this disease.[10,12,13]

In 2018, IDx-DR, which is an AI diagnostic system that autonomously diagnoses patients with diabetic retinopathy (including macular edema), was approved by the United States Food and Drug Administration (FDA) for classifying diabetic retinopathy. This was the first artificial intelligence device approved by that institution.

Ting et al.[12] evaluated the performance of artificial intelligence for screening for diabetic retinopathy, macular degeneration and glaucoma, using 494,661 images of the retina. This algorithm was then tested externally in 11 multiethnic cohorts. For detecting diabetic retinopathy, its sensitivity was 90.5% and specificity was 91.6%. For diabetic retinopathy with the risk of vision loss, its sensitivity was 100% and specificity was 91.1%. For macular degeneration, its sensitivity was 93.2% and specificity was 88.7%. For glaucoma, its sensitivity was 96.4% and specificity was 87.2%.

Tufail et al.[10] evaluated automated screening of patients with diabetic retinopathy by evaluating systems for automatic detection of diabetic retinopathy in comparison with human graders. EyeArt had sensitivity of 94.7% for detecting diabetic retinopathy and 93.8% for referable retinopathy (maculopathy, proliferative or pre-proliferative diabetic retinopathy). Retmaker had sensitivity of 73% for any retinopathy, 85% for referable retinopathy and 97.9% for proliferative retinopathy. AI models were trained to detect microaneurysms, retinal hemorrhages and hard or soft exudates. Retmaker is a system that has been used for screening diabetic retinopathy.[10]

Abràmoff et al.[14] evaluated an algorithm for automatic detection of diabetic retinopathy, with specificity of 59.45% and sensitivity of 96.8%. Gulshan et al.[15] developed an algorithm for screening diabetic retinopathy using 128,175 images of color fundus retinography, which had specificity of 90.3% and sensitivity of 98.1%, and

Table 1. Details of the search strategy

Database	Search strategies	Papers found
MEDLINE (via PubMed)	("artificial intelligence") and ("diabetic retinopathy")	226
MEDLINE (via PubMed)	("artificial intelligence") and ("macular degeneration age-related")	53
MEDLINE (via PubMed)	("artificial intelligence") AND ("glaucoma")	151
MEDLINE (via PubMed)	("artificial intelligence") and ("retinopathy of prematurity")	26
LILACS (via Biblioteca Virtual em Saúde)	("artificial intelligence") and ("diabetic retinopathy")	188
LILACS (via Biblioteca Virtual em Saúde)	("artificial intelligence") and ("macular degeneration age-related")	90
LILACS (via Biblioteca Virtual em Saúde)	("artificial intelligence") and ("glaucoma")	118
LILACS (via Biblioteca Virtual em Saúde)	("artificial intelligence") and ("retinopathy of prematurity")	21

LILACS = Latin American and Caribbean Literature in Health Sciences (Literatura Latino-Americana e do Caribe em Ciências da Saúde); MEDLINE = Medical Literature Analysis and Retrieval System Online.

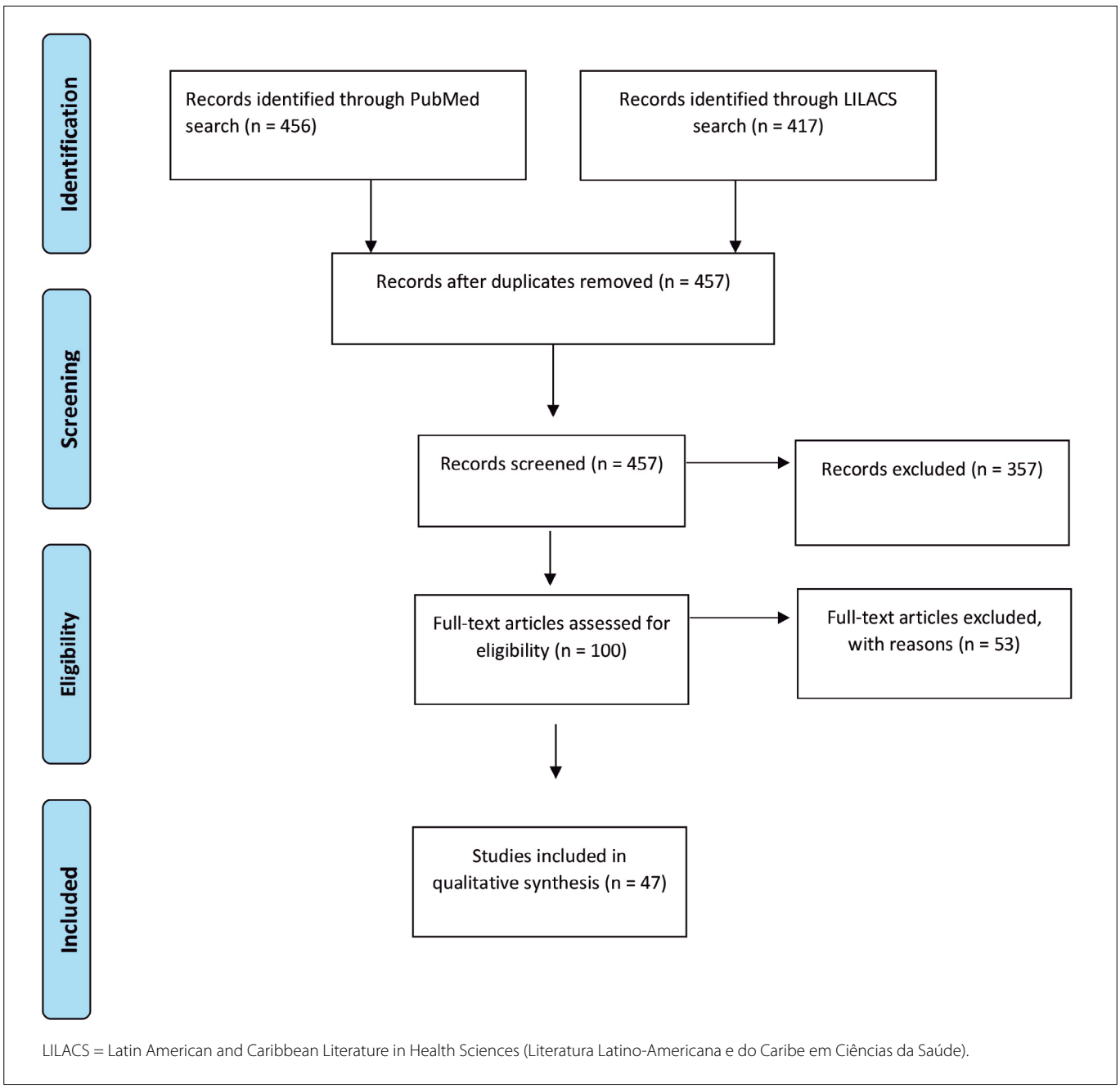
reached an area below the receiver operating characteristic (ROC) curve of 0.99 for detecting referable diabetic retinopathy.

Subsequently, Gulshan et al.[16] investigated use of an algorithm in 10 primary care centers for six months, which resulted in sensitivity of 87.2% and specificity of 90.8% for detecting clinically significant macular edema in at least one eye. This follow-up study emphasized the importance of testing an artificial intelligence algorithm in the real world.

Li et al.[13] developed an artificial intelligence-based model for detecting diabetic retinopathy based on the color of retinography photographs. Its sensitivity was 97.0% and specificity was 91.4%, as result of using more than 100,000 images. It reached an area below the ROC curve of 0.99 in validation and 0.955 in external validation using an independent multiethnic data set.

Gargeya et al.[17] published a study in which 75,137 fundus retinography photos from diabetic patients were used to train and test an artificial intelligence model. The model had sensitivity of 94% and specificity of 98%.

The data should preferably be validated using different camera systems and populations. Some diabetic retinopathy assessment



LILACS = Latin American and Caribbean Literature in Health Sciences (Literatura Latino-Americana e do Caribe em Ciências da Saúde).

Figure 1. Flow diagram of the study selection process.

systems only evaluate the central 45 degrees, close to the macula, and do not assess diabetic retinopathy lesions that may be occurring on the periphery of the patient's retina.[16]

Because of the great variation in the reference standards between different studies, it is difficult to compare the performance of the algorithms. To solve this challenge, algorithms could be tested on an independent data set with a single reference standard.

Age-related macular degeneration

Diabetic retinopathy and age-related macular degeneration (AMD) are the leading causes of blindness among adults over the age of 50 years in the United States. Just like in relation to diabetic retinopathy, development of algorithms for diagnosing and monitoring AMD has therefore been stimulated. AMD cases normally need to be referred to a tertiary-level eye service for clinical evaluation by experts.[18-20]

Algorithms evaluating color fundus photos

Ting et al.[12] used a database of 72,610 fundus retinography images to classify these patients into intermediate and advanced levels of macular degeneration, with sensitivity of 93.2% and specificity of 88.2%.

Burlina et al.[21] classified patients using software developed from 130,000 images on 4613 patients and reported that it showed 91.6% accuracy for identifying moderate and advanced macular degeneration. The findings from their study resulted in classification of these patients into four stages, ranging from 1 (without signs of macular degeneration) to 4 (advanced stage).

Grassmann et al.[22] tested an algorithm using 120,656 fundus retinography images from 3,654 patients and reported that it showed accuracy of 84.2% for differentiating between early and late macular degeneration and 94.3% for identifying healthy individuals. These investigators used 13 scales based on the Age-Related Eye Disease Study (AREDS), such that stage one showed no signs of degeneration of the macula, stages two to nine represented intermediate disease and stage ten represented the late stage of the disease.

Peng et al.[23] evaluated the severity and risk of progression of macular degeneration using fundus color photography. The performance of the algorithm was compared with that of retinal specialists, and it demonstrated accuracy of 0.94 for detecting large drusen, 0.93 for pigmentary abnormalities and 0.97 for advanced AMD.

Algorithms evaluating optical coherence tomography

Bogunovic et al.[24] developed a machine learning method for estimating a risk score and biomarkers associated with progression of macular degeneration in optical coherence tomography (OCT) examinations. In addition, Bogunovic et al.[25] evaluated an algorithm for analyzing OCT images in order to predict the best mode of treatment with intravitreal injection. The main predictive characteristic found in the latter study was the presence of subretinal fluid in the central 3 mm of the macular OCT image.

Schlegl et al.[26] developed an AI model for detecting and quantifying intra and subretinal fluid. This algorithm performed well in detecting these lesions in patients with macular degeneration and central retinal vein occlusion. The method had accuracy of 0.94 for detecting intraretinal fluid relating to macular degeneration, diabetic macular edema and retinal vein occlusion. The accuracy for detecting subretinal fluid was 0.92, with superior performance among patients with macular degeneration and retinal vein occlusion, compared with patients with macular edema due to diabetes.[27]

Venhuizen et al.[28] demonstrated the use of AI for classifying the severity of macular degeneration, with sensitivity of 98.2% and specificity of 91.2%. Using a database of 100,000 OCT B-scans (50% from examinations without alteration and 50% from examinations with macular degeneration), Lee et al.[29] reported that their algorithm showed accuracy of 87.6% with sensitivity of 84.6% and specificity of 91.5%. That algorithm was developed using images from OCT, diagnoses of macular degeneration provided by a specialist and worst vision of 20/30 in the better eye.

Thus, the main algorithms that have been developed are useful for detecting and segmenting injuries, estimating the risk of progression to advanced stages or evaluating the risk of conversion of dry AMD to an exudative form.

Glaucoma

Glaucoma is an important cause of loss of vision worldwide. In evaluating optic neuropathy, the cup disc needs to be characterized: its size and shape can vary between people. However, defining the cup disc is insufficient for diagnosing glaucoma, due to the large anatomical changes of the optic disc. Examination of the OCT retinal nerve fiber layer thickness and ganglion cell complex can be used for diagnosing glaucoma. Visual field examination is inexpensive and can be used to assess functional loss. However, the sensitivity and specificity of the diagnosis is lower than when a combination of visual field and OCT data is used.

Use of anatomical and functional data together is superior to anatomical data in isolation for diagnosing glaucoma. Artificial intelligence algorithms can combine these factors to aid in making diagnoses. In a study using a database of 125,189 fundus retinography images, Ting et al.[12] reported that their algorithm had sensitivity of 96.4% and specificity of 87.2% for detecting suspected glaucoma, defined as discs with an upper excavation of 0.8 and/or glaucomatous changes. Li et al.[30] evaluated a machine learning algorithm for detecting glaucoma based on 48,116 color fundus photographs, with sensitivity of 95.6%, specificity of 92% and an area under the ROC curve of 0.986. The main cause of false negatives in their study was patients with high myopia. Physiological excavation of the optic disc was the most common cause of false

positives in their study. A study using deep learning to classify suspected glaucoma using OCT examinations was developed to differentiate healthy eyes from initial glaucoma.[31]

Kim et al.[32] developed a model based on machine learning using three types of records including retinal nerve fiber layer thickness, visual field and ophthalmic clinical data. These investigators reported accuracy of 0.98, sensitivity of 0.983 and specificity of 0.975.

Ahn et al.[33] developed an algorithm that only required retinography data. Use of this limited data resulted in accuracy of 92.2% for identifying glaucoma cases. This model may be convenient with regard to helping with screening of glaucoma cases. Asaoka et al.[34] used artificial intelligence to analyze visual fields in patients with pre-perimetric open glaucoma and were able to differentiate them from patients with healthy eyes, with good accuracy (92.6%).

Using 3242 retinography images from eyes with confirmed glaucoma, Shibata et al.[35] developed a trained and tested algorithm, from which they reported an excellent area under the ROC curve, of 0.965. This algorithm was trained to detect cup size, optic disc notch, nerve fiber layer atrophy, peripapillary atrophy and optic disc hemorrhage.

Masumoto et al.[36] used 1,379 retinography images to detect glaucoma, and found 80.2% specificity and 81.3% sensitivity. The values were higher for severe cases of glaucoma.

Elze et al.[37] developed an AI system for identifying patterns of glaucomatous and non-glaucomatous visual field (VF) loss. Through an analysis on 13,231 reliable Humphrey VFs, they identified an ideal solution with 17 prototypes of glaucomatous vision loss. Algorithms show great difficulty in detecting the early stages of glaucoma when patients do not have defects in the visual field. Thus, studies using longitudinal data are needed in order to correctly identify patients who will develop glaucoma.

In patients with severe glaucoma, disease identification by means of algorithms usually has better results. However, caution needs to be exercised due to the great anatomical variability of optic nerves in populations, especially among patients with a high degree of myopia.

Retinopathy of prematurity

Retinopathy of prematurity (ROP), which has a prevalence of 6%-18%, is one of the main causes of loss of vision in childhood worldwide.[38] This disease, in its third epidemic, resulted in irreversible blindness in more than 50,000 premature newborns because of a shortage of trained specialists.[39,40]

Experts usually disagree about the clinical classification of ROP. In the cryotherapy (CRYO)-ROP study, the second examiner disagreed with the first regarding the diagnosis of threshold disease in 12% of the cases.[41] Also, in a multicenter telemedicine study on diagnosing ROP, almost 25% of the tests did not align with one of the three criteria for clinically significant ROP.[42]

The initial approaches to automated image analysis have been based on quantification of vascular tortuosity and vascular dilation. These systems were developed and validated for wide-angle RetCam images. They were evaluated based on the diagnoses of specialists but did not have any application in the real world because they are only semi-automated, thus requiring manual identification.[43]

The initial computational approaches for detecting this pathological condition focused on the vascular tortuosity of retinopathy of prematurity-plus (ROP-plus).[44] Recent work has suggested other possibilities for assessing vessel angles as resources for predictive values for this disease, using linear logistic regression models.[45]

Brown et al. developed and validated a fully automated deep learning system called informatics-retinopathy of prematurity deep learning (i-ROP DL), using a database of 5,511 retinography images obtained by means of a RetCam background camera. This enabled diagnosis of three levels of ROP (plus, pre-plus and normal), with an area under the ROC curve of 0.98 for a positive diagnosis of the disease, in comparison with a reference standard defined by specialists. The i-ROP DL system reached specificity of 94% and sensitivity of 93% for diagnosing ROP-plus and 94% specificity and 100% sensitivity for diagnosing ROP at pre-plus or worse levels.[46]

In an algorithm developed by Redd et al.,[47] an area under the ROC curve of 0.96 was found for identifying type 1 ROP and 0.91 for clinically significant ROP.[47] Xiao et al. developed an AI program that quantified the area of neovascularization in patients with ROP.[48] The AI program reached a higher range of correlation coefficients than that of specialists, for classification of areas with neovascularization. The algorithm works for quantification of key values of oxygen-induced retinopathy images, using deep learning neural networks. Ataer-Cansizoglu et al. developed an AI program with 95% accuracy for analyzing vascularization data.[49]

Current methods for detecting ROP can distinguish between mild and severe cases of ROP but are still unable to identify the stage of the disease.[50] Campbell et al.[51] demonstrated that automated diagnosis of ROP (i-ROP) had an accuracy of 95%, while the average accuracy of 11 specialists was 87%. Thus, algorithms with performance comparable to that of retinal specialists already exist.

DISCUSSION

Development of algorithms for diagnosing ophthalmic diseases requires many images in order to achieve a classification. When an algorithm is designed, the following need to be considered: the population in which it will be applied, whether it is aligned with current clinical evidence and whether use of the algorithm applies only to diagnosing the disease.[52]

Because diseases such as glaucoma, macular degeneration, diabetic retinopathy and retinopathy of prematurity have relatively high prevalence, this favors creation of algorithms, given the large

amount of data that has been documented. Rare diseases, with limited data, still present a challenge with regard to development of artificial intelligence programs. Among the topics selected for the present review, retinopathy of prematurity is one for which the fewest algorithms have been developed. This is thought to be due to the lower prevalence of this pathological condition in relation to the others analyzed and the greater difficulty in documenting data among preterm patients. Development of new portable devices that document retinopathy of prematurity may contribute towards development of new algorithms in the future.

Ethical and legal aspects should always be considered by groups that develop algorithms, with the aims of avoiding racial prejudice in healthcare and preserving fundamental rights to protection of personal data.

Currently, there are large databases (big data) of electronic medical records and digital images, which enable recognition of patterns in large volumes of data within a short period of time, thereby reducing errors in diagnostics and therapeutics and creating personalized medicine. In this context, a large database called Intelligent Research in Sight was created to store data on 17,363,018 patients from 7200 ophthalmologists in the United States, in order to improve individual care and public policies.[53]

The data of some algorithms can be used for three major groups of purposes: classification, segmentation and prediction. In classification, an image will be classified in different categories (presence or absence of disease, for example). This function is explored in disease screening and staging algorithms. In segmentation algorithms, different anatomical structures and lesions of importance in determining disease biomarkers are outlined. Prediction algorithms, on the other hand, address the relationship of data with future results, and thus help in estimating disease prognosis.

Some AI programs have multiple layers of information input and output, thus enabling a more efficient machine learning process that not only classifies the parameters, but also extracts the results. Most metrics within performance analysis have included calculation of sensitivity, specificity and the area under the ROC curve, which is calculated from sensitivity and specificity values. The closer to 1.0 that the area under the ROC curve reaches, the greater the sensitivity/specificity of the method is. Moreover, it is necessary to evaluate the sensitivity under a fixed specificity. An artificial intelligence system with a good area under the ROC curve may have low sensitivity at a high level of specificity, thus resulting in a high rate of false negatives (**Table 2**).[10,12,14-16,21-23,28-30,32-34,36,46,49,51]

It is important to highlight the reliability of the ground truth labels, which in ophthalmological studies are evaluations by specialists, who may nevertheless have divergent opinions. It is important that the sample used for training the algorithms should be specified.

Incorporation of machine learning technology within ophthalmology can improve medical care for the population in regions with limited medical resources, thus reducing some social inequalities.

Future directions, strengths and limitations

Development of enormous longitudinal studies to judge the artificial intelligence systems developed is important for assessing the real security and effectiveness of artificial intelligence systems. Narrative reviews contribute towards providing

Table 2. Comparison of accuracy, sensitivity, specificity and number and type of images analyzed

Authors	Pathological condition/ number of images analyzed	Precision
Ting et al.[12]	Diabetic retinopathy/76,370 images of retinal photographs	Sensitivity of 90.5% and specificity of 91.6%
Tufail et al.[10]	Diabetic retinopathy/20,258 images of retinal photographs	EyeArt (sensitivity of 93.8%) and Retmaker (sensitivity of 97.9%)
Abràmoff et al.[14]	Diabetic retinopathy/1,748 images of retinal photographs	Sensitivity of 96.8% and specificity of 59.4%
Gulshan et al.[15]	Diabetic retinopathy/9,963 images of retinal photographs	Sensitivity of 98.1% and specificity of 90.3%
Gulshan et al.[16]	Diabetic retinopathy/103,634 images of retinal photographs	Sensitivity of 87.2% and specificity of 90.8%
Ting et al.[12]	AMD/72,610 images of retinal photographs	Sensitivity of 93.2% and specificity of 88.2%
Burlina et al.[21]	AMD/130,000 images of retinal photographs	91.6% accuracy
Grassmann et al.[22]	AMD/120,656 images of retinal photographs	84.2% accuracy
Venhuizen et al.[28]	AMD/3,265 images of OCT	Sensitivity of 98.2% and specificity of 91.2%
Peng et al.[23]	AMD/58,402 images of retinal photographs	Accuracy of 97.0%
Lee et al.[29]	AMD/48,312 images of OCT	Sensitivity of 84.6% and specificity of 91.5%
Ting et al.[12]	Glaucoma/125,189 images of retinal photographs	96.4% sensitivity and 87.2% specificity
Li et al.[30]	Glaucoma/48,116 images of retinal photographs	Sensitivity of 95.6% and specificity of 92%
Kim et al.[32]	Glaucoma/399 images of visual field	Sensitivity of 98.3% and specificity of 97.5%
Ahn et al.[33]	Glaucoma/1,542 images of retinal photographs	92.2% accuracy
Asaoka et al.[34]	Glaucoma/171 images of visual field	92.6% accuracy
Masumoto et al.[36]	Glaucoma/982 images of visual field	Sensitivity of 81.3% and specificity of 80.2%
Brown et al.[46]	ROP/5,511 images of retinal photographs	93% sensitivity and 94% specificity
Ataer-Cansizoglu et al.[49]	ROP/77 images of retinal photographs	95% accuracy
Campbell et al.[51]	ROP/77 images of retinal photographs	95% accuracy

AMD = age-related macular degeneration; OCT = optical coherence tomography; ROP = retinopathy of prematurity.

updates on the medical knowledge available. These reviews help in formulating new research projects based on interpretation of the results from published studies after non-systematic analysis. New studies that use algorithms that combine analysis on OCT images, fundus retinography and visual fields can be useful for diagnosing and evaluating multiple pathological conditions simultaneously.[12]

Development of algorithms with real-time cloud information analysis is often helpful within the management and monitoring of eye diseases. However. studies need to be carried out with the aim of preventing certain decisions made by algorithms from going beyond certain ethical and moral precepts that have been established by society. Biases in data collection can substantially affect the generalization of the trained model beyond the population in which it was trained.

Thus, further studies are needed, with algorithms developed in different populations. The data used for external validation should come from a geographically distinct population, with validation by independent researchers.[54] Studies should be developed with protocols that promote transparency in clinical trials, in order to validate the use of algorithms.[55]

The current algorithms have been developed to evaluate two-dimensional images. Incorporation of multimodal images in the training of the algorithms can facilitate identification of three-dimensional ocular pathological conditions.

The articles included in this review generated heterogeneous data because of the diversity in the design of the studies. The main limitation of this review was the lack of tools for methodological assessment of the reviews. In addition, this narrative review does not provide quantitative answers to specific questions about studying artificial intelligence.

CONCLUSION

Use of technology, as embodied in artificial intelligence algorithms, is a way of providing an increasingly accurate service and enhancing scientific research. This forms a source of complement and innovation in relation to the daily skills of ophthalmologists. Thus, artificial intelligence adds technology to human expertise.

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Neuromodulation in acute traumatic brain injury: a tool in the rehabilitation process that needs to be investigated

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Dear Editor,

In 2014, while one of us (FZSA) was working towards his doctorate, he had the opportunity to follow about 200 patients who had suffered severe head trauma (traumatic brain injury, TBI), from the first day after the trauma until one year later. In relation to these cases, a variety of hypothetical questions arose: Could noninvasive brain stimulation (NIBS) help to contain the advancement of neurotoxicity, help with reorganization after brain injury and optimize brain neuroplasticity? In addition to the question of whether it was effective, would it be safe? What would be the barriers?

At that time, studies investigating the effects of NIBS in patients suffering from TBI had been conducted,[1-3] but none of them related to acute patients.

So far, little progress has been made in neuromodulation studies on this type of patient.[4] In fact, neuromodulation is a consolidated form of treatment for various neurological problems consequent to diseases such as depression, stroke, pain and others.[5] Neurophysiological effects are known in the literature, although some questions about mechanisms exist in relation to some diseases.[6]

However, various questions remain to be addressed in relation to TBI. This condition is a major public health problem worldwide and there is a need to move forward regarding its treatment. Neuromodulation may therefore form an important tool in the rehabilitation process for this disease condition.[7]

Many barriers exist in relation to how NIBS is performed in critically ill patients, especially with regard to transcranial direct current stimulation (TDCS) and transcranial magnetic stimulation (TMS). The issues involved include safety, clinical instability, extent of the injury, unfavorable hospital environment, heterogeneity of the injuries of TBI patients and treatment adherence after hospital discharge.[8] One interesting study showed good results from use of NIBS among patients with acute stroke and, although each condition has its specific characteristic, that study highlights the potential for use of NIBS among patients with acute brain injury in general.[1]

One of the great challenges in proposing clinical trials to test use of NIBS among patients with acute TBI concerns safety, considering that these are patients with great clinical instability. Thus, neurological stability needs to be ensured, given that patients with acute brain injury have high incidence of epilepsy, for example.[2] Another great challenge for researchers in preparing the study design is to fit the protocols to the sample homogeneity, considering that TBI cases are complex and have different characteristics. These complexities and differences form a great barrier to applying pre-established protocols such patients. Hence, patients' individuality needs to be respected and application of protocols and assemblies of equipment close to the target have to be guided by very careful evaluation. Use of tools such as functional magnetic resonance imaging, electroencephalograms, positron emission tomography (PET) scans and neuronavigation may perhaps be essential.[2]

Although results are only available from a few studies, methodologically well-designed works with good numbers of patients and with follow-ups need to be envisaged, so that not only can the effects of stimulation be identified over the short term, but also it can be known whether the effects persist. Identification of clinical predictors to identify possible impacts of acute-phase

variables on the outcomes of patients undergoing NIBS can also be suggested. In this way, it can be ensured that subjecting patients to stimulation retains a good cost-benefit relationship and is safe.

A wide range of measurements of effects is required, given that the sequelae of patient suffering from TBI have a wide spectrum. Therefore, motor, cognitive, psychiatric, functional and quality-of-life factors need to be assessed, without neglecting the patients' biopsychosocial characteristics. Among these measurements of effects, it can also be suggested that brain injury and recovery should be evaluated through biomarkers. This can strengthen the biological plausibility of the effects and be correlated with patients' clinical and functional improvements.

However, answers regarding the effects of NIBS on acute patients with head trauma over the short, medium and long terms are far from being obtained. The uncertainties are compounded by difficulties in designing and conducting a robust clinical trial. One interesting path would be to elaborate a feasibility study to identify barriers and facilitators regarding this approach among this type of patients. This could form an important study that would help in shaping the most appropriate methodology for clinical trials and even help in decision-making and clinical care for these patients.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

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

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

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

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

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

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Acknowledgements and funding

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

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

Authorship

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

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

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

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- they fail to adhere to the format for text and figures described here.

After peer review

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

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

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

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

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

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

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

Covering letter

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

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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;
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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;
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8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
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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;
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- 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.
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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.

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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.

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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.

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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.

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

DOCUMENTS CITED

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Conheça o Programa de Educação em Telemedicina e Saúde Digital da APM

O Programa de Educação em Telemedicina e Saúde Digital da APM foi desenvolvido para proporcionar conhecimentos e experiências para a prática dos profissionais nestas áreas.
A telemedicina é um método de cuidados às pessoas, e como tal, é fundamental a capacitação para seu uso com segurança, ética e qualidade.
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Inscreva-se

*Estes cursos têm como pré-requisito a realização do Curso Modular em Telemedicina do IESAPM

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APM
ASSOCIAÇÃO PAULISTA DE MEDICINA

III CONGRESSO BRASILEIRO DE NEUROGENÉTICA

9, 10 e 11 de março de 2023

SÃO PAULO - SP

O 3º Congresso Brasileiro de Neurogenética vai oportunizar o encontro dos congressistas com a fronteira do conhecimento em neurogenética e com informações essenciais para a prática clínica, para que possamos nos entusiasmar com os avanços científicos e trocas de informações, nos tornar mais ternos ao compartilharmos casos clínicos e experiências no cuidado de pacientes, para que juntos possamos elevar ainda mais o patamar da Neurogenética clínica brasileira.

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