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Are we preparing for the digital healthcare era?

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At a handful of moments over the history of human society, major revolutions have given rise to profound social changes. The creation of the wheel, Gutenberg's press machine, electricity, the telephone and, more recently, the internet have all changed human history.[1] Another tipping point was reached in early 2020, with the advent of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Although the coronavirus disease 2019 (COVID-19) pandemic cannot in itself be credited for the radical change in healthcare that has been experienced over the last two years, there is no doubt that the digital transformation of healthcare has accelerated worldwide because of this pandemic.[2,3]

In talking about the change that healthcare is going through, from the analogue to the digital world, many people may think that certain simplistic actions (such as "computerizing the process") will be enough to overcome the challenges imposed in this 21st century, in which we are increasingly digital beings. Perhaps they think that it will be enough to "digitize" healthcare as it is today and everything will be better, more beautiful and technological.

However, the process is not that simple. The patient healthcare system has developed centered on physical locations to which we are require to travel. All of this involves time: time to come or go; time to wait for care that never seems to arrive; and time to wait for the diagnosis. This time can often represent the patient's chance of survival or death. In the current healthcare model, which is now outdated, we must go to where the infrastructure and professionals are, in order to receive diagnoses and care. Digital healthcare is now changing this.

When the internet first became available for the public to use, in the late 1990s, many opportunities to apply digital technologies to healthcare were considered. Some were more like science fiction (such as autonomous robotic telesurgery), and others we already see today as a reality of our daily care, such as telemedicine.[4]

To illustrate the role that the pandemic played in the adoption of telemedicine, many hospitals were able to benefit from teleconsultation platforms and teleconsultation services to remotely assist patients in ICUs, train multidisciplinary teams and thus fight COVID-19. The Instituto do Coração of Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP) was one of the leaders in this movement in Brazil, having implemented a TeleICU service in record time to support several hospitals in the state of São Paulo that were on the front line of care for patients with COVID-19. The results so far have shown the great benefit of this telemedicine technological platform.[5]

New terms that were not part of our health vocabulary until recently, such as artificial intelligence, machine learning, virtual reality, big data, blockchain and wearables, among others, are revealing that we are now entering a completely new field, both for ordinary citizens and for medical professionals.

Another matter that needs to be considered is the change in the population's culture due to the arrival of these new technologies. We have seen how our habits have changed through the popularization of mobile phones, starting in the 1990s, and very recently, through the new wave of digital habits that have arisen with the growth in smartphone use. We now have devices with which there is no longer any need to make traditional phone calls. Instead, internet-based interactive messaging apps can be used to record and send audio, texts or images. We keep on communicating, only differently!

The market for new wearables and remote diagnostic solutions is growing all the time and is expected to reach US$ 116 billion by 2025, according to studies by specialized companies.[6] Today, this has become a new area of medicine and healthcare that is bringing in a revolution in the very way of understanding patients through the data that can be collected from them, thereby telling a much more trustworthy story of their health and habits.[7]

Time magazine featured the front-cover headline "Never Offline" in its September 11, 2014, edition.[8] The article highlighted the global launch of the Apple watch (a watch in the smartwatch category). An editorial mentioned: "The Apple Watch is just the beginning. How wearable technology will change your life - like it or not." After seven years, we can say they were right: we are now more connected than ever. We generate more data about ourselves than in all previous centuries put together. Today, with the technological resources available and those to come, we can monitor a huge variety of physiological, behavioral and emotional parameters of all human beings that are in some manner connected to this large digital data network that constitutes the internet.[9] Nonetheless, are we aware of what is really happening?

Issues of individual data protection, invasion of privacy, cybersecurity, interoperability, inclusive digital culture for the population (so as not to generate a new society of digitally excluded people), etc., are on the agenda today.[10,11] The implementation of digital healthcare is not only a matter of creating electronic clinical protocols, but also one of educating everyone involved: from physicians and healthcare professionals to patients and their caregivers. We are truly entering a digital social revolution.[12,13]

We are now born and are living "plugged into" the digital world. In healthcare terms, exabytes of data (big data) about our DNA, laboratory tests, clinical images and medical history, from electronic medical records registered in the blockchain, will increasingly become available. Data will also come from the wearables and smartphones that we use. All of these data will be analyzed through computers that make use of sophisticated artificial intelligence and exponential machine learning (machine learning and deep learning). Therefore, with regard to this essential issue of digital healthcare, which will determine much of our present and future, there is an absolute requirement for us to prepare ourselves for this today.

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Leydig and Sertoli cell function in individuals with genital ambiguity, 46,XY karyotype, palpable gonads and normal testosterone secretion: a case-control study

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ABSTRACT

BACKGROUND: Because normal male sexual differentiation is more complex than normal female sexual differentiation, there are more cases of disorders of sex development (DSDs) with 46,XY karyotype that have unclear etiology. However, Leydig and Sertoli cell markers are rarely used in distinguishing such individuals.

OBJECTIVES: To evaluate the function of Leydig and Sertoli cells in individuals with genital ambiguity, 46,XY karyotype, palpable gonads and normal testosterone secretion.

STUDY DESIGN AND SETTING: Case-control study with 77 patients, including eight with partial androgen insensitivity syndrome, eight with 5α-reductase deficiency type 2 (5ARD2) and 19 with idiopathic 46,XY DSD, and 42 healthy controls, from the Interdisciplinary Study Group for Sex Determination and Differentiation (GIEDDS), at the State University of Campinas (UNICAMP), Campinas, Brazil.

METHODS: Baseline levels of gonadotropins, anti-Müllerian hormone (AMH), inhibin B, insulin-like 3 (INSL3), testosterone and dihydrotestosterone in cases, and AMH, inhibin B, and INSL3 levels in controls, were assessed.

RESULTS: There was no significant difference in age between cases and controls ($P = 0.595$). AMH and inhibin B levels were significantly lower in cases than in controls ($P = 0.031$ and $P < 0.001$, respectively). INSL3 levels were significantly higher in cases than in controls ($P = 0.003$). Inhibin B levels were lower in 5ARD2 patients ($P = 0.045$) and idiopathic patients ($P = 0.001$), in separate comparisons with the controls.

CONCLUSION: According to our findings, we can speculate that inhibin B levels may be used to differentiate among DSD cases.

INTRODUCTION

Ambiguous genitalia are the most complex clinical manifestation of disorders of sex development (DSDs), an umbrella term that is used for congenital conditions characterized by atypical chromosomal, gonadal or anatomical development.[1] Because normal male sexual differentiation involves more genetically determined and hormonal events than those in normal female sexual differentiation, DSDs with 46,XY karyotype present greater etiological complexity.

Among the main etiologies of patients with genital ambiguity, 46,XY karyotype and normal testosterone secretion, partial androgen insensitivity syndrome (PAIS) (OMIM #312300) potentially presents with clinical features indistinguishable from those of other etiologies, particularly those of 5α-reductase type 2 deficiency (5ARD2) (OMIM #264600).[2] Both diagnoses are solely confirmed on the basis of molecular alterations in specific genes, which is a costly procedure and thus conducted at only a few centers.[3] Routine measurement of the function of Leydig cells, including testosterone and dihydrotestosterone (DHT) levels, is not always effective for differentiating PAIS from 5ARD2.[3,4]

There is a lack of data regarding insulin-like 3 (INSL3), which is also produced by Leydig cells, in relation to management of DSDs.[4] In some studies, high levels of anti-Müllerian hormone (AMH), a marker for Sertoli cells, were observed in patients with androgen insensitivity.[5-7] However, in patients with 5ARD2, low levels have been reported in only two studies.[8,9] Inhibin B is a good marker for Sertoli cells and gonadal function; nevertheless, data on cases of androgen

insensitivity and 5ARD2 remain limited.[4] Moreover, the role of these Leydig and Sertoli cell markers in patients with idiopathic 46,XY DSDs and genital ambiguity remains unclear.

OBJECTIVE

The aim of this study was to evaluate the function of Leydig cells (testosterone, dihydrotestosterone [DHT] and INSL3) and Sertoli cells (AMH and inhibin B) in patients with 46,XY DSDs and genital ambiguity.

METHODS

Patients and control group

The inclusion criteria were palpable gonads (in the scrotal and/or inguinal region, bilaterally), 46,XY karyotype and normal testosterone secretion during etiological investigation of genital ambiguity. The *AR* (OMIM *313700), *SRD5A2* (OMIM *607306) and *NR5A1* (OMIM *184757) genes were sequenced in all patients included in this study. All patients with PAIS had *AR* mutations, all patients with 5ARD2 had *SRD5A2* mutations and patients with idiopathic 46,XY DSDs had no mutations in these three genes sequenced.

The patients were selected from a sample of 408 patients first reported in 2016,[10] who had been diagnosed with DSDs between 1989 and 2016 by the Interdisciplinary Study Group for Sex Determination and Differentiation (GIEDDS) at the Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil. In this sample, among 189 individuals with 46,XY karyotype and both testicles, 107 patients had normal testosterone secretion. Among these 107 patients, 10 were diagnosed with PAIS (five prepubertal, four pubertal and one gonadectomized), 20 with 5ARD2 (five prepubertal, eight pubertal and seven gonadectomized) and 77 with idiopathic 46,XY DSDs (15 prepubertal, 61 pubertal and one gonadectomized). Furthermore, among these 107 patients, 98 met the inclusion criterion (not gonadectomized) for this study. However, only 54 continued with routine follow-up at the DSD outpatient clinic and, among these, 35 (65%) provided consent to participate in this study.

The control group comprised males aged three months to 40 years, including in-hospital patients, postgraduate students and their family members, with no comorbidities resulting in altered testicular function. The exclusion criteria for the control group were the following: birth weight less than 2500 g, previous history of genital ambiguity, hypospadias, varicocele, unilateral or bilateral cryptorchidism, infections or any disorder in the testicles, moderate-to-severe traumatic lesions in the testicles, testicular neoplasia, adrenal disease and use of testicular function-altering or gonadal axis-altering drugs.

This study was approved by the Research Ethics Committee of our institution (protocol number CEP: 434/2006, approved on August 26, 2014) and was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical evaluation

Upon recruitment, patients were clinically evaluated with regard to the following variables: age (in months), weight (in kg), height (in cm) and body mass index (BMI; in kg/m^2). These values were converted to z-scores using the NCHS 2000 data. Moreover, the patients' stage of puberty was assessed, and the patients were then classified as pubertal (Tanner stage ≥ 2) or pre-pubertal (Tanner stage 1). Furthermore, the following data were obtained from medical records: birth weight (in g), birth length (in cm) and features of the genitalia at initial presentation. The grade of masculinization of the genitalia was determined on the basis of the external masculinization score (EMS), in accordance with the method described by Ahmed et al.[11]

Laboratory evaluation

Karyotyping was performed at the cytogenetics laboratory at our institution, with a minimum count of 32 sets of metaphases. Only patients with a homogeneous 46,XY karyotype were included in the study.

For hormonal evaluation, the baseline levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, DHT, AMH, inhibin B and INSL3 were determined for all patients. Furthermore, all prepubertal patients underwent a stimulation test using human chorionic gonadotropin (hCG) (1,500 IU/d; via intramuscular injection on three consecutive days), and testosterone and DHT levels were measured 24 hours after the last dose. Testosterone secretion was considered normal in individuals presenting a total increase in testosterone of 1.5 ng/ml after stimulation relative to baseline levels.[3,12] In these cases, only testosterone and DHT levels after hCG administration were evaluated. Only baseline AMH, inhibin B and INSL3 levels were measured in the control group. Blood samples were collected through peripheral vein puncture, and serum was extracted via centrifugation at 2000 ×*g* for 10 minutes and was stored at -20 °C until evaluation.

Hormonal assays

The following hormonal assays were performed: LH, electrochemiluminescence (Roche Elecsys 2010, Roche Diagnostics, Switzerland); FSH, electrochemiluminescence (Roche Elecsys 2010); testosterone, electrochemiluminescence (Roche Elecsys 2010); DHT, enzyme immunoassay (ELISA, DIAsource, Belgium); AMH, enzyme immunoassay (AMH Gen II ELISA, Beckman-Coulter, Pasadena, CA, United States); inhibin B, enzyme immunoassay (Inhibin B ELISA RUO, Ansh Labs, Webster, TX, United States); and INSL3, enzyme immunoassay (Insulin-Like Protein 3 ELISA, Cloud-Clone Corp., China).

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., Chicago, IL, United States). The Shapiro-Wilk test was performed to verify data normality. Because most data were not normally distributed, we performed nonparametric tests. To compare variables between two groups (cases versus controls and pre-pubertal versus pubertal groups), the Mann-Whitney U test for independent samples was performed. To compare groups in accordance with the diagnoses (PAIS, 5ARD2 and idiopathic), the Kruskal-Wallis test was performed, followed by a multiple-comparisons test with Bonferroni adjustments to determine the differences among the groups, if necessary. Additionally, multivariate linear regression analysis using the stepwise method was performed to verify the influence of the dependent variables (age, puberty, weight, height, BMI, weight z-score, height z-score, BMI z-score, EMS, birth weight and birth length), with regard to explaining the variation in the expression of INSL3, inhibin B and AMH markers. The puberty variable was analyzed as a dummy (0 = no puberty and 1 = puberty). The linear regression parameters were presented as values of the unstandardized coefficients: beta (β) ± standard error and as values of the adjusted explanation coefficient (r^2). The significance level was set at 5% ($P < 0.05$).

RESULTS

Among the 35 patients included in the study, eight had PAIS (five prepubertal and three pubertal), eight had 5ARD2 (three prepubertal and five pubertal) and 19 were idiopathic (13 prepubertal and six pubertal). The baseline clinical and laboratory data of all the patients included are summarized in **Table 1**. The control group comprised 42 individuals aged 137.7 ± 125.9 months (mean ± standard deviation; median = 123 months, minimum = 3 months, and maximum = 408 months). Age (in months) at the time of the current assessment was not significantly different between cases and controls (Mann-Whitney U test; P = 0.595).

Regarding baseline levels among patients, no significant difference (Kruskal-Wallis test) was observed among the three subgroups with regard to age (months) at the current evaluation (P = 0.509), weight (P = 0.260), height (P = 0.257), BMI (P = 0.084), z-score of BMI (P = 0.375), EMS at initial presentation (P = 0.057), birth weight (P = 0.142), FSH (P = 0.320), LH (P = 0.169), testosterone (P = 0.122), DHT (P = 0.485), and testosterone-DHT ratio (T/DHT) (P = 0.989). However, significant differences (Kruskal-Wallis test) in the z-scores of current weight (P = 0.003) and height (P = 0.024) were observed, such that both of these were lower in the idiopathic group only, compared with the PAIS group. In contrast, length at birth was significantly shorter in the idiopathic group than in the 5ARD2 group (P = 0.030) (**Table 1**).

AMH levels were inversely proportional to age, with a moderate correlation between cases (r = -0.68; P < 0.0001) and controls (r = -0.83; P < 0.0001). Subgroup analysis revealed that this age-based correlation was strong in the 5ARD2 group (r = -0.95; P < 0.0001) and moderate in the idiopathic group (r = -0.71;

Table 1. Baseline clinical and laboratory data of the 35 cases with 46,XY DSDs

	PAIS (n = 8)			5ARD2 (n = 8)			Idiopathic (n = 19)			P-value
	Median	Min	Max	Median	Min	Max	Median	Min	Max	
Age (months)	92	46	430	196	5	469	98	9	217	0.509
Weight (kg)	29	16	91	54	9	90	27	7	65	0.260
Height (cm)	130	102	169	168	68	180	129	68	169	0.257
BMI (kg/m²)	16.6	15.3	32.0	19.6	18.0	27.6	16.3	12.3	24.5	0.084
Weight (z-score)	**1.5**	**-0.02**	**2.4**	1.0	-1.5	1.5	**-0.2**	**-3.1**	**1.4**	**0.003***
Height (z-score)	**0.4**	**-0.9**	**2.6**	0.6	-1.3	1.0	**-0.9**	**-3.1**	**0.9**	**0.024***
BMI (z-score)	0.4	-1.2	3.0	1.0	-0.9	1.5	0.3	-3.6	1.3	0.375
EMS	6	5	9	4	2	9	6	5	9	0.057
Birth weight (g)	2910	1510	3950	2900	1500	3500	2290	700	3600	0.142
Birth length (cm)	46	42	52	**49**	**43**	**53**	**44**	**31**	**49**	**0.033†**
FSH (IU/l)[a]	1.48	0.67	6.44	7.60	0.25	35.07	0.96	0.42	16.28	0.320
LH (IU/l)[a]	0.15	0.10	14.71	6.22	0.10	16.93	0.14	0.10	6.17	0.169
Testosterone (ng/ml)[b]	2.09	1.51	8.72	5.08	1.83	10.97	3.18	1.53	7.79	0.317
DHT (pg/ml)	103.10	52.70	674.40	362.65	37.60	1652.20	148.10	25.90	1454.80	0.472
T/DHT	21.0	7.5	30.0	14.7	6.6	54.0	19.8	2.5	59.1	0.697

DSD = disorders of sex development; PAIS = partial androgen insensitivity syndrome; 5ARD2 = 5α-reductase type 2 deficiency; Min = minimum; Max = maximum; BMI = body mass index; EMS = external masculinization score; FSH = follicle-stimulating hormone; LH = luteinizing hormone; DHT = dihydrotestosterone; T = testosterone.

[a]Baseline levels of all subjects; [b]Post-human chorionic gonadotropin (hCG) levels in prepubertal subjects, baseline levels in pubertal subjects; *Significant differences between PAIS and 5ARD2 groups (post-hoc adjustment through Bonferroni test); †Significant differences between 5ARD2 and idiopathic groups (post-hoc adjustment through Bonferroni test).

P = 0.001), but not significant in the PAIS group (r = -0.33; P = 0.420). Furthermore, AMH was positively correlated with inhibin B only in the idiopathic group (r = 0.56; P = 0.039): there was only a positive correlation between these two hormones in this group, among all the groups (r = 0.55; P = 0.002). On the other hand, this correlation was not observed in relation to the 5ARD2 (r = 0.061; P = 0.148) and PAIS (r = 0.19; P = 0.651) subgroups. Serum AMH levels were significantly lower in cases than in the control group (P = 0.031). Nonetheless, subgroup comparisons with the control group and among the groups did not reveal any significant differences in AMH levels (**Table 2**).

Inhibin B levels could not be evaluated in one case with 5ARD2 (aged 27 years 10 months) and in five cases in the idiopathic subgroup (aged 1 year 5 months, 6 years 6 months, 7 years 3 months, 8 years 2 months and 8 years 4 months). Inhibin B levels were evaluated in all patients in the PAIS and control groups, and no correlation with age was observed, either among cases or controls. As described above, inhibin B was positively correlated with AMH only in the idiopathic group. Inhibin B levels were significantly lower in cases than in controls (P < 0.001) (**Table 2**). Comparison of all subgroups of cases (PAIS, 5ARD2 and idiopathic) with the control group and with each other only showed significantly lower values in the 5ARD2 (P = 0.045) and idiopathic groups (P = 0.001) than in controls, using Bonferroni's adjusted multiple comparison test (**Table 3**). No significant differences were observed in subsequent comparisons.

INSL3 levels could not be evaluated in one case with 5ARD2 (aged 18 years), two cases in the idiopathic subgroup (aged 8 years 4 months and 18 years 1 month) and 11 controls (aged 10 months, 11 months, 1 year 7 months, 2 years 1 month, 2 years 10 months, 8 years 3 months, 14 years 1 month, 14 years 10 months, 28 years, 29 years and 34 years). INSL3 was not significantly correlated with age in any of the groups analyzed (controls: r = 0.251; p = 0.177; PAIS: r = 0.000; p = 1.00; 5ARD2: r = -0.236; P = 0.610; and idiopathic: r = -0.202; P = 0.437). Moreover, INSL3 levels were not correlated with inhibin B (controls: r = -0.327; P = 0.072; PAIS: r = -0.195; P = 0.643; 5ARD2: r = -0.213; P = 0.686; and idiopathic: r = 0.000; P = 1.00) or AMH levels (controls: r = -0.182; P = 0.328; PAIS: r = 0.053; P = 0.773; 5ARD2: r = 0.059; P = 0.900; and idiopathic: r = 0.100; P = 0.703). Intergroup comparisons revealed that INSL3 levels were significantly higher in cases than in controls (P = 0.003) (**Table 2**). Subgroup comparisons among each other and with the control group revealed higher values in the 5ARD2 and PAIS subgroups than in the control group; however, these differences were not significant (Bonferroni test) (**Table 3**).

Table 4 shows the hormone levels in pubertal and pre-pubertal individuals in each subgroup. In pre-pubertal individuals, none of the hormone levels differed significantly among the three subgroups of etiological diagnosis (Kruskal-Wallis test, P > 0.05). However, among pubertal individuals, serum inhibin B levels (Kruskal-Wallis test, P = 0.040) and AMH levels (Kruskal-Wallis test, P = 0.036) were significantly higher in the PAIS group than in the 5ARD2 and idiopathic groups.

In the stepwise multivariate linear regression analysis, we observed that among all the variables analyzed, the weight z-score ($\beta = 0.006 \pm 0.003$; P = 0.049) significantly explained 12% of the

Table 2. Comparison of anti-Müllerian hormone, inhibin B and INSL3 levels between cases and controls

	Cases					Controls					P-value
	n	Median	IQR	Min	Max	n	Median	IQR	Min	Max	
Age (months)	35	100.00	135.00	9.00	469.00	42	123.00	162.25	3.00	408.00	0.595
AMH (pMol/l)	35	**243.51***	228.52	8.96	295.85	42	292.90	314.07	20.06	420.55	< 0.001
Inhibin B (pg/ml)	29	**65.14***	106.86	14.18	381.37	42	151.59	149.86	57.11	926.84	0.003
INSL3 (ng/ml)	32	**0.35***	0.03	0.33	3.51	31	0.21	0.26	0.10	1.04	0.031

INSL3 = insulin-like 3; IQR = interquartile range; AMH = anti-Müllerian hormone; Min = minimum; Max = maximum.
*Significant differences, compared with the controls (independent-samples Mann-Whitney U test).

Table 3. Comparison of anti-Müllerian hormone, inhibin B and INSL3 levels between subgroups of cases and controls

	n	PAIS		n	5ARD2		n	Idiopathic		n	Control	
		Median	IQR		Median	IQ		Median	IQR		Median	IQ
Age (months)	8	92.0	267.7	8	196.5	259.5	19	98.0	113.0	42	123.0	162.2
AMH (pMol/l)	8	261.50	112.37	8	42.05	243.15	19	247.04	210.84	42	292.90	314.04
Inhibin B (pg/ml)	8	93.49	156.59	7	**50.70***	**101.41**	14	**59.52†**	**81.89**	42	**151.59**	**149.86**
INSL3 (ng/ml)	8	0.36	0.04	7	0.35	0.05	17	0.35	0.02	31	0.21	0.26

INSL3 = insulin-like 3, PAIS = partial androgen insensitivity syndrome; 5ARD2 = 5α-reductase type 2 deficiency; IQR = interquartile range; AMH = anti-Müllerian hormone.
*Significant difference (lower values), compared with the control group (post-hoc adjustment through Bonferroni test; P = 0.045); †Significant difference (lower values), compared with the control group (post-hoc adjustment through Bonferroni test; P = 0.001).

Table 4. Comparison of laboratory data among the three subgroups of cases, according to the presence or absence of puberty

	Partial androgen insensitivity syndrome			5α-reductase type 2 deficiency			Idiopathic		
	Puberty								
	Yes (n = 3)	No (n = 5)	P	Yes (n = 5)	No (n = 3)	P	Yes (n = 6)	No (n = 13)	P
LH (IU/l)	7.65 ± 3.76	0.10 ± 0.02	0.036*	11.03 ± 2.07	0.10 ± 0.30	**0.036***	4.52 ± 0.61	0.10 ± 0.39	**0.001***
FSH (IU/l)	1.91 ± 1.57	1.16 ± 0.22	0.143	14.05 ± 5.18	0.91 ± 0.39	**0.036***	9.19 ± 2.48	0.88 ± 0.60	**0.001***
Testosterone (ng/ml)	7.95 ± 2.10	1.82 ± 0.26	0.143	5.32 ± 1.20	2.03 ± 2.71	0.393	3.57 ± 0.80	2.06 ± 0.47	0.127
DHT (pg/ml)	571.90 ± 185.36	86.80 ± 33.89	0.393	496.60 ± 246.36	60.30 ± 65.68	**0.036***	566.75 ± 167.49	113.80 ± 18.81	**0.001***
T/DHT	15.25 ± 4.89	24.71 ± 4.14	0.571	8.78 ± 2.06	41.02 ± 6.83	**0.036***	6.95 ± 1.96	23.45 ± 4.40	**0.001***
AMH (pMol/l)	169.65 ± 61.28	279.49 ± 21.68	0.786	31.92 ± 3.40	274.82 ± 6.41	**0.036***	42.30 ± 10.83	253.43 ± 18.86	**0.001***
Inhibin B (pg/ml)	219.51 ± 18.80	81.30 ± 11.73	**0.036***	42.32 ± 25.93	57.11 ± 109.58	0.400	50.34 ± 25.87	61.53 ± 24.45	0.662
INSL3 (ng/ml)	0.36 ± 0.02	0.35 ± 0.01	1.000	0.36 ± 0.01	0.35 ± 0.02	1.000	0.34 ± 0.01	0.35 ± 0.26	0.234

LH = luteinizing hormone; FSH = follicle-stimulating hormone; DHT = dihydrotestosterone; T = testosterone; AMH = anti-Müllerian hormone; INSL3 = insulin-like 3.
*Statistical difference between puberty (yes) and prepuberty (no) in the same diagnosis, through the Mann-Whitney test (median ± standard error of the mean).

INSL3 variations ($r^2 = 0.121$); the BMI z-score ($\beta = -27.342 \pm 12.972$; $P = 0.047$) significantly explained 13% of the variation in inhibin B ($r^2 = 0.130$); and body weight ($\beta = -3.812 \pm 0.499$; $P < 0.001$) significantly explained 68% of the variation in AMH ($r^2 = 0.680$).

DISCUSSION

To our knowledge, our study was the first to evaluate the function of Leydig and Sertoli cells in patients with genital ambiguity, 46,XY karyotype, palpable gonads and normal testosterone secretion. This particular group of DSDs was selected because of the difficulty in distinguishing such patients, especially those with 5ARD2 and PAIS, which comprise most 46,XY DSDs, based on clinical and laboratory findings before puberty.[2,10] Thus, the present study provides promising results, especially with regard to inhibin B levels.

Our results show that the severity of external genital ambiguity, evaluated on the basis of the EMS, did not differ among these three subgroups of 46,XY DSDs with normal testosterone secretion. From a clinical viewpoint, the only difference observed was the shorter length at birth and the lower z-scores for height in the idiopathic group. These findings have already been reported previously because approximately 10%-25% of cases of 46,XY DSDs with no defined etiology are associated with intrauterine growth restriction.[13-15]

Furthermore, the present study confirmed that traditional methods of evaluation, such as measurement of the levels of gonadotrophins (LH and FSH) and androgens (testosterone, DHT and T/DHT), are not sufficient to differentiate among the subgroups analyzed. Currently, the recommendations indicate use of more sensitive methods, including mass spectrometry or other hormone markers, for this evaluation.[16,17] However, Chan et al. reported that even with highly sensitive methods, androgen evaluation may be ineffective in differentiating among 46,XY DSD individuals with normal testosterone secretion.[18]

Serum AMH levels were low in all groups of 46,XY DSD individuals, relative to the control group. However, serum AMH levels were not a useful parameter for differentiating among the three subgroups of our study, in line with the findings from previous studies[5,6,8] and with the current DSD consensus.[19]

Inhibin B, which was not indicated as a diagnostic marker in the 2016 DSD consensus,[19] was also evaluated in this study. It has been demonstrated to be an useful parameter in evaluating DSDs, especially among individuals with 46,XY karyotype.[20,21] The clinical significance of inhibin B is particularly evident in cases of cryptorchidism, which is a frequent clinical manifestation in patients with 46,XY DSDs with normal testosterone secretion; and in assessing fertility, which is an important aspect in DSD management.[22-26] Studies on cryptorchidism have revealed an association between inhibin B levels and testicular volume, and have suggested that inhibin B acts as a marker for testicular recovery after treatment for cryptorchidism.[22,23]

Some studies evaluating inhibin B levels in patients with infertility have reported that a direct association between this hormone and sperm parameters was observed, which would suggest that inhibin B is also a good marker for spermatogenesis.[24-26] Moreover, serum inhibin B levels are low in individuals with 46,XY gonadal dysgenesis,[27] and in some cases, this disorder may present even with normal serum testosterone levels.[28] In such cases, inhibin B could be used for differential diagnosis and in the prognosis for gonadal viability.

From a physiological point of view, inhibin B is useful for assessing 46,XY DSDs because it is present at measurable levels for most of an individual's lifespan.[21,29] In addition, this hormone is already present at measurable levels at birth, even in cord blood samples, and its level increases more rapidly during the first week of life, unlike the levels of the hormones traditionally used to assess genital ambiguities (e.g. testosterone and AMH).[29-31]

Furthermore, the present study showed that, similar to AMH, inhibin B levels were lower in cases than in controls. No age-related changes were observed in inhibin B levels; however, again similar to AMH, inhibin B levels were higher in pubertal patients in the

PAIS group than in those in the 5ARD2 and idiopathic groups.[7] In general, the 5ARD2 and idiopathic groups displayed lower inhibin B levels than those of the controls. This finding indicates that individuals with 5ARD2 potentially have defects in Sertoli cell maturation.[32,33] Moreover, DHT potentially influences spermatocyte growth and differentiation,[32] thus explaining the reduction in inhibin B levels in this group. These findings suggest that inhibin B has good potential as a biochemical marker that can differentiate patients with 5ARD2 from those with PAIS. Similar results were obtained previously among idiopathic individuals.[20] However, it is difficult to establish a causal relationship because the underlying etiology is unclear, although differences in height at birth suggest that there may be an association with intrauterine growth restriction.

INSL3 levels were higher in cases than in controls, which suggests that the etiology of 46,XY DSDs involves not only normal testosterone secretion but also the functioning of preserved Leydig cells. INSL3 levels may increase from the intrauterine period onwards. Anand-Ivell et al. reported that individuals with ambiguous genitalia (hypospadias and cryptorchidism) had elevated levels of INSL3 in the amniotic fluid in the second trimester, compared with those in controls.[34] Analyzing the groups separately, the 5ARD2 and PAIS groups showed an increasing trend with regard to INSL3 levels, compared with individuals in the control group. This trend may have been associated with two functional aspects of INSL3: firstly, this hormone may be present at high levels to protect against apoptosis in germ cells,[35,36] a mechanism that is potentially exacerbated in individuals with 5ARD2 and PAIS, thus resulting in infertility;[36] and secondly, this increment in INSL3 levels is potentially associated with its induction of steroidogenesis in the context of both relative (5ARD2) and partial (PAIS) androgen insufficiency.[32,37-39]

Another potential explanation for this increment in INSL3 levels is Leydig cell hyperplasia. This has been already reported among individuals with 5ARD2 and PAIS at puberty, occurring after LH hyperstimulation through a negative feedback mechanism in 5ARD2, with reductions in DHT and in PAIS, owing to testosterone activity.[33] However, further research on INSL3 behavior in 46,XY DSD patients is required in order to elucidate this trend.

Multivariate analysis was performed, and no data that would correlate the findings regarding inhibin B, AMH and INSL3 levels with puberty, age and anthropometric data were found, except for weight and BMI. However, there was low explanatory power for these two variables.

One limitation of this study was the small cohort, which may have influenced the statistical power of some of our findings. However, it should be noted that it is not easy to recruit individuals with such rare disorders, through molecular diagnosis at a single center. In addition, the lack of evaluation of testicular histology and its correlation with hormonal levels formed another study limitation, thus further restricting the elucidation of cellular patterns. However, gonadal biopsy is not usually performed for management of 5ARD2 and PAIS.

CONCLUSIONS

To our knowledge, our study was the first to report that individuals with 5ARD2 have low levels of inhibin B, thus suggesting that this hormone may be a biochemical marker that can differentiate the diagnosis of 5ARD2 from that of other etiologies with a similar clinical presentation (particularly PAIS). Our study was also the first to report that INSL3 levels were higher in patients with 46,XY karyotype, palpable gonads and normal testosterone secretion. However, further evaluation of each etiological group analyzed is necessary. Lastly, for differentiation of these groups, the AMH levels did not show promising results.

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Are physical inactivity, sitting time and screen time associated with obstructive sleep apnea in adults? A cross-sectional study

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ABSTRACT

BACKGROUND: Sitting time, screen time and low physical activity (PA) levels have been associated with several diseases and all-cause mortality. PA is related to better sleep quality and absence of daytime sleepiness, along with lower risks of obstructive syndrome apnea (OSA). However, studies on the relationship between sitting time, screen time and OSA are scarce in the literature.

OBJECTIVE: To analyze associations between PA levels, sitting time, screen time and OSA among adults with suspected sleep disorder.

DESIGN AND SETTING: Cross-sectional study conducted at Hospital Israelita Albert Einstein.

METHODS: Data were collected from 369 adults with suspected sleep disorders who visited the hospital's neurophysiology clinic between August 2015 and January 2017.

RESULTS: Correlations between hypopnea and PA indicators were demonstrated for total sitting time (0.123; P = 0.019) and total screen time (0.108; P = 0.038). There was also a correlation between latency for rapid-eye-movement sleep (REM_LAT) and total sitting time (0.103; P = 0.047) and a negative correlation between mean oxyhemoglobin saturation (SaO_Avg) and total PA time (-0.103; P = 0.048). There were no associations between PA parameters and apnea-hypopnea index. After adjusting for confounding factors (body mass index, age and gender), sitting time and screen time were not associated with OSA.

CONCLUSION: After adjusting for anthropometric and clinical factors, excessive sitting time or screen time was not associated with OSA in adults suspected of sleep disorders. Age, gender, hypertension, body mass index and waist circumference were associated with OSA.

INTRODUCTION

Obstructive syndrome apnea (OSA) is characterized by repetitive collapse of the upper airways during sleep and is defined by an apnea-hypopnea index (AHI) ≥ 15 events / hour, with reduced airflow, oxygen desaturation and sleep interruption.[1] OSA is associated with chronic diseases such as hypertension, metabolic comorbidities and increased all-cause mortality.[2-5]

The potential serious adverse consequences of untreated OSA are a major reason for emphasizing early diagnosis and treatment.[6,7] The main risk factors for OSA are obesity, age, cranial issues and gender (men).[6,8,9] Moreover physical activity (PA) levels and sedentary behavior (SED, characterized as sitting time, screen time and low energy expenditure)[10] have been identified as new risk factors for most chronic diseases, such as cardiovascular disease, diabetes and some cancers.[11-13] There is evidence demonstrating associations between these risk factors and OSA.[14]

Although previous studies have explored the association between OSA, PA and SED, no study has analyzed these associations using overnight polysomnography (PSG) as a method for diagnosing OSA.

OBJECTIVE

The purpose of this study was to analyze associations between PA levels, SED and OSA among adults with suspected sleep disorders that were diagnosed at a neurophysiology laboratory for OSA.

METHODS

This study had a cross-sectional design. The ethics committee of Hospital Israelita Albert Einstein approved the study protocol (SGPP: 1.150.084/2015 and CAAE: 45354215.4.0000.0071; date: July 15, 2015). Subsequently, individuals who visited the neurophysiology clinic at this hospital between August 2015 and January 2017 were invited to participate and signed a written consent statement in order to participate. The following inclusion criteria for participation were adopted: age over 18 years and indication for undergoing overnight laboratory PSG due to suspected OSA. Patients were excluded if they were already receiving treatment for OSA, had a disease that would make it impossible to complete the questionnaires or had technical problems during the overnight laboratory PSG.

Overnight laboratory polysomnography

All individuals participated in an overnight laboratory PSG as previously described.[15-17] Individuals were prepared between 8:30 pm and 10:30 pm and were woken up between 6:00 am and 7:00 am, when the recording was ended. The following signals were recorded: electroencephalograms (C3M2, C4M1 and O2M1), bilateral electrooculograms, electromyograms of the chin muscles and right and left anterior tibialis, movement of the rib cage and abdomen (piezoelectric crystal), oxygen saturation (SaO_2) from pulse oximetry, electrocardiogram (lead 1) and body position. Airflow was assessed from nasal airway pressure and oronasal thermistry. Trained PSG technicians, blinded to the study, positioned the patients and monitored them throughout the night, as recommended in the American Academy of Sleep Medicine Manual.[10] Apnea events were defined as ≥ 90% airflow reduction for ≥ 10 seconds. Hypopnea events were defined as ≥ 30% airflow reduction in association with ≥ 3% drop in oxygen desaturation or sleep fragmentation. To classify the presence and severity of OSA, the cutoff points for apnea were used: ≥ 15 and < 30 events/hour (moderate apnea); and ≥ 30 events/hour (severe apnea).[18,19]

Physical activity and sedentary behavior

To analyze PA levels and SED, we used the International Physical Activity Questionnaire (IPAQ),[20] which evaluates frequency, intensity and duration of physical activity, classifying individuals into four categories (very active, active, non-active and sedentary), as well as evaluating the total sitting time and screen time per week and at weekends.[21-24] Cutoff scores were used for sitting and screen time using different models (model 1: < 6 and ≥ 6 hour/day; model 2: < 10 and ≥ 10 hour/day) and different PA levels, according to the criteria below:

a- Active individuals, in line with the following recommendations for PA: (1): a) vigorous: ≥ 5 days / week and ≥ 30 minutes per session and/or b) vigorous: ≥ 3 days/week and ≥ 20 minutes per session + moderate PA and/or c) walking: ≥ 5 days / week and ≥ 30 minutes per session; or (2): a) vigorous: ≥ 3 days/week and ≥ 20 minutes per session and/or b) moderate or walking: ≥ 5 days / week and ≥ 30 minutes per session and/or any activity accumulated: ≥ 5 days / week and ≥ 150 minutes/week (walking + moderate +vigorous);

b- Inactive individuals, who did PA but insufficiently to be classified as active because they did not comply with the recommendations regarding frequency or duration. In this classification, we included the frequency and duration of different types of activities (vigorous + moderate + walking). Thus, individuals were considered inactive if they met at least one of the criteria of the recommendation regarding frequency or duration of the activity: a) frequency: 5 days/ week or b) duration: 149 minutes/week; or if they failed to perform continuous physical activity for at least 10 minutes during the week.

Anthropometric and study covariates

The characteristics of interest included age, gender, body mass index (BMI), waist circumference and presence of hypertension (HTN). Anthropometric assessments of height, body weight and abdominal circumference were made in accordance with standard procedures.

Body weight was determined by using the InBody 270 scale (Ottoboni, Rio de Janeiro, Brazil). Individuals positioned themselves on this calibrated scale by placing their feet (without socks or shoes) on the metal region of the platform, with feet facing forward. Height was determined using a stadiometer with an accuracy of 0.1 mm. Individuals were positioned with their heels, gluteal scapulas and occipital surfaces in contact with the wall. During the measurement, the individuals performed inspiratory apnea, looking to the horizon, and at that point the evaluator placed the cursor of the stadiometer on the apex of the head. The measurement was performed three times and the final result was the mean of the three measurements.

From these measurements, the individuals' BMI was calculated. The classification adopted for BMI followed the criteria outlined by the World Health Organization for adults: eutrophic (18.5-24.9 kg/m²); overweight (25.0-29.9 kg/m²); and obese (≥ 30.0 kg/m²).

For waist circumference (WC) measurements, individuals remained in the orthostatic position, with a relaxed abdomen. A tape measure was positioned in the horizontal plane at the midpoint between the last costal arch and the iliac crest. Measurements were made three times and the final result was the mean of the three measurements. The cutoff point for waist circumference measurements was in accordance with the World Health Organization guidelines for adults: men ≥ 94 cm and women ≥ 80 cm; and for elderly people: men ≥ 102 cm and women ≥ 88 cm.

Blood pressure was measured in accordance with international standards, using an aneroid sphygmomanometer with a Dormed pedestal (Dormed, Belo Horizonte, Minas Gerais, Brazil). In the supine position, the arms were kept alongside the body, one of them with a slightly abducted cuff; for patients with an extremely developed thorax, cushions were used to secure the arm at the level of the heart. HTN was considered present when the blood pressure was ≥ 140/90 mmHg. In addition, patients with a history of HTN and patients who were using antihypertensive medications were considered to have HTN.

Statistical analyses

Multinominal models were constructed for each explanatory variable and for each outcome. The odds ratio (OR) was calculated with the respective confidence interval and P-value.

The first model compared moderate (15 ≥ AHI ≥ 30) with absent apnea (< 15 AHI), and the second model compared severe (≥ 30 AHI) with absent apnea. Pearson's correlation coefficients were used to evaluate the relationships between weekly PA indicators (total physical activity time, total sitting time and total screen time) and sleeping indicators monitored by means of PSG. In addition, groups formed by the combination of PA time (active or inactive) with screen time (short or long time) were compared with sleep indicators obtained by means of PSG, using generalized linear models. Different probability and bond function distributions were tested, and the best-fit model was chosen in accordance with the AIC44 fit quality criterion.

The results were presented as mean values estimated through the models at 95% confidence intervals. In comparing the groups formed by the combination of PA time (active or inactive) with sitting time (short or long time), the same procedure was used for the analysis as was used for groups investigating screen time. Multiple logistic regression models were built to investigate the relationship between PA level and SED, controlling for age, gender and BMI.

All the analyses were done using the Statistical Package for the Social Sciences (SPSS) software, version 21 (IBM, SPSS Inc., Chicago, United States),[25] and the significance level used was 5%.

RESULTS

Table 1 shows the demographic data of the sample, together with the ORs of the variables in relation to OSA severity. The sample was characterized as middle-aged (between 34 and 56 years old); 66.94% were men; and there was high prevalence of overweight or obesity in OSA presence (between 25.88 and 34.58 kg/m^2). The diagnosis of HTN was observed in 16.29% of participants without OSA, 26.44% of those with moderate OSA and 30.77% of those with severe OSA, respectively. Clinical characteristics such as male gender, obesity, elevated WC and HTN presence were associated with moderate and severe OSA among individuals with suspected sleep disorders.

Table 1. Association between obstructive syndrome apnea severity obtained from polysomnography and anthropometric factors

Variable	Presence of obstructive syndrome apnea			OR [95% CI (moderate to absent)]	P-value	OR [95% CI (severe to absent)]	P-value
	AHI < 15	15 ≥ AHI < 30	AHI ≥ 30				
Age (years)							
Mean (SD)	42.05 (11,95)	46.94 (11.18)	48.67 (12)	1.04 [1.01; 1.06]	0.002	1.05 [1.03; 1.07]	< 0.001
Median [Q1; Q3]	42.00 [34.00; 49.75]	47.00 [39.50; 54.00]	48.00 [39.00; 56.25]				
N	178	87	104				
Gender							
Women	84 (47.19%)	19 (21.84%)	19 (18.27%)	1 (Reference)		1 (Reference)	
Men	94 (52.81%)	68 (78.16%)	85 (81.73%)	3.20 [1.78; 5.76]	< 0.001	3.99 [2.24; 7.12]	< 0.001
N	178	87	104				
BMI (kg/m^2)							
Mean (SD)	26.72 (4.41)	28.95 (4.66)	31.25 (5.22)	1.12 [1.05; 1.19]	< 0.001	1.22 [1.15; 1.29]	< 0.001
Median [Q1; Q3]	26.45 [23.38; 29.12]	28.40 [25.88; 30.79]	30.70 [27.67; 34.58]				
N	178	87	104				
WC							
0	48 (30.97%)	13 (19.4%)	8 (9.76%)	1 (Reference)		1 (Reference)	
1	107 (69.03%)	54 (80.6%)	74 (90.24%)	1.86 [0.93; 3.73]	0.08	4.15 [1.85; 9.28]	0.001
N	155	67	82				
Hypertension							
Absence	149 (83.71%)	64 (73.56%)	72 (69.23%)	1 (Reference)		1 (Reference)	
Presence	29 (16.29%)	23 (26.44%)	32 (30.77%)	1.85 [0.99; 3.43]	0.05	2.28 [1.28; 4.06]	0.005
N	178	87	104				

AHI = apnea-hypopnea index (events per hour); BMI = body mass index; WC = waist circumference; CI = confidence interval; OR: odds ratio. Waist circumference category 0: men < 94 cm and women < 80 cm; elderly men: < 102 cm and elderly women: < 88 cm. Waist circumference category 1: men ≥ 94 cm and women ≥ 80 cm; elderly men: ≥ 102 cm and elderly women: ≥ 88 cm. Data are presented as mean, median and standard deviation.

The correlation between PA and SED indicators (total physical activity time, sitting time and screen time) and sleep indicators from PSG are shown in **Table 2**. The correlation coefficients obtained indicated that there was a low correlation between REM_LAT and total sitting time (r = 0.103; P = 0.047) and a low negative correlation between SaO_Avg and total PA time (r = -0.103; P = 0.048). In addition, no correlations were found between AHI and total physical activity time (r = 0.084, P = 0.107), total sitting time (r = 0.067, P = 0.202) or total screen time (r = 0.036, P = 0.485).

Screen time and physical activity

Comparisons of sleep indicators obtained from PSG in relation to PA level and screen time are shown in **Table 3**. For this evaluation, four groups were created, combining the levels of PA: active (≥ 150 minutes) or inactive (< 150 minutes) with short screen time (< 6 hours and < 10 hours) or long screen time (≥ 6 hours and ≥ 10 hours). We observed differences between the groups in terms of percentage REM sleep (%REM; P = 0.030) and awakening from sleep (SLEEP_WAKE, P = 0.028). In relation to %REM, the average for the inactive group with short screen time was lower than the averages for the inactive group with long screen time (P = 0.019) and the active group with long screen time (P = 0.032). In relation to SLEEP_WAKE, the average for the inactive group with short screen time was higher than the average for the active group with short screen time (P = 0.044). Moreover, we did not see any evidence of differences between PA indicators in PSG measurements (P > 0.05 in all comparisons).

Sitting time and physical activity

Table 4 shows the comparisons between sleep indicators obtained from PSG in relation to the levels of PA and sitting time using the same combinations of screen time. Using the 6-hour cut-off time it was not possible to adjust the models to compare these groups. In the adjusted models for comparing the PA and sitting time group, considering the 10-hour cutoff, no evidence of differences in PSG measurements (P > 0.05 in all comparisons) were found between the groups.

Logistic regression analysis: sitting time and screen time.

Multiple-approach logistic regression models were built in order to explain physical inactivity and sitting time (**Table 5**) or screen time (**Table 6**), with adjustments for age, gender and BMI. We found no evidence of association between physical inactivity and sleep quality (P > 0.05 in all analyses).

Table 2. Correlation between coefficients of measurements of physical activity indicators (total physical activity time, total sitting time and total screen time) and sleep quality indicators obtained from polysomnography, among patients who underwent the examination

Polysomnography	TAFT	P	TST	p	TTT	P
TTR	-0.062	0.237	0.003	0.960	0.038	0.473
SLEEP_LAT	-0.049	0.350	-0.043	0.409	0.035	0.498
REM_LAT	-0.057	0.278	0.103	0.047*	0.013	0.810
TTS	-0.013	0.805	0.035	0.504	0.036	0.488
%NI	-0.054	0.302	0.046	0.378	0.033	0.522
%NII	0.018	0.736	0.026	0.613	0.058	0.268
%NIII	0.005	0.931	-0.033	0.529	-0.064	0.223
%REM	0.037	0.478	-0.042	0.421	-0.035	0.504
SLEEP_WAKE	-0.028	0.593	0.001	0.987	-0.057	0.272
NARO	-0.094	0.073	0.072	0.169	0.034	0.521
IND_NARO	-0.097	0.063	0.047	0.369	0.049	0.351
RESP_BREAKS	-0.079	0.130	0.089	0.088	0.045	0.386
APNEA	-0.069	0.185	0.032	0.544	-0.022	0.667
OBS_APNEA	-0.080	0.126	0.048	0.361	-0.007	0.896
CENT_APNEA	-0.006	0.904	-0.063	0.227	-0.051	0.330
MIX_APNEA	-0.001	0.978	-0.010	0.855	-0.016	0.766
HYPOPNEA	-0.075	0.151	0.123	0.019*	0.108	0.038*
SaO_Avg	-0.103	0.048*	0.021	0.689	0.063	0.227
SaO_Min	0.066	0.208	-0.074	0.155	0.039	0.459
%SAO	-0.042	0.418	-0.016	0.755	-0.042	0.420
AHI	-0.084	0.107	0.067	0.202	0.036	0.485

Data are shown as Pearson correlation coefficients. TAFT = total physical activity time; TST = total sitting time; TTT = total screen time; TTR = total recording time; SLEEP_LAT = sleep latency; REM_LAT = REM sleep latency; TTS = total sleep time; %NI = percentage sleep stage 1; %NII = percentage sleep stage 2; %NIII = percentage sleep stage III; %REM = percentage REM sleep; SLEEP_WAKE = awakening from sleep; NARO = nightly arousals; IND_NARO = nightly arousals index; RESP_BREAKS = respiratory breaks; OBS_APNEA = obstructive apnea; CENT_APNEA = central apnea; MIX_APNEA = mixed apnea; HYPOPNEA = hypopnea; SaO_Avg = average oxygen saturation; SaO_Min = minimum oxygen saturation; %SAO = percentage oxygen apnea; AHI = apnea-hypopnea index (events per hour). *P < 0.05.

Table 3. Estimated average values and 95% confidence intervals for sleep quality indicators obtained from polysomnography, among patients undergoing the examination according to physical activity and screen time

PSG	Physical activity time and screen time (< 6 h or ≥ 6 h)					Physical activity time and screen time (< 10 h or ≥ 10 h)				
	Inactive with short screen time (n = 31)	Inactive with long screen time (n = 135)	Active with short screen time (n = 32)	Active with long screen time (n = 171)	P-value	Inactive with short screen time (n = 65)	Inactive with long screen time (n = 101)	Active with short screen time (n = 91)	Active with long screen time (n = 112)	P-value
TTR	449.4 (433.7; 464.3)	442.2 (434.6; 449.6)	437.4 (421.4; 452.6)	439.5 (432.7; 446.2)	0.654	448.8 (438.0; 459.1)	440.2 (431.4; 448.8)	439.3 (429.9; 448.3)	439.1 (430.7; 447.3)	0.497
SLEEP_LAT	22.8 (14.0; 37.2)	23.6 (18.7; 29.8)	16.3 (10.1; 26.3)	17.6 (14.3; 21.7)	0.230	20.5 (14.7; 28.8)	25.5 (19.4; 33.3)	17.2 (12.9; 22.9)	17.6 (13.6; 22.8)	0.165
REM_LAT	111.5 (77.0; 161.3)	99.6 (83.5; 119.0)	118.6 (82.4; 170.7)	106.3 (90.8; 124.4)	0.828	104.3 (80.8; 134.6)	100.2 (81.6; 123.0)	116.2 (93.7; 144.2)	101.8 (83.8; 123.7)	0.765
TTS	350.3 (327.7; 371.3)	367.2 (357.2; 376.9)	376.0 (355.7; 394.7)	371.6 (362.9; 380.0)	0.265	365.7 (351.1; 379.6)	363.1 (351.3; 374.4)	369.4 (357.2; 381.0)	374.6 (363.9; 384.9)	0.513
%NI	10.1 (8.0; 12.8)	9.6 (8.6; 10.7)	8.6 (6.8; 10.7)	9.5 (8.6; 10.5)	0.774	9.3 (7.9; 10.9)	9.9 (8.7; 11.3)	9.3 (8.1; 10.7)	9.4 (8.3; 10.6)	0.897
%NII	56.8 (53.4; 60.3)	53.9 (52.3; 55.5)	57.5 (54.2; 61.1)	53.8 (52.4; 55.2)	0.095	54.0 (51.7; 56.2)	54.7 (52.9; 56.5)	53.9 (52.0; 55.8)	54.7 (53.0; 56.5)	0.881
%NIII	16.9 (13.9; 19.9)	16.5 (15.1; 18.0)	15.2 (12.2; 18.1)	17.4 (16.1; 18.7)	0.540	17.9 (15.8; 20.0)	15.8 (14.1; 17.4)	17.3 (15.6; 19.1)	16.8 (15.3; 18.4)	0.403
%REM	14.7 (12.3; 17.1)	18.7 (17.5; 19.8)	18.2 (15.9; 20.6)	18.3 (17.3; 19.3)	0.030*	17.7 (16.0; 19.4)	18.1 (16.7; 19.4)	18.7 (17.3; 20.1)	17.9 (16.7; 19.2)	0.810
SLEEP_ WAKE	62.4 (47.8; 81.5)	41.4 (36.5; 47.1)	37.1 (28.6; 48.3)	44.2 (39.5; 49.5)	0.028*	50.0 (41.5; 60.2)	42.0 (36.2; 48.7)	44.9 (38.3; 52.5)	41.6 (36.1; 47.9)	0.412
NARO	118.9 (92.9; 152.2)	113.3 (100.6; 127.5)	100.0 (78.4; 127.5)	113.3 (102.0; 125.9)	0.770	113.5 (95.7; 134.6)	114.8 (100.1; 131.7)	105.4 (91.3; 121.7)	115.9 (101.8; 132.0)	0.780
IND_NARO	21.2 (16.3; 26.7)	20.3 (18.0; 22.9)	17.0 (12.7; 21.9)	18.8 (16.8; 21.0)	0.513	19.3 (16.0; 22.9)	21.3 (18.5; 24.3)	17.8 (15.1; 20.7)	19.1 (16.6; 21.8)	0.397
RESP_ BREAKS	130.1 (85.4; 198.2)	113.5 (92.8; 138.9)	76.0 (50.2; 115.0)	105.8 (88.4; 126.6)	0.285	121.0 (90.5; 161.9)	113.7 (90.0; 143.6)	88.1 (68.9; 112.6)	111.7 (89.5; 139.4)	0.321
APNEA	3.8 (2.0; 6.5)	2.4 (1.7; 3.2)	3.0 (1.5; 5.2)	2.5 (1.9; 3.3)	0.566	3.0 (1.9; 4.4)	2.4 (1.6; 3.3)	2.5 (1.7; 3.6)	2.7 (1.9; 3.7)	0.882
OBS_ APNEA	2.1 (1.0; 3.9)	1.2 (0.8; 1.7)	1.3 (0.5; 2.6)	1.3 (0.9; 1.8)	0.584	1.8 (1.2; 2.9)	1.1 (0.8; 1.5)	1.4 (1.0; 2.0)	1.3 (0.9; 1.7)	0.349
CENT_ APNEA	0.67 (0.25; 1.23)	0.51 (0.31; 0.73)	0.70 (0.28; 1.26)	0.59 (0.40; 0.80)	0.838	0.56 (0.27; 0.90)	0.52 (0.29; 0.78)	0.52 (0.28; 0.80)	0.68 (0.44; 0.96)	0.786
MIX_ APNEA	0.34 (0.05; 0.72)	0.23 (0.09; 0.39)	0.29 (0.01; 0.65)	0.28 (0.15; 0.42)	0.924	0.32 (0.11; 0.56)	0.21 (0.06; 0.39)	0.30 (0.12; 0.50)	0.27 (0.11; 0.45)	0.883
HYPOPNEA	88.1 (61.1; 126.9)	90.4 (75.9; 107.6)	56.9 (39.6; 81.6)	82.3 (70.4; 96.1)	0.155	86.1 (66.8; 110.8)	92.5 (75.5; 113.2)	69.6 (56.2; 86.2)	85.1 (70.2; 103.1)	0.278
SaO_Avg	93.4 (92.5; 94.1)	93.4 (93.0; 93.8)	93.7 (93.0; 94.5)	93.5 (93.2; 93.9)	0.837	93.2 (92.6; 93.7)	93.5 (93.1; 94.0)	93.5 (93.0; 93.9)	93.6 (93.2; 94.0)	0.589
SaO_Min	83.0 (80.3; 85.4)	83.9 (82.7; 85.1)	84.7 (82.2; 87.0)	84.4 (83.3; 85.4)	0.708	83.0 (81.2; 84.7)	84.2 (82.8; 85.5)	84.7 (83.3; 86.1)	84.2 (82.9; 85.4)	0.489
%SAO	1.6 (0.8; 2.6)	0.8 (0.5; 1.1)	0.5 (0.1; 1.1)	0.8 (0.6; 1.1)	0.131	1.2 (0.7; 1.7)	0.8 (0.5; 1.2)	0.7 (0.4; 1.1)	0.8 (0.5; 1.2)	0.494
AHI	23.0 (16.0; 31.1)	20.5 (17.2; 24.1)	14.2 (8.8; 20.7)	17.9 (15.1; 20.8)	0.195	20.8 (16.1; 26.1)	21.1 (17.2; 25.3)	15.6 (12.1; 19.5)	18.7 (15.2; 22.5)	0.199

Data are presented as estimated averages (95% CI); active (≥ 150 minutes) or inactive (<150 minutes); short time (<6 hours and < 10 hours) or long time (≥ 6 hours and ≥ 10 hours). TAFT = total physical activity time; TST = total sitting time; TTT = total screen time; TTR = total recording time; SLEEP_LAT = sleep latency; REM_LAT = REM sleep latency; TTS = total sleep time; %NI = percentage sleep stage 1; %NII = percentage sleep stage 2; %NIII = percentage sleep stage III; %REM = percentage REM sleep; SLEEP_WAKE = awakening from sleep; NARO = nightly arousals; IND_NARO = nightly arousals index; RESP_BREAKS = respiratory breaks; OBS_APNEA = obstructive apnea; CENT_APNEA = central apnea; MIX_APNEA = mixed apnea; HYPOPNEA = hypopnea; SaO_Avg = average oxygen saturation; SaO_Min = minimum oxygen saturation; %SAO = percentage oxygen apnea, AHI: apnea-hypopnea index. *P < 0.05.

Table 4. Estimated average values and 95% confidence intervals for sleep quality indicators obtained from polysomnography, among patients who underwent the examination, according to physical activity (active or inactive) and sitting time (< 10 hours or ≥ 10 hours).

Polysomnography	Physical activity group and sitting time				P-value
	Inactive with short sitting time (n = 41)	Inactive with long sitting time (n = 125)	Active with short sitting time (n = 40)	Active with long sitting time (n = 163)	
TTR	451.7 (438.2; 464.6)	440.9 (433.0; 448.6)	438.2 (423.9; 451.8)	439.4 (432.5; 446.2)	0.421
SLEEP_LAT	25.0 (16.4; 38.2)	23.0 (18.0; 29.3)	20.4 (13.3; 31.4)	16.7 (13.5; 20.7)	0.170
REM_LAT	100.6 (72.9; 138.8)	102.2 (85.0; 122.9)	103.9 (75.0; 143.9)	109.3 (93.0; 128.4)	0.943
TTS	356.8 (337.7; 374.8)	366.5 (356.1; 376.6)	364.6 (345.8; 382.2)	374.1 (365.3; 382.7)	0.323
%NI	9.3 (7.6; 11.3)	9.8 (8.7; 11.0)	8.1 (6.6; 10.0)	9.7 (8.7; 10.7)	0.442
%NII	54.1 (51.3; 57.1)	54.5 (52.9; 56.2)	56.4 (53.5; 59.6)	53.9 (52.4; 55.3)	0.498
%NIII	17.7 (15.1; 20.3)	16.3 (14.8; 17.7)	16.3 (13.7; 19.0)	17.2 (15.9; 18.5)	0.690
%REM	17.6 (15.5; 19.7)	18.0 (16.8; 19.2)	18.4 (16.3; 20.5)	18.2 (17.2; 19.3)	0.946
SLEEP_WAKE	47.6 (37.7; 60.2)	44.2 (38.6; 50.5)	42.0 (33.1; 53.2)	43.3 (38.5; 48.7)	0.881
NARO	99.7 (80.5; 123.5)	119.3 (105.5; 134.9)	106.1 (85.4; 131.8)	112.4 (100.9; 125.2)	0.497
IND_NARO	19.4 (15.3; 24.0)	20.9 (18.4; 23.5)	17.7 (13.7; 22.2)	18.7 (16.7; 21.0)	0.527
RESP_BREAKS	104.4 (72.4; 150.7)	120.7 (97.8; 148.9)	89.5 (61.7; 129.7)	103.6 (86.2; 124.6)	0.517
APNEA	3.0 (1.7; 4.9)	2.5 (1.8; 3.3)	2.4 (1.3; 4.1)	2.7 (2.0; 3.5)	0.939
OBS_APNEA	1.7 (0.8; 3.0)	1.2 (0.8; 1.8)	1.2 (0.5; 2.3)	1.3 (0.9; 1.9)	0.852
CENT_APNEA	0.34 (0.04; 0.72)	0.61 (0.40; 0.86)	0.61 (0.25; 1.08)	0.60 (0.41; 0.82)	0.607
MIX_APNEA	0.23 (-0.01; 0.53)	0.26 (0.11; 0.43)	0.29 (0.03; 0.60)	0.28 (0.15; 0.43)	0.987
HYPOPNEA	74.2 (53.9; 101.9)	95.5 (79.6; 114.5)	71.4 (51.7; 98.5)	79.6 (67.9; 93.4)	0.279
SaO_Avg	93.3 (92.6; 94.0)	93.4 (93.0; 93.8)	93.4 (92.7; 94.1)	93.6 (93.3; 93.9)	0.790
SaO_Min	84.0 (81.7; 86.0)	83.6 (82.4; 84.9)	84.7 (82.5; 86.7)	84.4 (83.3; 85.4)	0.791
%SAO	1.2 (0.6; 1.9)	0.9 (0.6; 1.2)	0.6 (0.2; 1.1)	0.8 (0.6; 1.1)	0.516
AHI	20.3 (14.6; 27.0)	21.2 (17.7; 25.0)	16.8 (11.5; 23.1)	17.4 (14.6; 20.4)	0.344

Data are expressed as estimated averages (95% confidence interval); active (≥ 150 minutes) or inactive (< 150 minutes); short time (< 10 hours) or long time (≥ 10 hours). TTR = total recording time; SLEEP_LAT = sleep latency; REM_LAT = REM sleep latency; TTS = total sleep time, %NI = percentage sleep stage 1; %NII = percentage sleep stage 2; %NIII = percentage sleep stage III; %REM = percentage REM sleep; SLEEP_WAKE = awakening from sleep; NARO = nightly arousals; IND_NARO = nightly arousals index; RESP_BREAKS = respiratory breaks; OBS_APNEA = obstructive apnea; CENT_APNEA = central apnea; MIX_APNEA = mixed apnea; HYPOPNEA = hypopnea; SaO_Avg = average oxygen saturation; SaO_Min = minimum oxygen saturation; %SAO = percentage oxygen apnea; AHI = apnea-hypopnea index (events per hour).

Table 5. Logistic regression model, evaluating the association between physical activity practice and sleep quality, controlled for age, gender, body mass index (BMI) and sitting time (6-hour and 10-hour cutoffs)

Variable	6 hours				Variable	10 hours			
	Physical activity		OR (95% CI)	P-value		Physical activity		OR (95% CI)	P-value
	Active (n = 203)	Inactive (n = 166)				Active (n = 203)	Inactive (n = 166)		
Sleep quality (AHI)					**Sleep Quality (AHI)**				
< 15 (n = 178)	107 (60.1%)	71 (39.9%)	0.892 (0.511; 1.558)	0.687	< 15 (n = 178)	107 (60.1%)	71 (39.9%)	0.919 (0.524; 1.609)	0.767
15-29.9 (n = 87)	40 (46.0%)	47 (54.0%)	1.468 (0.816; 2.641)	0.200	15-29.9 (n = 87)	40 (46.0%)	47 (54.0%)	1.477 (0.820; 2.662)	0.194
≥ 30 (n = 104)	56 (53.8%)	48 (46.2%)	reference	---	≥ 30 (n = 104)	56 (53.8%)	48 (46.2%)	reference	---
Age (years)					**Age (years)**				
Average (SD)	45.4 (12.5)	44.7 (11.7)	0.991 (0.973; 1.009)	0.331	Average (SD)	45.4 (12.5)	44.7 (11.7)	0.990 (0.972; 1.008)	0.276
Gender					**Gender**				
Female (n = 122)	73 (59.8%)	49 (40.2%)	0.849 (0.529; 1.362)	0.497	Female (n = 122)	73 (59.8%)	49 (40.2%)	0.802 (0.495; 1.300)	0.371
Male (n = 247)	130 (52.6%)	117 (47.4%)	reference	---	Male (n = 247)	130 (52.6%)	117 (47.4%)	reference	---
BMI (kg/m²)					**BMI (kg/m²)**				
Average (SD)	28.1 (4.9)	29.1 (5.3)	1.035 (0.989; 1.083)	0.140	Average (SD)	28.1 (4.9)	29.1 (5.3)	1.038 (0.992; 1.087)	0.106
Sitting time					**Sitting time**				
< 6 h (n = 18)	8 (44.4%)	10 (55.6%)	1.822 (0.684; 4.855)	0.230	< 10 h (n = 81)	40 (49.4%)	41 (50.6%)	1.582 (0.933; 2.684)	0.089
≥ 6 h (n = 351)	195 (55.6%)	156 (44.4%)	reference	---	≥ 10 h (n = 288)	163 (56.6%)	125 (43.4%)	reference	---

OR = odds ratio; CI = confidence interval; SD = standard deviation; n = number; AHI = apnea-hypopnea index (events per hour).

Table 6. Logistic regression model. evaluating the association between physical activity practice and sleep quality, controlled for age, gender, body mass index (BMI) and screen time (6-hour and 10-hour cutoffs).

6 hours					10 hours				
Variable	Physical activity		OR (95% CI)	P-value	Variable	Physical Activity		OR (95% CI)	P-value
	Active (n = 203)	Inactive (n = 166)				Active (n = 203)	Inactive (n = 166)		
Sleep quality (AHI)					**Sleep quality (AHI)**				
< 15 (n = 178)	107 (60.1%)	71 (39.9%)	0.902 (0.516; 1.578)	0.718	< 15 (n = 178)	107 (60.1%)	71 (39.9%)	0.881 (0.505; 1.538)	0.656
15 - 29.9 (n = 87)	40 (46.0%)	47 (54.0%)	1.473 (0.819; 2.651)	0.196	15 - 29.9 (n = 87)	40 (46.0%)	47 (54.0%)	1.469 (0.818; 2.640)	0.198
≥ 30 (n = 104)	56 (53.8%)	48 (46.2%)	reference	---	≥ 30 (n = 104)	56 (53.8%)	48 (46.2%)	Reference	---
Age (years)					**Age (years)**				
Average (SD)	45.4 (12.5)	44.7 (11.7)	0.990 (0.972; 1.008)	0.273	Average (SD)	45.4 (12.5)	44.7 (11.7)	0.994 (0.975; 1.012)	0.498
Gender					**Gender**				
Female (n = 122)	73 (59.8%)	49 (40.2%)	0.817 (0.505; 1.322)	0.410	Female (n = 122)	73 (59.8%)	49 (40.2%)	0.891 (0.554; 1.431)	0.632
Male (n = 247)	130 (52.6%)	117 (47.4%)	reference	---	Male (n = 247)	130 (52.6%)	117 (47.4%)	Reference	---
BMI (kg/m^2)					**BMI (kg/m^2)**				
Average (SD)	28.1 (4.9)	29.1 (5.3)	1.038 (0.991; 1.086)	0.115	Average (SD)	28.1 (4.9)	29.1 (5.3)	1.031 (0.985; 1.079)	0.194
Screen time					**Screen time**				
< 6 hours (n = 63)	32 (50.8%)	31 (49.2%)	1.506 (0.838; 2.705)	0.171	< 10 hours (n = 156)	91 (58.3%)	65 (41.7%)	0.899 (0.571; 1.414)	0.644
≥ 6 hours (n = 306)	171 (55.9%)	135 (44.1%)	reference	---	≥ 10 hours (n = 213)	112 (52.6%)	101 (47.4%)	reference	---

OR = odds ratio; CI = confidence interval; SD = standard deviation; n = number; AHI = apnea-hypopnea index (events per hour).

DISCUSSION

Our study showed a correlation between sleep quality and SED and was concordant with the findings from a previous study.[14] In this study, we used PSG indicators to outline the results. We identified correlations between sitting time and hypopnea and between screen time and hypopnea. In addition, we observed a negative correlation between average oxygen saturation and total physical activity time.

Further to this, we identified that individuals with suspected sleep disorders who were inactive and had short screen time (< 6 hours) had a lower percentage of REM sleep than did individuals with suspected sleep disorders who were inactive and had long screen time (≥ 6). We also showed that awakening from sleep occurred more among individuals with suspected sleep disorders who were inactive and had short screen time (< 6 hours) than among individuals with suspected sleep disorders who were active and had long screen time (≥ 6 hours). This had also been demonstrated in a previous study.[14] Therefore, screen time may be associated with a decrease in sleep quality.

The main finding of our study was that after adjusting for anthropometric and clinical factors, SED analyzed in terms of sitting time and screen time was not associated with sleep quality. Previous studies also suggested that OSA was affected by age, because the prevalence of OSA increased up to the age of 65 years, at which point, for unclear reasons, the prevalence reached a threshold. Previous data also suggested the interaction between body weight, BMI and OSA in elderly people may be different to that of young adults. Therefore, obesity predisposes and potentiates OSA.[26] In this regard, the prevalence among obese or severely obese patients is almost twice that of normal obese adults. In addition, patients with moderate OSA who gain 10% of their baseline weight present a sixfold increased risk of OSA progression. However, individuals who reduce the same percentage of weight can present an improvement of 20% in the severity of OSA.[26]

It is possible that obesity may worsen OSA due to fat deposition at specific sites. Deposition of fat in the tissues surrounding the upper airways seems to result in a lower lumen and greater collapsibility of the upper airways, thus predisposing to apnea.[27,28] In addition, fat deposits around the thorax (truncal obesity) reduce thoracic complacency and functional residual capacity and may increase the demand for oxygen.[29]

In this sense, visceral obesity is also considered to be a risk factor for OSA. However, the relationship between OSA and visceral obesity is complex. Although there is evidence showing obesity,

as well as visceral obesity, may predispose to OSA and that weight loss results in OSA improvement, previous studies have suggested that OSA may itself cause weight gain.[30,31] Some anthropometric indices, including waist circumference, are widely used as markers for obesity or central obesity.[32] In a recent study, a 1 cm increase in waist circumference gave rise to an 11% increase in the risk of development of OSA.[33]

The prevalence of OSA varies according to gender: it is approximately 30% in men and 15% in women. Mechanisms that potentially explain gender differences in the prevalence and severity of OSA include significant variation in body fat distribution, upper airway collapsibility, hormonal status and ventilatory control.[34-36]

In addition, OSA is a recognized cause of secondary hypertension.[37] Episodes of OSA impose multiple injury; however, intermittent hypoxia (rather than hypercapnia, sleep disruptions or intrathoracic pressure oscillations) is thought to be the most important prohypertensive.[37] Although the mechanisms underlying OSA-related hypertension are not fully understood, the current concept suggests that the sympathetic nervous system and the renin-angiotensin system alter vascular function and structure, resulting in blood pressure elevation. Sympathetic nervous system activity during sleep and wakefulness is heightened in patients with OSA. The mechanisms that sustain sympathetic activation after withdrawal of chemical stimuli are not known; however, it appears that this chronic sympathetic excitation has both reflex and central nervous system origins.[37]

Sitting time and screen time have been associated with less favorable serum biomarkers, besides being considered to be new risk factors for chronic diseases, including cardiovascular diseases, diabetes and cancers, and new risk factors for a higher mortality rate, regardless of PA levels. In contrast to a previous study[14] that showed that SED presented a high risk of severe OSA, in our study it was not associated with moderate or severe OSA after adjusting for clinical factors (BMI, gender and age). One possible explanation for our findings relates to the sample composition and the diagnostic method used for OSA.

Previous studies did not investigate the association between PA levels and OSA in populations.[14,38] One study only used a female sample.[38] Our study was composed of individuals of both genders who visited the neurophysiology clinic, with a referral to undergo overnight laboratory polysomnography due to suspected sleep disorders. The data presented in our study and previous studies[14,38] enable us to hypothesize that populations with suspected sleep disorders can influence the results demonstrated, if anthropometric data such as BMI are different. Polysomnography is considered to be the gold-standard method for evaluating OSA, and the diagnoses thus obtained reinforce our findings. A recent study[14] that investigated the association between screen time and the risk of OSA used a questionnaire to diagnose the risk of developing this condition.

Screen time (predominantly seated leisure time) has been consistently correlated with adverse health outcomes. A recent study demonstrated the association between screen time and OSA[14] and indicated that screen time may be an important risk factor for sleep disorders and the risk of apnea. In our study, associations between screen time per week or weekend and OSA were observed only through correlations. We failed to find any clear explanation for these results. One possibility would be to consider that there may have been errors in completing questionnaires, which was also suggested in another recent study,[38] because of individuals' altered perceptions of screen time. In a study that identified an association between screen times and OSA risk, it was speculated that the main factor could be the proximity of television viewing to going to sleep,[14] thus assuming that screen time would happen at night, close to bedtime. We emphasize that the sleep measurements in this study were not evaluated using questionnaires, especially when checking the risk of OSA. Questionnaires cannot diagnose OSA and can introduce errors into the results obtained. Our study used the gold standard method to assess OSA, which therefore strengthens the findings obtained.

In relation to PA levels, experimental and intervention studies support the notion that there is a bi-directional relationship between sleep and PA.[38] However, these studies do not necessarily provide insight into sleep and PA patterns. From a clinical standpoint there is growing evidence that aerobic exercise training could be beneficial for adults with a diagnosed sleep disorder.[39]

Results from previous studies have indicated that men and women with low PA levels have the highest odds of OSA.[40] Furthermore, there seems to be an inverse relationship between PA level and OSA severity.[41] Reduced PA is associated with increased OSA severity, independent of gender, age and BMI.[41,42] These findings also indicate that efforts to prevent OSA should include encouraging patients to engage in at least some form of moderate-to-vigorous PA.[43] In addition, findings regarding PA may be different among patients with a wide distribution of OSA severity. The reasons for limiting exercise among patients with OSA are unclear. Some potential contributing factors comprise dyspnea, muscle weakness in the lower limbs, cardiac dysfunction, respiratory muscle dysfunction, arterial hypoxemia, demotivation and peripheral vascular diseases.[39,44]

The strengths of the current study included, first, its use of PSG for diagnosing OSA. Second, it used total sitting time and total screen time per week and on weekends. Third, it incorporated information on BMI, age, gender, waist circumference, AH presence and PA level, which allowed us to limit the effects of confounding variables. It is possible, however, that additional confounding effects may have been present.

The limitations of the current study included, first, the cross-sectional nature of this study, which limited the effects of causal

inferences. A second limitation related to the sample size, which meant that only a specific population could be analyzed. Lastly, other limitations related to the administration of self-reported measurements of PA and SED levels, and lack of investigation of the specific periods during which individuals remained in front of screens. In a general manner, the present study may serve to generate hypotheses for future research. Future studies should longitudinally investigate the associations between sitting time, screen time, PA and sleep.

CONCLUSIONS

We did not identify any relationship between screen time and sitting time and OSA among adults with suspected sleep disorders, after adjusting for anthropometric and clinical factors.

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Scanning of paroxysmal atrial fibrillation as an etiological risk factor in patients with acute ischemic stroke: prospective study

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ABSTRACT

BACKGROUND: Prevention of recurrence of stroke depends on recognition of the underlying mechanism of ischemia.

OBJECTIVE: To screen patients who were hospitalized with diagnosis of acute ischemic stroke in terms of atrial fibrillation (AF) with repeated Holter electrocardiography recordings.

DESIGN AND SETTING: Prospective study conducted at Konya Education and Research Hospital, Turkey.

METHODS: Patients with a diagnosis of acute ischemic stroke, without atrial fibrillation on electrocardiography (ECG), were evaluated. Their age, gender, histories of previous ischemic attack, occurrences of paroxysmal atrial fibrillation (PAF) and other risks were assessed during the first week after acute ischemic stroke and one month thereafter. ECG recordings were obtained from 130 patients through 24-hour ambulatory Holter. Patients without PAF attack during the first Holter were re-evaluated.

RESULTS: PAF was detected through the first Holter in 33 (25.4%) out of 130 acute ischemic stroke patients. A second Holter was planned for 97 patients: 53 (54.6%) of them could not attend due to COVID-19 pandemic; while 44 (45.3%) patients had the second Holter and, among these, 4 (9.1%) had PAF. The only parameter associated with PAF was older age. Four (10.8%) of the 37 patients with PAF had also symptomatic carotid stenosis.

CONCLUSIONS: Detecting the presence of PAF by screening patients with no AF in the ECG through Holter ECG examinations is valuable in terms of changing the course of the treatment. It should be kept in mind that the possibility of accompanying PAF cannot be ruled out in the presence of other factors that pose a risk of stroke.

INTRODUCTION

Atrial fibrillation (AF) consists of atrial arrhythmia characterized by loss of P waves on electrocardiography, with one or more attacks for at least 30 seconds. Although AF is more common in the elderly or individuals with other cardiovascular risk factors, it is the most common type of arrhythmia, affecting approximately 3% of the adult population. Symptoms associated with AF can be observed in all of its subtypes, seen as paroxysmal, persistent or permanent AF. However, some patients with AF associated with stroke during or after stroke are also asymptomatic. It is known that AF increases the risk of ischemic stroke four to fivefold.[1]

It is important to reveal the etiology of stroke and to reduce the risk of stroke recurrence through putting appropriate treatment options into effect. However, in approximately a quarter of all ischemic strokes, the underlying factor cannot be revealed.[2] For example, in the TOAST classification, this group is called cryptogenic stroke.

With developments in the field of neuroradiology and cardiological examination, and widespread access to these examinations, the definition of cryptogenic stroke has been questioned as a result of clarification of the etiology. This has been achieved through advanced examination methods among some of the patients who had previously been diagnosed as presenting cryptogenic stroke. Thus, the term 'Embolic Stroke of Undetermined Source' (ESUS) has been introduced.[3]

ESUS is held responsible for 20% of ischemic strokes.[4] By definition, ESUS consists of a non-lacunar brain infarction with no demonstrable proximal arterial stenosis or cardioembolic source, and with a clear indication for anticoagulation.[1] Studies have focused on the idea that a large proportion of ESUS patients may have silent paroxysmal AF (PAF).[5]

In the 2020 guidelines of the European Society of Cardiology (ESC) for patients with acute ischemic stroke or transient ischemic stroke (TIA) without known AF, it is recommended that after a short electrocardiography (ECG) recording in the first 24 hours, continuous ECG monitoring should be implemented for at least 72 hours, if possible (class 1, level B). It is recommended that AF should be scanned through long-term non-invasive ECG monitors or implantable cardiac monitors in selected patients with no known AF (class 2a, level B).[6]

However, not all stroke patients benefit from long-term ECG monitoring. Long-term ECG recording should be selected for patients who are considered to be at risk of developing AF (e.g. elderly individuals with cardiovascular risk factors or patients with presence of comorbidities, high left atrium remodeling index and high C2HEST score), patients whose condition is suggestive of embolic stroke and patients with cryptogenic stroke.[6]

Although it is recommended in the guidelines that Holter monitoring should be implemented 72 hours after stroke, it is obvious that each center should do its own planning according to the possibilities available. It needs to be borne in mind that some treatment centers do not have Holter monitoring opportunities; and that in centers that do have Holter monitoring, the devices are often limited to 24-hour recording.

OBJECTIVE

In our center, where 72-hour Holter monitoring is not available, we planned our study based on the idea that recurrent 24-hour Holter recordings could increase the chance of picking up AF attacks that could not be detected in the first Holter. Moreover, we investigated whether Holter monitoring would produce different results in stroke patients whose stroke etiology could not be elucidated or correlated with other reasons.

METHODS

The protocol for this prospective study was approved by the Ethics Committee of Selcuk University Medical Faculty (protocol number: 2019/347; date: November 27, 2019) and was funded by the Medical Specialty Education Board of the Saglik Bilimleri University, Konya Education and Research Hospital (protocol number: 48929119/774; date: May 2, 2020), in Turkey.

In our study, patients who were hospitalized in the Department of Neurology, Saglik Bilimleri University, Konya Education and Research Hospital, with a diagnosis of acute ischemic stroke, who did not show AF on ECG and who had not previously been diagnosed with PAF, were included. We sought to include patients who were euthyroid. In addition, we determined that the patients should not have valvular heart disease, which would be an indication for anticoagulant therapy on echocardiography (ECHO). The results from 24-hour Holter monitoring examinations completed in the first week, at the acute ischemic stroke clinic and at the end of the first month, among patients who we recruited over a six-month period, were evaluated according to age, gender, histories of previous ischemic attack and other risk factors.

Holter ECG monitoring was planned and implemented for patients during their hospitalization in the first week (days 0-7) and at the end of the first month (days 30-45), during which routine outpatient clinic control was planned after discharge, twice for 24 hours. No control Holter was required for patients who presented PAF in the first Holter.

Patients for whom it was planned to continue their post-discharge check-ups at an external center and patients whose general condition was bad enough to require monitoring in intensive care were not included in the study group. The examination and treatment plans for any patients who were hospitalized in the neurology clinic with a diagnosis of acute ischemic stroke but did not want to be included in the study were arranged by the neurologist who followed these patients.

Twenty-four hour ambulatory Holter ECG recordings were obtained from all the 130 patients who agreed to participate in the study and whose conditions were in accordance with what was desired for this study (Risingmed cv3L Holter system, Beijing, China). Rapid irregular atrial activity, characterized by absence of P waves that was observed for longer than 30 seconds in 24-hour Holter recordings, was reported as PAF.

Holter ECG appointments were given to patients who did not have a PAF attack in the first Holter, for dates that complied with the outpatient clinic controls one month later, at discharge. Control Holter results were collected and the data were transferred to a computer environment.

The data were analyzed using the SPSS 22.0 program (SPSS Inc., Chicago, Illinois, United States). Frequency and percentage values were used for categorical (nominal and ordinal) data. For numerical data, minimum and maximum values were given, along with the median value. In comparisons of categorical data, Fisher's exact test was used when it met the assumptions required for the test, and when those of the chi-square test could not be met. In the analyses on all hypothesis tests, the significance level (P-value) was taken as 0.05.

RESULTS

The ages of the 130 patients included in the study ranged from 31 to 92 years (interquartile range, IQR 62-78), with a median value of 69.5 years. The sample consisted of 70 men (53.8%) and 60 women (46.2%). There was no significant relationship between the sexes and the presence of PAF.

While 106 of the patients (81.5%) were evaluated after their first ischemic stroke attack, 19 (14.6%) were evaluated after their second and five (3.8%) after their third attack. All 11 patients (8.5%)

who were evaluated as presenting transient ischemic attack were at their first attack. There was no statistically significant association between recurrent stroke attacks and the presence of PAF.

Regarding concomitant diseases, 87 patients (66.9%) had essential hypertension, 47 (36.2%) had diabetes mellitus, 28 (21.5%) had coronary artery disease and six (4.6%) had congestive heart failure. No statistically significant association was found between any of these diseases and the presence of PAF.

The number of patients using antiaggregant (acetylsalicylic acid, 100-300 mg) for various reasons was 35 (26.9%). No relationship could be established between presence of PAF and occurrence of ischemic stroke despite antiaggregant treatment. The patients' characteristics are presented in **Table 1**.

Twenty (16%) of the patients were over 80 years old. While PAF was detected in 24 (21.8%) of the 110 patients who were under 80 years of age, nine (45%) of the 20 patients aged 80 and over had PAF. There was a statistically significant difference (P = 0.028) between these age groups, such that the presence of PAF was found to be associated with increasing age (**Table 2**).

The median value of the modified Rankin score (mRs) was 3 (IQR 1-3); 62 patients (47.7%) were independent (mRs 0-2) and 67 (51.5%) were dependent (mRs 3-5). One patient (0.8%) died due to non-neurological causes (mRs 6). There was no significant relationship between mRs and the presence of PAF.

The median value on the National Institutes of Health Stroke Scale (NIHSS) was 6 (IQR 4-9). No significant difference was found between a group with NIHSS 0-4 and a group with NIHSS 5 and above, in terms of PAF relationship.

Table 1. Demographic characteristics

	n (%)
Male/female	70/60
Median age in years (IQR)	69.5 (IQR 62-78)
Evaluation time	
First stroke attack	106 (81.5%)
Second stroke attack	19 (14.6%)
Third stroke attack	5 (3.8%)
Concomitant diseases	
Essential hypertension	87 (66.9%)
Diabetes mellitus	47 (36.2%)
Coronary artery disease	28 (21.5%)
Congestive heart failure	6 (4.6%)
Using antiaggregant	35 (26.9%)

IQR = interquartile range.

Table 2. Evaluation of PAF in the first Holter, according to the age group of the patients with stroke

	PAF	
	Positive	**Negative**
< 80 years old (n = 110)	24 (21.8%)	86 (78.2%)
≥ 80 years old (n = 20)	9 (45.0%)	11 (55.0%)

P-value: 0.028. PAF = paroxysmal atrial fibrillation.

The median value for CHA2DS2-VASc was 5 (IQR 4-6). No statistical relationship between CHA2DS2-VASc score and PAF was revealed.

PAF was detected in the first Holter in 33 (25.4%) of the 130 patients included in the study. Control Holter appointments for 53 (54.6%) out of the 97 patients who were not found to have PAF in the first Holter were canceled during the period when elective examinations were delayed in our hospital due to the COVID-19 pandemic. The other 44 patients (45.3%) were scanned through a second Holter, and four (9.1%) of these patients had a PAF attack during this control (**Table 3**).

The first choice for carotid-vertebral artery imaging was as follows: Doppler ultrasonography for 116 (89.2%) of the patients, computed tomography (CT) angiography for nine (6.9%) and magnetic resonance imaging (MRI) angiography for five (3.85).

As the first examination or a further examination, 19 patients underwent CT angiography and 24 patients underwent MRI angiography. For seven patients who underwent CT angiography and six patients who underwent MRI angiography, evaluation of advanced stenosis was planned, to be performed using digital subtraction angiography (DSA). For four patients with advanced stenosis on CT angiography or MRI angiography, presence of PAF in the first Holter was also revealed.

Thrombolytic therapy and/or thrombectomy were applied to all patients who were evaluated in the hyperacute period and for whom these were indicated. In 14 patients, only intravenous thrombolytic therapy was applied, in three patients only thrombectomy was applied and in four patients intravenous thrombolytic therapy and thrombectomy were applied. There was no significant relationship between the patients who underwent thrombolytic therapy and/or thrombectomy and the presence of PAF.

DISCUSSION

If persistent AF is detected through routine ECG evaluation during stroke, it is easy to demonstrate its relationship with stroke. However, it may not always be easy to detect short-term episodes of paroxysmal atrial fibrillation that are expected to end spontaneously within seven days. Some of the cases that are not evaluated with adequate examinations can be considered as included in the cryptogenic stroke group.[7]

Although the association of persistent atrial fibrillation with stroke is better known, paroxysmal atrial fibrillation is also blamed for the same risk of ischemic stroke as persistent atrial fibrillation and as a potential source of cryptogenic stroke.[8]

Table 3. PAF results from first and control Holters

	Number of patients		PAF	
	Planned	**Performed**	**Positive**	**Negative**
First Holter	130	130	33 (25.4%)	97 (74.6%)
Second Holter	97	44	4 (9.1%)	40 (90.9%)

PAF = paroxysmal atrial fibrillation.

In a retrospective study on 3,480 patients with TIA or ischemic stroke, paroxysmal atrial fibrillation was found in 237 (19%) of the patients. In univariate analyses, the following were identified as important markers for paroxysmal atrial fibrillation: increasing age, female gender, previous ischemic stroke, myocardial infarction, other heart diseases, pathological troponin, embolic stroke and stroke in different arterial regions.[9]

Conditions that are known to be risk factors for both AF and stroke, such as age, male gender, hypertension, diabetes mellitus, valvular heart disease, heart failure, coronary heart disease, chronic kidney disease, inflammatory disorders, sleep apnea and tobacco use, have been shown to be responsible for the association between AF and stroke.[10] In our study, no significant associations between presence of PAF and any factors other than advanced age were found.

About a quarter of strokes are recurrent.[11] In our study, no significant relationship was found between the presence of PAF and the number of recurrent strokes. It is important to investigate the etiological factors in ischemic stroke and to arrange appropriate treatment, because this reduces the risk of recurrence of stroke. Since the presence of atrial fibrillation requires anticoagulant treatment, its detection is of particular importance. In the presence of atrial fibrillation, anticoagulation is the main treatment method for limiting systemic complications.[12]

In fact, the risk of stroke, which varies between 0 and 18% per year according to individuals' clinical situation and risk profile, is not equally distributed among patients with atrial fibrillation. For this reason, it is important to evaluate thromboembolic risk in a personalized manner. A variety of scoring systems can be used for individualized patient selection. The CHA2DS2-VASc score is one of the most widely used scoring systems and is an effective method for considering the risk of stroke and the rate of anticoagulant benefit in patients with atrial fibrillation.[12] Guidelines have recommended that anticoagulant therapy should be started if patients present nonvalvular AF with a CHA2DS2-VASc score of 2 or more.[13] Since all the patients included in our study received a score of 2 points only because of ischemic stroke and this score increased in the presence of other risk factors, patients with AF are considered to be the patient group that will benefit from anticoagulant treatment. It is vital to reveal AF through Holter monitoring in these patients.

Since the 1960s, Holter monitoring has been the cornerstone for diagnosing suspected arrhythmias in patients of all ages. The length of the recording in the most commonly used monitoring systems is limited to 24-48 hours, while newer Holter monitors allow continuous electrocardiogram recording for two weeks.

Prolonging the ECG recording time will increase the diagnostic efficiency of Holter monitoring, especially for rare but recurrent rhythm disorders.[14] However, long-term monitoring has disadvantages such as reduced patient compliance and increased cost. Ischemic stroke leads to the possibility of cognitive impairment, which may impair compliance among patients. Criteria for appropriate patient selection need to be developed.

Studies have shown that AF can be detected in approximately 10% of patients by extending the follow-up to 30 days, among patients who are examined with the diagnosis of ESUS. Moreover, AF can be detected in one fourth of patients by using continuous monitoring, for example, with implantable loop recording devices. However, attention has been drawn to the need for an algorithm for patient selection and for diagnosing progressive rhythm, considering that not all stroke patients can receive such intense monitoring.[15]

In a study in which 11,658 patients with stroke and atrial fibrillation were evaluated retrospectively between 1980 and 2014, the cardiac monitoring methods used were divided into four groups. In the first stage (in the emergency room), an admission electrocardiogram was performed. In stage 2 (in the hospital), serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry and in-hospital Holter monitoring were performed. In stage 3 (first ambulatory period), ambulatory Holter was performed. In stage 4 (second ambulatory period), mobile cardiac telemetry, external loop recording and implantable loop recording were performed. The summary proportions of patients diagnosed with post-stroke atrial fibrillation were 7.7% in stage 1, 5.1% in stage 2, 10.7% in stage 3 and 16.9% (13.0-21.2) in stage 4. The overall yield of atrial fibrillation detection after all the stages of sequential cardiac monitoring was 23.7%.[16]

In our study, 33 (25.4) of the 130 patients had PAF attacks during the first Holter. Only 44 (45.4%) of the 97 patients whose participation in the second stage was planned were actually included in the study, and four (9.1%) of these 44 patients had PAF. Although the positivity rate decreased, the important point is that PAF was diagnosed as a result of investigative Holter among patients who had previously been examined. However, in order to gain statistical significance, this needs to be evaluated with a larger population.

Since Holter monitoring at our facility is limited to 24 hours, we aimed to evaluate the advantages and disadvantages of extending this period through repeated Holter recordings. We predicted that patients could become dependent on someone else due to their stroke, and that this could reduce compliance with appointment dates. In fact, 67 patients (51.5%) in our study had a score of 3 or more on mRs, and this was considered to be the dependent group. However, the major factor that reduced participation in the control Holter was the COVID-19 pandemic. It was not possible for this group of advanced age with chronic diseases to adapt to hospital controls during the pandemic period. The fact that PAF was only detected in the second recording, in four of the 44 patients who could be included in the control Holter, even though they had been scanned through 24-hour recording previously, draws attention to the insufficiency of 24-hour recording. The low participation in

the control Holter suggests that it would be more appropriate to complete the examinations on this patient group, in which about half of these individuals were dependent on someone else to perform their daily activities, during hospitalization.

Another issue that we want to draw attention to in this study is the possibility of overlooking PAF if it is not evaluated through further examination, in the presence of other risk factors. Most of the chronic diseases that are considered to be risk factors for stroke, such as essential hypertension and congestive heart failure, are also closely related to atrial fibrillation. Therefore, their presence may play a role in the etiology of stroke, but is not sufficient to rule out the risk of PAF.

In our study, simultaneous PAF was detected in four of the 13 patients with symptomatic carotid stenosis detected through CT angiography and MRI angiography. This patient group was considered to present large-artery atherosclerosis according to the TOAST classification. Although the recommended Holter monitoring time for cases of cryptogenic stroke and ESUS was extended to 72 hours in the updated guidelines,[6] the possibility that stroke might be multifactorial was ignored and no recommendations were made for these patients.

CONCLUSION

Detecting the presence of PAF by scanning patients who did not show AF on ECG, through Holter ECG examination, is valuable in terms of changing the course of the treatment. It should be kept in mind that the possibility of accompanying PAF cannot be ruled out in the presence of other factors that pose a risk of stroke.

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Grief and ruminative thought after perinatal loss among Turkish women: one-year cohort study

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ABSTRACT

BACKGROUND: Among women who have suffered loss of pregnancy, the level of grief decreases gradually. Age, mental health status and childlessness are the factors known to mostly affect women's levels of grief.

OBJECTIVES: To assess the levels of grief among women who experienced perinatal loss and the changes in their ruminative thought styles over the first year after their loss.

DESIGN AND SETTING: One-year follow-up study carried out in a university hospital in Turkey.

METHODS: The study population included 70 women who experienced loss of pregnancy in the hospital. The sample size was calculated using G*Power V3.1. Data were collected at 48 hours, at the third month, at the sixth month and at one year after pregnancy loss, between June 2018 and June 2019. A personal information form, the Perinatal Grief Scale and the Ruminative Thought Style Questionnaire were used for data collection.

RESULTS: The women's highest levels of grief and ruminative thought style were in the first 48 hours. Their tendency towards grief and ruminative thought styles decreased over the repeated measurements during the follow-up. Women aged 20-29 years had the highest levels of grief at the third month after perinatal loss.

CONCLUSIONS: Nursing assessments regarding grief and ruminative thought style over the first 48 hours after perinatal loss should be integrated into nursing care for these women. Grief follow-up programs for these women can be developed through nursing research.

INTRODUCTION

Perinatal loss is the loss of a baby prematurely or at a short time after birth. The most common forms of perinatal losses are miscarriage, stillbirth and neonatal death.[1] Despite all the improvements in medicine, perinatal losses still occur frequently and affect millions of families.[1,2] It has been estimated that approximately 15%-20% of all pregnancies end in miscarriage or spontaneous abortion within the first 12 weeks, worldwide.[3] The miscarriage and stillbirth rate in Turkey was 18.6% in 2018.[4] The perinatal death rate was reported to be 6 in 1000 live births in the United States in 2016; it was 11 in 1000 live births in Turkey in 2018.[5,6]

Perinatal loss is one of the most painful and unbearable life experiences for parents, and it causes emotional responses such as grief and depression. Fear, disappointment, anger, self-pity, feelings of failure, etc., are experienced during the period of grief.[2] Sex, age, perception of loss, life changes, coping styles, support systems and rumination can affect the duration of grief.[2,7]

Ruminative thought has effects on individuals' negative responses.[8] Rumination consists of repetitively thinking through a negative emotion or situation.[9] Individuals with ruminative thoughts isolate themselves, continually focusing on their problems, and feel the results of negative situations for longer times. They think that, through such behavior, they are trying to find a solution.[10] Studies have shown that rumination is associated with various psychological problems such as depressive symptoms,[11-14] anxiety, worry and symptoms of prolonged grief.[7,13,15] In the literature, it has been noted that women have ruminative tendencies more than men do.[10,11,13,14,16]

Determining the gradual changes in women's grief levels and their ruminative thought styles may be the starting point and first step in planning nursing care for individuals who

have experienced perinatal loss. In this regard, there is one previous study assessing the level of grief among women with pregnancy loss in Turkey.[17] To the best of our best knowledge, no studies have evaluated the gradual changes in grief levels and ruminative thought styles among women who suffered perinatal loss in Turkey.

OBJECTIVE

The aim of this study was to evaluate differences in grief levels and ruminative thought styles among women who have experienced perinatal loss, by means of repeated measurements over the first year after the event.

METHODS

This was a one-year follow-up study carried out in a university hospital. The study population consisted of women who had experienced pregnancy loss in the hospital. The number of women who used the hospital's delivery service between April 1 and May 1, 2018, was 49. The sample size was calculated using the G*Power software (version 3.1.9.2; Universität Düsseldorf, Düsseldorf, Germany), in terms of the change in R^2 in multiple linear regression approximation. The minimum sample size required for seven predictors with 80% power and medium effect size ($f^2 = 0.15$) was calculated as 43 subjects.[18,19] However, through considering abandonment over the course of the repeated measurements of the study, we decided to include a total of 70 women in the study.

The women who were included in this study were voluntary participants who had experienced pregnancy loss in any trimester of pregnancy, and who had the ability to speak and write in Turkish. Women who had previously had a psychological disorder were not included in the study, and women whom the researchers were unable to reach during the repeated follow-ups were excluded.

Data collection forms and tools

Data were collected using a personal information form, the Perinatal Grief Scale (PGS) and the Ruminative Thought Style Questionnaire (RTSQ).

Personal information form

This form was prepared by the researchers. It consisted of 10 questions regarding sociodemographic and obstetric characteristics.

Perinatal grief scale

The PGS was developed by Toedter et al. and assesses the level of grief experienced after perinatal loss.[20] The original scale consists of 33 items on a five-point Likert-type scale and includes three subscales.[21] These three subscales are named Active Grief, Difficulty Coping and Despair. These levels represent progression of the pathological condition on the overall scale. An Overall Grief score of 91 or higher means that grief is present. An Active Grief score of 34, a Difficulty Coping score of 30 and a Despair score of 27 are used as cutoff points on the three subscales. The Cronbach's α values lie between 0.86 and 0.92. A validity and reliability study was conducted in Turkey by Özgür Köneş et al. in 2017, and its Cronbach's alpha was found to be 0.95.[22] In the present study, the Cronbach's alpha values were between 0.793 and 0.857 for the subscales of the PGS and 0.930 for the total score.

Ruminative thought style questionnaire

The RTSQ was developed by Brinker and Dozois in 2009, and its adaptation to Turkish culture was published by Karatepe et al., in 2013.[14,23] This scale has 20 items. Assessments are made based on the total score. The lowest score is 20 and the highest score is 140. Its Cronbach's alpha in the above studies was 0.907.[14,23] In the present study, Cronbach's alpha was 0.886.

Data collection

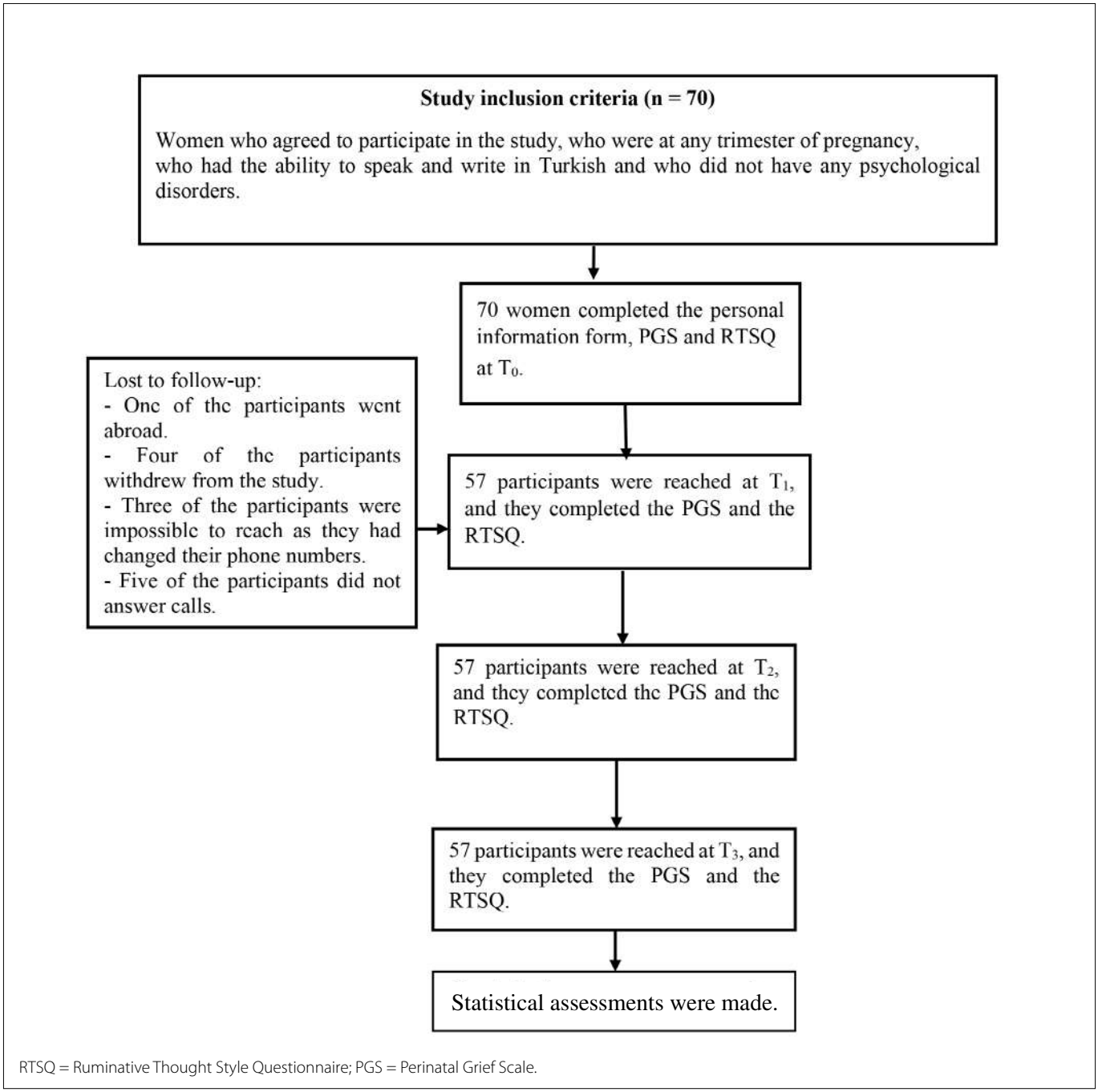
Data were collected in four steps from June 2018 to June 2019. In the first step, the questionnaires were completed for the first time just before the participants were discharged. These women had stayed in the hospital for 48 hours (T_0) after their pregnancy loss. The women's phone numbers and addresses were obtained at this time.

The same questionnaires were filled out through phone calls at the third month (T_1) and sixth month (T_2) and at one year (T_3) after discharge. The questionnaires at T_0 were filled out through face-to-face interviews conducted by the researchers. They explained to the participants that later on they would call them by phone, to fill out the same questionnaires again. The first interviews lasted approximately 30 minutes. The repeated interviews lasted approximately 15 minutes each.

At T_0, 70 participants were involved in the study, but 13 participants did not answer the call at T_1. The researchers were able to reach all of the T_1 participants again, at both T_2 and T_3, and thus the study was completed with 57 participants. The researchers called all the women who did not answer the phone, at least three times before deciding to drop them from the study. All the details regarding the study process are explained in the study flowchart (**Figure 1**).

Data analysis

Statistical analyses were done using the IBM SPSS Statistics software V23 (IBM Corporation, Armonk, New York, United States) and the R Studio software (R Studio, Boston, United States). The normal distribution compliance of the data was examined using the



RTSQ = Ruminative Thought Style Questionnaire; PGS = Perinatal Grief Scale.

Figure 1. Study flowchart.

Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as the mean (standard deviation [SD]); non-normal variables were reported as the median (minimum-maximum [min-max]). Categorical variables were presented as the number of events and percentages. The frequencies of categorical variables were compared using Pearson's χ^2 or Fisher's exact test, as appropriate. The Mann-Whitney U test was used to compare differences between two independent groups when the independent variable was not normally distributed, and Student's t test was used for normally distributed variables. Repeated measurements of scales were evaluated via the repeated-measurement analysis of variance (ANOVA) test, the Friedman test and nonparametric analysis of longitudinal data in factorial experiments. For experiments with F1-LD-F1 design, Wald-type statistics (WTS) were calculated for

testing group and time effects, and interactions. The Kruskal-Wallis test and one-way ANOVA test were used for comparisons of more than two independent groups. Relationships between two continuous variables were tested by means of the Spearman rank correlation. The multiple linear regression-backward elimination technique was used for estimation of RTSQ scores via independent variables. The significance level accepted was $P < 0.05$.

Ethical considerations

Ethics approval (number: 2018.02.22/3-10; date: February 22, 2018) was obtained from the University Scientific Research and Publication Ethics Committee of the Osmaniye Korkut Ata University. The procedures used in this study adhered to the tenets of the Declaration of Helsinki. Informed consents were obtained from the participants after we had explained the objectives of the study to them.

RESULTS

The mean age of the participants was 30.34 ± 6.55 years, and the mean week in which pregnancy loss occurred was 15.42 ± 6.61. Among all the participants, 45.7% had miscarriages and 54.3% had stillbirths. The perinatal deaths all occurred at between 4 and 32 weeks of gestation. **Table 1** shows the sociodemographic and obstetric characteristics of the participants.

The median values of the total scores on the PGS ($P < 0.001$) and the mean scores on the RTSQ ($P < 0.001$) differed over time (**Table 2**).

A statistically significant difference was found between total score median values on the PGS at T_1 in terms of the variables of age and childlessness ($P < 0.05$). The difference based on the age variable was caused by the 20 to 29-year age group ($P < 0.05$). The total median scores on the PGS among women who were unable to have children were higher at T_1 than at other times ($P < 0.05$) (**Table 3**; **Figure 2**). **Figure 2** shows the changes in the variables of age and childlessness on the PGS and RTSQ over the one-year follow-up.

According to the correlation results from the scales, positive medium-level correlations were found between the total scores on the RTSQ and the PGS and their subscales at T_0, T_1 and T_2 ($P < 0.05$) (**Table 4**). Also, it was found that the percentages of the women who had PGS total scores ≥ 91 were 55.7% at T_0, 21.1% at T_1, 3.5% at T_2 and 3.5% at T_3. A score higher than this cutoff point means having grief. The changes in the RTSQ scores based on the PGS cutoff points over time are shown in **Figure 3**.

The multiple linear regression-backward elimination technique was used for RTSQ score estimation. The regression model included family type, childlessness, working status and PGS T_3. PGS T_3 contained active grief, difficulty coping and despair. Dummy variables were created for categorical variables in the model. Active

Table 1. Sociodemographic and obstetric characteristics of the participants

	n	%
Age (years)		
20-29	31	44.3
30-39	33	47.1
40-49	6	8.6
Education level		
Primary school	21	30.0
Secondary school	13	18.6
University and above	36	51.4
Working status		
Not working	55	78.6
Working	15	21.4
Educational level of spouse		
Primary school	15	21.4
Secondary school	20	28.6
University and above	35	50.0
Income level perception		
Poor	5	7.1
Moderate	42	60.0
Good	23	32.9
Residence		
Village	9	12.9
District	19	27.1
City	42	60.0
Family type		
Nuclear family	56	80.0
Large family	14	20.0
Number of pregnancies		
Primiparous	18	25.7
Multiparous	52	74.3
Childlessness		
Yes	28	40.0
No	42	60.0
Number of pregnancy losses		
One	39	55.7
Two	20	28.6
Three or more	11	15.7
Number of this pregnancy		
First	20	28.6
Second	21	30.0
Third	14	20.0
Fourth or more	15	21.4
Type of loss		
Miscarriage	32	45.7
Stillbirth	38	54.3

Table 2. Descriptive statistics on the Perinatal Grief Scale (PGS) and the Ruminative Thought Style Questionnaire (RTSQ)

	Time	$\chi \pm$ standard deviation	Median (minimum-maximum)	Test statistics	P
Total PGS	T_0^A	95.94 ± 22.81	93 (43-143)	$\chi^2 = 91.363$	**< 0.001**
	T_1^A	76.70 ± 20.26	75 (42-130)		
	T_2^B	58.40 ± 18.73	57 (36-120)		
	T_3^B	53.79 ± 17.98	47 (36-125)		
Active grief	T_0^A	27.75 ± 7.26	26 (14-44)	$\chi^2 = 60.886$	**< 0.001**
	T_1^B	25.07 ± 7.62	24 (11-44)		
	T_2^C	20.70 ± 7.60	20 (10-40)		
	T_3^B	19.12 ± 7.30	16 (10-43)		
Difficulty coping	T_0^A	36.47 ± 7.96	36 (14-52)	$\chi^2 = 92.065$	**< 0.001**
	T_1^B	23.18 ± 6.09	23 (13-40)		
	T_2^C	18.88 ± 5.05	16 (13-34)		
	$T3^B$	18.21 ± 5.33	16 (13-41)		
Despair	T_0^A	34.40 ± 9.20	35 (15-52)	$\chi^2 = 118.790$	**< 0.001**
	T_1^B	25.77 ± 8.29	25 (11-47)		
	T_2^C	18.82 ± 7.65	18 (11-46)		
	T_3^B	15.19 ± 6.15	13 (10-38)		
RTSQ	T_0^A	91.26 ± 25.61	95 (21-140)	F = 8.450	**< 0.001**
	T_1^B	79.51 ± 23.04	82 (20-131)		
	T_2^C	79.96 ± 25.44	82 (25-139)		
	T_3^B	77.89 ± 24.93	80 (25-132)		

F = repeated analysis of variance; χ^2= Friedman test statistic; A-C = there are no differences between times that have the same letter for each subscale/total score.

grief and family type were found to be statistically significant in the regression model (P < 0.05). They explained 15.6% of the change in RTSQ score (**Table 5**).

DISCUSSION

The aim of this study was to evaluate grief and ruminative thought after a perinatal loss, among Turkish women. This study was specific for perinatal grief in a prospective manner and it makes a valuable contribution to the literature relating to grief, given that this was the first study in Turkey to evaluate grief and ruminative thought style prospectively over a one-year period.

In this study, more than half of the women were experiencing grief at the interview after the first 48 hours. The median values of the grief score periodically decreased over the course of the follow-up measurements.

The grief levels of women who had experienced pregnancy loss have been reported in the literature.[17,21,24-27] Özgür and Yıldız determined in their study conducted among women over the first three months after pregnancy loss that the average total PGS score did not change within three months.[17] However, the majority of the studies showed that women experienced various level of grief right after a perinatal loss, and that their grief tended to decrease gradually.[21,24-27] In a qualitative study, Avelin et al. reported that after the loss of a baby, couples stated that they were still crying and experiencing physical pain at the third month after the loss. On the other hand, one year later, they felt stronger.[26] This result indicated that couples experience active grief within the first three months and that their feelings change positively over time. The results from many studies have indicated that there are high levels of grief among women who recently had the loss of a pregnancy, and that perinatal grief decreases over time.[28-31]

The results from the current study are in line with data in the literature. In Turkish society, individuals believe that they have something in their destiny and that this cannot be changed. According to faith in one's destiny, the time of death and the time of marriage are predetermined; therefore, individuals do not have control over them. In Turkish culture, pregnancy or having a baby is blessed. When it comes to losing a most precious thing that people can ever have, society shares all the sad feelings of women and supports them. Accepting their own faith and the support receiving from society may help women to accept their loss and provide positive feelings.

The age variable had a significant effect on the median PGS total score at T_1 after the loss. Women aged 20-29 years had higher PGS

Table 3. Distribution of scale scores in terms of some variables over time

	PGS T_0 Median (min-max)	PGS T_1 Median (min-max)	PGS T_2 Median (min-max)	PGS T_3 Median (min-max)	Statistical significance P-value	RTSQ T_0 $\chi \pm SD$	RTSQ T_1 $\chi \pm SD$	RTSQ T_2 $\chi \pm SD$	RTSQ T_3 $\chi \pm SD$	Statistical significance P-value
Age (years)										
20-29	88 (66-138)	77 (50-130)	56.5 (39-105)	48.5 (38-125)	Age: WTS = 1.194 P = 0.551 Time: WTS = 70.631; P < 0.001 Age*Time: WTS = 10.480; P = 0.105	97.11 ± 22.05	81.31 ± 16.42	57.95 ± 16.42	53.09 ± 18.76	Age: F = 0.348; P = 0.708 Time: F = 2.855; P = 0.069 Age*Time: ATS = 1.626; P = 0.180
30-39	96 (43-143)	70 (43-122)	52 (36-120)	44 (36-101)		96.42 ± 23.87	74.51 ± 20.43	58.07 ± 21.13	55.25 ± 18.22	
40-49	101.5 (50-130)	57 (42-83)	52.5 (36-90)	43.5 (39-90)		95.83 ± 28.21	60.83 ± 18.02	59.33 ± 20.70	52.16 ± 19.46	
	$\chi^2 = 0.016$ P = 0.992	**$\chi^2 = 7.169$ P = 0.028†**	$\chi^2 = 0.286$ P = 0.867	$\chi^2 = 0.157$ P = 0.924		F = 0.784 P = 0.484	F = 0.071 P = 0.931	F = 0.607 P = 0.548	F = 0.411 P = 0.904	
Childlessness										
Yes	88 (50-143)	80 (50-130)	60 (39-105)	45 (39-125)	Childlessness: WTS = 0.547; P = 0.459 Time: WTS = 135.88; P < 0.001 Childlessness*Time: WTS = 7.730; P = 0.051	88.82 ± 27.45	77.95 ± 26.46	78.38 ± 28.89	77.38 ± 29.62	Childlessness: ATS = 0.112; P = 0.739 Time: ATS = 7.707; P = 0.001 Childlessness*Time: ATS = 0.032; P = 0.955
No	100 (43-138)	71.5 (42-122)	55.5 (36-120)	48 (36-101)		89.80 ± 25.41	80.41 ± 21.13	80.88 ± 23.57	78.19 ± 27.22	
	Z = -1.167 P = 0.243	**Z = -2.326 P = 0.020†**	Z = -0.985 P = 0.324	Z = -0.025 P = 0.980		t = -0.154 P = 0.878	t = -0.387 P = 0.701	t = -0.356 P = 0.723	t = -0.118 P = 0.907	
Number of pregnancy losses										
One	99 (63-143)	77 (50-130)	60 (37-120)	48 (39-125)	Number of pregnancy losses: WTS = 7.508; P = 0.023 Time: WTS = 42.07; P = < 0.001 Number of pregnancy losses*Time: WTS = 4.445; P = 0.617	90.46 ± 22.05	85.70 ± 22.86	85.09 ± 26.64	81.80 ± 26.34	Number of pregnancy losses: ATS = 2.141; P = 0.127 Time: F = 12.094; P = 0.095 Number of pregnancy losses*Time: ATS = 2.094; P = 0.095
Two	90 (50-138)	71 (42-91)	47 (37-90)	44 (38-90)		80.20 ± 30.68	69.94 ± 20.15	72.17 ± 20.65	72.05 ± 20.65	
Three or more	84 (43-114)	77 (43-97)	52 (36-87)	54 (36-80)		102.45 ± 26.19	76.22 ± 24.20	77.00 ± 27.79	75.44 ± 27.50	
	$\chi^2 = 1.116$ P = 0.572	$\chi^2 = 4.173$ P = 0.124	$\chi^2 = 3.579$ P = 0.167	$\chi^2 = 0.928$ P = 0.629		F = 2.799 P = 0.068	F = 2.859 P = 0.066	F = 1.516 P = 0.229	F = 0.887 P = 0.418	
Type of loss										
Miscarriage	94.5 (50-143)	73.5 (42-117)	57 (36-90)	48 (36-90)	Type of loss: WTS= 3.065; P = 0.079 Time: WTS = 18.04; P < 0.001 Type of loss*Time: WTS = 0.579; P = 0.761	91.50 ± 25.22	79.98 ± 23.21	80.31 ± 25.55	78.21 ± 25.05	Type of loss: ATS = 0.136; P = 0.714 Time: ATS = 3.374; P = 0.044 Type of loss*Time: ATS = 0.016; P = 0.975
Stillbirth	92 (43-130)	75 (47-130)	55 (37-120)	45 (38-125)		89.17 ± 31.28	75.50 ± 23.04	77.00 ± 26.59	75.17 ± 26.00	
	Z = -0.343 P = 0.731	Z = -1.366 P = 0.172	Z = -0.415 P = 0.678	Z = -0.240 P = 0.810		t = -0.332 P = 0.741	t = 0.615 P = 0.541	t = 0.083 P = 0.934	t = -0.444 P = 0.659	

PGS = Perinatal Grief Scale; RTSQ = Ruminative Thought Style Questionnaire; min-max = minimum-maximum; SD = standard deviation; χ^2 = Kruskal-Wallis test; Z = Mann-Whitney U test; F = one-way analysis of variance (ANOVA) test; ATS = repeated-measurement ANOVA test; WTS = Wald-type statistics, t: Student's t test; †P < 0.05.

total scores than other age groups. Robert et al. stated that maternal age was a significant predictor of the level of grief and that there was a negative relationship between maternal age and perinatal grief level.[30] The results from the current study are consistent with those from that study. At early ages in the cycle of life, individuals may not yet have experienced any loss, and a pregnancy loss might be the first major loss in their lives. Women might become more capable of managing negative emotions as they acquire more experiences of life.

In this current study, it was found out that already having children had a significant effect on the median value of the PGS total score at T_1. Childless women had higher levels of PGS scores at T_1. Childlessness has been determined to be an important factor with regard to the duration of perinatal grief.[25] Moreover, Tseng et al. indicated that being a childless woman

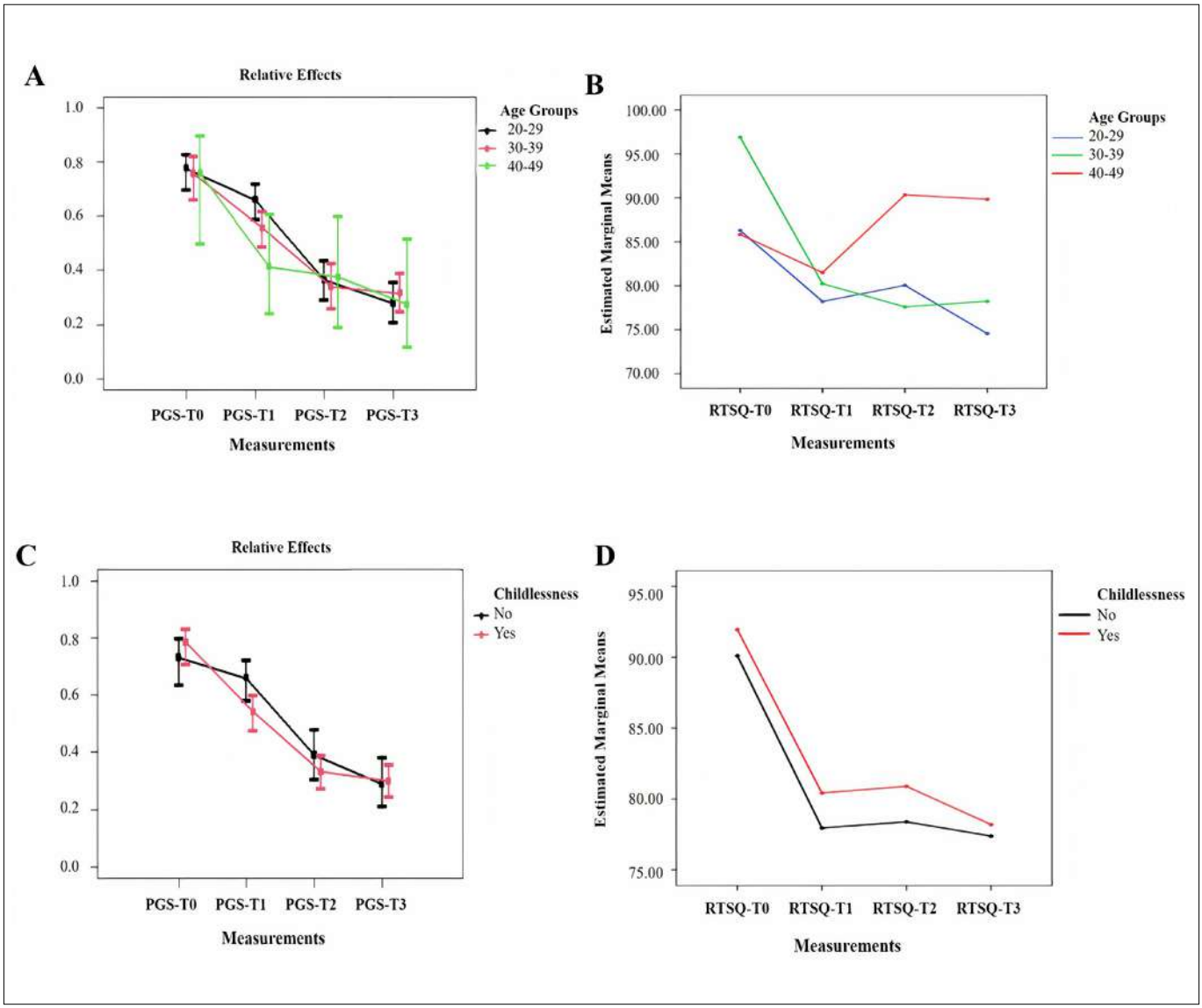


Figure 2. Changes in the age groups and childlessness variables of the Perinatal Grief Scale (PGS) and Ruminative Thought Style Questionnaire (RTSQ) at one-year follow-up: a) age groups of the PGS; b) age groups of the RTQS; c) childlessness of the PGS; D) childlessness of the RTQS.

is a major risk factor for perinatal grief.[27] The results from our study were similar to those of all these studies. In Turkish society, individuals believe that women who lost their pregnancy may heal through have another living child. Being childless may cause a higher level of grief than that of women who have living children.

We found that the mean RTSQ score of the women was highest at T_0. The mean scores on the RTSQ showed decreases over the course of the one year of measurements. Thus, the rumination level was highest in the early period of the loss, and it tended to decrease from high to medium rumination gradually. Rumination is considered a cognitive process, in that it has an important role in various psychiatric disorders such as anxiety and mood state disorders.[23] Studies have reported that among women the risk of experiencing depression increases when their ruminative tendencies increase.[11,14,32,33] There are no studies in the literature that have evaluated ruminative thought styles among women after perinatal loss. However, several studies have assessed the correlations between rumination levels and anxiety, depression and psychological parameters. Previous studies have shown that rumination causes depressive symptoms because of negative thinking, weak problem-solving skills, insufficient coping

behaviors and lack of social support.[33,34] Rumination has also been found to have positive correlations with depression, anxiety and negative automatic thoughts, and a negative correlation regarding satisfaction with life.[8,11,13-16,33-35] Additionally, some studies have found that grief may occur in various pathological forms, and that chronic grief may cause depression, anxiety, phobias, obsessions and psychotic reactions.[36] Therefore, determining the level of rumination after pregnancy loss is quite important in terms of psychopathological conditions such as depression during the early days after the loss.

The results from this study showed that as rumination increases among women in the early period after their loss, grief also increases. This result was supported by the regression analysis in this study. In this current study, the results showed that almost all the women had recovered by the sixth month after the perinatal loss. However, women who are not recovering from grief present more rumination over time than do women who improve. There are no studies evaluating the relationship between perinatal grief and ruminative thought styles in the literature. However, a positive correlation has been reported in the literature between perinatal grief and depression.[24,29,37]

It has been observed that the majority of the women who experienced perinatal loss showed depressive symptoms.[24,29] Also, similar studies have shown that the risk of incidence of depression after perinatal loss is high.[25,37] Determining the relationship between perinatal grief and ruminative thought styles might be a starting point for planning qualitative nursing care aimed at protecting and improving women's mental health after perinatal loss.

Limitations

The sample size was limited because of the number of dropouts. For this reason, the study results can be generalized only for this population.

CONCLUSION

In this study, the levels of perinatal grief and ruminative thought styles among women who experienced pregnancy loss were assessed at the first 48 hours and at three months, six months and one year later. These women had high levels of grief and ruminative thought styles in the first 48 hours. However, their levels of grief and ruminative thought styles tended to decrease over the repeated measurements during the follow-up. Based on the results from this study, the following recommendations can be made:

- Nursing assessments regarding grief and ruminative thought style over the first 48 hours after perinatal loss should be integrated into nursing care for these women.
- In clinics, nurses should be trained regarding to how to approach these women, especially during the first 48 hours after the loss.
- Grief follow-up programs for these women can be developed through nursing research, especially during the first six months after the loss.
- Institutions should provide counseling services.

Table 4. Correlation analyses on the scales

		Active grief	Difficulty coping	Despair	Total PGS
T_0					
Difficulty coping	r	**0.481**			
	P	**< 0.001**			
Despair	r	**0.697**	**0.787**		
	P	**< 0.001**	**< 0.001**		
Total PGS	r	**0.798**	**0.855**	**0.957**	
	P	**< 0.001**	**< 0.001**	**< 0.001**	
Total RTSQ	r	**0.373**	**0.309**	**0.395**	**0.461**
	P	**0.001**	**0.009**	**0.001**	**0.001**
T_1					
Difficulty coping	r	**0.666**			
	P	**< 0.001**			
Despair	r	**0.811**	**0.734**		
	P	**< 0.001**	**< 0.001**		
Total PGS	r	**0.898**	**0.853**	**0.912**	
	P	**< 0.001**	**< 0.001**	**< 0.001**	
Total RTSQ	r	**0.369**	**0.288**	**0.401**	**0.360**
	P	**0.005**	**0.030**	**0.002**	**0.006**
T_2					
Difficulty coping	r	**0.583**			
	P	**< 0.001**			
Despair	r	**0.888**	**0.667**		
	P	**< 0.001**	**< 0.001**		
Total PGS	r	**0.943**	**0.748**	**0.961**	
	P	**< 0.001**	**< 0.001**	**< 0.001**	
Total RTSQ	r	**0.338**	0.246	**0.323**	**0.303**
	P	**0.010**	0.065	**0.014**	**0.022**
T_3					
Difficulty coping	r	**0.474**			
	P	**0.000**			
Despair	r	**0.836**	**0.510**		
	P	**0.000**	**0.000**		
Total PGS	r	**0.939**	**0.641**	**0.928**	
	P	**0.000**	**0.000**	**0.000**	
Total RTSQ	r	**0.306**	0.124	0.240	**0.289**
	P	**0.021**	0.357	0.072	**0.029**

PGS = Perinatal Grief Scale; RTSQ = Ruminative Thought Style Questionnaire; r = Spearman correlation.

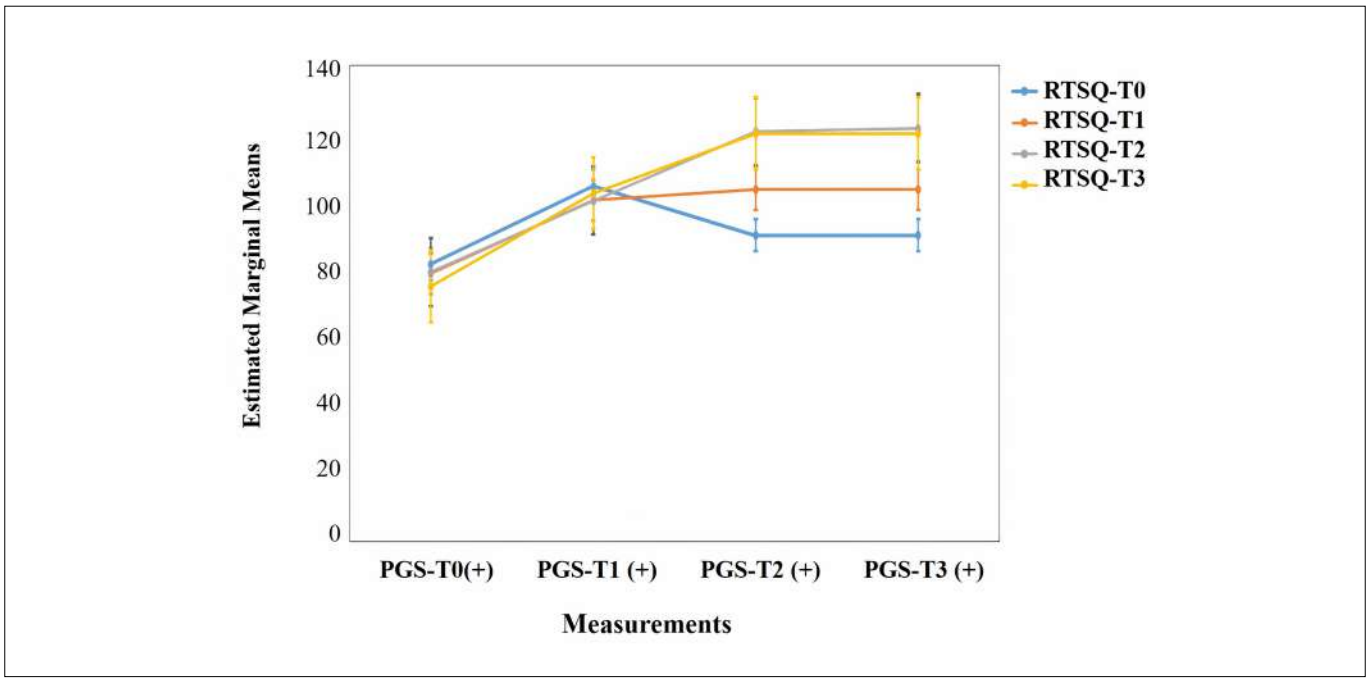


Figure 3. The changes in the Ruminative Thought Style Questionnaire (RTSQ) scores based on the Perinatal Grief Scale (PGS); cutoff points at one-year follow-up.

Table 5. Regression model for estimation of Ruminative Thought Style Questionnaire (RTSQ) scores

Model	B	t	P-value	95% confidence interval for B		Adjusted R^2
				Lower boundary	Upper boundary	
(Constant)	49.519	5.514	< 0.001	31.513	67.524	
Active grief_PGST$_3$	1.325	3.125	0.003	0.475	2.174	0.156
Family type: large	15.781	2.031	0.047	0.204	31.357	

Full model includes the following: family type; childlessness; working status; PGST$_3$ (Perinatal Grief Scale T$_3$); active grief; difficulty coping; despair.

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High prevalence of functional dyspepsia in nonalcoholic fatty liver disease: a cross-sectional study

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Diabetes mellitus.

AUTHORS KEYWORDS:
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NAFLD.
Indigestion.
Body weight.

ABSTRACT

BACKGROUND: Gastrointestinal (GI) symptoms are frequent complaints from individuals with nonalcoholic fatty liver disease (NAFLD). Dyspepsia is a universal clinical symptom and is among the most common GI complaints observed in the general population, but its prevalence in the population with NAFLD has not been previously investigated.

OBJECTIVE: To compare the prevalence of functional dyspepsia (FD) between patients with NAFLD and controls without liver disease.

DESIGN AND SETTING: Cross-sectional study at the Outpatient Liver Clinic, University Hospital, Belo Horizonte, Brazil.

METHODS: We included 96 NAFLD patients and 105 controls without liver disease. All participants were assessed for GI symptoms in accordance with the Rome III criteria. Evaluation methods included a questionnaire for FD (validated in Brazil), laboratory tests and upper GI endoscopy.

RESULTS: Mean age and sex were similar between the groups. The NAFLD group presented higher frequency of proton-pump inhibitor usage (31.3% vs 4.8%; P < 0.001) and prevalence of FD (25.0% versus 12.4%; P = 0.021). The symptom frequencies were as follows: postprandial distress, 22.9% versus 11.4% (P = 0.030); postprandial fullness, 18.8% versus 10.5% (P = 0.095); early satiation, 8.3% versus 5.7% (P = 0.466); and epigastric pain or burning, 18.8% versus 5.7% (P = 0.004), in NAFLD patients and controls, respectively. Multivariate analysis demonstrated that female sex (odds ratio, OR 6.97; 95% confidence interval, CI: 1.51-32.12; P = 0.013) and NAFLD diagnosis (OR 2.45; 95% CI: 1.14-5.27; P = 0.021) were independently associated with FD occurrence.

CONCLUSION: FD occurs more frequently in individuals with NAFLD than in controls without hepatic disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is currently considered to be a public health problem in many countries, affecting both adults and children. This condition is characterized by hepatic steatosis, which is detected through ultrasound (US) or histological examination of the liver in individuals without a history of excessive alcohol consumption and with no other causes of liver disease.[1] NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocarcinoma. Obesity, insulin resistance, type 2 diabetes mellitus (DM) and other components of metabolic syndrome are common related comorbidities.[1] The global incidence of NAFLD is unknown since it depends on the population studied and on the methods used to diagnose this condition (e.g. liver biopsy, magnetic resonance spectroscopy or US). Despite these limitations, the prevalences of NAFLD and NASH in the general population in Western countries have been estimated to reach 20%-30% and 1%-3%, respectively.[1,2]

NAFLD is considered to be a silent disease with asymptomatic evolution until its advanced stages. Studies have demonstrated a lack of specific symptoms in 45%-100% of patients.[3-5] The diagnosis is made unintentionally in asymptomatic patients through detecting elevated serum aminotransferase levels or steatosis on US performed as a routine test or during investigation of other comorbidities related to NAFLD. However, more recently, it has been suggested that NAFLD patients may present with multiple symptoms related to the gastrointestinal (GI) tract. For example, a high proportion of the patients with NAFLD that was incidentally detected

through US examination initially sought medical attention due to the presence of functional GI symptoms.[6] Moreover, patients with functional dyspepsia (FD) who underwent US have also been described as having high prevalence of fatty liver.[7] Nevertheless, published data regarding the prevalence of GI symptoms specifically in the NAFLD population are scarce.

Dyspepsia is one of the most frequent GI symptoms observed in the general population. It is defined as a digestive disorder characterized by a set of symptoms related to the upper GI tract, such as pain, burning or discomfort in the upper abdomen, which may be associated with early satiety, postprandial nausea, vomiting, bloating or a feeling of abdominal distention.[8] The Rome III consensus defines FD as the presence of one or more of the following: epigastric pain or epigastric burning, bothersome postprandial fullness and early satiety with no evidence of a structural disease (including upper endoscopy evaluation) that would explain the symptoms.[9] Patients with these symptoms but without any structural disease upon diagnostic evaluation probably have FD, even though according to the Rome III guidelines, these criteria should be met during the last three months with symptom onset at least six months before the diagnosis.

OBJECTIVE

Considering the current increasing burden of NAFLD and the lack of knowledge regarding the characterization of GI symptoms in this population, we conducted this study to test the hypothesis that individuals with NAFLD have higher prevalence of FD than do subjects without fatty liver disease.

METHODS

Study population and data collection

This cross-sectional study included 201 subjects who were prospectively selected between August 2015 and December 2016. The patients were consecutively recruited from the Outpatient Liver Clinic, University Hospital, Belo Horizonte, Brazil, after they had been diagnosed with NAFLD. This institution is a referral center within the Brazilian public healthcare system for treating liver diseases. A control group was also formed, and this included 105 individuals without known liver disease. These subjects were the companions of patients treated in the Outpatient Liver Clinic, and they were selected based on their clinical history of no liver diseases. The local ethics committee approved the study (CAAE 26228014.7.0000.5149) on March 12, 2014, and all patients signed an informed consent statement. The sample was obtained according to convenience after inclusion of prospective patients' inclusion, since the prevalence of FD among NAFLD subjects was unknown.

The diagnosis of NAFLD was established in accordance with the criteria of international guidelines.[10] The inclusion criteria comprised (a) steatosis on US and/or liver biopsy (performed based on clinical judgment); (b) exclusion of other causes of liver disease (i.e. alcoholic disease, autoimmune disorders, viral hepatitis, hemochromatosis, Wilson's disease and alpha-1-antitrypsin deficiency); (c) no history of prior gastric or jejunoileal bypass and no exposure to hepatotoxins; (d) no use of steatogenic medications within the past six months; and (e) 18 years of age or older. The inclusion criteria for controls were that they needed to be adults aged between 18 and 75 years and without any history of liver disease. The exclusion criteria for both groups were the presence of a diagnosis of decompensated liver cirrhosis, use of oral contraceptives or nonsteroidal anti-inflammatory drugs, corticosteroid treatment or history of organic GI diseases.

Clinical and laboratory investigations

Demographic characteristics, anthropometric data, use of proton-pump inhibitors and prevalence of comorbidities were evaluated in all patients. Anthropometric data comprised weight (kg), height (m), waist circumference (cm) (measured midway between the lower limit of the rib cage and the iliac crest, with the participant in a standing position) and body mass index (BMI), which was calculated as weight/height^2 (kg/m^2). For analysis purposes, obesity was defined as BMI $\geq$ 30 kg/m^2.

Metabolic syndrome was defined in accordance with the criteria adopted by the International Diabetes Federation:[11] central obesity (waist circumference $\geq$ 90 cm in men and $\geq$ 80 cm in women), along with two or more of the following conditions: hypertriglyceridemia ($\geq$ 150 mg/dl), low high-density lipoprotein (HDL) cholesterol levels (< 40 mg/dl in men and < 50 mg/dl in women), hypertension (systolic blood pressure $\geq$ 130 mmHg and diastolic $\geq$ 85 mmHg) and fasting glucose $\geq$ 100 mg/dl.

All patients who had GI symptoms underwent upper GI endoscopy to investigate the presence of structural disease. We excluded patients with findings suggestive of structural diseases that may cause dyspeptic symptoms, such as peptic ulcers, erosive duodenitis, intestinal metaplasia or gastric mucosal atrophy. Since erosive esophagitis and gastroesophageal reflux disease (GERD) do not usually cause dyspeptic symptoms,[12] they were not excluded. Nonspecific findings such as enanthematous gastritis/pangastritis and hiatal hernia were described. Esophageal varices were considered to be manifestations of portal hypertension related to progressive steatohepatitis, as long as a diagnosis of NAFLD was previously present.

Helicobacter pylori infection was tested by means of histopathological assessment, and individuals with positive tests were treated for its eradication. Patients with persistent dyspeptic symptoms after six months, despite adequate *H. pylori* treatment proved through a respiratory test, were diagnosed as presenting FD.[13]

The laboratory assessment included total cholesterol and fractions, triglycerides, fasting blood glucose and insulin,

glycohemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin, hemoglobin and platelet count. Insulin resistance in nondiabetic patients was calculated using the homeostatic model assessment index (HOMA), i.e. serum insulin (μU/ml) × fasting glucose (mmol/l)/22.5, and presence of insulin resistance was defined as HOMA values ≥ 3. Presence of DM was diagnosed if patients were on regular oral hypoglycemic drugs and/or insulin, and/or they had a fasting glucose level ≥ 126 mg/dl on two different occasions.

The NAFLD fibrosis score was calculated for all NAFLD patients. This score is a noninvasive method for determining the presence of advanced liver fibrosis in these patients. Scores above 0.676 indicate advanced liver fibrosis, and scores below -1.455 indicate the absence of advanced liver fibrosis.[14]

Rating of functional dyspepsia between the groups

The presence of GI symptoms was assessed by administering a questionnaire adapted from the criteria proposed in the Rome III[15] consensus, which has been validated for use in the Portuguese language.[16] The interpretation was also based on the Rome III definitions for functional disorders. Therefore, the criteria for all diagnosed symptoms had to be met within the last three months and symptom onset needed to be at least six months ago. Functional gastroduodenal disorders such as dyspepsia were diagnosed when there was no evidence of structural disease in upper endoscopy examination, or of abnormal behavior (e.g. self-induced vomiting), central nervous system abnormalities or metabolic diseases that could explain the symptoms.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 18 (SPSS Inc, Chicago, Illinois, United States). Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as the mean ± standard deviation when the data were normally distributed, while the median and interquartile range were used for variables with skewed distribution.

For univariate analyses, continuous variables were compared between groups using the nonparametric Mann-Whitney U test. To compare proportions, the chi-square test or Fisher's exact test was used, as appropriate. For the multivariate analysis, we used logistic regression, with the backward method, to verify predictors of FD and confounding factors. The results were presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). The variables were removed from the model one by one until only variables with a P-value < 0.05 remained. Significance was indicated by a P-value < 0.05.

RESULTS

Characteristics of the patients

The present study included 96 patients with NAFLD with a mean age of 55.9 ± 12.7 years and 105 controls with a mean age of 55.2 ± 12.8 years. The demographic characteristics, anthropometric data and prevalence of comorbidities are shown in **Table 1**.

Six patients were not included, based on the following exclusion criteria: four patients had Crohn's disease (two NAFLD subjects and two controls) and two patients had previously undergone gastroduodenal anastomosis (NAFLD group). Upper gastrointestinal endoscopy revealed peptic ulcers and/or erosive duodenitis in three patients in the NAFLD group. These patients were not included.

There was no difference between the groups regarding sex distribution or median age. NAFLD patients presented significantly higher frequencies of obesity, hypertension, DM, hypercholesterolemia, low HDL-cholesterol levels, metabolic syndrome and use of proton-pump inhibitors than did the controls (**Table 1**). In the whole sample, 35 patients had been using omeprazole: 30 NAFLD patients (13 with GERD, 10 with FD, seven with both conditions and 14 who were using this drug for other indications) and five control individuals (two had GERD, none had FD and three were using this drug for other indications).

DM was observed in 42.1% of the NAFLD patients. NAFLD fibrosis score analysis demonstrated that, out of the 96 NAFLD patients, 41 (42.7%) did not have significant fibrosis and 13 (13.5%) presented significant fibrosis; in 42 (43.8%) patients, the stage of fibrosis could not be determined from the score.

Functional gastrointestinal symptoms

All the patients with dyspeptic symptoms underwent upper endoscopy in order to map any presence of organic diseases, as shown in **Table 2** (five control individuals did not have this test

Table 1. Demographic, anthropometric and clinical data on the NAFLD patients and controls

Variable	Groups		P-value
	NAFLD (n = 96)	Control (n = 105)	
Female sex	78 (81.3)	82 (78.1)	0.579†
Age (years)	59 (49.5-64.0)	58 (48.5-64.0)	0.638§
BMI (kg/m²)	32 (28-36)	26 (23-29)	< 0.001§
Obesity (BMI ≥ 30)	62/94 (66)	22/104 (21.2)	< 0.001‡
Central obesity	93/96 (96.9)	48/105 (45.7)	< 0.001†
Hypertension	67/95 (70.5)	36/105 (34.3)	< 0.001†
Diabetes	40/95 (42.1)	14/105 (13.3)	< 0.001†
Hypertriglyceridemia	49/90 (54.4)	13/91 (14.3)	< 0.001†
Low HDL cholesterol	43/88 (48.9)	11/91 (12.1)	< 0.001†
Metabolic syndrome	71/95 (74.7)	13/105 (12.4)	< 0.001†
Proton-pump inhibitor use	30/96 (31.3)	5/105 (4.8)	< 0.001†

Data are expressed as absolute numbers (percentages) and medians (interquartile ranges). NAFLD = nonalcoholic fatty liver disease; BMI = body mass index; HDL = high-density lipoprotein; †chi-square test; ‡Fisher's exact test; §Mann-Whitney U test.

because they refused to undergo the procedure). Although FD and epigastric burning or pain occurred more frequently in the NAFLD patients, the frequencies of *Helicobacter pylori* infection, gastritis and pangastritis were similar in the two groups.

Out of the 27 NAFLD patients who underwent upper endoscopy, eight were diagnosed with *Helicobacter pylori* (29.6%) and were treated with conventional therapy. After six months of treatment, three of these patients achieved resolution of the dyspeptic symptoms, while the other five had persistent symptoms, despite undergoing a respiratory *Helicobacter pylori* test that confirmed that the treatment had been adequate. Patients with resolution after *Helicobacter pylori* eradication were not considered to have had FD.

Table 2. Comparison between endoscopic findings among NAFLD patients and controls with dyspeptic symptoms

Variable	Groups		P-value
	NAFLD (n = 27)	Control (n = 9)	
Peptic ulcers	0 (0.0)	0 (0.0)	1.000†
Erosive duodenitis	0 (0.0)	0 (0.0)	1.000†
Erosive esophagitis	5 (18.5)	0 (0.0)	0.302†
Enanthematous gastritis	7 (25.9)	4 (44.4)	0.409†
Enanthematous pangastritis	14 (51.9)	1 (11.1)	0.051†
Esophageal varices	2 (7.4)	0 (0.0)	1.000†
Hiatal hernia	2 (7.4)	1 (11.1)	1.000†
Helicobacter pylori infection	8 (29.6)	1 (11.1)	0.266†

Data are expressed as absolute number (percentage); †Fisher's exact test.

Figure 1 shows the frequency and type of FD in the NAFLD individuals and controls, respectively: FD, 24 (25.0%) and 13 (12.4%) (P = 0.021); postprandial distress syndrome, 22 (22.9%) and 12 (11.4%) (P = 0.030); postprandial fullness, 18 (18.8%) and 11 (10.5%) (P = 0.095); early satiation, 8 (8.3%) and 6 (5.7%) (P = 0.466); and epigastric burning or pain, 18 (18.8%) and 6 (5.7%) (P = 0.004).

For better characterization of the patients with FD, we compared the individuals with and without FD inside each of the groups (i.e. NAFLD and controls) according to age, sex and features of metabolic syndrome (**Table 3**). Although the overall NAFLD group presented higher frequency of obese patients (**Table 1**) than the control group, when the subjects in each group were separated according to the presence or absence of FD, the frequencies of DM, central obesity and other metabolic features were similar among those with NAFLD, and also inside the control group.

Multivariate analysis was performed in order to investigate predictors for FD occurrence in the whole population studied, by adding the variables of age, sex and NAFLD diagnosis to a logistic regression model. After adjustment, the variables independently associated with FD occurrence were female sex (OR 6.97; 95% CI 1.51-32.12; P = 0.013) and NAFLD diagnosis (OR 2.45; 95% CI 1.14-5.27; P = 0.021).

The NFS categories were not associated with any functional gastrointestinal symptom or disorder: FD (P = 0.689), postprandial

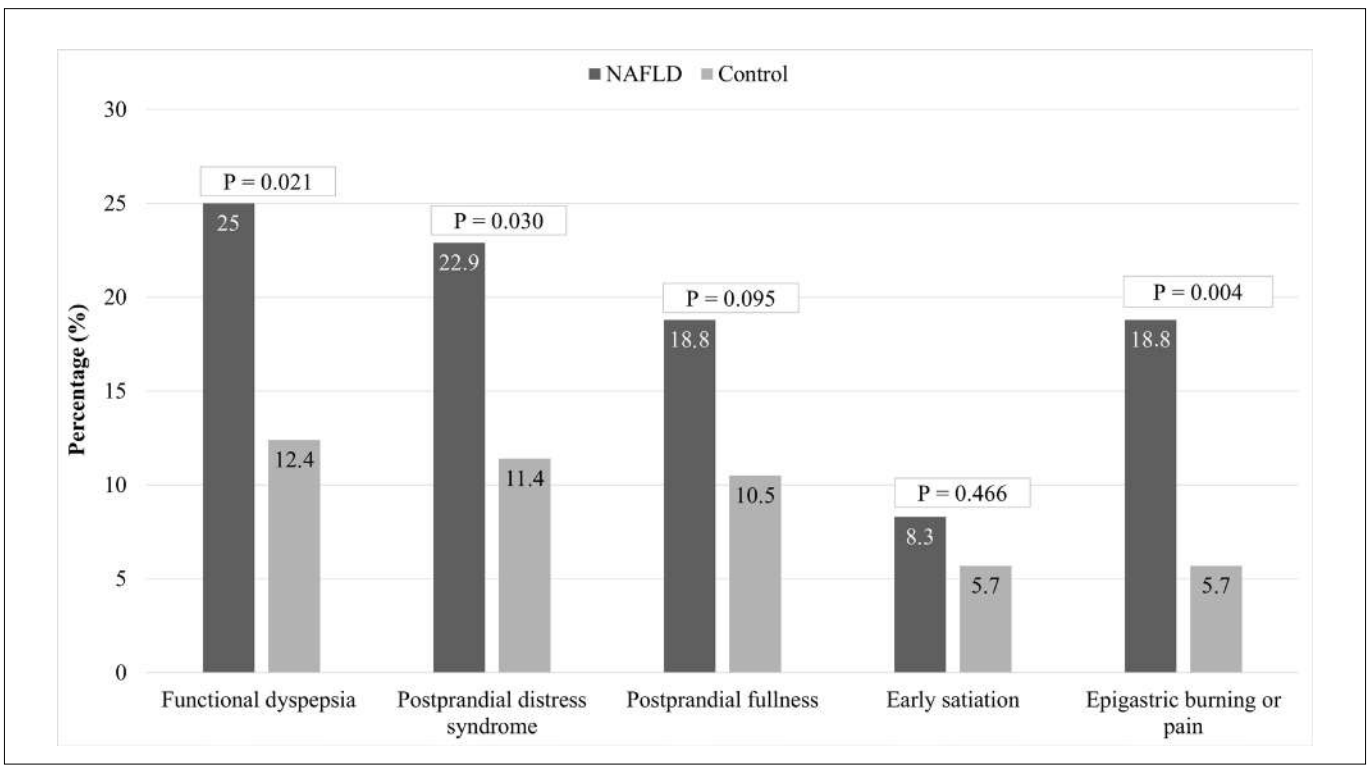

Figure 1. Comparison of frequencies and types of functional dyspepsia syndromes and symptoms between nonalcoholic fatty liver disease (NAFLD) and control groups. Chi-square test.

distress syndrome (P = 0.784), postprandial fullness (P = 0.944), early satiation (P = 0.612) and epigastric pain/discomfort syndrome (P = 0.489).

DISCUSSION

In this study, we found high prevalence of FD, according to the Rome III criteria, in the NAFLD group in comparison with its prevalence in the control group without hepatic disease. The frequency of FD was 25.0% in the NAFLD group and only 12.4% in the control group. The prevalence of FD in the control group was similar to what had previously been described in the general population, which ranged from 5.3% to 20.4%.[17] Although postprandial distress syndrome was more frequent among the patients with FD in the NAFLD group, the frequencies of early satiation and postprandial fullness were similar between the NAFLD and control individuals. The reasons for these findings are unknown and should be addressed in future studies. Corroborating our findings, a recent study that included 195 patients with FD showed high prevalence of associated NAFLD (67%), diagnosed through US.[7]

Our results also showed that a higher percentage of individuals with NAFLD used proton-pump inhibitors and had epigastric burning or pain complaints, than among the controls. To our knowledge, this was the first study evaluating FD according to the Rome III criteria among NAFLD patients. Two previous studies showed higher prevalence of GERD among NAFLD patients,[18,19] but no study had evaluated functional GI symptoms. We did not investigate functional heartburn because although all the patients with this complaint underwent endoscopy, they were not subjected to further investigations in order to make differential diagnoses regarding this condition. Thus, all the subjects with normal endoscopy results and complaints of heartburn were considered to have GERD. Interestingly, a recent meta-analysis showed high frequency of dyspepsia among subjects with GERD symptoms, which may suggest that that these conditions can overlap.[20]

A heterogeneous group of pathophysiological mechanisms has been implicated in the pathogenesis of FD, including delayed gastric emptying, antral hypomotility, impaired intestinal motility, decreased gastric accommodation, increased visceral sensitivity, abnormal sensitivity to carbohydrates, poor fatty acid duodenal digestion, infiltration of the digestive tract by immune cells and psychological factors. Despite years of intense research, many controversies about the role of these factors and their causal relationship with FD symptoms remain to be elucidated.[20]

Although the pathogenesis of NAFLD has not been fully elucidated, it is well known that this condition is strongly associated with insulin resistance, obesity and dyslipidemia.[1] Additionally, previous studies demonstrated that FD is associated with central obesity and DM. DM patients frequently report GI symptoms such as postprandial fullness, heartburn, bloating, abdominal pain, early satiety, vomiting and nausea. These symptoms were previously attributed to diabetic gastropathy as an expression of autonomic neuropathy; however, more recent data have suggested that those symptoms are probably due to multifactorial mechanisms.[21,22] Indeed, controversies regarding the association of DM with GI symptoms still exist. Some studies[23,24] did not show any differences in the prevalence of GI symptoms between individuals with and without DM, except for lower prevalence of heartburn in individuals with type 1 DM. In contrast, in other investigations,[25,26] subjects with DM reported significantly more GI symptoms than did control individuals without DM. However, those authors did not use the Rome III criteria for diagnosing FD. We did not find any association between FD and DM within the NAFLD group, or among the controls (**Table 3**). Female sex has also been associated with FD in diabetic and control populations.[26]

It has been suggested that obesity may cause dyspeptic symptoms by means of different mechanisms, such as alterations in the function of GI neuropeptides;[27] excess visceral adiposity, which may increase intra-abdominal pressure; and secretion of adipokines and proinflammatory cytokines by visceral adipose tissue.[28]

Table 3. Comparison between patients with and without functional dyspepsia, according to age, sex and features of metabolic syndrome

Variable	NAFLD (n = 96)			Control (n = 105)		
	FD (n = 24)	No FD (n = 72)	P-value	FD (n = 13)	No FD (n = 92)	P-value
Female	23 (95.8)	55 (76.4)	0.037*†	12 (92.3)	70 (76.1)	0.289‡
Age (years)	56 (42-63)	60 (53-65)	0.140§	61 (44-65)	58 (50-64)	0.489§
Central obesity	23 (95.8)	70 (97.2)	> 0.999‡	6 (46.2)	42 (45.7)	0.973†
Hypertension	19 (79.2)	48 (67.6)	0.283†	5 (38.5)	31 (32.7)	0.761‡
Diabetes	10 (41.7)	30 (42.3)	> 0.999†	1 (7.7)	13 (14.1)	> 0.999‡
Hypertriglyceridemia	16 (66.7)	33 (45.8)	0.091†	0 (0.0)	13 (14.1)	0.354‡
Low HDL-c	15 (62.5)	28 (38.9)	0.036*†	0 (0.0)	11 (13.8)	0.348‡
Metabolic syndrome	20 (83.3)	51 (70.8)	0.262†	1 (7.7)	12 (13.0)	> 0.999‡

NAFLD = nonalcoholic fatty liver disease; FD = functional dyspepsia; HDL-c = high-density lipoprotein cholesterol. Data are expressed as number (percentage) and median (interquartile range); †chi-square test; ‡Fisher's exact test; §Mann-Whitney U test.

However, the epidemiological data linking obesity to functional GI disorders are inconsistent.[29] Although it is well established that obesity is associated with GERD, it remains unclear whether obesity is a risk factor for common functional GI disorders.[30]

Recent studies have demonstrated an association between high BMI and increased risk of FD among females.[31,32] In the current study, we found an association between female sex and FD, thus corroborating the results from previous studies. Interestingly, one study identified a positive correlation between visceral adiposity and FD. Regarding GI symptoms, only epigastric pain was found to be associated with visceral adiposity.[33] Those results were different from ours, as our NAFLD patients and controls with FD did not present higher frequency of central obesity, considering each group individually (**Table 3**).

Our study had limitations that should be noted. Firstly, there was subjectivity in applying the questionnaire and there are inherent clinical difficulties in making assertive diagnoses of functional disturbances. On the other hand, the Rome III questionnaire has been validated in Brazil. Additionally, a specific team was trained for individual and standardized administration of questionnaires. This strength is relevant in comparison with other observational studies in which the questionnaires were administered online or by telephone, or were handed to patients to be returned later.[31,34] Furthermore, we used the Rome III criteria instead of Rome IV because our team already had experience with its administration; and because Rome IV only presents minor changes in relation to Rome III. These changes were an attempt to increase the specificity of appropriate patient inclusion in clinical trials, whereas in clinical practice this precision may not be required.[35] Lastly, the controls did not undergo abdominal ultrasonography for diagnosing NAFLD. Thus, the study results may constitute an underestimation, considering that after excluding possible controls with undiagnosed NAFLD, the association between FD and the group with diagnosed fatty liver could even have been stronger than we found. Further studies are needed to confirm this.

CONCLUSION

In conclusion, the present study provides new evidence regarding the association between FD and NAFLD. The prevalence of FD was higher among individuals with NAFLD. Further studies are required in order to validate these observations and to establish optimal strategies for managing dyspeptic symptoms in these individuals.

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Self-reported depression and anxiety among COPD patients. A case-control study

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ABSTRACT

BACKGROUND: Anxiety and depression are the most prevalent mental disorders worldwide. However, the exact mechanisms linking chronic obstructive pulmonary disease (COPD) with depression and anxiety have not been identified.

OBJECTIVES: To compare self-reported depression and anxiety among patients diagnosed with COPD in relation to healthy controls.

DESIGN AND SETTING: Case control study at a public hospital institution in Spain.

METHODS: We designed a case-control study. Patients were recruited using a consecutive sampling method from a single institution. Two groups were created: COPD and healthy controls. Data on medical history and demographic background were collected from the medical records. Self-reported depression levels were assessed using Beck's depression inventory (BDI). Self-reported anxiety was measured using the State-trait anxiety inventory (STAI).

RESULTS: Fifty-two patients with COPD and fifty healthy patients were included in this study. BDI scores were higher for COPD patients (10.23 ± 6.26) than in the control group (5.2 ± 6.56). STAI-state scores were higher for COPD patients (41.85 ± 12.55) than for controls (34.88 ± 9.25). STAI-trait scores were higher for COPD patients (41.42 ± 10.01) than for controls (34.62 ± 9.19).

CONCLUSIONS: This study showed that there were higher levels of depression and anxiety among COPD patients than among healthy controls.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death worldwide.[1] It is a major cause of chronic morbidity and mortality throughout the world. Many people die prematurely from it or its complications.[2]

COPD is defined as a respiratory disease, mainly caused by tobacco abuse and characterized by persistent symptoms such as chronic cough with or without expectoration and chronic airflow limitation, that usually manifests as progressive dyspnea.[3]

According to the World Health Organization (WHO), common mental disorders refer to two main diagnostic categories: depressive disorders and anxiety disorders. Both of these are highly prevalent in the population and can affect people of all ages. Over 300 million people are estimated to suffer from depression, equivalent to 4.4% of the world's population, and this number seems to be increasing.[3]

Depressive disorders are characterized by symptoms such as sadness, loss of interest or pleasure, feelings of worthlessness or guilt, sleep difficulties, fatigue, appetite or weight changes, feelings of tiredness, psychomotor disturbances, poor ability to concentrate and even suicidality.[4] Depression can be long-lasting or recurrent, and causes impairment to activities of daily life.

Anxiety is associated with physical and psychological discomfort. All anxiety disorders share common symptoms, such as fear, anxiety and avoidance. Other anxiety-related symptoms include fatigue, restlessness, irritability, sleep disturbances, reduced concentration, lack of memory and muscle tension.

Depression and anxiety often co-occur. Up to 90% of patients with anxiety develop symptoms of depression, and nearly 85% of patients with depression show some kind of anxiety symptom.[5,6] The prevalence of depression and anxiety is two to three times higher among people with chronic medical conditions than among healthy people.[7] People with a long-term condition and

depression or anxiety have worse health status than people with depression or anxiety alone, and even people with any combination of long-term conditions without depression.[8]

Nearly 40% of the population are affected by an anxiety disorder at some point.[9] The consequences of both anxiety and depression in terms of loss of health are substantial and have considerable effects on patients' health-related quality of life. Depression is considered to be the largest single contributor to overall disability around the world.[10] The most common underlying disorder among individuals who attempt suicide is depression.[11]

We hypothesized that people with COPD would have worse levels of self-perceived depression and anxiety traits and states, compared with healthy people.

OBJECTIVE

The main objective of this study was to determine self-perceived depression and anxiety trait and state levels in a subset of COPD patients, compared with healthy people. To our knowledge, this was the first time that both Beck's depression inventory (BDI) (second edition) and the state-trait anxiety inventory (STAI) had been used altogether to evaluate depression and anxiety among COPD patients, in comparison with healthy participants.

METHODS

Study design

The guidelines for reporting observational studies of the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement were followed.[12] A case-control study was designed to compare self-assessed depression severity, anxiety traits and anxiety states among patients diagnosed with COPD and among healthy controls.

Ethics statement

This study was approved by the ethics committee for clinic research of Galicia, Spain, under registration number 2019/431, with the application date of October 22, 2019. The Helsinki declaration and all national and international ethical standards for human experimentation were respected.[13] Furthermore, all participants signed an informed consent statement before their inclusion in the present research.

Sample size calculation

In order to determine the sample size required to ascertain differences between two different means, we applied a T test by using the G*Power 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf; Düsseldorf, Germany). We focused on BDI as our principal outcome measurement in the preliminary study (n = 28 participants) with two groups (mean + standard deviation, SD): 14 patients with COPD (9.28 ± 6.16 points) and 14 healthy controls (4.92 ± 3.64 points). Moreover, the following variables were used for the sample size calculation: effect size of 0.86, α error of 0.01 and power (1-β error) of 0.90.

In the end, the sample size determined through adjustments to calculations was 84 participants, i.e. 42 for each group, which was found necessary in order to achieve an actual power of 0.901. From this, a total sample of 150 subjects with 50 participants in each group was included in the present study, taking into consideration a possible 30% loss due to errors in data acquisition or incomplete questionnaires.

Participants

We used a consecutive sampling method in order to recruit participants from the pneumology department of the Complexo Hospitalario de Ourense, Ourense, Spain. All the data collection was supervised by the same researcher. We established two groups: COPD (case group) and healthy participants (control group). COPD patients were diagnosed and classified in accordance with the GesEPOC guidelines (Spanish practical guidelines for COPD patient diagnosis and treatment).[14] The inclusion criteria for both groups were that the subjects needed to be older than 18 years of age, agree to sign the informed consent statement and show a lack of history of psychiatric disease or use of antidepressants or anxiolytics. For the control group, healthy participants older than 18 years of age were included, without any chronic respiratory disease or known psychiatric medical history, and with agreement to sign the informed consent statement. The exclusion criterion was a lack of compliance with the inclusion criteria described above.

Descriptive data

Descriptive data on sex, age, weight, height, body mass index (BMI; calculated through the Quetelet index as kg/m^2)[15] and smoking habit were collected.

Outcome measurements

Self-perceived depression, anxiety traits and states were considered to be the primary outcomes.

Self-reported depression

We used the "BDI-II", which is a widely used instrument for assessing the severity of depression worldwide. This tool has been validated for use in Spanish, with Cronbach's $\alpha = 0.87$ and high diagnostic validity (receiver operating characteristic, ROC = 0.91) in the general population.[16]

This questionnaire consists of 21 groups of sentences that are scored on a 4-point Likert scale (scores of 0-3). The results can range from 0 to 63 points. Greater scores suggest increased severity of depression. As an example, the first group of sentences states:

"I do not feel sad" (0 points), *"I feel sad"* (1 point), *"I am sad all the time and I can't snap out of it"* (2 points) and *"I am so sad and unhappy that I can't stand it"* (3 points).

Total scores of 0-13 indicate minimal signs of depression; 14-19, mild depression; 20-28, moderate depression; and 29-63, severe depression.[17]

Self-reported anxiety trait and state

The STAI is a self-reported scale that is used for assessment of anxiety states (STAI-S) and anxiety traits (STAI-T) in research and clinical practice. This inventory consists of 40 statements about the participants' feelings, divided into two parts. In the first part, they are instructed to indicate the intensity of their feelings of anxiety at a particular moment (state anxiety), on a 20-item scale. In the second part, they describe how they generally feel (trait anxiety) by reporting the frequency of their symptoms of anxiety, again on a 20-item scale. Both parts use 4-point Likert scale scores ranging from 1 (hardly ever) to 4 (often).[18]

The items in both STAI-S and STAI-T can score positively (for example, item 13 from the STAI-T *"I feel secure"*). However, there are also items that score negatively (for example, item 17 from the STAI-S *"I am worried"*). The final result is obtained using a correction factor. Higher scores suggest higher levels of anxiety. The Spanish version of the STAI was used and the final score was converted to a number on a scale from 0 to 80, as described by Buela-Casal, to be uniform with the original version of the STAI.[19,20] This test has good internal consistency, with Cronbach's $\alpha = 0.92$ for anxiety states (95% confidence interval, CI: 0.91-0.93) and Cronbach's $\alpha = 0.91$ for anxiety traits (95% CI: 0.90-0.92).[21] The test-retest reliability coefficients on initial development ranged from 0.31 to 0.86.[18]

Statistical analysis

Statistical analyses were carried out by means the of the SPSS software, version 25.0 for Windows (IBM, Armonk, New York, United States), using an α error of 0.05 in conjunction with a 95% CI.

For quantitative data, the Kolmogorov-Smirnov test was applied to evaluate normality. All data were described as the mean ± SD and range (minimum-maximum), given that the median ± interquartile range did not accurately reflect the differences for some nonparametric data. For parametric data (Kolmogorov-Smirnov P-value ≥ 0.05), between-group differences were analyzed by means of Student t tests for independent samples. For nonparametric data (Kolmogorov-Smirnov P-value < 0.05), between-group differences were analyzed by means of Mann-Whitney U tests for independent samples. For categorical data, frequencies and percentages were applied to describe these values and their between-group differences were analyzed by means of Fisher exact tests and chi-square (χ^2) tests.

RESULTS

The study population included 102 participants: 60 men and 42 women. Their sociodemographic characteristics are shown in **Table 1**. Ten participants (9.80%) were smokers, 50 (49.01%) were former smokers and 42 (41.17%) were non-smokers. In the COPD group, there were 52 patients (10 females and 42 males), with a mean age of 70 ± 10.46 years. Only three patients were active smokers, while 45 were former smokers. The patients were treated with inhaled steroids, short-acting beta agonist (SABA), long-acting beta agonist (LABA), short-acting muscarinic antagonist (SAMA), long-acting muscarinic antagonist (LAMA) and alpha-1 antitrypsin. The control group was formed by 50 healthy participants (64% female and 36% male), with a mean age of 42.84 ± 15.69 years. None of them were receiving chronic medication.

Fifty-two patients with COPD and fifty healthy patients were included in this study. The BDI scores were higher for COPD patients (10.23 ± 6.26) than the control group (5.2 ± 6.56). The STAI-state score (P < 0.005) was higher among the COPD patients (41.85 ± 12.55) than among the controls (34.88 ± 9.25). The STAI-trait scores (P < 0.001) were also higher among the COPD patients (41.42 ± 10.01) than among the controls (34.62 ± 9.19). These data are shown in **Table 2**.

Table 1. Sociodemographic and clinical characteristics of the sample population

	Sample	Control	COPD	P-value
	Mean ± SD (range) n = 102	Mean ± SD (range) n = 50	Mean ± SD (range) n = 52	
Age (years)	56.70 ± 19.4007 (19-88)	42.84 ± 15.69 (19-83)	70.02 ± 10.47 (36-88)	< **0.001**†
Weight (kg)	72.59 ± 13.83 (43-115)	70.37 ± 13.9 (47-115)	77.06 ± 14.87 (47.5-120)	0.017†
Height (m)	1.68 ± 0.083 (1.50-1.89)	1.69 ± 0.92 (1.50-1.89)	1.68 ± 0.74 (1.50-1.83)	0.740†
BMI (kg/m^2)	25.89 ± 3.98 (17.59-37.04)	24.48 ± 3.42 (17.59-33.79)	27.25 ± 4.04 (19.20-37.04)	< **0.001**†
Sex (female/male)	42/60	32/18	10/42	< **0.001**‡
Smoker (no/yes/former)	42/10/50	38/7/5	4/3/45	< **0.001****

COPD = chronic obstructive pulmonary disease; BMI = body mass index; SD = standard deviation; P < 0.05 with a 95% confidence interval was considered statistically significant. †Mann-Whitney U test was used; ‡Fisher exact test was used; **Chi-square (χ^2) test was used.

In the case group, we found that 36 patients had scores in the range 0-13, which indicated minimal signs of depression; ten patients were within the range 14-19, which indicated mild depression; six patients were within the range 20-28, which indicated moderate depression; and none were within the range 29-63, which would have indicated severe depression.[17] In the control group, we found that 47 patients were within the range 0-13 (minimal signs of depression); one patient was within the range 14-19 (mild depression); one patient was within the range 20-28 (moderate depression); and one patient was within the range 29-63 (severe depression).

COPD could be classified into three subgroups, according to its severity, as shown in **Table 3**:

- Mild COPD: with a BDI score of 11.15 ± 6.78; STAI-S score of 44.15 ± 12.63; and STAI-T score of 42.92 ± 11.27.
- Moderate COPD: with a BDI score of 7.38 ± 5.12; STAI-S score of 38.31 ± 11.63; and STAI-T score of 38.63 ± 8.72.
- Severe COPD: with a BDI score of 11.70 ± 6.60; STAI-S score of 43 ± 12.21; and STAI-T score of 42.52 ± 10.14.

DISCUSSION

The relationship between COPD and depression is likely to be bidirectional, considering that depression may be both a consequence of COPD and also the cause of increased morbimortality. Depression or anxiety confers an increased risk of exacerbation of COPD and possibly death. Moreover, COPD increases the risk of developing depression.[22] However, the exact mechanisms linking COPD with depression and anxiety have not been identified.

In the present study, we found higher self-reported anxiety state scores among COPD patients than among healthy participants. Bailey et al.[23] described the so-called breathlessness/anxiety/breathlessness cycle and explained how, when people with COPD experience dyspnea, they become anxious. This anxiety causes more breathlessness, and thus these individuals enter a vicious circle of increasing anxiety and breathlessness. An increment in the patient's experience of dyspnea will cause emotional distress and/or some form of help-seeking action. The most common help-seeking behavior often includes emergency admission to a hospital.[23]

The anxiety trait scores among patients with COPD were also higher than those of healthy participants. This can be explained through the understanding that patients with COPD know that their disease is irreversible and progressive. Lung disease limits the daily activities of many of these patients, and many of them are forced to change their occupation or even to retire prematurely. In addition, their social relations are also adversely affected.[24] Associations between anxiety disorders and COPD appear to be largely explained by confounding factors, such as previous history of cigarette smoking and nicotine dependence.[25]

Regarding self-reported depression, the BDI scores among COPD patients in our study were higher than those of healthy participants. This was consistent with the data previously published by Schneider et al.[26] and Jiménez-Cebrián.[27] These authors reported that people with other chronic diseases, for example Parkinson disease, had

Table 2. Depression and anxiety score differences between COPD and healthy participants

	Sample	Control	COPD	P-value
	Mean ± SD (range) n = 52	Mean ± SD (range) n = 50	Mean ± SD (range) n = 52	
STAI-State	38.43 ± 11.54 (20-68)	34.88 ± 9.25 (21-66)	41.85 ± 12.55 (20-68)	**0.005**†
STAI-Trait	38.03 ± 10.20 (20-65)	34.62 ± 9.19 (20-65)	41.37 ± 10.10 (22-61)	< **0.001**†
BDI	7.76 ± 6.86 (0-36)	5.20 ± 6.56 (0-36)	10.23 ± 6.26 (0-24)	< **0.001**†

COPD = chronic obstructive pulmonary disease; SD = standard deviation; STAI = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory; P < 0.05 with a 95% confidence interval was considered statistically significant. †Mann-Whitney U test was used.

Table 3. Depression and anxiety score differences between COPD severity classification subgroups

	Mild COPD	Moderate COPD	Severe COPD	P-value
	Mean ± SD (range) n = 13	Mean ± SD (range) n = 16	Mean ± SD (range) n = 23	
BDI score	11.15 ± 6.78 (1-21)	7.38 ± 5.12 (0-21)	11.70 ± 6.60 (2-24)	< **0.001**†
STAI-S	44.15 ± 12.63 (20-68)	38.31 ± 11.63 (20-60)	43 ± 12.21 (24-66)	< **0.001**†
STAI-T	42.92 ± 11.27 (24-59)	38.63 ± 8.72 (26-54)	42.52 ± 10.14 (22-61)	< **0.001**†

COPD = chronic obstructive pulmonary disease; SD = standard deviation; BDI = Beck Depression Inventory; STAI-S = State-Trait Anxiety Inventory - State; STAI-T = State-Trait Anxiety Inventory - Trait; P < 0.05 with a 95% confidence interval was considered statistically significant. †Mann-Whitney U test was used.

results similar to those of patients with COPD, with higher prevalence of depression than in the general population. Depression itself is a risk factor for development of chronic illnesses such as diabetes and coronary heart disease, and it adversely affects the course and management of chronic medical illness.[7] Moreover, the relative risk of developing depression is higher among patients with severe COPD.

Although the BDI, STAI-S and STAI-T scores were higher in the case group, we did not find any direct correlation between COPD severity and the scores of the three questionnaires. Goodwing et al. reported that the relationship between COPD and depressive disorders could be attributable to confounding due to cigarette smoking and lifetime nicotine dependence.[25]

There is also another possible explanation: the neurobiological theory. This maintains that depression is associated with activation of some aspects of cellular immunity, thus resulting in hypersecretion of proinflammatory cytokines and hyperactivity of the hypothalamic-pituitary-adrenal axis. Inflammatory deregulation as the etiological factor appears to be a plausible hypothesis for explaining why up to 50% of depressive patients do not respond to conventional therapy. The levels of pro-inflammatory cytokines in the brain can cause neurotransmitter imbalance, neuroinflammation and neurodegeneration.[28]

Recognizing the possibility of a psychological disorder in COPD patients is very important, in order to be able to establish adequate treatment if needed. Untreated anxiety and depression among patients with COPD have negative consequences for both patients and their caregivers, and may increase healthcare service utilization.[29] Both anxiety and depression are associated with worse quality of life, greater functional deterioration and mortality, especially in the case of depression.[14] The bidirectional association and the adverse prognostic impact of comorbid COPD and depression or anxiety need to be taken into consideration by physicians.[22] Some good results have been obtained through treatments consisting of pulmonary rehabilitation, smoking cessation and psychological and antidepressant drug therapy, for reducing anxiety and depressive symptoms among patients with COPD.[29]

Future studies and clinical implications

Limitations

Some limitations of our study need to be mentioned. A consecutive sampling method was used in order to recruit participants and should be considered in future studies. Although this was significant, a larger matched-paired sample size might be necessary to achieve more reliable results. Also, a further study taking the role of medication into consideration should be conducted.

The use of self-reported questionnaires, even though they have been validated, does not replace diagnoses of specific anxiety or depressive disorders that are made by a qualified mental health professional through a structured clinical interview.

CONCLUSIONS

COPD patients showed higher scores for self-reported depression, anxiety state and anxiety trait than controls.

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Association between neck circumference and non-alcoholic fatty liver disease: cross-sectional analysis from ELSA-Brasil

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ABSTRACT

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) has become a public health problem worldwide. Neck circumference (NC) is a simple anthropometric adiposity parameter that has been correlated with cardiometabolic disorders like NAFLD.

OBJECTIVES: To investigate the association between NC and NAFLD, considering their obesity-modifying effect, among participants from the Longitudinal Study of Adult Health (ELSA-Brasil) baseline study.

DESIGN AND SETTINGS: Cross-sectional study at the ELSA-Brasil centers of six public research institutions.

METHODS: This analysis was conducted on 5,187 women and 4,270 men of mean age 51.8 (± 9.2) years. Anthropometric indexes (NC, waist circumference [WC] and body mass index [BMI]), biochemical and clinical parameters (diabetes, hypertension and dyslipidemia) and hepatic ultrasound were measured. The association between NC and NAFLD was estimated using multinomial logistic regression, considering potential confounding effects (age, WC, diabetes, hypertension and dyslipidemia). Effect modification was investigated by including the interaction term NC x BMI in the final model.

RESULTS: The frequency of NAFLD and mean value of NC were 33.6% and 33.9 (± 2.5) cm in women, and 45.8% and 39.4 (± 2.8) cm in men, respectively. Even after all adjustments, larger NC was associated with a greater chance of moderate/severe NAFLD (1.16; 95% confidence interval [CI] for women; 1.05, 95% CI for men; $P < 0.001$). Presence of multiplicative interaction between NC and BMI ($P < 0.001$) was also observed.

CONCLUSION: NC was positively associated with NAFLD in both sexes, regardless of traditional adiposity indexes such as BMI and WC. The magnitude of the association was more pronounced among women.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by a primary form of excessive fat accumulation in hepatocytes, which stands out because of its potential to evolve into inflammatory conditions, steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma.[1-3] Although diagnosed worldwide, it has variations in prevalence. In Brazil, its prevalence is estimated to reach about 20%-30%, with an increasing trend, such that it is becoming a public health problem.[4]

NAFLD is highly associated with excess weight, obesity, diabetes and dyslipidemia[5] and more often affects men. On the other hand, premenopausal women are protected from developing NAFLD.[6] In addition, NAFLD is a hepatic manifestation of metabolic syndrome, because it is associated with components such as insulin resistance (IR), abdominal fat, glucose intolerance and hypertension.[6]

The main methods for evaluating body fat and NAFLD are based on imaging. Particularly for NAFLD, ultrasound (USG) is considered to be a more accessible and reasonable diagnostic examination, compared with other imaging tests and with hepatic biopsy (the gold standard method).[7] Transaminases tests, in turn, are not good diagnostic parameters because of their low specificity, since NAFLD does not always lead to liver enzyme abnormalities. These tests should therefore only be used as complements for another method.[6,8,9] Both in epidemiological studies and in clinical practice, anthropometric indicators have been used as a proxy for NAFLD because they are more available, noninvasive and cost-effective than other existing methods used for assessing NAFLD.[10]

Neck circumference (NC) presents advantages over traditional anthropometric indices,[11] given that this provides a separate estimate for the upper body subcutaneous adipose fat, which is considered to be just as pathogenic as visceral adipose fat. Presence of upper body adipose fat has been associated with several metabolic disorders,[12,13] including NAFLD.[14-16] Previous studies conducted among the Longitudinal Study of Adult Health (ELSA-Brasil) baseline participants already showed associations of NC with metabolic risk factors and with carotid intimal-media thickness, thus suggesting that NC measurement may be a potential marker for the risk of subclinical atherosclerosis and cardiovascular events.[17,18] Additionally, it was concluded from a recent Brazilian study that NC can be used for screening of insulin resistance (IR) in patients with NAFLD.[19] Some studies in other countries have demonstrated use of NC measurements as a predictor of NAFLD among obese and non-obese adult individuals, independent of other anthropometric indexes.[14-16,19,30]

OBJECTIVE

The aim of the present study was to investigate the association between NC and NAFLD and whether this association is modified according to obesity status, among participants of the ELSA-Brasil baseline study.

METHODS

Design

This cross-sectional analysis used baseline data from ELSA-Brasil, a multicenter prospective cohort that enrolled 15,105 civil servants aged 35-75 years, from public institutions of higher education and/or research located in six Brazilian state capitals: Universidade Federal de Minas Gerais/ Centro Federal de Educação Tecnológica de Minas Gerais (UFMG-CEFET); Universidade de São Paulo (USP); Fundação Oswaldo Cruz (FIOCRUZ); Universidade Federal do Espírito Santo (UFES); Universidade Federal da Bahia (UFBA); and Universidade Federal do Rio Grande do Sul (UFRGS). The ELSA-Brasil baseline was established between 2008 and 2010 and further information about that study can be found in other publications.[21-23] Approvals were obtained from the Research Ethics Committees of the institutions (CAAE 0016.1.198.000-06), and from the National Research Ethics Committee (CONEP 13065, Brasília, August 4, 2006). All the subjects signed an informed consent statement.

Population study

Out of the total of 15,105 ELSA-Brasil baseline participants, we included in the present analysis all participants for whom complete data regarding the presence of non-alcoholic fatty liver through ultrasound USG and NC measurements were available. Participants for whom data on NC (n = 4) and liver ultrasound (n = 2,878) were missing, or for whom no images of reasonable/good or excellent quality were available, were excluded. We also excluded participants with the following characteristics: excessive alcohol intake (n = 712), self-reported history of cirrhosis and/or hepatitis (n = 989) and presence of thyroid dysfunction and/or use of medicine for thyroid dysfunction (n = 1065).

Excessive alcohol intake was assessed in terms of the types of drinks consumed, and their frequency and consumption patterns, and was classified as > 210 g of alcohol per week for men, and > 140 g per week for women. Cirrhosis and/or hepatitis was defined from self-reports of previous medical diagnosis and thyroid dysfunction, which was defined as changes in thyroid stimulating hormone (TSH) and T4 levels and/or levothyroxine or propylthiouracil use. The cutoff levels for hyperthyroidism were TSH < 0.4 mIU/l and free T4 > 1.9 ng/dl; and for hypothyroidism, TSH > 4.0 mIU/l and free T4 < 0.8 ng/dl.

In the end, 9,457 participants (5,187 women and 4,270 men) remained in the analytical sample of this study.

Non-alcoholic fatty liver evaluation

Liver ultrasound examinations were performed by board-certified radiologists or by radiology technicians, after adequate training, using the same equipment: a high-resolution B-mode scanner (SSA-790A, Aplio XG, Toshiba Medical System, Tokyo, Japan) and a convex array transducer (model PVT-375BT, Toshiba Medical System, Tokyo, Japan), with a central frequency of 3.5 MHz and a fundamental frequency of 1.9-5.0 MHz. Subsequently, these B-mode hepatic ultrasound images were read by board-certified radiologists at the ELSA-São Paulo site, which was established as the ELSA-Brasil ultrasound reading center. The quality control protocol was verified by a senior ultrasound radiologist, by crosschecking the data. All examiners who performed ultrasound examinations were kept blind to the diagnosis of NAFLD.

The criterion for classifying hepatic attenuation of the ultrasound beam consisted of a standard B-mode ultrasound evaluation using a four-point visual classification system based on the degree of visualization of the diaphragm posterior to the right hepatic lobe.[24] For the present study, the hepatic attenuation was classified as normal (complete viewing of the diaphragm), mild (partial, i.e. > 50% viewing of the diaphragm); or moderate/severe (< 50% viewing of the diaphragm or none). NAFLD was defined as mild or moderate/severe according to the above criterion.

Anthropometric variables

NC was measured in centimeters (cm) using an inelastic tape, immediately above the cricoid cartilage and perpendicular to the

long axis of the neck, with the participant in a sitting position and with head upright and eyes directed horizontally forward, in accordance with a standardized protocol.

Body mass index (BMI) was calculated by dividing the body weight measurement in kilograms by the squared height in meters (kg/m^2). It was then classified as follows: normal (18.5 kg/m^2 ≤ BMI < 25 kg/m^2); overweight (BMI ≥ 25 and < 30 kg/m^2); and obesity (BMI ≥ 30 kg/m^2). Waist circumference (WC) was measured using standardized procedures and equipment and was used as a continuous variable (WHO, 1998). The participants were classified according to the obesity status presented, considering the BMI. All anthropometric measurements were performed by trained examiners.[25]

Covariates

The demographic and socioeconomic characteristics that were evaluated were age, gender and education (elementary incomplete and complete, high school and college/university).

Presence of diabetes was defined as the presence of one of the following: medical history of diabetes; use of medication for diabetes treatment; fasting plasma glucose ≥ 126 mg/dl; two-hour glucose post load test ≥ 200 mg/dl; or HbA1C ≥ 6.5%. Presence of hypertension was defined as use of medication to treat hypertension, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Presence of dyslipidemia was defined as use of lipid-lowering agents or alterations in one of the following biochemical tests: cholesterol ≥ 200 mg/dl; triglycerides ≥ 150 mg/dl; high-density lipoprotein-cholesterol (HDL-C) < 50 mg/dl (women) and < 40 mg/dl (men); or low-density lipoprotein-cholesterol (LDL-C) ≥ 160 mg/dl.

Statistical analysis

All analyses were stratified according to gender. Continuous variables were reported as the mean and standard deviation (± SD) and categorical variables as the frequency and percentage. The means for NC between the different degrees of NAFLD were compared by means of one-way analysis of variance (ANOVA). Multinomial logistic regression models were used to estimate the association between NC and NAFLD, considering the potential effects of the confounding variables. First, the crude odds ratios (ORs) were adjusted for age (continuous) (model 1); then adjusted for WC (continuous) (model 2); and subsequently adjusted for diabetes, hypertension and dyslipidemia (model 3). Lastly, a further adjustment was made through inclusion of the interaction term NC x BMI, which was inserted into the final model (model 4). The magnitude of the association was estimated using the OR and its respective 95% confidence interval (95% CI). All variables that presented associations in univariate analyses with a significance level lower than 0.20 were considered in the multivariable analysis, and only those that remained associated with the response variable at the $P < 0.05$ level were retained in the final model. All analyses were performed using the Stata 12.0 software (Stata Corporation, College Station, Texas, United States).

RESULTS

Out of the 9,457 participants evaluated 5,187 were women and 4,270 were men, with a mean age of 51.8 ± 9.2 years. Among them, 33.6% of the women and 45.8% of the men presented some degree of NAFLD. The prevalence of a moderate/severe degree of NAFLD was 11.6% among the women and 20.3% among the men. In both sexes, the NC was larger at higher degrees of NAFLD. The main characteristics of our study participants are described according to their degree of NAFLD, for each gender, in **Table 1**.

Table 2 shows the crude and adjusted OR of NC in relation to NAFLD in the logistic models. NC was associated with NAFLD with a higher OR in relation to a mild degree of NAFLD (OR = 1.23, 95% CI: 1.19-1.27 for women; OR = 1.20, 95% CI: 1.17-1.24 for men) and a moderate/severe degree of NAFLD (OR = 1.56, 95% CI: 1.50-1.62 for women; OR = 1.45, 95% CI: 1.40-1.50 for men), compared with the reference category. Additionally, inclusion of WC in model 2 significantly altered the results.

Among women, the magnitude of the association between NC and mild NAFLD (OR = 1.06; 95% CI: 1.02-1.10; $P < 0.001$) and moderate/severe NAFLD (OR = 1.20; 95% CI: 1.14-1.26; $P < 0.001$) NAFLD was significantly reduced after adjustment for WC. Among men, after adjustment for WC, the association of NC remained statistically significant only in relation to moderate/severe NAFLD (OR = 1.06; 95% CI: 1.01-1.10; $P < 0.05$). Adjustments for diabetes, hypertension and dyslipidemia did not modify the results found, in relation to either of the sexes.

To evaluate the effect modification due to obesity status (according to BMI) on the association between NC and NAFLD, the presence of multiplicative interaction between NC and BMI ($P < 0.001$) among women and men was also investigated. However, these analyses stratified according to normal weight (≥ 18.5 and < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2) and obesity (> 30 kg/m^2), and with adjustment for all confounding factors, including WC, only showed that NC was associated with a higher OR for having NAFLD (moderate/severe degree) among women with obesity. No such finding was observed among men (**Tables 3** and **4**).

DISCUSSION

In this cross-sectional analysis on ELSA-Brasil participants, NC and NAFLD were independently associated, regardless of traditional anthropometric indexes and the presence of effect modification on

Table 1. Main characteristics of the men and women participating in the study according to degree of non-alcoholic fatty liver disease (NAFLD). ELSA-Brasil, 2008-2010 (n = 9,457)

Variables	Women (n = 5,187)			Men (n = 4,270)		
	NAFLD			NAFLD		
	Normal	Mild	Moderate/ severe	Normal	Mild	Moderate/ severe
	3,442 (66.4)	1,142 (22.0)	603 (11.6)	2,315 (54.2)	1,087 (25.5)	868 (20.3)
Age, years (SD)	50.9 (8.9)	52.1 (8.6)	53.6 (8.5)	51.4 (9.7)	52.3 (9.2)	52.9 (8.9)
Education, n (%)						
Elementary incomplete	129 (3.8)	63 (5.5)	41 (6.8)	179 (7.7)	96 (8.8)	69 (8.0)
Elementary complete	164 (4.8)	87 (7.6)	42 (7.0)	206 (8.9)	101 (9.3)	62 (7.1)
High school	1278 (37.1)	459 (40.2)	250 (41.5)	790 (34.1)	362 (33.3)	290 (33.4)
College/university	1871 (54.4)	533 (46.7)	270 (44.8)	1140 (49.2)	528 (48.6)	464 (51.5)
Diabetes, n (%)						
No	3,061 (88.9)	910 (79.7)	370 (61.4)	1,962 (84.8)	810 (74.5)	506 (58.4)
Yes	380 (11.0)	232 (20.3)	233 (38.6)	352 (15.2)	277 (25.5)	361 (41.6)
Hypertension, n (%)						
No	2,599 (75.5)	705 (61.8)	305 (50.8)	1,573 (68.1)	628 (57.8)	414 (47.8)
Yes	841 (24.5)	436 (38.2)	296 (49.3)	740 (32.0)	458 (42.2)	452 (52.2)
Dyslipidemia, n (%)						
No	838 (24.4)	178 (15.6)	71 (11.8)	603 (26.1)	172 (15.8)	89 (10.3)
Yes	2,604 (75.7)	964 (84.4)	532 (88.2)	1,712 (73.9)	915 (84.2)	779 (89.8)
Neck circumference, mean (SD)	33.3 (2.2)	34.5 (2.5)	36.1 (2.7)	38.6 (2.6)	39.8 (2.7)	41.2 (2.8)
BMI, n (%)						
Normal	1,698 (49.3)	310 (27.2)	49 (8.1)	1112 (48.1)	267 (24.6)	80 (9.2)
Overweight	1,236 (35.9)	470 (41.2)	176 (29.2)	978 (42.3)	573 (52.7)	385 (44.3)
Obesity	508 (14.8)	362 (31.7)	377 (62.6)	224 (9.7)	247 (22.7)	403 (46,4)
Waist circumference, mean (SD)	83.9 (10.9)	90.7 (12.0)	99.4 (11.8)	90.6 (10.2)	96.9 (10.1)	104.4 (11.2)

n (%) or mean (standard deviation, SD); BMI = body mass index; ELSA= Estudo Longitudinal da Saúde do Adulto – Brasil.

Table 2. Crude and adjusted odds ratio between neck circumference (NC) and non-alcoholic fatty liver disease (NAFLD) for women and men, ELSA-Brasil, 2008-2010

	NAFLD	Model 0	Model 1	Model 2	Model 3	Model 4
Women	**Normal**	1.00	1.00	1.00	1.00	1.00
	Mild					
	NC	1.23 (1.19-1.27)**	1.22 (1.19-1.26)**	1.06 (1.02-1.10)*	1.04 (1.00-1.09)*	0.99 (0.95-1.05)
	WC	-	-	1.04 (1.04-1.05)**	1.04 (1.03-1.05)**	1.02 (1.01-1.04)**
	NC x BMI	-	-	-	-	1.00 (1.00-1.00)
	Moderate/severe					
	NC	1.56 (1.50-1.62)**	1.55 (1.50-1.62)**	1.20 (1.14-1.26)**	1.16 (1.10-1.23)**	1.06 (1.00-1.14)*
	WC			1.08 (1.07-1.09)**	1.08 (1.06-1.09)**	1.04 (1.03-1.06)**
	NC x BMI	-	-	-	-	1.00 (1.00-1.00)
Men	**Normal**	1.00	1.00	1.00	1.00	1.00
	Mild					
	NC	1.20 (1.17-1.24)**	1.20 (1.17-1.24)**	1.01 (0.97-1.05)	1.01 (0.97-1.05)	0.93 (0.88-0.99)
	WC			1.06 (1.05-1.07)**	1.06 (1.05-1.07)**	1.04 (1.02-1.05)**
	NC x BMI	-	-	-	-	1.00 (1.00-1.00)
	Moderate/severe					
	NC	1.45 (1.40-150)**	1.45 (1.40-1.50)**	1.06 (1.01-1.10)*	1.05 (1.00-1.10)*	0.95 (0.89-1.02)
	WC			1.12 (1.11-1.14)**	1.12 (1.10-1.13)**	1.09 (1.07-1.11)**
	NC x BMI	-	-	-	-	1.00 (1.00-1.00)

Reference for NAFLD = normal; *P < 0.05; **P < 0.001. Model 0: univariate; Model 1: adjusted for age; Model 2: model 1 + WC (waist circumference); Model 3: model 2 + diabetes, hypertension and dyslipidemia; Model 4: model 3 + interaction term NC x BMI (body mass index).

the association due to obesity status, particularly among women. Our results support the hypothesis that obesity status (as assessed via BMI) modifies the association between NC and NAFLD in both sexes. However, after stratification according to BMI category, NC remained associated with a greater chance of moderate/severe NAFLD only among obese women, and not among men.

Table 3. Crude and adjusted odds ratio between neck circumference (NC) and non-alcoholic fatty liver disease (NAFLD), stratified according to BMI (normal, overweight and obesity) among women, ELSA-Brasil, 2008-2010

	WOMEN				
	NAFLD	**Model 0**	**Model 1**	**Model 2**	**Model 3**
Normal Weight	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.09 (1.01-1.17)*	1.08 (1.00-1.16)*	0.99 (0.91-1.07)	0.98 (0.90-1.07)
	WC	-	-	1.05 (1.03-1.08)**	1.04 (1.02-1.06)*
	Moderate/Severe				
	NC	1.19 (1.01-1.41)*	1.18 (0.99-1.39)	0.99 (0.82-1.21)	0.99 (1.82-1.20)
	WC	-	-	1.09 (1.04-1.15)**	1.08 (1.03-1.15)*
Overweight	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.15 (1.08-1.22)**	1.14 (1.08-1.21)**	1.08 (1.02-1.16)*	1.07 (1.00-1.14)*
	WC	-	-	1.04 (1.02-1.06)**	1.04 (1.02-1.06)**
	Moderate/Severe				
	NC	1.24 (1.13-1.35)**	1.23 (1.12-1.34)**	1.10 (1.00-1.21)*	1.06 (0.96-1.17)
	WC	-	-	1.09 (1.06-1.13)**	1.08 (1.05-1.11)**
Obesity	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.11 (1.04-1.18)**	1.11 (1.04-1.18)**	1.07 (0.99-1.14)	1.05 (0.98-1.13)
	WC	-	-	1.02 (1.00-1.04)*	1.02 (1.00-1.04)*
	Moderate/Severe				
	NC	1.29 (1.22-1.38)**	1.29 (1.22-1.38)**	1.23 (1.15-1.32)**	1.20 (1.11-1.28)**
	WC	-	-	1.03 (1.01-1.05)*	1.03 (1.01-1.05)*

Reference for NAFLD = normal; *P < 0.05; **P < 0.001. Model 0: univariate; Model 1: adjusted for age; Model 2: model 1 + WC (waist circumference); Model 3: model 2 + diabetes, hypertension and dyslipidemia.

Table 4. Crude and adjusted odds ratio between neck circumference (NC) and non-alcoholic fatty liver disease (NAFLD), stratified according to BMI (normal, overweight and obesity) among men, ELSA-Brasil, 2008-2010

	MEN				
	NAFLD	**Model 0**	**Model 1**	**Model 2**	**Model 3**
Normal Weight	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.13 (1.05-1.22)**	1.13 (1.05-1.22)**	0.96 (0.88-1.05)	0.96 (0.88-1.05)
	WC	-	-	1.09 (1.07-1.13)**	1.09 (1.06-1.12)**
	Moderate/Severe				
	NC	1.43 (1.26-1.61)**	1.43 (1.26-1.61)**	1.09 (0.94-1.27)	1.11 (0.96-1.29)
	WC	-	-	1.19 (1.13-1.25)**	1.17 (1.11-1.23)*
Overweight	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.05 (0.99-1.10)	1.05 (0.99-1.10)	1.00 (0.95-1.07)	1.00 (0.94-1.06)
	WC	-	-	1.03 (1.01-1.06)*	1.03 (1.01-1.05)*
	Moderate/Severe				
	NC	1.18 (1.11-1.26)**	1.18 (1.11-1.26)**	1.05 (0.99-1.13)	1.03 (0.96-1.10)
	WC	-	-	1.11 (1.08-1.14)**	1.10 (1.07-1.13)**
Obesity	**Normal**	1.00	1.00	1.00	1.00
	Mild				
	NC	1.06 (0.99-1.14)	1.06 (0.99-1.14)	1.01 (0.93-1.10)	0.99 (0.92-1.09)
	WC	-	-	1.04 (1.01-1.07)*	1.04 (1.00-1.06)*
	Moderate/Severe				
	NC	1.14 (1.07-1.22)**	1.14 (1.07-1.22)**	1.03 (0.95-1.11)	1.03 (0.95-1.11)
	WC	-	-	1.07 (1.05-1.10)**	1.08 (1.05-1.10)**

Reference for NAFLD = normal; *P < 0.05; **P < 0.001. Model 0: univariate; Model 1: adjusted for age; Model 2: model 1 + WC (waist circumference); Model 3: model 2 + diabetes, hypertension and dyslipidemia.

Recent studies on Asian populations also showed that NC was associated with NAFLD, in addition to the traditional indexes used (BMI and WC). One potential explanatory mechanism for the association between NC and NAFLD is that upper body subcutaneous fat, as estimated via NC, causes metabolic abnormalities such as accumulation of free fatty acids in the neck region. In addition, free fatty acids will generate a high amount of triglycerides to be stored in the liver, thus contributing to the accumulation of fat and to NAFLD.[15] Another study showed that the upper region of the body, and more specifically the neck, is responsible for higher release of systemic free fatty acids than is the visceral region.[26]

NC measurement is feasible for use as an anthropometric method in investigations on metabolic disorders, given its harmlessness, low cost and lack of cultural restrictions. It therefore has good applicability in clinical practice and epidemiological studies with large samples, among other eternal measurements of body dimensions.[27] Among these measurements, WC is frequently used and is known as a marker of abdominal fat, especially visceral adipose tissue, which makes this a measurement traditionally associated with cardiometabolic risks.[20,28,29]

However, WC has some important limitations that NC can highlight and overcome. One of these limitations is that the different anatomical parameters used for WC measurement (smallest circumference, umbilical scar, iliac crest, midpoint between the last rib and the iliac crest, among others) may significantly influence the measurement.[30] Another is the variation that can occur in the abdominal region during the day, through with food intake, such that measurements are influenced by the time of day at which they are made.[30] Moreover, it is not as practical and rapid to perform WC measurements in large population-based epidemiological studies. In particular, clothing is an obstacle during cold weather.[11] In contrast, NC shows advantages because it is simple, easy and low-cost, has no intraindividual variation and is also considered to be a proxy measurement of upper body subcutaneous fat, since it is the only fat compartment that is separated and individualized without interference from other adipose tissues, and may be more easily measured.[13,16,30,31]

In addition, several studies have shown that NC measurements have positive associations with different cardiometabolic outcomes, such as type 2 diabetes,[32-34] chronic kidney disease[35] and metabolic syndrome.[36] There is still a scarcity of data in the literature but, in agreement with our findings, three recent cross-sectional studies investigated the association between NC and NAFLD among Chinese adults with or without excess weight and suggested that NC measurement formed a marker for NAFLD.[14-16] The findings of Hu et al. showed that NC was more effective for predicting NAFLD in women than in men, similar to our results.[14] Huang et al. found a strong positive association in the highest NC quartile for the presence of NAFLD in both men and women, even after adjusting for age, BMI, WC and hip circumference (HC).[15] Li et al. showed that among other anthropometric indices (BMI, WC and HC), NC tended to be higher with increased liver attenuation in both sexes.[16] In addition, they concluded that although obesity is the major risk factor for the development of NAFLD (even a small increase in weight may increase the risk of fat in the liver), NC may be a useful and convenient indicator for detecting NAFLD in men with normal weight (BMI ≥ 18 kg/m^2 and < 25 kg/m^2), but not in women.

Regarding the differences in predicting moderate/severe NAFLD from NC measurements that were observed in our study between the sexes, the data in the literature are concordant with our findings. According to previous analyses from the Framingham Heart Study, which investigated the association of NC with cardiometabolic risk factors, fat deposits are more strongly associated with adverse risk factors among women than among men, because women store a higher proportion of free fatty acids in upper body subcutaneous adipose tissue, and especially because of the differences in the anatomical distribution of body fat that exists between the sexes.[13] Women concentrate excess adipose tissue in the hip region (gynoid obesity, or "pear-shaped"); while men concentrate this in the central abdominal region (central obesity, or "apple-shaped").[37] Additionally, one recent study showed that although estrogen was a protective factor against NAFLD in women, it was not just men who were at increased risk of developing NAFLD. Significant age-related changes in NAFLD epidemiology among women may also potentially have physiopathological, clinical and therapeutic significance. For women for example, NAFLD epidemiology and physiopathology are modulated by the age at menarche and postmenopausal status. Those findings showed that, after the menopause, women displayed similar or even higher prevalence of NAFLD, compared with men, thus corroborating the effect of estrogens.[6,38]

In addition to finding that NC measurements were more effective for predicting the risk of NAFLD in women, Hu et al. concluded that these measurements might be more used among women in healthcare practices such as care and prevention of NAFLD.[14] The findings from previous studies suggested that NC was a measurement that could contribute together with other anthropometric indices (BMI, WC and waist/hip ratio [WHR]). Thus, a synergistic effect towards better prediction of NAFLD, and possibly other risk factors for cardiovascular disease, was reported, due to the significant additive interaction that was found.[13,15]

Our study was the first to investigate and demonstrate the independent association of NC and NAFLD among Brazilian adults, and the results also support the hypothesis that obesity status modifies the association between NC and NAFLD. We found a statistically significant difference when the interaction term (NC x BMI) was added, among both men and women with moderate to severe NAFLD. Although different populations are compared

in the literature, the synergistic effect also found in our study can be explained by differences in lifestyle, eating habits, distribution and body composition, as well as gender and race. In addition, the etiology of NAFLD also reflects complex interactions between genetic, neurohumoral, metabolic and stress-related factors.[9,26]

Moreover, the present study was carried out on a large sample of Brazilian adults, and strengthens the existing literature with data on the importance of measuring NC as a simple and easy predictor of NAFLD. However, it is important to highlight some limitations to the present study. First, the cross-sectional design does not allow inferences regarding causality in the association found. Second, the specificity and sensitivity of hepatic ultrasound for detecting NAFLD is variable. A study conducted by Goulart et al. using a subsample of ELSA-Brasil participants showed sensitivity of 85.1% and specificity of 73.4%, which may have impacted both the estimated prevalence of NAFLD and its association with NC.[24] Lastly, the NAFLD data was not complete, because of exclusions of some hepatic ultrasound scans of poor quality. However, we do not believe that this loss was differential. Longitudinal analyses on ELSA-Brasil may contribute to better elucidation of the role of NC as a marker of cardiovascular risk.

CONCLUSION

Our findings demonstrated that NC was significantly associated with NAFLD, after all adjustments in both sexes. We also observed the presence of multiplicative interaction between NC and BMI. These findings reinforced the positive association between NC and NAFLD, regardless of traditional adiposity indexes such as BMI and WC. Particularly among women, the magnitude of the association between NC and NAFLD was more pronounced.

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Impact of quality of response on survival outcomes among multiple myeloma patients treated with novel agents – a retrospective analysis

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ABSTRACT

BACKGROUND: In this era of target therapies, novel data on the correlation between response endpoints and survival outcomes in multiple myeloma have arisen.

OBJECTIVE: To determine the impact of quality of response on clinical outcomes, using first-line treatment, and identify risk factors influencing progression-free survival (PFS) and overall survival (OS) among myeloma patients.

DESIGN AND SETTING: Retrospective analysis on myeloma patients who were treated at the Clinic of Hematology and Clinical Immunology, University Clinical Centre, Niš, Serbia, over a four-year period.

METHODS: A total of 108 newly diagnosed patients who received first-line therapy consisting of conventional chemotherapy or novel agent-based regimens were included in this analysis.

RESULTS: The quality of response to first-line therapy for the whole cohort was classified as follows: complete response (CR) in 19%; very good partial response (VGPR) in 23%; partial response (PR) in 38%; and less than PR for the remaining patients. After a median follow-up of 25.4 months, the three-year PFS and OS for the entire study population were 47% and 70%, respectively. Achievement of CR was the main factor associated with significantly prolonged PFS and OS, in comparison with patients who reached VGPR and PR. Likewise, addition of the new drugs bortezomib and thalidomide to standard chemotherapy led to considerably extended PFS and OS, compared with conventional therapy alone.

CONCLUSIONS: This analysis demonstrated that the quality of response after application of first-line treatment using novel agent-based regimens among multiple myeloma patients was a prognostic factor for PFS and OS, which are the most clinically relevant outcomes.

INTRODUCTION

Multiple myeloma (MM) is an incurable plasma cell neoplasm exemplified by changeable survival ranging from several months to more than 15 years. The prognosis can be impacted by disease biology, type of therapy, quality of response and patient-related factors. Several recent studies have shown improved outcomes for patients with myeloma, regarding both relapses of the disease and diagnoses, through treatments with new myeloma-directed drugs, autologous stem cell transplants and combination therapeutic approaches.[1,2]

Enhancing long-term outcomes is the primary aim of current treatment strategies, including overall survival (OS) and progression-free survival (PFS). First-line treatment response is one of the most crucial prognostic factors related to PFS and OS among patients with newly diagnosed MM.[3] Use of a combination of thalidomide, melphalan and prednisone as first-line treatment in patients with multiple myeloma, in comparison with melphalan-prednisone, was shown to provide significant improvements, both in PFS (15.0 versus 11.0 months) and in OS (two-year OS rates were 67% versus 43%).[4] The time to progression among patients receiving bortezomib plus melphalan-prednisone was significantly longer than the time among those receiving melphalan-prednisone alone (24.0 versus 16.6 months).[5] Moreover, the VISTA study confirmed longer OS (three-year OS rates were 68.5% versus 54.0%) and other clinical benefits through use of bortezomib plus melphalan-prednisone versus use of melphalan-prednisone.[6] Assessment on the influence of the degree of treatment response on PFS and OS showed that the three-year PFS and OS were significantly prolonged among patients who achieved complete response (CR), compared with those who achieved very good partial response (VGPR) or partial response (PR).[7]

Data from a meta-analysis indicated that achievement of CR subsequent to high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT), after first-line therapy with novel versus non-novel agents, has more prognostic influence for enhanced long-term outcomes.[8]

OBJECTIVE

The aim of this study was to assess the impact of the quality of therapeutic response with first-line treatment on progression-free survival and overall survival, among newly diagnosed myeloma patients, along with extensive analysis on prognostic factors in relation to survival outcomes.

METHODS

Consecutive newly diagnosed MM patients who were treated at our institution over the period from January 2015 to December 2018 were retrospectively evaluated. This study included patients whose response data after first-line therapy were available. The diagnosis of MM was determined in accordance with the updated criteria of 2014 from the International Myeloma Working Group (IMWG).[3] Staging and risk assessment were done in accordance with the international staging system for multiple myeloma.[9]

Patients were treated either with conventional chemotherapy or with novel agent-based induction comprising regimens that included either thalidomide or bortezomib. Therapeutic response assessment was carried out in accordance with the IMWG consensus response criteria.[10,11]

Briefly, CR was defined as negative serum and urine immunofixation, presence of less than 5% plasma cells in bone marrow and disappearance of any soft tissue plasmacytoma. VGPR was characterized as a reduction in serum M-protein of 90% or more; and urinary M-protein of less than 100 mg/24 hours or M-protein noticeable through immunofixation but not through electrophoresis. Partial response (PR) was defined as a reduction in serum M-protein levels from baseline of 50% or more; and a reduction in 24-hour urine M-protein excretion of 90% or more, or a level of less than 200 mg/24 hours. The disease was classified as stable if did not fulfil the criteria for PR, VGPR, CR or progressive disease. Any of the following was defined as progressive disease: an increase of 25% or more from the lowest response value in serum M-protein (absolute ≥ 0.5 g/dl) or urine M-protein (absolute ≥ 200 mg/24 hours).

OS was estimated from the time of diagnosis until death or the last follow-up. PFS was calculated from the time of diagnosis to disease progression, relapse or death from any cause or the last follow-up.

The Pearson χ^2 test was used to compare patient characteristics regarding discrete variables while the Mann-Whitney test was applied to continuous variables. The prognostic influence of therapeutic and clinical factors on PFS and OS was assessed based on the hazard ratio (HR) with 95% confidence interval (Cl) from multivariate Cox's proportional hazards regression. All statistical tests were two-sided, and P-values < 0.05 were considered statistically significant. Survival analysis, regarding PFS and OS, was performed by applying the Kaplan-Meier method. Survival outcomes were analyzed for patients who achieved CR, VGPR or PR after induction therapy.

This study was approved by our institution's ethics committee (date: January 19, 2021; number: 1399/2).

RESULTS

This retrospective analysis included 108 patients who were newly diagnosed with multiple myeloma. Their median age at diagnosis was 63.8 years (range 40-82 years), and 53% were males. At the time of diagnosis, the majority of the patients (62; 57%) were in clinical stage III of Durie & Salmon,[12] while 52 patients (48%) had high-risk disease.

The number of patients who initially had substantial renal impairment with creatinine clearance (CrCl) < 40 ml/minute was 26 (24%), while 12 (11%) patients were undergoing hemodialysis. More than half of the patients had Charlson's comorbidity index (CCI) ≥ 2, and a smaller percentage of these patients achieved CR and VGPR, compared with patients who had CCI < 2. Equal distribution between international staging system (ISS) stages I, II and III was recorded among patients in the CR, VGPR and PR groups; this equal distribution was also seen in relation to clinical stages. The types of therapy administered and baseline characteristics of the patients who achieved CR, VGPR and PR are shown in **Table 1**.

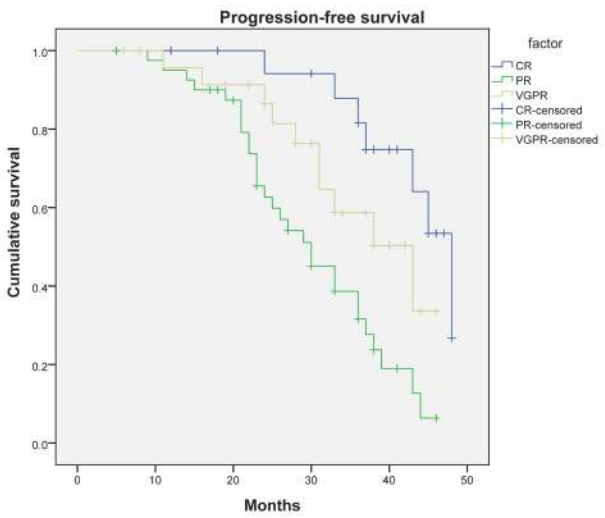
Novel agent-based induction therapy was applied to 97 patients, among whom 74 received a drug combination with thalidomide and 23 received a drug combination with bortezomib. The other 11 patients underwent conventional chemotherapy. The quality of response to first-line therapy was assessed as follows: CR was reported in 20 cases (19%), VGPR in 25 (23%) and PR in 41 (38%); the remaining patients achieved less than PR. Patients who achieved CR were generally treated with novel agent-based regimens: 55% of these patients received combination therapy with thalidomide, 40% combination therapy with bortezomib and only 5% conventional chemotherapy. In contrast, in the PR group, the highest number of patients (78%) received combined therapy with thalidomide, 12% combination therapy with bortezomib and 10% standard chemotherapy.

The influence of new therapeutic modalities on the recovery of renal function and whether its recovery affected the OS was analyzed. The rate of achieving complete renal response in accordance with the IMWG criteria among patients with CrCl < 40 ml/minute at diagnosis was higher in the group of patients initially treated with bortezomib-based protocols than in the group that received

Table 1. Baseline characteristics of patients with multiple myeloma

Variable	All patients n = 108	CR n = 20	VGPR n = 25	PR n = 41
Sex				
Male, n (%)	57 (53)	11 (55)	13 (52)	21 (51)
Age, years				
Median	63.8	42-72	62.7	63.3
Range	40-82	64.5	49-79	41-85
≥ 70 years, n (%)	31 (29)	4 (20)	4 (16)	9 (22)
Charlson's comorbidity index, n (%)				
CCI < 2	47 (43.5)	11 (55)	15 (60)	18 (44)
CCI ≥ 2	61 (56.5)	9 (45)	10 (40)	23 (56)
Durie & Salmon stage, n (%)				
I	14 (13)	2 (10)	2 (8)	7 (17)
II	32 (30)	6 (30)	7 (28)	13 (32)
III	62 (57)	12 (60)	16 (64)	21 (51)
Creatinine clearance, n (%)				
CrCl < 40 ml/min	26 (24)	4 (20)	7 (28)	13 (32)
CrCl ≥ 40 ml/min	82 (76)	16 (80)	18 (72)	28 (68)
ISS stage, n (%)				
I	18 (17)	4 (20)	4 (16)	7 (17)
II	38 (35)	7 (35)	9 (36)	14 (34)
III	52 (48)	9 (45)	12 (48)	20 (49)
Type of therapy, n (%)				
Conventional	11 (10)	1 (5)	2 (8)	4 (10)
Thalidomide	74 (69)	11 (55)	16 (64)	32 (78)
Bortezomib	23 (21)	8 (40)	7 (28)	5 (12)

CR = complete response; VGPR = very good partial response; PR = partial response; ISS = international staging system.



CR = complete response; PR = partial response; VGPR = very good partial response.

Figure 1. Kaplan-Meier estimate of progression-free survival according to quality of response. Estimated progression-free survival among patients receiving first-line therapy, according to quality-of-response group.

thalidomide protocols: 40% versus 22% (P = 0.061). There was a significant difference in median OS in the group of patients who had CrCl < 40 ml/minute at diagnosis and corrected this to CrCl ≥ 40 ml/minute, compared with the group that continued to present CrCl < 40 ml/minute after therapy: 32.5 months versus 18.6 months (P = 0.019).

After a median follow-up of 25.4 months (range 6-48 months), the three-year PFS and OS for all the patients analyzed were 47% and 70%, respectively. The outcomes according to quality of treatment response to first-line therapy among multiple myeloma patients are shown in **Figure 1** and **Figure 2**. The three-year PFS was 75% among patients who achieved CR after first-line treatment, 49% among patients who achieved VGPR (HR = 0.19; 95% Cl, 0.12-0.23; P < 0.001) and 32% among those who only reached PR (HR = 0.11; 95% Cl, 0.06-0.17; P < 0.001) (**Figure 1**). Likewise, the three-year OS was 87% among patients who achieved CR after first-line treatment, 72% among those who reached VGPR (HR = 0.17; 95% Cl, 0.10-0.27; P < 0.001) and 66% among those who only achieved PR (HR = 0.09; 95% Cl, 0.05-0.18; P < 0.001) (**Figure 2**).

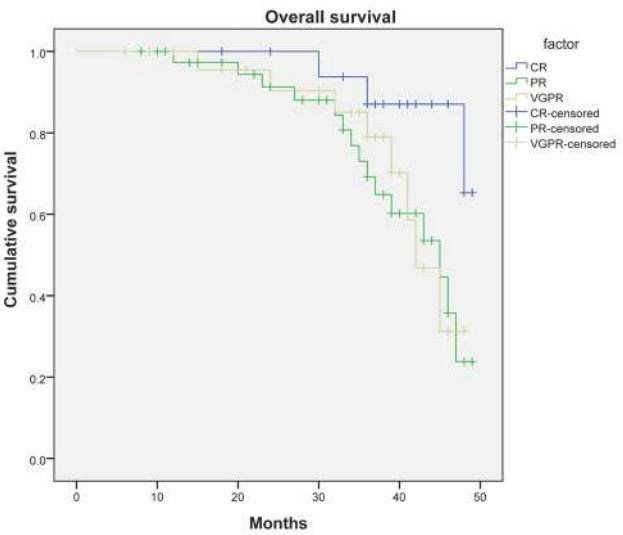
The effects of comorbidities on OS and PFS were assessed using Charlson's comorbidity index, in which patients with CCI < 2 were considered to be fit and patients with CCI ≥ 2, frail. In this cohort, according to CCI, fit patients accounted for 43.5% and frail for 56.5%. Fit patients were found to have higher rates for three-year OS than frail patients (80% versus 57.6%; HR = 0.13; 95% Cl, 0.05-0.37; P = 0.011). Also, the rates for three-year PFS were higher in the group of fit patients than in the group of frail patients (67% versus 24.6%; HR = 0.28; 95% Cl, 0.14-0.48; P = 0.005).

The findings from the assessment of prognostic factors that influenced survival are presented in **Table 2**. Multivariate analysis showed that novel agent-based induction, namely the addition of bortezomib or thalidomide to conventional chemotherapy, was linked to substantial enhancement of PFS: (HR = 0.55; 95% CI, 0.23-0.87; P < 0.001) and (HR = 0.79, 95% CI, 0.38-1.13, P < 0.001), respectively. Achievement of CR after first-line treatment, compared with VGPR (HR = 0.31; 95% CI, 0.13-0.54; P < 0.001) and PR (HR = 0.22; 95% CI, 0.10-0.46; P < 0.001), was significantly associated with prolonged PFS. Shorter PFS was related to age of more than 65 years, existence of comorbidities (CCI ≥ 2) and renal impairment that continued even after therapy (CrCl < 40 ml/minute). On the other hand, this association was not established for clinical stages II and III, or for the existence of intermediate and high-risk diseases.

Regarding OS, patients who received combined therapy with bortezomib (HR = 0.42; 95% CI, 0.19-0.88; P < 0.001) or a therapeutic combination with thalidomide (HR = 0.68; 95% CI, 0.44-1.09; P < 0.001) showed a significant association with superior survival, compared with patients treated with conventional chemotherapy. Achievement of CR was the factor most strongly correlated with significantly prolonged OS, in comparison with VGPR (HR = 0.39; 95% CI, 0.16-0.63; P < 0.001) and PR (HR = 0.27; 95% CI, 0.11-0.50; P < 0.001). Age greater than 65 years, presence of comorbidities (CCI ≥ 2) and absence of recovery of renal function after therapy (CrCl < 40 ml/minute) were the factors that were found to significantly reduce OS, while higher clinical stage and high-risk disease did not have any impact.

DISCUSSION

The prognostic influence of the quality of response has been proven mainly among patients newly diagnosed with MM who were treated with HDT/ASCT. Patients who achieved a maximal response were more likely to have better long-term survival than those reaching lesser responses.



CR = complete response; PR = partial response; VGPR = very good partial response.

Figure 2. Kaplan-Meier estimate of overall survival according to quality of response. Estimated overall survival among patients receiving first-line therapy, according to quality-of-response group.

Table 2. Multivariate analysis on factors possibly influencing progression-free survival and overall survival

Factor	PFS HR (95% CI)	P-value	OS HR (95% CI)	P-value
Age, years				
> 65 versus ≤ 65	1.18 (1.09-1.23)	0.02	1.36 (1.18-1.52)	< 0.001
Charlson's comorbidity index				
CCI ≥ 2 versus CCI < 2	0.59 (0.41-0.78)	0.04	0.91 (0.64-1.21)	0.003
ISS stage				
2 versus 1	1.10 (0.67-1.45)	0.39	1.25 (0.89-1.65)	0.57
3 versus 1	1.32 (0.83-1.75)	0.19	1.45 (0.91-1.83)	0.10
Durie & Salmon stage				
II versus I	1.48 (1.02-1.78)	0.17	1.67 (1.23-1.97)	0.27
III versus I	1.40 (1.14-1.81)	0.12	1.59 (1.19-1.92)	0.09
Creatinine clearance after therapy				
Retained CrCl < 40 ml/min versus reversed CrCl ≥ 40 ml/min	1.29 (1.17-1.49)	0.01	1.12 (0.84-1.37)	< 0.001
Therapy				
Bortezomib combination versus conventional	0.55 (0.23-0.87)	< 0.001	0.42 (0.19-0.88)	< 0.001
Thalidomide combination versus conventional	0.79 (0.38-1.13)	< 0.001	0.68 (0.44-1.09)	< 0.001
Response				
CR versus VGPR	0.31 (0.13-0.54)	< 0.001	0.39 (0.16-0.63)	< 0.001
CR versus PR	0.22 (0.10-0.46)	< 0.001	0.27 (0.11-0.50)	< 0.001

PFS = progression-free survival; OS = overall survival; HR = hazard ratio; ISS = international staging system; CR = complete response; VGPR = very good partial response; PR = partial response.

Lahuerta et al.[13] assessed therapeutic responses among patients with newly diagnosed MM that was treated through chemotherapy induction regimens tracked by means of HDT/ASCT. There was a considerable correlation between depth of response and outcomes, such that there was a five-year OS rate of 74% among patients who achieved CR, compared with 50% for patients who achieved PR (P = 0.01). In a study by Moreau et al.,[14] PFS was significantly longer for patients who achieved VGPR later in induction therapy, compared with patients who achieved VGPR only after HDT/ASCT (median of 41.2 versus 31.1 months; P = 0.01). This evidently suggests that achievement of VGPR or better after induction has prognostic significance for longer PFS.

A recently published meta-analysis on 24 studies among newly diagnosed myeloma patients undergoing ASCT that examined the connectivity between responses and long-term outcomes showed that the association between achieving CR and outcomes seemed to be better for patients achieving CR through use of novel rather than non-novel agents.[8]

After the introduction into clinical practice of target therapy using the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide, as part of combination treatments, these therapies have enabled greater emphasis on the depth and duration of responses and their influence on improvements in disease control and survival.[1,15] In a study by Offidani et al.,[16] the efficiency of thalidomide-based regimens among untreated patients with MM was assessed and was shown to provide a higher response rate, while the response to treatment was significantly predictive of survival. The estimated three-year time to progression was 60%, event-free survival was 57% and OS was 84%, and these parameters were significantly higher among patients who achieved a response level of CR/VGPR than among those who did not.

The results from the VISTA study[17] showed that the quality of response was correlated with improved long-term outcomes among patients treated with bortezomib-based regimens. These analyses indicated that achievement of CR was correlated with substantially longer periods to progression, length of time to next therapy and greater treatment-free interval, but there was no significant difference in OS. Falcon et al.[18] reported that patients treated with lenalidomide-based regimens had significantly longer OS than patients treated with conventional chemotherapy (59.1 versus 49.1 months; P = 0.0144). In addition, the four-year PFS rate was more than doubled in the lenalidomide group, to 32.6%, compared with 14.6% in the group treated with standard therapy (P < 0.0001), thus proving that lenalidomide-based regimens significantly improved PFS.

Gay et al.[7] performed a pooled analysis on 1,175 newly diagnosed myeloma patients who were treated with melphalan-prednisone with or without thalidomide and/or bortezomib. The highest CR rate was detected among patients treated with bortezomib and thalidomide plus melphalan-prednisone (49%), while the lowest rate was among patients treated with melphalan-prednisone (5%), with a strong correlation between depth of response and outcomes. After a median follow-up of 29 months, the three-year PFS and OS were 67% and 27% (P < 0.001), and 91% and 70% (P < 0.001), among patients who achieved CR and those who achieved VGPR, respectively.

The present analysis demonstrated that the CR rates were similar in the groups of patients treated with thalidomide-based regimens (55%) and bortezomib-based regimens (40%), and were lowest in the group treated with conventional therapy (5%). This study also showed that after a median follow-up of 25.4 months, the three-year PFS and OS were 75% and 49% (P < 0.001), and 87% and 72% (P < 0.001), among patients who achieved CR and those who achieved VGPR, respectively. Moreover, multivariate analysis indicated that novel agent-based induction, achievement of CR after first-line treatment, recovery of renal function, absence of significant comorbidities and age less than 65 years were the factors that were clearly linked with considerably prolonged PFS and OS.

Multivariate risk factor analysis by other researchers has shown that novel agent-based induction, administration of maintenance therapy and achievement of CR were significantly linked with prolonged PFS. Regarding OS, novel agent-based induction and maintenance therapy were significantly associated with superior survival.[19] Multidrug regimens combining proteasome inhibitors with immunomodulatory drugs have enhanced the depth of response, have shown satisfactory tolerability and are being recommended as a standard treatment approach.[20] The rapidity of achievement of a deep response after up-front therapy, applied either early or late during the treatment, does not influence survival.[21] Treatment should be personalized to the disease characteristics, for individual patients, with the goal of achieving better disease control and longer survival.[20]

CONCLUSION

The findings from the present analysis indicate that the quality of response to first-line treatment has a positive prognostic impact. Patients who achieved a maximal response had significantly longer progression-free survival and overall survival, compared with patients who reached lesser responses. In our study, the patients who were treated with novel agent-based induction regimens had significantly prolonged progression-free survival and superior overall survival, in comparison with the patients who were treated with conventional chemotherapeutic agents. The data from this study support the conclusion that achievement of a deeper response after first-line treatment with novel targeted

therapies, among multiple myeloma patients, is a prognostic factor for improved survival outcomes.

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Hospitalization due to mental and behavioral disorders caused by use of alcohol and psychoactive substances among older adults and elderly people in Brazil: a cross-sectional study

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AUTHORS' KEYWORDS:
Psychiatric conditions.
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CAPS.

ABSTRACT

BACKGROUND: It has been estimated that 17% of individuals aged 50 years or older suffer from addiction to legal or illegal drugs. Use of alcohol and psychoactive substances has been correlated with several diseases, e.g. psychiatric conditions and cardiovascular and sexual dysfunctions.

OBJECTIVE: To discuss the Brazilian profile of mental and behavioral disorders caused by use of alcohol and psychoactive substances among older adults and elderly people, over the period from 2008 to 2019.

DESIGN AND SETTING: Cross-sectional study conducted among Brazilians aged 50 years or older.

METHODS: Hospitalization due to mental and behavioral disorders caused by use of alcohol and psychoactive substances was assessed through data obtained from the National Health System Department of Informatics (Departamento de Informática do Sistema Único de Saúde, DATASUS).

RESULTS: Decreasing and steady trends of hospitalization due to mental and behavioral disorders caused by use of alcohol among both men and women at all ages were observed. Similar trends were reported for all age ranges among men and women aged 60 years and older. In contrast, a slight increase was seen among women aged 50 to 59 years.

CONCLUSION: These data are crucial for qualifying mental healthcare for older adults and elderly people and for planning mental health services.

INTRODUCTION

Drug addiction is a common issue reported among adolescents and young adults. However, it has been estimated that 17% of individuals aged 50 years old or older suffer from addiction to legal or illegal drugs.[1,2] There is evidence from several studies showing that sexual and psychological abuse, maltreatment and trauma during childhood are closely related to substance use in later years.[3,4]

Accumulating evidence has shown that significant levels of psychological distress are present among older adults and elderlies. A previous study[5] showed that there was an increasing rate of hospitalization due to drug substance abuse and a decreasing rate due to alcohol among older adults and elderly people in the United States from 1992 to 2005. In addition, increasing rates of first hospitalization due to substance abuse were reported among older adults and elderly people from 1998 to 2008.[6] Increasing suicide rates were reported among women and men aged up to 74 years from 2000 to 2014, and the rate is expected to increase further over the next few years.[7]

Among older adults and elderly people, the symptoms of substance abuse are more challenging to treat and may be consequences of other diseases, e.g. cardiovascular diseases,[8] urological diseases,[9] diabetes[10] and cancer.[11] There are also significant relationships between abusive use of alcohol and psychoactive substances and occurrence of mental and behavioral disorders. For example, in a cross-sectional study on the clinical characteristics of drug users hospitalized in an intensive care unit, it was found that 31.2% of the individuals had psychiatric comorbidities, and that the most common of these were depression, anxiety and bipolar affective disorder.[12] In the psychological and psychiatric literature, it is indicated that abusive use of alcohol and drugs can act both as an aggravator and as a consequence of mental illness.[13,14]

Alcohol and substance abuse disorders are a risk factor for several diseases, e.g. psychiatric conditions, cardiovascular conditions and sexual dysfunctions, and have become a public health issue that potentially affects individuals' lives, employment and family relationships.[15,16] One explanation for this the influence of cultural factors that normalize alcohol abuse and facilitate increasing alcohol consumption, as seen in Brazil. Another important explanation is that alcohol and substance abuse negatively affect family relationships. Thus, conflict-ridden, violent and unstructured family relationships act as a predisposing factor for alcohol abuse. A similar dynamic can be observed in relation to work: while it is true that alcohol and substance abuse affects working relationships, it is also true that frustration in labor relations and unemployment are also factors that give rise to vulnerability to abusive use of alcohol and substances.[17] Cumulative studies[18-20] within the fields of social psychology and occupational medicine have shown that the organizational structure of work relationships can lead individuals to emotional distress, which can turn into mental health issues such as depression, stress and anxiety. Furthermore, one common consequence of depression is increased consumption of alcohol and substances.[19,21]

Treatment of alcohol and substance abuse remains challenging. It is important to mention the difficulties reported by healthcare service professionals, such as the difficulty of establishing clear criteria for discharge processes for individuals with substance abuse issues.[22] These difficulties relate to the following: divergences in professional teams; omnipotence of professionals; difficulties relating to rupture of bonds; institutional dependency; patient instability; and difficulties in making connections within the healthcare network. Previous research has indicated that the treatment and discharge process is complex and is characterized by combinations of social, economic, political, subjective and institutional dimensions.[22]

The National Household Sampling Survey (Pesquisa Nacional por Amostra de Domicílios, PNAD) investigates the general characteristics of the Brazilian population and its living conditions every year. It includes health-related questions every three years, and accesses individual information on demographic and socioeconomic characteristics and selected health indicators, including risk factors and self-reported chronic diseases. According to PNAD, less than 10% of the subjects who reported having alcohol and drug-related problems have received treatment for their disorders.[23] Understanding the national profile of individuals who need treatment for alcohol and substance abuse is a key point for planning public policies and improving the quality of treatment for these disorders.[17]

In this regard, cross-sectional studies on mental health are an important tool for analyzing the distribution and frequency of mental disorders. Such studies contribute to planning, executing and evaluating strategic interventions for prevention, control and treatment.

OBJECTIVE

Since mental health during the aging process and use of psychoactive drugs and alcohol in later life are still unrecognized problems, the aim of the present study was to analyze hospitalization due to mental and behavioral disorders related to alcohol and psychoactive substance abuse in Brazil over the period from 2008 to 2019.

METHODS

Clinical data

This cross-sectional study was conducted in September 2020. It included data from hospital admissions that were reported as mental and behavioral disorders due to use of alcohol or psychoactive substances among individuals aged 50 years or older who were living in Brazil. The period surveyed was from January 1, 2008, to December 31, 2019.

The data were extracted from the database of the Department of Informatics of the Brazilian National Health System (Departamento de Informática do Sistema Único de Saúde, DATASUS), which is part of the Ministry of Health (Ministério da Saúde, MS) and is available through the DATASUS website.[24] The data available through DATASUS are part of the universal accessibility policy of the Brazilian public healthcare system and include the hospital information system, which is composed of the registers collected through municipal health departments. The data collection methodology did not change during the study period.

The subjects whose information was extracted were not individually identified. Therefore, this study did not require approval from a research ethics committee.[25]

The information in DATASUS includes the basic and associated cause based on the 10th edition of the International Classification of Diseases (ICD). We used the ICD version 10 (ICD-10) codes, among which F10 corresponds to mental and behavioral disorders due to use of alcohol and F11 to F19 correspond to mental and behavioral disorders due to psychoactive substance use, which includes use of opioids, cannabinoids, sedative-hypnotics, cocaine, other stimulants such as caffeine, hallucinogens and volatile solvents and multiple drug use of other psychoactive substances.

Demographic data

Demographic data were obtained from the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE).[26] The IBGE is the official provider of geographical and statistical information in Brazil, and it conducts a census every 10 years to verify the profile of the Brazilian population by collecting several variables from every household in the country. The sociodemographic profile in the years between censuses are estimated through projections.

Data analysis

Data analyses were conducted using the Prism software, version 6.0 (GraphPad Software, San Diego, California, United States). For analyses on the differences across age groups, the one-way analysis of variance (ANOVA) test was used as described previously.[27] The statistical tests were considered significant when $P < 0.05$.

For the proportional rates of hospitalization, we used the total number of hospitalizations according to age as the numerator, and the respective population as the denominator, as shown in the following equation:

$$Hospitalization_{age} = \frac{number\ of\ hospitalizations}{total\ population\ in\ the\ range} \text{ x}10^5$$

RESULTS

The aim of this epidemiological study was to evaluate the hospitalization profile of mental and behavioral disorders due to use of alcohol and psychoactive substances among Brazilians aged 50 years and older.

Between 2008 and 2019, 184,930 individuals were hospitalized in Brazil due to mental and behavioral disorders caused by alcohol. Interestingly, the hospitalization rate was nine times higher among males than among females. In both genders, individuals aged 50 to 59 years were the ones most affected, followed by the age ranges of 60 to 69 years, 70 to 79 and 80 or older **(Table 1)**.

In order to analyze the real rates of hospitalization, considering the demographic increase of the population, we cross-referenced the demographic data and hospital admission registers over the period studied. In proportional terms, males **(Figure 1 A)** showed massively higher rates of hospitalization, compared with females **(Figure 1 B).** However, the two sexes presented similar trends, with significantly decreasing rates ($P < 0.05$) among individuals aged 50 to 59, a slight decrease among those aged 60 to 69 years and steady rates among those aged 70 years and older.

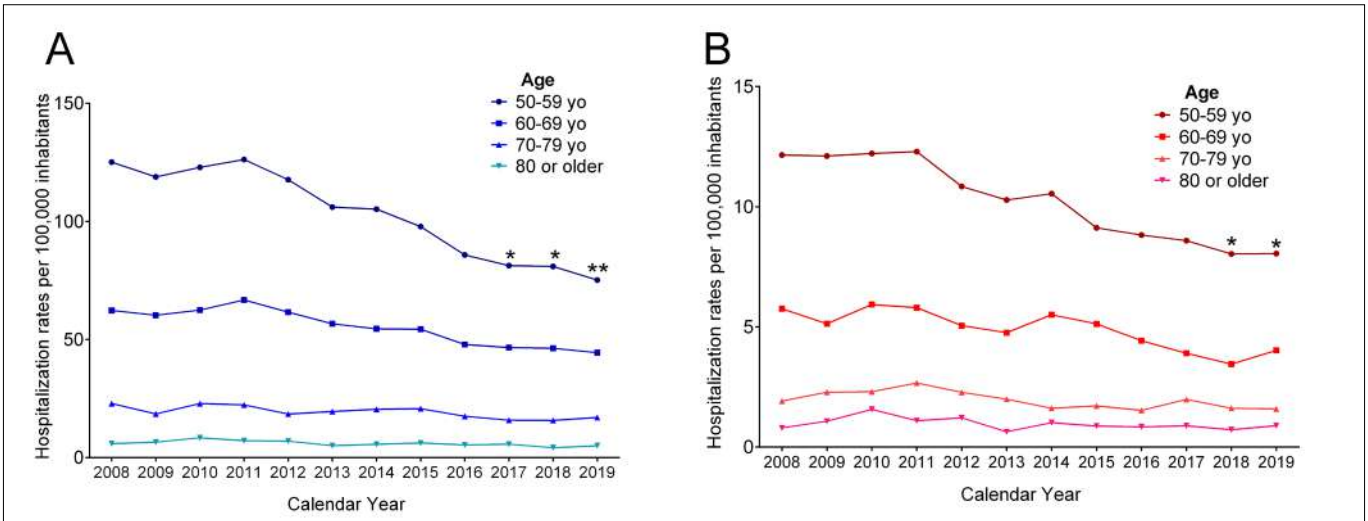
Over the same period, 31,586 Brazilians were hospitalized due to mental and behavioral disorders caused by psychoactive substance use. Among these individuals, the hospital admission rate for men was approximately three times higher than the rate for women. Again, comparing the age ranges within the genders, there were similar profiles: male and female individuals aged 50 to 50 were the ones most hospitalized, followed by those aged 60 to 69, 70 to 79 and 80 or older **(Table 2)**.

In proportional terms, hospitalization among males was always higher. At all ages, there was a slight decrease in the rates ($P > 0.05$) **(Figure 2 A)**. However, among females, a statistical increase ($P < 0.05$) was reported among those aged 50 to 59 years, while a steady rate at all ages from 60 years onwards was observed **(Figure 2 B)**.

Table 1. Frequency of hospitalization due to mental and behavioral disorders caused by psychoactive substance use among Brazilians between 2008 and 2019

Age	Men		Women	
(years)	n	% (95% CI)	n	% (95% CI)
50-59	18,503	77.98 (78.50 ± 77.44)	5,454	69.40 (70.42 ± 68.37)
60-69	3,923	16.53 (17.01 ± 16.06)	1,478	18.80 (19.69 ± 17.95)
70-79	947	3.99 (4.25 ± 3.74)	613	7.81 (8.41 ± 7.21)
≥ 80	355	1.50 (1.65 ± 1.34)	313	3.99 (4.43 ± 3.56)
Total	**23,728**	**100**	**7,858**	**100**

Data source: Hospital Information System, available from the Department of Informatics of the Brazilian National Health System. CI = confidence interval.



Values represents the rates per 100,000 inhabitants; *P < 0.05; **P < 0.01 when compared to the initial year of the analysis (2008), as reference. yo = years old.

Figure 1. Proportional hospitalization due to mental and behavioral disorders caused by use of alcohol (International Classification of Diseases version 10, ICD-10: F10) among males (A) and females (B) according to their respective populations.

Lastly, comparing hospitalization due to alcohol with hospitalization due to psychoactive substances (**Tables 1** and **2**), the hospitalization rate for mental and behavioral disorders due to alcohol abuse was approximately six times higher (184,930 individuals) than for psychoactive substances (31,586 individuals).

DISCUSSION

In the present epidemiological study, we analyzed the hospitalization profile of mental and behavioral disorders due to use of alcohol and psychoactive substances in Brazil over the period 2008-2019. We also evaluated their prevalence according to sex, age ranges and calendar-year incidence of hospitalization. Over the period studied, we observed that the hospitalization rate for mental and behavioral disorders due to alcohol abuse was approximately six times higher than the rate due to psychoactive substances. In addition, men were hospitalized more, due to both use of alcohol and use of psychoactive substances. Our results showed that hospital admission due to alcohol use has been decreasing in both sexes aged 50 to 69 years, while a steady rate profile was observed among individuals aged 70 years and older. Different profile was seen with regard to hospitalization due to psychoactive substances; females aged 50 to 59 years presented an increasing rate over the years, while steady rates were observed among females aged 60 years and older and at all ages among men.

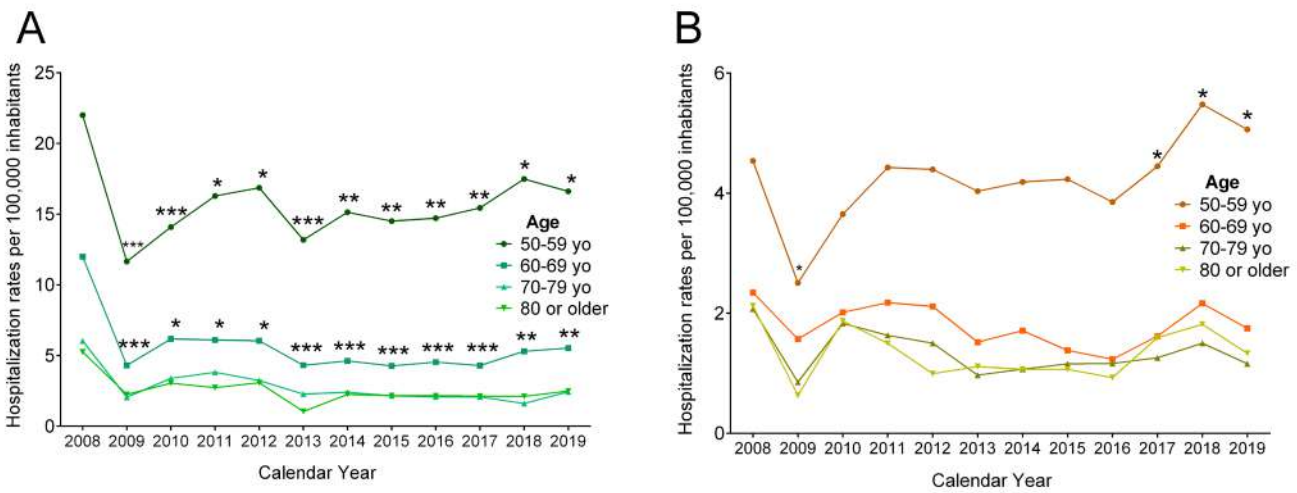
According to the World Health Organization (WHO),[28] abuse of alcohol results in approximately three million deaths per year (5% of all deaths worldwide). This mortality rate is higher than the rates for diseases such as diabetes, tuberculosis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In 2016, 133 million cases of alcohol-attributable disability were reported worldwide. Among these disabilities induced by alcohol abuse, 49% were due to non-communicable and mental health conditions, 40% due to accidents and 11% due to digestive, cardiovascular and infectious diseases, and to cancers. In Brazil, about 9% of all disabilities are related to mental and behavioral disorders, according to the Brazilian Ministry of Labour.[29]

It is widely known that alcohol consumption is more prevalent among males than among females. Among all deaths, 7.7% of those among males and 2.6% of those among females are related to alcohol worldwide.[30] Our results showed that hospitalization due to mental and behavioral disorders caused by use of alcohol was nine times higher among males. Drinking habits can be influenced by several factors, e.g. demographic, social and attitudinal variables.[31] One plausible explanation for the higher levels of drinking among

Table 2. Frequency of hospitalization due to mental and behavioral disorders caused by alcohol use among Brazilians between 2008 and 2019

Age	Men		Women	
(years)	n	% (95% CI)	n	% (95% CI)
50-59	120,502	72.19 (72.40 ± 71.96)	12,895	71.65 (72.31 ± 70.99)
60-69	38,926	23.32 (23.52 ± 23.11)	3,991	22.19 (22.79 ± 21.57)
70-79	6,667	3.99 (4.08 ± 3.90)	887	4.91 (5.25 ± 4.61)
≥ 80	839	0.50 (0.53 ± 0.46)	223	1.23 (1.41 ± 1.08)
Total	**166,934**	**100**	**17,996**	**100**

Data source: Hospital Information System, available from the Department of Informatics of the Brazilian National Health System. CI = confidence interval.



Values represents the rates per 100,000 inhabitants; *P < 0.05; **P < 0.01 and ***P < 0.001 when compared to the initial year of the analysis (2008), as reference. yo = years old.

Figure 2. Proportional hospitalization due to mental and behavioral disorders caused by psychoactive substance use For Review Only (International Classification of Diseases version 10, ICD-10: F11-F19) among males (A) and females (B) according to their respective populations.

men relates to the traditional form of masculinity, in which being a man and consumption of alcohol are strongly associated. The massive difference between men and women can also be explained by the fact that drinking behavior has traditionally been condemned by women. In a survey conducted recently among young men in Brazil, there was a positive correlation between alcohol consumption and adherence to these traditional norms of masculinity[32] (such as heterosexuality, aggressiveness and a tendency to engage in risky behavior,[33-34] which reinforces our point of view. It is also important to point out that the conventional forms of masculinity are closely associated with the worst health outcomes.[35]

Addiction to legal and illegal drugs is commonly an issue related to early adulthood[36] and adolescence.[37] Interestingly, consumption of drugs tends to decrease in later adulthood (approximately at the age of 50 years) in both genders,[38] with the exception of tobacco. In our results, we showed that there were higher rates of hospitalization due to alcohol use in the younger population in both genders. According to a study conducted by the Brazilian government,[39] 8% of Brazilians aged 45 to 59 years old consume alcohol every day, 16% up to four times per week, 14% up to three times per month, 9% up one time per month and 53% less than once per year or have never used alcohol. Among elderly people aged 60 years or older, 7% drink alcohol every day, 8% up to four times per week, 10% up to three times per month, 8% up to one time per month and 68% have never drunk alcohol or less than once per year. In Brazil, 50,296 psychiatric hospital admissions due to alcohol use were reported in 2010 and 34,249 in 2017, which was a decrease of about 32%.[40] We attributed the decline in hospitalization to: i) efficient implementation and popularization of centers for psychosocial care (Centros de Atenção Psicossocial, CAPS) in Brazil; and ii) culturally, drinking habits are lower in the older population.

A previous study[41] showed that the use of illicit drugs among individuals aged 50 to 59 years old increased from 5.1% in 2002 to 9.4% in 2007, and 90% of this population started using them when they were younger than 30 years old. In the United States, it was estimated that in 2000, 1.7 million people aged 50 years or older needed treatment due to drug abuse, and 4.4 million in 2020.[42]

In this study, we showed that hospitalization due to psychoactive substance use (which includes use of opioids, cannabinoids, sedative-hypnotics, cocaine, other stimulants such as caffeine, hallucinogens and volatile solvents and multiple drug use of other psychoactive substances) and due to alcohol is approximately three and nine times higher, respectively, among men than among women. One key point in this scenario is that recreational use of psychoactive substances and alcohol is more condemned among women, which may be reflected in the lower rates of hospitalization among females.

In addition to the cultural factors that influence the differences in the levels of alcohol and psychoactive substance abuse among men and women, another cultural factor that is very influential within the Brazilian reality is religiosity. It is important to highlight the great influence of religion in Brazil and its role in the use of alcohol and psychoactive substances. Self-declared Roman Catholics accounted for 95% of the Brazilian population in 1945 and 65% in 2010; in contrast, over the same period, there were growing numbers of Protestants (up from 3% to 22%) and people with no religion people (up from 1% to 8%) and other religions (up from 2% to 5%).[43] According to the Roman Catholic and Protestant religions, conservative behaviors should be practiced by their followers. Thus, use of illicit drugs is extremely condemned. In this regard, a previous study[44] showed that religion is a protective factor against drug use. The lower rates of hospitalization due to psychoactive substance use among women than among men may be also associated with the fact that women are more religious than men.

A different profile was seen with regard to mental and behavioral disorders due to psychoactive substances: a slight increase rate among women aged 50 to 59 years was reported in this study, while a steady rate among women aged 60 and older and at all ages among men was observed. The increasing rate among women aged 50 to 59 years may indicate significant distress in this age range. In a previous study,[45] it was reported that during this period in life, the rates of suicide and suicide attempts among women are higher, and this was correlated with the experience of menopause and some cultural factors that accompany this phase of life among women in Brazil. Hormonal changes can act as facilitators of melancholic processes, and this can be accompanied by a possible feeling of "an end to femininity", accompanying the loss of reproductive capacity. Menopause, as a symbol of the aging process, can bring sadness, low self-esteem and frustration.

Another external psychological factor that can trigger melancholic feelings at this time in life is the possibility that this may coincide with the phase in which grown-up sons and daughters usually leave the maternal home in Brazil. For women who have taken motherhood as their main objective in life, or who have invested most of their time and energy in this, the departure of their offspring can generate a feeling of intense emptiness.[45,46]

We therefore believe that the sum of these factors can lead to an increase in alcohol consumption and psychoactive substance abuse, which would explain the growth in hospitalization rates for women in this age group.

Some methodological limitations to this study need to be noted: i) our data were acquired from electronic records and, although registration of these records is mandatory, potential for lack of data or incorrect recording may exist; ii) we could not distinguish between the first hospitalization and re-hospitalization

episodes; and iii) the recorded data does not include emergency departments, where entries are mostly due to suicide attempts.[47]

CONCLUSION

Collectively, we present a comprehensive report on hospitalization due to mental and behavioral disorders caused by abuse of alcohol and other psychoactive substances across Brazil, covering the period from 2008 to 2019. This study provides valuable information about hospitalization according to age, sex and year. Decreasing and steady trends of hospitalization due to mental and behavioral disorders caused by use of alcohol among men and women at all ages were demonstrated. Similar trends were reported for all age ranges among men and women aged 60 years and older. In contrast, a slight increase was seen among women aged 50 to 59 years. These data are crucial for planning mental health services targeting older adults and elderly people who are hospitalized due to mental and behavioral disorders caused by use of alcohol and psychoactive substances.

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Biceps tenotomy or tenodesis in association with rotator cuff repair: is there an influence on functional results? A retrospective cohort study

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Biceps tenodesis.
Rotator cuff repairs.
Arthroscopy.

ABSTRACT

BACKGROUND: Instability or tears of the long head of the biceps tendon (LHBT) may be present in more than 35% of rotator cuff repairs (RCR).

OBJECTIVE: To compare clinical results from patients undergoing arthroscopic RCR, according to the procedure performed at the LHBT.

DESIGN AND SETTING: Retrospective cohort study designed at the shoulder and elbow clinic of Instituto de Ortopedia e Traumatologia, Hospital das Clinicas, Faculdade de Medicina, Universidade de Sao Paulo, Brazil.

METHODS: Functional results among patients were compared using the American Shoulder and Elbow Surgeons (ASES) and University of California Los Angeles (UCLA) scales, according to the LHBT approach adopted: no procedure, tenotomy or tenodesis.

RESULTS: We evaluated 306 shoulders (289 patients): 133 underwent no procedure at the LHBT, 77 tenotomy and 96 tenodesis. The ASES scale at 24 months showed no difference (P = 0.566) between the groups without LHBT procedure (median 90.0; interquartile range, IQR 29), tenotomy (median 90.0; IQR 32.1) or tenodesis (median 94.4; IQR 22.7); nor did the UCLA scale (median 33; IQR 7 versus median 31; IQR 8 versus median 33; IQR 5, respectively, P = 0.054). The groups differed in the preoperative functional assessment according to the ASES and UCLA scale, such that the tenodesis group started from higher values. However, there was no difference in pre and postoperative scores between the groups.

CONCLUSION: Tenodesis or tenotomy of the LHBT, in the sample analyzed, did not influence the clinical results from RCR, as assessed using the ASES and UCLA scales.

INTRODUCTION

Instability or tears of the long head of the biceps tendon (LHBT) may be present in more than 35% of the arthroscopies performed to repair the rotator cuff.[1,2] Although LHBT disorders may occur in isolation, in most cases involvement of the LHBT is associated with rotator cuff syndrome.[3]

Tenotomy and tenodesis of this tendon are frequently performed during shoulder arthroscopy.[3] The low number of studies comparing these techniques has been highlighted in published meta-analyses,[4-6] and in one of them 50% of the studies only present level IV evidence.[4] The results pointed towards better functional results through tenodesis, but no minimally significant clinical difference was reached.[5,6] However, no analysis on confounding factors was performed in these meta-analyses,[6] and the samples may have been subject to selection bias, especially in non-randomized studies. In addition, most of the published studies compared the results obtained through tenodesis and tenotomy, and only a few reports included a control group of patients without biceps procedures.[7]

OBJECTIVE

The aim of this study was to compare the clinical results from patients undergoing rotator cuff repair, divided into three groups according to the procedure performed at the LHBT: control group (without any LHBT approach), tenotomy or tenodesis.

METHODS

Design, place and dates

We performed a retrospective cohort study, with data collected prospectively, comparing the functional results between three groups of patients according to the intraoperative approach to the LHBT that had been used: no procedure, tenotomy or tenodesis. The procedures were performed between 2014 and 2017, in a single institution, by three different surgeons.

The local institutional review board approved the study: the Ethics Committee for Review of Research Projects ("CAPPesq") of the Clinical Board of the Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, under research protocol number 2.133.213, dated June 22, 2017.

Eligibility criteria

We included patients who underwent arthroscopic rotator cuff repair and had preoperative magnetic resonance imaging, without the use of intra-articular contrast, in a device rated at 1.5T or higher, regardless of tendon thickness, retraction or fatty degeneration. Patients with irreparable or partially repaired rotator cuff tear, tear of the subscapularis alone, complete tear of the LHBT, rotator cuff arthropathy, moderate or severe glenohumeral arthrosis (as described by Samilson and Prieto)[8] or previous shoulder surgery were excluded. Patients who had not undergone pre or postoperative functional evaluation were also excluded.

Outcome

The primary outcome was the evaluation on the American Shoulder and Elbow Surgeons (ASES)[9,10] and University of California Los Angeles (UCLA)[11,12] scales at a follow-up conducted 24 months after the operation. As a secondary outcome, we assessed the influence of sex, age, dominance, smoking, diabetes, previous injection, traumatic tear, supraspinatus tear pattern, subscapularis repair, fatty degeneration of rotator cuff muscles, acromioplasty and lateral clavicle resection on the clinical results from the LHBT procedure.

Variables analyzed

The following variables were evaluated:

- Variables relating to patients: age, sex, involvement of the dominant side, smoking, diabetes, previous injection and previous trauma to the affected shoulder.
- Variables relating to the lesion: thickness of the supraspinatus tear (partial or full thickness), retraction of the supraspinatus tear (< 30 mm or ≥ 30 mm) and degree of fatty infiltration of the rotator cuff muscles, as described by Fuchs et al.[13]
- Variables relating to the procedure: subscapularis repair, acromioplasty and distal resection of the clavicle.
- Variables relating to the intraoperative approach towards the LHBT: no procedure, tenotomy or tenodesis. In cases of tenodesis, we specified the method of fixation and site of tenodesis.

All variables referring to the lesion, with the exception of fatty degeneration, were determined by means of arthroscopic inspection. The clinical evaluations using the ASES[9,10] and UCLA[11,12] scales were performed one week before and 24 months after the surgical procedure.

Arthroscopy

The procedures were performed under general anesthesia in association with interscalene brachial plexus block. We positioned the patients on a beach chair or in lateral decubitus, depending on the surgeon's preference, and conventional portals were used. The inspection was performed using a 30° arthroscope positioned in the posterior portal. Using a probe, the LHBT was palpated and mobilized, looking for signs of instability, through the "ramp test",[14] as well as any injuries to its substance or insertion. The variables described above were inspected in a standardized manner.

The indications for LHBT procedures were subluxation or dislocation, partial lesions affecting more than 25% of the thickness or superior labrum lesions of types 2, 3 or 4. For patients aged 60 years or older, tenotomy was performed. Tenodesis was performed on younger or active patients or on those with a body mass index (BMI) below 25, regardless of age. Tenotomy was performed close to the origin of the glenoid labrum. Tenodesis, when indicated, was performed using anchors. In the procedure, one of the anchor sutures used to repair the subscapular or supraspinatus could be used, or an additional anchor positioned in the bicipital groove could be used.

The rotator cuff repair was performed using a simple row technique. Acromioplasty was performed according to the surgeon's preference, and distal resection of the clavicle was performed in patients with symptomatic arthritis. After surgery, patients remained immobilized through use of a sling for six weeks.

Passive shoulder movements were started in the third week, and active shoulder movements were started after the sling was removed. Strengthening started at 12 weeks. Movements of the hand, wrist and elbow were allowed from day one.

Statistical analysis

We subjected continuous variables to assessment of normality, using the Shapiro-Wilk test, and assessment of homogeneity, using the Levene test.

Categorical variables were described in terms of absolute and percentage values. Continuous variables were expressed as the median and interquartile range (IQR). The general characteristics of the sample were compared between groups using the chi-square test (categorical variables) or the Kruskal-Wallis test (continuous variables).

Comparisons between pre and postoperative times for each group, according to the measurements on the ASES and UCLA scales, were performed using the Wilcoxon test. The comparison between functional results before surgery and at 24 months, according to the approach taken to the LHBT, was performed using the Kruskal-Wallis test, with Bonferroni post-hoc correction.

Multiple regression analysis was performed with the objective of identifying confounding factors in the final result, and this analysis including all variables that presented $P < 0.2$.

We used the SPSS software (version 21.0; IBM, Armonk, New York, United States) for data analysis. A 5% significance level was used.

RESULTS

During the study period, we performed 399 arthroscopies to treat rotator cuff tears. Patients who underwent debridement (11), subscapularis repair alone (5), reoperations (3) or rotator cuff partial repair (34), patients with complete tears of the LHBT (19) and those without clinical information (21) were not included in the analysis. Thus, the sample analyzed consisted of 306 shoulders (289 patients), among which 133 shoulders did not undergo any procedure on the long head of the biceps, while 77 underwent tenotomy and 96 underwent bicipital tenodesis. Tenodesis was performed on at the supraspinatus repair anchor in the cases of 62 shoulders and at the subscapular anchor in 24 cases. Tenodesis was performed in the bicipital groove in 10 shoulders.

The variables relating to the patients demonstrated that the groups differed in terms of age and sex ($P = 0.022$ and $P < 0.001$, respectively). Cases involving tenotomy presented higher mean age and were predominantly among women, while cases involving tenodesis were predominantly among men. There were no differences in the other analyses (**Table 1**).

The variables relating to the injury and the procedure showed statistically significant differences in all analyses, except for distal clavicle resection. The group without any procedure at the LHBT had fewer full-thickness tears of the supraspinatus, less retraction of the supraspinatus tear, lesser degree of fatty degeneration and a lower index of subscapularis repair. The tenotomy group had more retracted lesions and more fatty degeneration, compared with the tenodesis group. These data can be seen in **Table 2**.

The multiple regression analysis showed that only age proved to be an independent factor for the postoperative clinical outcome ($P = 0.007$), such that older patients correlated with better functional results. These data are shown in **Table 3**.

All three groups improved significantly through the procedure, according to the two scales used ($P < 0.001$). The ASES scale at 24 months showed no significant difference ($P = 0.566$) between the groups without LHBT procedure (median 90.0; IQR 29), tenotomy (median 90.0; IQR 32.1) and tenodesis (median 94.4; IQR 22.7). Likewise, the UCLA scale did not differ between the groups

Table 1. Variables relating to the patients

	Biceps procedure						
	None (n = 133)		Tenotomy (n = 77)		Tenodesis (n = 96)		P
Age, years [median, IQR]	53	10	62	12	56	9	0.022
Sex [n (%)]							
Male	53	39.8	17	22.1	58	60.4	< 0.001
Female	80	60.2	60	77.9	38	39.6	
Dominant side affected [n, %]							
Yes	95	71.4	56	72.7	69	71.9	0.980
No	38	28.6	21	27.3	27	28.1	
Smoking [n, %]							
Smoker	16	12.0	9	11.7	15	15.6	
Former smoker	26	19.5	11	14.3	17	17.7	0.768
Never smoked	91	68.4	57	74.0	64	66.7	
Diabetes [n, %]							
Yes	18	13.5	13	16.9	11	11.5	0.586
No	115	86.5	64	83.1	85	88.5	
Previous injection [n, %]							
Yes	24	18.0	11	14.3	13	13.5	0.604
No	109	82.0	66	85.7	83	86.5	
Traumatic tear [n, %]							
Yes	11	8.3	8	10.4	11	11.5	0.712
No	122	91.7	69	89.6	85	88.5	

IQR = interquartile range.

Table 2. Variables relating to the lesion and the procedure

	Biceps procedure						
	None (n = 133)		Tenotomy (n = 77)		Tenodesis (n = 96)		P
Supraspinatus tear [n, %]							
Partial thickness	28	21.1	4	5.2	4	4.2	< 0.001
Full thickness	105	78.9	73	94.8	92	95.8	
Retraction of the supraspinatus [n, %]							
< 30 mm	119	89.5	46	59.7	74	77.1	< 0.001
≥ 30 mm	14	10.5	31	40.3	22	22.9	
Subscapularis repair [n, %]							
Yes	19	14.3	44	57.1	54	56.3	< 0.001
No	114	85.7	33	42.9	42	43.8	
Fuchs classification (supraspinatus) [n, %]							
Grade I	123	92.5	51	66.2	84	87.5	
Grade II	9	6.8	20	26.0	12	12.5	< 0.001
Grade III	1	0.8	6	7.8	0	0.0	
Fuchs classification (infraspinatus) [n, %]							
Grade I	122	91.7	57	74.0	86	89.6	
Grade II	11	8.3	16	20.8	9	9.4	0.002
Grade III	0	0.0	4	5.2	1	1.0	
Fuchs classification (subscapularis) [n, %]							
Grade I	130	97.7	65	84.4	93	96.9	
Grade II	3	2.3	11	14.3	3	3.1	< 0.001
Grade III	0	0.0	1	1.3	0	0.0	
Acromioplasty [n, %]							
Yes	114	85.7	50	64.9	81	84.4	0.001
No	19	14.3	27	35.1	15	15.6	
Distal clavicular resection [n, %]							
Yes	6	4.5	1	1.3	0	0.0	0.063
No	127	95.5	76	98.7	96	100.0	

(median 33; IQR 7 versus median 31; IQR 8 versus median 33; IQR 5, respectively, P = 0.054). The groups differed significantly in the preoperative functional assessment, according to both the ASES scale (P = 0.017) and the UCLA scale (P = 0.008), and the tenodesis group started from higher values. However, there was no difference in pre and postoperative scores between groups (P = 0.642 and 0.371, respectively). These data are shown in **Table 4**.

We performed a subgroup analysis, categorizing patients by age, according to the result from the multivariate analysis. From the ASES scale, patients aged 60 years or older had similar scores in the preoperative evaluation (medians for the control group 36.1; tenotomy group 27.1; tenodesis group 50; P = 0.105) and at 24 months (medians of 99, 93.9 and 94.7, respectively; P = 0.247). Likewise, among the patients under the age of 60 years, the scores were similar between the groups in the preoperative assessment (medians of 38.9, 32.4 and 42.8, respectively; P = 0.096) and in the assessment at 24 months (medians of 88.2, 84.4 and 93.2, respectively; P = 0.224). In the evaluation using the UCLA scale, patients under 60 years of age who underwent tenodesis showed slightly higher postoperative results (median of 33), compared with patients in the control group (32) and in the tenotomy group (31), with a statistically significant difference (P = 0.027). In the preoperative assessment, the difference also favored the tenodesis group (median of 15), compared with the groups without the procedure (13.5) and tenotomy (12), with a statistically significant difference (P = 0.024). In the subgroup of patients older than 60 years, there were no statistically significant differences in the preoperative evaluation using the UCLA scale (medians of 14, 14 and 17, respectively; P = 0.193), or in the 24-month evaluation (35, 32 and 35; P = 0.248).

The location of LHBT tenodesis did not influence the results. The 86 patients who underwent intra-articular tenodesis had a median score of 94.4 (IQR 24.1) using the ASES scale and 33.5 (IQR 6) using the UCLA scale, while the 10 patients who underwent tenodesis in the bicipital groove had a median score of 93.2 (IQR 20.4) and 33 (IQR 4), respectively. The P values were 0.590 for the ASES scale and 0.695 for the UCLA scale.

Table 3. Multiple regression analysis to control for confounding factors

	Coefficient	95% confidence interval		P
		Lower	Upper	
Sex	-0.082	-8.692	1.726	0.189
Age	0.170	0.116	0.711	0.007
Supraspinatus tear	0.023	-6.032	9.064	0.693
Supraspinatus retraction	-0.077	-10.816	2.985	0.265
Subscapularis repair	-0.089	-8.998	1.245	0.137
Fuchs classification (supraspinatus)	-0.024	-8.416	6.111	0.755
Fuchs classification (infraspinatus)	-0.088	-12.026	2.792	0.221
Fuchs classification (subscapularis)	0.072	-3.984	15.989	0.238
Acromioplasty	0.030	-4.842	8.041	0.625
Distal clavicular resection	-0.015	-17.934	13.720	0.793
Preoperative ASES score	0.106	-0.014	0.250	0.079

ASES = American Shoulder and Elbow Surgeons.

DISCUSSION

Our results showed that, at 24 months, the functional results from arthroscopic rotator cuff repair did not differ between patients undergoing tenotomy, tenodesis or no procedure at the LHBT. These results are in line with those presented by Kukkonen et al.,[7] in a cohort study that, similarly to ours, compared three groups of patients according to the procedure performed at the LHBT, including a control group. However, in our series, the patients started from statistically different scores at the baseline, such that the tenotomy group had a lower score than the tenodesis group before surgery. Nonetheless, this difference did not reach clinical relevance, and its detection may have been due to our larger sample (about three times more patients underwent procedures at the LHBT). Those authors had a less detailed baseline than ours, and they evaluated their sample only according to sex and age, without analyses on other possible confounding factors. Several other factors such as comorbidities and associated lesions and procedures can influence the results, especially due to the fact that procedures relating to the LHBT are performed together with rotator cuff repair in most cases.

Table 4. ASES and UCLA scores according to biceps procedure

	Biceps procedure						P
	None (n = 133)		Tenotomy (n = 77)		Tenodesis (n = 96)		
	Median	IQR	Median	IQR	Median	IQR	
ASES							
Preoperative	38.3	25.5	34.6	26.7	44.8	25.7	0.017*
24 months	90	29	90	32.1	94.4	22.7	0.566
Difference***	43.9	41.6	45	44	43.4	29.9	0.642
UCLA							
Preoperative	14	6	14	6	15	8	0.008**
24 months	33	7	31	8	33	5	0.054
Difference***	17	9	16	8	15	8	0.371

ASES = American Shoulder and Elbow Surgeons; UCLA = University of California Los Angeles; *Post-hoc test: tenotomy vs. tenodesis, P = 0.017; other comparisons, P > 0.05; **Post-hoc test: tenotomy versus tenodesis, P = 0.033; none versus tenodesis, P = 0.014; other comparisons, P > 0.05; ***Difference between postoperative and preoperative scores.

It is important to highlight that although the patients presented statistically significant differences regarding their preoperative scores (such that the tenodesis group started with higher baseline scores), the values found at the end of 24 months did not differ between the groups; nor was there a difference between the pre and postoperative states. The lack of significant difference between the groups regarding the improvement obtained (calculated as the difference between pre and postoperative states) was maintained even after analyzing the subgroups according to age.

In a recent systematic review comparing the effects of tenodesis and tenotomy, Na et al.[6] observed that there was a statistically significant difference favorable to the tenodesis group, according to the Constant-Murley score (96.5 versus 95.6). However, some points should be highlighted. The difference found did not reach clinical relevance[15] and, in addition, the study did not evaluate the baseline score, which may be higher in the tenodesis group, as shown in our study, which may be a confounding factor for the analysis. Most of the published comparative studies have not found any statistically significant difference regarding clinical scales,[7,16-25] and those that did demonstrate a statistical difference did not reach clinical relevance.[20,26]

Our study did not evaluate complications relating to procedures at the LHBT. Popeye's sign occurs in 3%-6% of the cases undergoing tenodesis, and in 9%-20% of those undergoing tenotomy, according to randomized studies.[22-24] In a systematic review of level II clinical evidence, Na et al.[6] demonstrated a statistically significant difference, such that 24% of the patients in the tenotomy group showed Popeye's sign, compared with 9% in the tenodesis group. Other complications, such as postoperative pain level, presence of cramping and elbow flexion strength and forearm supination, have not been found to differ between tenotomy and tenodesis groups.[6] Furthermore, arm deformity is not a source of concern for most patients.[16,17] Among 24 patients with Popeye's sign, Boileau et al.[17] noted that only 16 noticed the deformity and none of the patients cared about it. Biz et al.,[16] similarly, reported that only 25% of the patients with Popeye's sign had noticed the deformity.

In our series, procedures at the LHBT were necessary in 56% of the arthroscopies, i.e. a higher proportion than the 40% reported by other authors.[7,27] This was probably due to inclusion of a greater number of patients with tears not restricted to the supraspinatus.

Our results, which showed similarity between those from tenodesis performed with an anchor next to the rotator cuff and those performed in the bicipital groove with an anchor, should be viewed with caution, given the small sample of patients in the second group. Franceschetti et al,[28] in a randomized study, observed that the clinical results from subpectoral tenodesis were superior to those from high tenodesis with anchors. However, those authors performed open subpectoral tenodesis using a screw, whereas they performed high tenodesis using anchors and arthroscopically. Thus, it is not possible to say whether the difference found was due to the method or to the site of fixation. Most studies have aimed to compare tenodesis with tenotomy, and not to make comparisons between different types of tenodesis.[5,6,23]

Our study had some limitations. First, it was a retrospective cohort study, with the biases inherent to this design. It is important to highlight that the groups were heterogeneous regarding baseline characteristics and preoperative functional assessments. To reduce bias, we performed multivariate and subgroup analysis. Future randomized studies may bring more knowledge on this topic. It is noteworthy that, despite the initial differences, the groups converged to similar functional results at the end of the follow-up.

In addition, we did not perform postoperative resonance imaging (MRI), and structural analysis on the cuff repair or tenodesis was not possible. However, it is known that the functional results do not reach any clinically important difference between patients with and without structural integrity of the rotator cuff,[29] and most studies that have evaluated the results of procedures at the LHBT did not carry out this analysis.[6] Furthermore, although we applied scales that are widely used for functional assessment of the shoulder (ASES and UCLA), we did not evaluate specific physical findings of involvement of the LHBT in the physical examination, such as anterior shoulder pain or the incidence of Popeye's sign.

Our sample was more heterogeneous than that of other authors,[7] including massive rotator cuff tears and involvement not restricted to the supraspinatus. It is already known that the dimension of the rotator cuff tear correlates with LHBT lesions, and this factor may have biased our results.[30] On the other hand, this approach increased the external validity of the data.

It is also worth noting that our data are applicable only to suprapectoral tenodesis with anchors, and cannot be generalized to other techniques. In addition, the surgical technique used was not standardized, and included different tenodesis sites and use of an anchor for the LHBT independently or in association with rotator cuff repair. Most comparative studies have evaluated tenodesis with anchors,[7,19-22,25] and few have evaluated use of interference screws.[17,24]

Among the favorable points regarding our study, we can mention the inclusion of the control group in which no surgical approach was performed at the LHBT. This strategy was previously only used by Kukkonen et al.[7] and Godenèche et al.,[26] to the detriment of the other cohorts[16-21,26] or randomized studies.[22-24] Our sample was quite robust, and superior to that of most other comparative studies,[16-24,26] even though we only considered patients who underwent one of the biceps procedures. Furthermore, all the patients underwent preoperative MRI. We made a detailed description of the baseline, associated with multivariate regression, in order to search for factors that might confound the clinical outcome. This statistical approach, which is important in cohort studies, has

only been implemented in a few studies.[17,26] Lastly, our postoperative clinical evaluation was carried out at a standardized time, at 24 months after the operation, by a research assistant who did not participate otherwise in the study, which therefore reduced the measurement bias.

Thus, according to our results and supported by the current literature,[5,6,23] we concluded that the procedure performed at the LHBT did not influence the final result when performed in association with rotator cuff repair. Future research analyzing the influence of the LHBT on functional results and on patient satisfaction and quality of life, along with development of clinical scales for assessing this tendon and studies comparing different types of tenodesis, are needed for better understanding of the role of different approaches to the biceps with regard to the clinical results.

CONCLUSION

The choice between tenodesis and tenotomy of the long head of the biceps, in the sample analyzed, did not influence the clinical results from rotator cuff repair evaluated using the ASES and UCLA scales.

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Effects of COVID-19 pandemic on colorectal cancer surgery

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ABSTRACT

BACKGROUND: The coronavirus disease-19 (COVID-19) pandemic has changed the course of diseases that require emergency surgery.

OBJECTIVE: To evaluate the effect of the COVID-19 pandemic on colorectal cancer disease stage.

DESIGN AND SETTING: Retrospective analysis in the city of Rize, Turkey.

METHODS: This was a comparative analysis on two groups of patients with various symptoms who underwent surgical colorectal cancer treatment. Group 1 comprised patients operated between March 11, 2019, and December 31, 2019; while group 2 comprised patients at the same time of the year during the COVID-19 pandemic.

RESULTS: Groups 1 and 2 included 56 and 48 patients, respectively. The rate of presentation to the emergency service was higher in Group 2 ($P < 0.02$). The stage of the pathological lymph nodes and the rate of liver metastasis was higher in Group 2 ($P < 0.004$ and $P < 0.041$, respectively). The disease stage was found to be more advanced in Group 2 ($P < 0.005$). The rate of postoperative complications was higher in Group 2 ($P < 0.014$).

CONCLUSION: The presentation of patients with suspicious findings to the hospital was delayed, due both to the fear of catching COVID-19 and to the pandemic precautions that were proposed and implemented by healthcare authorities worldwide. Among the patients who presented to the hospital with emergency complaints and in whom colorectal cancer was detected, their disease was at a more advanced stage and thus a higher number of emergency oncological surgical procedures were performed on those patients.

INTRODUCTION

Cancer is a problem with worldwide importance and is the second leading cause of death globally.[1] Colorectal cancers, with an incidence of 9%, are the fourth among all cancers, following lung, breast and prostate cancer. This rate varies between different countries and ethnicities.[2] The countries with the highest incidence rates include Australia, New Zealand, Canada, the United States and parts of Europe. The countries with the lowest risk include China, India and parts of Africa and South America.[3]

During the last 30 years, the incidence of colorectal cancer has decreased from 66.3 to 45.3 per 100,000 population in the United States.[4] The most important cause of this reduction has been the development and extensive implementation of colorectal cancer screening programs, which have made a positive contribution to the prognosis for the disease, through early detection and diagnosis.[5]

The first cases of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that were reported were in Wuhan, China, in December 2019.[6] A global pandemic was declared by the World Health Organization on March 11, 2020.[7] Coronavirus disease-19 (COVID-19) has seriously jeopardized the health of the whole world, but especially that of healthcare workers.[8]

The number of cases of all other diseases presenting to hospitals and emergency services decreased significantly after cases of COVID-19 began to be seen on March 11. A decision was made by the Turkish Ministry of Health on March 17, to delay all elective surgical procedures while pandemic precautions were continuing to be implemented. In addition to these precautions, the fear of contracting COVID-19 also impacted the rate of access to the country's healthcare services.[9]

This raises various questions, such as: "If patients' presentations to hospitals were delayed despite the presence of suspicious symptoms, were the procedures of colorectal cancer surgery

more complicated during the COVID-19 pandemic; did COVID-19 affect the staging of colorectal cancer; and were the rates of emergency colorectal surgery, postoperative complications and mortality changed by the COVID-19 pandemic?"

OBJECTIVE

The aim of this study was to evaluate the effects of the pandemic precautions suggested and applied by healthcare authorities worldwide and the impact of the fear of becoming infected by SARS-CoV-2, on delay in detection and diagnosis of colorectal cancer, disease stage at the time of diagnosis and emergency surgery rates, during the COVID-19 pandemic.

METHODS

This study was conducted retrospectively, after obtaining ethics board approval from the Ministry of Health (2021-01-06T14_53_45) and from the Ethics Board of the School of Medicine of Recep Tayyip Erdoğan University (approval number: 2021/27; date: February 4, 2021).

This study involved comparative analysis between patients who were treated for colorectal cancer during the COVID-19 pandemic and patients treated for colorectal cancer one year before the pandemic but at the same time of year. The patients were divided into two groups. Group 1 included patients who were treated for colorectal cancer between March 11, 2019, and December 31, 2019, while Group 2 included patients treated for colorectal cancer between March 11, 2020, and December 31, 2020, during the COVID-19 outbreak.

The patients' age and gender, emergency status of the operations, treatment modality applied and surgical procedure, localization of the tumor, histopathological result from the surgical specimen, disease stage, postoperative complications and duration of postoperative stay were recorded separately in Group 1 and Group 2. The differences between the groups were compared.

An analysis on the data was made using PASW Statistics (version 18.0; SPSS Inc., Chicago, Illinois, United States). The Mann-Whitney U test was used to analyze continuous variables. Variables such as age and gender were compared with Student's t test. Pearson's chi-square test was used to evaluate numerical data between groups. The level of statistical significance was set at a P-value of less than 0.05.

RESULTS

A total of 104 patients were included in this study. Among these patients, 63 (60.5%) were male and 41 (39.5%) were female, with a mean age of 64 years. Groups 1 and 2 included 56 and 48 patients, respectively. There were 32 males (57%) and 24 females (43%) in Group 1; while Group 2 comprised 31 males (64%) and 17 females (36%). No statistical significance in terms of gender was found between the groups (P = 0.439). No significant difference in mean age was found between the groups, either: Group 1, 64.9 years (range = 41-89); Group 2, 63.2 years (range = 22-90; P = 0.492 (**Table 1**).

The numbers of emergency and elective operations were 13 (23%) and 43 (77%) in Group 1, respectively; and 25 (52%) and 23 (48%) in Group 2, respectively. The number of patients undergoing emergency surgery was significantly higher in Group 2 (P = 0.02) (**Table 1**). Among the patients undergoing emergency surgery, the indication for the operation was ileus in 10 (18%) and tumor perforation in three (5%) in Group 1; while in Group 2 it was ileus in 16 (33%), tumor perforation in eight (17%) and gastrointestinal (GIS) bleeding in one (2%) (**Table 1**).

Laparotomy and laparoscopic surgery was performed in 40 (71%) and 16 patients (29%), respectively in Group 1; while 39 patients (81%) underwent laparotomy and nine patients (19%) underwent laparoscopic procedures in Group 2 (P = 0.243) (**Table 2**). No significant difference in the surgical procedure performed and the localization of the tumor was found (P = 0.663 and P = 0.511, respectively) (**Table 1**).

The mean duration of the postoperative hospital stay was 9.3 days and 10.8 days in Group 1 and Group 2, respectively, with no difference between the groups (P = 0.332) (**Table 1**).

Postoperative complications occurred in 11 (20%) and 20 patients (42%) in Groups 1 and 2, respectively, and the rate of postoperative complications was significantly higher in Group 2 (P = 0.014) (**Table 1**). The complications seen were hematoma in one patient (1.8%), ileus in five (8.9%), anastomotic leakage in two (3.6%) and extraperitoneal complications in three (5.4%) in Group 1; while they were wound site infection in seven (14.6%), ileus in two (4.2%), evisceration in one (2.1%), anastomotic leakage in one (2.1%) and extraperitoneal complications in nine (18.8%) in Group 2 (**Table 1**).

Mortality in the early period was seen in three cases (5%) and four cases (8%) in Group 1 and Group 2, respectively with no difference between the groups (P = 0.209) (**Table 1**).

The histopathological diagnosis was adenocarcinoma in all patients in Group 1 (100%); while in Group 2 it was adenocarcinoma in 46 patients (96%), medullary carcinoma in one patient (2%) and neuroendocrine carcinoma in one patient (2%). No difference in terms of histopathological diagnosis was found between the groups (P = 0.304) (**Table 2**).

No significant difference in the pathological tumor stage (T) was found between the two groups (P = 0.240) (**Table 2**). However, the pathological lymph node stage (N) was significantly higher in Group 2 (N0 70% versus 44%, respectively; N1 7% versus 31%, respectively; and N2 23% versus 25%, respectively; P = 0.004) (**Table 2**).

The disease stage at presentation was stage 1 in nine patients (16%), stage 2 in 29 (52%), stage 3 in 13 (23%) and stage 4 in five

Table 1. Demographic and perioperative data of the patients

	Group 1 (2019)	Group 2 (2020)	P
Number of patients, n (%)	56 (54)	48 (46)	
Gender, n (%)			
Male	32 (57)	31 (64)	0.439
Female	24 (43)	17 (36)	
Age, mean (minimum-maximum)	64.9 (41-89)	63.2 (22-90)	0.492
Emergency/elective, n (%)			
Emergency	13 (23)	25 (52)	0.02
Elective	43 (77)	23 (48)	
Reason for surgery, n (%)			
Elective		23 (48)	
Ileus	43 (77)	16 (33)	
Tumor perforation	10 (18)	8 (17)	
Gastrointestinal bleeding	3 (5)	1 (2)	
Treatment modality, n (%)			
Laparotomy	40 (71)	39 (81)	0.243
Laparoscopy	16 (29)	9 (19)	
Surgical procedure, n (%)			
Hemicolectomy		24 (50)	
Low anterior resection	30 (54)	20 (42)	
Abdominoperineal resection	21 (37)	3 (6)	0.663
Total colectomy	5 (9)	1 (2)	
Tumor localization, n (%)			
Cecum	5 (8)	11 (23)	
Ascending colon	15 (27)	1 (2)	
Transverse colon	1 (2)	2 (4)	
Descending colon	8 (14)	1 (2)	0.511
Sigmoid colon	2 (4)	9 (19)	
Rectosigmoid	3 (5)	13 (27)	
Rectum	22 (40)	11 (23)	
Length of stay, mean (minimum-maximum)	9.3 (1-54)	10.8 (1-56)	0.332
Postoperative complications, n (%)			
Yes	11 (20)	20 (42)	0.014
No	45 (80)	28 (58)	
Complications, n (%)			
Wound site infection			
Ileus		7 (14.6)	
Hematoma/bleeding	5 (8.9)	2 (4.2)	
Anastomotic leak	1 (1.8)	1 (2.1)	
Evisceration	2 (3.6)	1 (2.1)	
Extraperitoneal complications (lung and cardiac problems)	3 (5.4)	9 (18.8)	
Mortality, n (%)			
Yes	3 (5)	4 (8)	0.209
No	53 (95)	44 (92)	

Table 2. Pathological characteristics and postoperative data

	Group 1 (2019) n (%): 56 (54)	Group 2 (2020) n (%): 48 (46)	P
Pathological diagnosis, n (%)			
Adenocarcinoma	56 (100)	46 (96)	0.304
Medullary carcinoma		1 (2)	
Neuroendocrine tumor		1 (2)	
Pathological tumor stage, n (%)			
T1	3 (5)	0 (0)	0.240
T2	6 (10)	8 (17)	
T3	34 (62)	25 (52)	
T4	13 (23)	15 (31)	
Pathological lymph node stage, n (%)			
N0	39 (70)	21 (44)	0.004
N1	4 (7)	15 (31)	
N2	13 (23)	12 (25)	
Pathological stage, n (%)			
Stage 1	9 (16)	5 (10)	0.005
Stage 2	29 (52)	11 (23)	
Stage 3	13 (23)	21 (44)	
Stage 4	5 (9)	11 (23)	
Liver metastasis, n (%)			
Yes	4 (7)	10 (21)	0.041
No	52 (93)	38 (79)	
Synchronous tumor, n (%)			
Yes	4 (7)	2 (4)	0.516
No	52 (93)	46 (96)	
Peritoneal carcinomatosis, n (%)			
Yes	2 (4)	1 (2)	0.651
No	54 (96)	47 (98)	
Colostomy, n (%)	21(37)	22 (46)	0.390

(9%) in Group 1; while it was stage 1 in five patients (10%), stage 2 in 11 (23%), stage 3 in 21 (44%) and stage 4 in 11 (23%) in Group 2. Patients in Group 2 were diagnosed at a later stage than were patients in Group 1 (P = 0.005) (**Table 2**). Similarly, the rate of liver metastasis was also significantly different between the groups, in favor of Group 2. Liver metastasis was present in four patients (7%) and 10 patients (21%) in Group 1 and Group 2, respectively (P = 0.041) (**Table 2**). The presence of synchronous tumors and peritoneal carcinomatosis was similar in the two groups (P = 0.516 and P = 0.651, respectively) (**Table 2**).

DISCUSSION

The COVID-19 outbreak seriously changed the structure of health-care systems globally. Many surgical associations recommended that elective surgical operations should cease and that permission should only be granted for presentation of patients with emergency conditions, while cancer surgery could continue.[10-12]

Many papers have highlighted the precautions that would need to be taken while carrying out emergency and elective surgical procedures during the COVID-19 pandemic.[13-16] Consequent to the COVID-19 pandemic, there have been many new changes regarding

re-planning of departments within hospitals, with measures applied to reduce the risk of transmission to the hospital staff, and emphasis on the importance of using of personal protective equipment.[17,18] These changes have greatly extended operating times and the time taken to clean operating rooms between surgeries. Moreover, given that surgeons and operating room workers do not want to endanger their own health, they may have even been avoiding operations on cancer cases unless emergency conditions occur.

At the same time, the protective equipment that surgeons and the entire operating team had to use due to the pandemic restricted the movement of the entire operating team, especially surgeons. Benitez et al. reported that the use of personal protective equipment adversely affected the performance of the surgeons.[19]

Here, in the present study, our aim was to evaluate the situation regarding delayed colorectal cancer disease diagnosis and its consequences. In our study, the age and gender of the patients operated on were similar in the two groups (**Table 2**).

Syllaios et al. reported that the number of emergency colorectal cancer surgeries increased by approximately 30% and that the number of minimally invasive surgical procedures decreased during the COVID-19 outbreak.[20] The rate of occurrence of emergency surgery was found to be significantly higher in Group 2 in the present study (**Table 2**). Hence, it can be stated that patients with suspicious findings probably ignored their situation and preferred to wait at home. This result raises two possibilities: either the patients feared contracting the disease through exposure to the outside environment and consequently stayed at home, or delays in accessing healthcare services and in getting a diagnosis occurred due to pandemic precautions.

Algorithms relating to the approach to be taken in cases of emergency surgery have changed many times during the pandemic. For example, conservative approaches such as antibiotic therapy instead of surgery in acute appendicitis cases and application of laparotomy instead of laparoscopy have been preferred.[21-23] Laparotomy was performed at a rate of 81% during the COVID-19 period with no significant difference between the groups, according to the results from our study (P = 0.243) (**Table 1**).

Comorbidities and disease stage have been investigated in order to determine the outcomes from colorectal surgical treatment.[24,25] In a study involving 887 patients undergoing major colorectal surgery, Ragg et al. reported that a high number of comorbidities was a risk factor for morbidity and mortality.[26] Postoperative complications are known to be an important surgical factor affecting morbidity. In the present study, the rate of postoperative complications was also found to be significantly higher in Group 2 (P = 0.014) (**Table 1**). The rate of postoperative complications may have increased through reduction of the capacity to exert effort due to insufficient physical activity levels during the COVID period, diminished immunity due to advanced stage tumor and greater complexity of surgery.

In the literature, the rate of postoperative mortality has been reported to be 3-8%.[27,28] The mortality rates in Group 1 and Group 2 of the present study were 5% and 8%, respectively, and these rates were consistent with findings in the literature. Although there was no significant difference in these mortality rates, mortality was high in Group 2 (**Table 1**).

In the present study, no significant increase in the pathological tumor stage (T) was seen during the pandemic. However, pathological lymph node (N) status was significantly higher (**Table 2**). In addition, liver metastasis was seen at a significantly higher rate in Group 2 (**Table 2**). According to these factors, the pathological stage of the patients in the pandemic was observed to be significantly more advanced (P = 0.005) (**Table 2**).

The Hartman procedure is frequently preferred in colorectal cancer surgery performed under emergency conditions.[29] In parallel with the increase in the number of emergency surgeries during the pandemic period, we observed that colostomy was performed more often in Group 2 in our study. However, no significant difference was found between the groups (P = 0.390) (**Table 2**).

Individuals with suspicious findings relating to colorectal cancer disease may have preferred to wait at home and self-treat, instead of presenting to a healthcare institution. This may have been due either to limitations on the number of outpatient examinations and substantial selectivity regarding endoscopic and surgical procedures, or due to the precautions taken; or because of the fear of contracting COVID-19. This idea is supported by the observation that emergency operations on the symptoms manifested were performed more frequently and that tumors were only detected at more advanced stages.

CONCLUSION

Through the COVID-19 pandemic, surgeons have been faced with patients presenting greater complications and disease at more advanced stages, due to delayed presentation at healthcare facilities.

In addition to irreversible complications due to these delays in presentation, the increased rates of morbidity and mortality, longer duration of hospital stay and higher patient costs also need to be taken into consideration.

More advanced social understanding is needed in order to address patients' fears, in order to ensure that patients will promptly attend healthcare facilities in the event of a new COVID-19 wave with variant strains.

Moreover, if the course of colorectal cancers during such occurrences can be ascertained, policymakers and healthcare providers can become better organized with regard to disease management.

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Effects and implications of the COVID-19 pandemic on medicine use by employees of a Brazilian public university: a cross-sectional study

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ABSTRACT

BACKGROUND: During the COVID-19 pandemic, universities have had to adopt remote education, a strategy that caused sudden changes of routine for everyone involved in academia.

OBJECTIVE: To assess the profile of medicine use by the employees of a Brazilian public university during the COVID-19 pandemic.

DESIGN AND SETTING: Cross-sectional study at a Brazilian public university.

METHODS: Employees were invited to answer an online self-administered questionnaire, containing questions on sociodemographic features, medicine use, mental health and lifestyle habits during the COVID-19 pandemic. The outcome variable was the use of medicines stratified according to occupation. Descriptive, bivariate and multivariate (Poisson regression) statistical analyses were performed.

RESULTS: A total of 372 employees participated in the study and use of medicine was reported by 53.2%. Among professors, suicide attempts (prevalence ratio [PR], 1.81; 95% confidence interval [CI], 1.20-2.74), physical activity (PR, 1.53; 95% CI, 1.11-2.11) and poor self-rated health (PR, 1.29; 95% CI, 1.01-1.66); and among technicians, decreased workload during the COVID-19 pandemic (PR, 1.41; 95% CI, 1.00-1.99), excess body weight (PR, 1.39; 95% CI, 1.02-1.88) and poor self-rated health (PR, 1.48; 95% CI, 1.14-1.92) were positively associated with use of medicines. In addition, among technicians, engaging in physical activity (PR, 0.60; 95% CI, 0.46-0.78) was a protective factor against medicine use.

CONCLUSION: The profile of medicine use among these employees was similar to that of the Brazilian population. However, some associated factors may have been influenced by the COVID-19 pandemic, thus highlighting the need to examine this topic in a longitudinal study.

INTRODUCTION

The COVID-19 pandemic, caused by exponential transmission of the severe acute respiratory syndrome coronavirus 2, has had serious consequences worldwide.[1,2] In Brazil, since the first case was reported, the number of infections and deaths has been increasing, reaching 18,557,141 confirmed cases on June 30, 2021, at 7 pm. The average numbers of cases and deaths have tended to fluctuate considerably among Brazil's states and regions. However, the southeastern region currently (2021) has the highest moving average of COVID-19 cases.[3]

In order to reduce the transmission rates, some coping measures have been adopted, such as quarantine or social distancing,[4,5] and Brazilian universities have adopted distance learning. This strategy has caused sudden changes to the routines of all people involved in academia.[6]

In this context, professors and technicians who carry out face-to-face activities with students have had to adapt to a new reality and develop new teaching skills. These changes associated with social distancing may have affected these employees' mental health because they normally interact with different people as part of their workload. Additionally, the feeling of anxiety related to an unstable future may have led to mental health issues among those who faced such situations.[7,8] This situation had the potential to increase their use of psychotropic medicines. In addition, data from the Federal Pharmacy Council (Conselho Federal de Farmácia, CFF) indicated that the use of psychotropic medicines during the pandemic (January to July 2020), especially medicines in the anticonvulsant and antidepressant classes, increased by 12.8% and 13.84%, respectively.[9]

To the best of our knowledge, no study has explored the use of medicines among employees of higher education institutions during the COVID-19 pandemic and whether the profile of medicine use by this specific population is similar to that of the general adult population.

OBJECTIVE

The aim of the present study was to assess the profile of medicines consumed by the employees of a Brazilian public university during the COVID-19 pandemic and the factors associated with this use of medicines.

METHODS

Study design and participants

This cross-sectional study was integrated with a project on anxiety and depression among university students (PADu) that was conducted by researchers at the Universidade Federal de Ouro Preto (UFOP), titled "Effect of the COVID-19 pandemic on mental and nutritional health and on the home food environment of the academic community: longitudinal evaluation - PADu-COVID". Currently, UFOP has 11,993 students enrolled in 55 undergraduate courses, 726 technicians (administrative and laboratory technicians) and 934 professors. The study population consisted of all technicians and professors at UFOP.[10]

For this article, only employees (university professors and technicians) were evaluated, and the participants were recruited through a virtual invitation. This constituted convenience sampling, in which all employees were invited by email to participate and the sample consisted of those who answered the questionnaire.

Ethical issues

All potential participants were asked to read and agree to the informed consent statement online before they could participate in the study. A copy of this statement was made available for download. This step was necessary before they could start answering the questionnaire. The PADu-COVID project received ethical approval under number CAAE 31077320.7.1001.5150 on June 28, 2020.

Data collection

The employees' e-mail addresses were obtained through the UFOP Information Technology Center. These e-mail addresses were used with the university's consent. Information about this study was also spread via the university's website, social networks, unions and academic directories that supported the project.

All UFOP employees were invited to participate in the study between July 20 and August 27, 2020, through virtual invitations sent out by email and through social network channels, using snowball sampling. The questionnaire was made available on an online platform (Google Forms) and the invitations were sent out once a week, on alternate days, over a period of one month.

Outcome and explanatory variables

The questionnaire consisted of questions on sociodemographic characteristics, medicine use, mental health, lifestyles and health conditions during the COVID-19 pandemic. The outcome variable of the study was the use of medicines by the employees. The data on this variable was obtained through the question: "In the last 30 days, have you taken any medicine?". The answer options were "no" or "yes". If the response was yes, the participant was asked to report the name of the medicine. Subsequently, the medicines reported were grouped into classes in accordance with the second level of Anatomical Therapeutic Chemical (ATC).[11]

The explanatory variables were the following: age (< 45 years or ≥ 45 years); sex (female or male); sexual orientation (heterosexual, homosexual, bisexual or asexual); housing situation (living alone, with family/relatives, in student housing or with friends); skin color (white; or others: East Asian, brown or black); marital status (single/divorced/widowed, married or common-law marriage); religious belief (no or yes); family income (up to six minimum monthly wages in Brazil or greater than or equal to six minimum monthly wages in Brazil); decreased income due to the pandemic (no, yes or yes, more than 50%); symptoms of anxiety (no or yes), depression (no or yes), stress (no or yes) or suicidal ideation (no or yes), or suicide attempts (no or yes) or social distancing (no or yes); workload (still the same, increased or decreased); alcohol consumption (no or yes) and alcohol consumption since the pandemic started (still the same, increased or decreased); smoking (never smoked, quit smoking or currently smoking); illicit drug use (no or yes); engaging with physical activity (no or yes); body mass index (no excess body weight or excess body weight); and self-rated health (good or poor).

The monetary values for the monthly minimum wage were presented in Brazilian reais, converted into United States dollars (USD) using the purchasing power parity (PPP) method. Thus, the value of 1 USD was equivalent to 2.25 Brazilian reais, according to the conversion rate for the year 2019.[12]

Statistical analyses

The data from the survey questionnaire were automatically stored in a database in the Excel software, 2019 version (Microsoft, Washington, United States) and were coded. Statistical analyses were performed using the STATA 13.0 software (StataCorp LLC, Texas, United States), namely:

1) Descriptive analysis according to frequencies.

2) Bivariate analysis according to Pearson's chi-square and Fisher's exact tests, to determine associations between the outcome of interest, i.e. medicine use stratified according to occupation, and the sociodemographic, mental health, lifestyle and health condition variables during the COVID-19 pandemic. Only the explanatory variables that showed an association with a level of significance of ≤ 0.20 in the bivariate analysis were included in the subsequent multivariate analysis.
3) Multivariate analysis using Poisson regression was carried out to determine the possible factors associated with the use of medicine. For this analysis, a significance level of 0.05 was adopted. In the multiple regression model, the data entry method of backward selection was used, i.e. all the variables selected in the bivariate analysis were inserted at the same time in the model and were removed one-by-one, starting from the least significant. The final model was adjusted for age and sex.

RESULTS

A total of 372 employees participated in the study: 213 university professors and 159 technicians. Most of the participants were younger than 45 years (66.1%), female (56.4%), heterosexual (90.9%), living with their family (76.4%), of self-declared white skin color (59.4%) and married (60.0%); and had a religious belief (71.0%) and a family income greater than or equal to six minimum monthly wages in Brazil (81.4%). In addition, 60.7% of the participants did not experience any decrease in family income during the COVID-19 pandemic (**Table 1**).

Regarding the use of medicines, 53.2% of the employees took some medicine, among whom 2.7% used five or more medicines simultaneously, known as polypharmacy. Furthermore, the professors reported using 183 medicines, of which 37 (20.2%) were prescribed after the onset of the COVID-19 pandemic; the technicians reported using 149 medicines, of which 25 (16.8%) were prescribed after the onset of the pandemic. Psychotropic medicines were the most frequently used medicines, especially after the onset of the pandemic, and antiepileptics (N03), antidepressants (N06) and analgesics (N02) were the most frequently cited pharmacological classes.

Antidepressants were the most widely used medicines. Among the professors and technicians, the prevalences of antidepressant use were 13.7% and 16.8%, respectively. Analgesics were also widely cited by the participants, at a prevalence rate of 9.3% among the professors and 10.1% among the technicians. Among cardiovascular system medicines, the most frequently cited ones were angiotensin II antagonists, at a prevalence of 11.5% among the professors and 10.1% among the technicians. The percentages of medicines used, in accordance with the first and second levels of Anatomical Therapeutic Chemical (ATC), by professors and technicians, are presented in **Figure 1**. Medicines for the nervous and

Table 1. Descriptive analysis on sociodemographic variables, medicine use, mental health conditions and lifestyle habits during the COVID-19 pandemic, among employees of the Universidade Federal de Ouro Preto, Ouro Preto, 2020 (n = 372)

Variables	n	%
Sociodemographic characteristics		
Age		
< 45 years	246	66.1
≥ 45 years	126	33.9
Occupation		
University professor	212	57.0
Technicians	169	43.0
"Gratified" functions		
No	322	86.6
Yes	50	13.4
Sex		
Female	210	56.4
Male	162	43.6
Sexual orientation		
Heterosexual	338	90.9
Homosexual, bisexual, and asexual	34	9.1
Housing situation		
Living alone	57	15.3
With family/relatives	284	76.4
In student housing or with friends	31	8.3
Skin color		
White	221	59.4
Others (East Asian, brown or black)	151	40.6
Marital status		
Single/divorced/widowed	149	40.0
Married or common-law marriage	223	60.0
Religious belief		
No	108	29.0
Yes	264	71.0
Family income		
Up to six minimum monthly wages in Brazil	69	18.6
Greater than or equal to six minimum monthly wages in Brazil	303	81.4
Income decrease due to pandemic		
No	226	60.7
Yes	142	38.2
Yes, more than 50%	4	1.1
Use of medicines		
Were medicines used?		
No	174	46.8
Yes, 1-4	188	50.5
Yes, 5 or more	10	2.7
Cardiovascular medicines		
No	328	88.2
Yes	44	11.8

Continue...

Table 1. Continuation

Variables	n	%
Nervous system medicines		
No	309	83.1
Yes	63	16.9
Mental health		
Symptoms of anxiety		
No	307	82.5
Yes	65	17.5
Symptoms of depression		
No	287	77.2
Yes	85	22.8
Symptoms of stress		
No	288	77.4
Yes	84	22.6
Suicidal ideation		
No	314	84.4
Yes	58	15.6
Suicide attempt		
No	365	98.1
Yes	7	1.9
Lifestyle and health conditions during the COVID-19 pandemic		
Social distancing		
No	22	5.9
Yes	350	94.1
After the start of the pandemic, your workload was:		
Still the same	140	37.6
Increased	79	21.3
Decreased	153	41.1
Alcohol consumption		
No	123	33.1
Yes	249	66.9
After the start of the pandemic, your alcohol consumption was:		
Still the same	160	64.3
Increased	34	13.6
Decreased	55	22.1
Smoking		
No, I never smoked	305	82.0
I quit smoking	39	10.5
I currently smoke	28	7.5
Illicit drug use		
No	356	95.7
Yes	16	4.3
Physical activity		
No	103	27.7
Yes	269	72.3
Body mass index		
No excess body weight	202	54.3
Excess body weight	170	45.7
Self-rated health		
Good SRH	308	82.8
Poor SRH	64	17.2

One Brazilian minimum monthly wage was equivalent to 464.44 United States dollars, when converted according to purchasing power parity (PPP $) in 2019.[12]

Common-law marriage: long-lasting, public affective relationship between two individuals who want to build a family, as acknowledged through the Brazilian Federal Constitution.[13,14]

SRH: self-rated health.

"Gratified" functions are those involving direction, leadership, advisory or secretariat functions, among others, which give rise to additional payments.

cardiovascular systems were the ones most frequently reported by the professors and technicians.

The frequencies of medicine use, stratified according to occupation, in relation to sociodemographic, mental health and lifestyle variables during the COVID-19 pandemic, are shown in **Table 2**.

In the bivariate analysis (**Table 2**), statistically significant differences were observed between university professors who used medicines and the variables of age, suicidal ideation and physical activity. Among the technicians, this association occurred in relation to the variables of age, sex, symptoms of anxiety, alcohol consumption, physical activity, body mass index and self-rated health.

The results from the multivariate analysis for medicine use stratified according to occupation were adjusted for age and sex in order to minimize possible confounding factors (**Table 3**). Among the professors, suicide attempts (prevalence ratio [PR], 1.81; 95% CI, 1.20-2.74), physical activity (PR, 1.53; 95% CI, 1.11-2.11) and poor self-rated health (PR, 1.29; 95% CI, 1.01-1.66) were positively associated with the use of medicines.

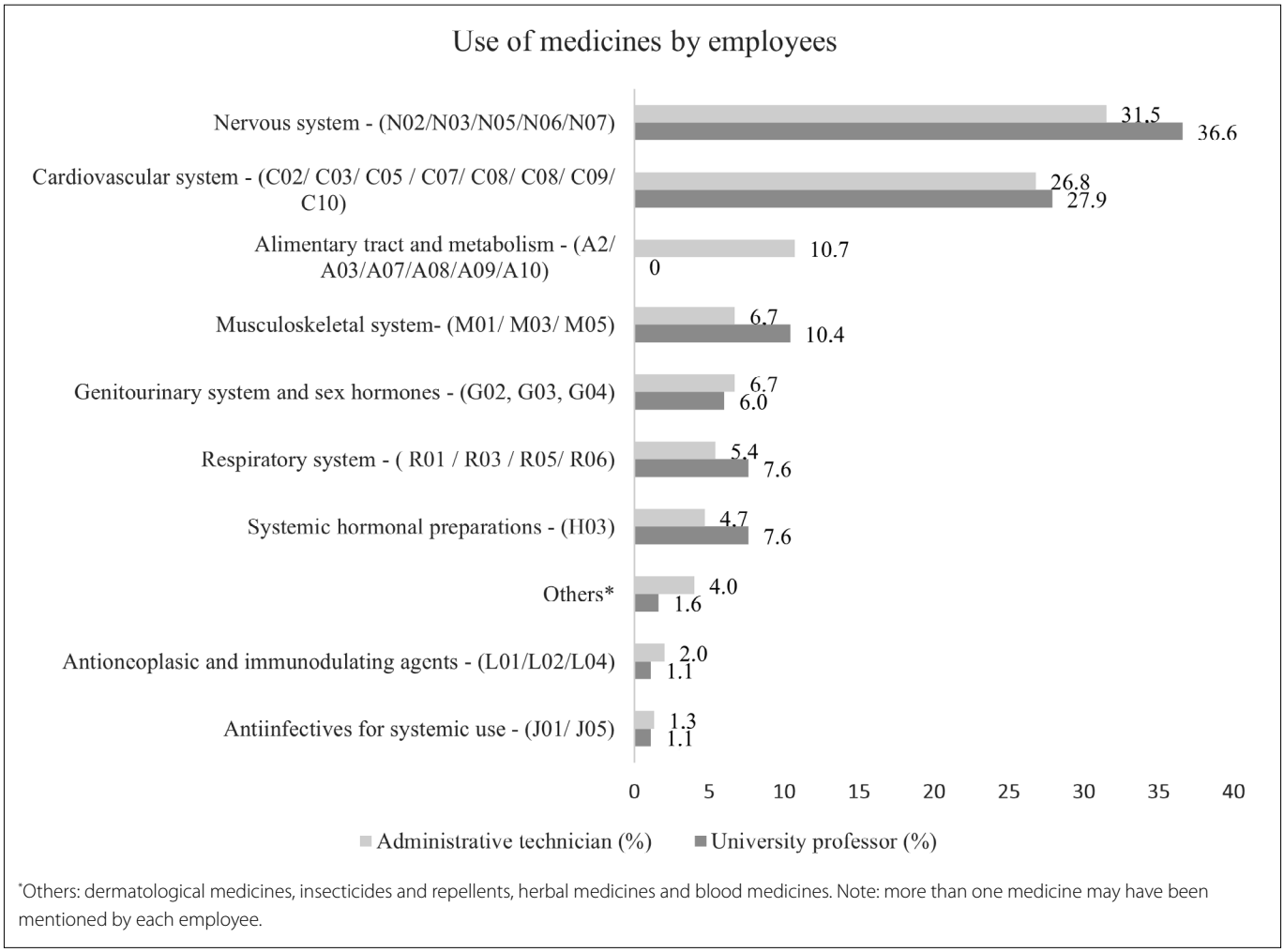
Among the technicians, decreased workload during the COVID-19 pandemic (PR, 1.41; 95% CI, 1.00-1.99), excess body weight (PR, 1.39; 95% CI, 1.02-1.88) and poor self-rated health (PR, 1.48; 95% CI, 1.14–1.92) were associated with increased medicine use. On the other hand, physical activity (PR, 0.60; 95% CI, 0.46-0.78) was negatively associated with medicine use, thus indicating that it was a protective factor against medicine use (**Table 3**).

DISCUSSION

To the best of our knowledge, this was the first study to assess the use of medicines by the employees of a Brazilian public university during the COVID-19 pandemic. Important results were found for this population.

The results showed that there was high prevalence of medicine use among these employees (53.23%). Corroborating our findings, the National Survey on Access, Use and Promotion of Rational Use of Medicines of 2015 (Pesquisa Nacional de Acesso, Utilização e Promoção do Uso Racional de Medicamentos, PNAUM), which investigated the use of medicines in a representative sample of the Brazilian population, found an overall prevalence of medicine use of 50.70%.[15] In addition, other studies on adult populations found similar overall prevalences of medicine use.[16,17] In our study, medicines for the nervous and cardiovascular systems were the ones most cited, as also observed in other studies involving adult populations.[18,19]

de Mesquita Mororó et al. analyzed population-based data from the National Health Survey and found that access to medicines is unequal between the regions of Brazil and that higher education levels are related to increased access.[20] This aspect of education, as a determinant of access to medicines, has also been



*Others: dermatological medicines, insecticides and repellents, herbal medicines and blood medicines. Note: more than one medicine may have been mentioned by each employee.

Figure 1. Prevalence of medicine use among technicians and professors, according to the first and second levels of Anatomical Therapeutic Chemical (ATC).[11]

found in other studies.[21,22] However, despite the fact that access to medicines is linked to their profile of use, the prevalence of medicine use among the population in the present study was similar to that reported in studies involving the adult population in general.

For these university professors and technicians, the prevalence of use of new medicines after the pandemic started was around 31%. Use of psychotropic medicines was frequently reported, with emphasis on antiepileptics, analgesics and antidepressants. High use of medicines for mental health issues is a common response to moments of crisis, such as the COVID-19 pandemic. In a systematic review conducted by Xiong et al. (2020), the negative impacts on the mental health of individuals during this period were highlighted, especially the indications for pharmacological treatment.[23] Thus, the COVID-19 pandemic may have contributed to the beginning of the use of this class of medicines in the UFOP academic community.

Chronic non-communicable diseases, such as hypertension, diabetes mellitus and other comorbidities, are known to be risk factors for the occurrence of severe symptoms of COVID-19.[24-26] In the present study, medicines for the cardiovascular system formed the second most reported class. Use of some cardiovascular medicines, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may be associated with severe COVID-19 infection.[25,27] Mehra et al. (2020) indicated that cardiovascular diseases themselves and not the use of medicines are related to increased mortality among patients hospitalized with COVID-19. Thus, several independent authorities have recommended that the use of these medicines should not be interrupted among patients with COVID-19, considering the absence of robust clinical evidence.[28]

The use of medicines during the pandemic by the professors and technicians was associated with several socioeconomic, mental health, lifestyle and physical health condition characteristics

Table 2. Bivariate analysis on the prevalence of medicine use, stratified according to occupation, in relation to sociodemographic variables, medicine use, mental health conditions and lifestyle habits during the COVID-19 pandemic among employees of the Universidade Federal de Ouro Preto, Ouro Preto, 2020 (n = 372)

Variables	Use of medicines			
	University professor (%)	P	Technicians (%)	P
Sociodemographic characteristics				
Age				
< 45 years	46.6	**< 0.001**	42.6	**0.009**
≥ 45 years	71.9		65.9	
"Gratified" functions				
No	56.3	0.911	46.4	**0.083**
Yes	55.2		66.7	
Sex				
Female	61.3	0.280	62.6	**< 0.001**
Male	50.0		30.9	
Sexual orientation				
Heterosexual	53.6	**0.055***	49.3	0.846
Homosexual, bisexual and asexual	84.2		46.7	
Housing situation				
Living alone	48.3		32.1	
With family/relatives	57.1	0.611*	51.7	**0.123**
In student housing or with friends	64.3		58.8	
Skin color				
White	54.8	0.503	53.3	0.308
Others (East Asian, brown or black)	59.7		45.2	
Marital status				
Single/divorced/widowed	50.7	0.253	47.5	0.693
Married or common-law marriage	59.0		50.6	
Religious belief				
No	52.7	0.435	38.2	**0.155**
Yes	58.3		52.0	
Family income				
Up to six minimum monthly wages in Brazil	60.0	0.619*	45.3	0.438
Greater than or equal to six minimum monthly wages in Brazil	56.2		51.6	
Income decrease due to pandemic				
No	56.6		43.3	
Yes	57.3	0.361*	55.2	**0.091***
Yes, more than 50%	0.0		100.0	
Mental health				
Symptoms of anxiety				
No	54.	**0.103**	44.5	**0.020**
Yes	67.6		67.7	
Symptoms of depression				
No	54.7	0.340	47.0	0.389
Yes	62.8		54.8	
Symptoms of stress				
No	56.5	0.905	45.0	**0.073**
Yes	55.6		61.5	
Suicidal ideation				
No	53.4	**0.049**	50.7	0.303
Yes	71.4		39.1	
Suicide attempt'				
No	55.3	**0.055***	49.0	0.742*
Yes	100.0		50.0	

Continue...

Table 2. Continuation

Variables	Use of medicines			
	University professor (%)	P	Technicians (%)	P
Lifestyle and health conditions during the COVID-19 pandemic				
Social distancing				
No	60.0	0.540*	58.3	0.357*
Yes	56.2		48.3	
After the start of the pandemic, your workload was:				
Still the same	54.0		39.4	
Increased	58.1	0.885	52.1	**0.091**
Decreased	57.4		60.0	
Alcohol consumption				
No	59.1	0.587	59.6	**0.046**
Yes	55.1		43.1	
After the start of the pandemic, your alcohol consumption was:				
Still the same	54.8		46.3	
Increased	70.6	0.307*	35.3	0.661
Decreased	48.6		38.9	
Smoking				
No, I never smoked	56.3		48.8	
I quit smoking	61.5	0.684*	53.8	0.925
I currently smoke	46.1		46.7	
Illicit drug use				
No	56.2	0.540	49.7	0.359*
Yes	60.0		33.3	
Physical activity				
No	41.8	**0.012**	72.9	**< 0.001**
Yes	61.4		38.7	
Body mass index				
No excess body weight	51.7	**0.128**	36.9	**0.001**
Excess body weight	62.1		62.7	
Self-rated health				
Good SRH	53.4	**0.060**	40.9	**< 0.001**
Poor SRH	70.3		88.9	

One Brazilian minimum monthly wage was equivalent to 464.44 United States dollars, when converted according to purchasing power parity (PPP $) in 2019.[12] Common-law marriage: long-lasting, public affective relationship between two individuals who want to build a family, as acknowledged through the Brazilian Federal Constitution.[13,14] SRH: self-rated health.

"Gratified" functions are those involving direction, leadership, advisory or secretariat functions, among others, which give rise to additional payments.

*Value obtained through Fisher's exact test.

Table 3. Multivariate analysis using Poisson regression adjusted for sex and age, according to the occupation of employees of the Universidade Federal de Ouro Preto, Ouro Preto, 2020 (n = 372)

Variables	Use of medicines			
	University professor		Technicians	
	PR (95% CI)	P	PR (95% CI)	P
Suicide attempt				
No	1	0.005	–	–
Yes	1.81 (1.20-2.74)		–	
After the start of the pandemic, your workload was:				
Still the same	–		1	
Increased	–	–	1.19 (0.84 - 1.68)	0.316
Decreased	–		1.41 (1.00 - 1.99)	0.047
Physical activity				
No	1	0.009	1	< 0.001
Yes	1.53 (1.11-2.11)		0.60 (0.46 - 0.78)	
Body mass index				
No excess body weight	–	–	1	0.035
Excess body weight	–		1.39 (1.02-1.88)	
Self-rated health				
Good SRH	1	0.040	1	0.003
Poor SRH	1.29 (1.01-1.66)		1.48 (1.14-1.92)	

SRH = self-rated health; PR = prevalence ratio; 95% CI = 95% confidence interval.

during the COVID-19 pandemic. Among the professors, suicide attempts, physical activity and poor self-rated health were associated with the use of medicines.

Many professors experienced mental illnesses during the COVID-19 pandemic, as they entered an environment of great pressure and had to adapt to new technological and digital resources quickly, while reconciling remote work and personal life in the same environment.[29] Stress in the work environment is associated with occurrence of mental disorders and can be a risk factor for use of antidepressants.[30]

Physical activity was associated with increased use of medicines among the professors. The association between physical activity and increased medicine use may have been influenced by the presence of chronic cardiovascular diseases among the professors and the recommendations to remain active to ensure good quality of life.[31,32]

Poor self-rated health was associated with increased use of medicines among the professors. In a systematic review carried out during the COVID-19 pandemic, Vindegaard and Benros (2020) observed that negative self-assessment of health can lead to an increased risk of psychiatric symptoms or worsening of psychological wellbeing, which consequently leads to use of medicines.[33] In addition, the presence of comorbidities was also associated with negative self-rated health.[34]

For the technicians, the decrease in the workload during the pandemic, excess body weight and poor self-rated health were associated with increased use of medicines, while physical activity was a protective factor against use of medicines. The decrease in the workload, which occurred in the first months of the COVID-19 pandemic, coincided with the period of data collection. This variable was associated with increased use of medicines among the technicians. During this period, the employees had to adapt to a new scenario; they also had to face a loss of daily routines and impaired personal and social contacts. In addition, the pandemic period was accompanied by the emergence of heightened emotions, especially the fear of contracting or transmitting COVID-19. When academic activities were being organized for distance learning, this may have provided some leisure initially, but it eventually led to high levels of stress and anxiety while waiting for new ways of working.[35,36] Consequently, it may have become necessary to start pharmacological treatment in order to minimize psychological damage.

Another factor associated with the use of medicines among technicians was excess body weight. Overweight and obesity are related to the presence of chronic diseases such as cardiovascular diseases.[37,38] As a large percentage of the technicians reported using cardiovascular medicines, this may explain the association between being overweight and use of medicines. Similar to the professors' profile of use, poor self-rated health was associated with increased medicine use among technicians. This relationship can be explained by the fact that, in most cases, the medicine use was directly related to disease conditions, thus resulting in poor self-perception of health.[39,40]

Physical activity was associated with reduced use of medicines among the technicians. It is known that physical activity prevents the onset of numerous diseases and, consequently, it may have been a protective factor. The relationship between engagement with physical activity and good health has been widely described in the literature.[41,42] Good physical and mental health may reduce the need for psychotropic medications.

Although these two classes of employees showed medicine use profiles similar to that of the general population, there were differences in the characteristics associated with the use of medicines, such as the relationship between suicide attempts and use of medicines among the professors and between decreased workload and increased use of medicines among the technicians. Such associations may have been impacted by the COVID-19 pandemic. In order to better understand the profile of medicine use and the differences between these employees, it is necessary to continue the present study in a longitudinal manner.

This study had a cross-sectional design, so the influence of memory bias when reporting medicine use in the last 30 days cannot be ruled out. Data relating to additional occupations such as participation in working groups or postgraduate programs were not collected. In addition, there are many challenges in collecting online data, such as limitations on access to and reliability of the internet network, high non-response rate, selection bias toward those who have access to the internet and familiarity with the platform used for the research. The response rate was 22.6%, which was similar to what is expected for studies involving online surveys.[43,44] Despite these challenges, online studies have proven to be an important alternative for conducting research during the COVID-19 pandemic.[45]

Lastly, this was an innovative study that highlighted the importance of studies involving employees of educational institutions, especially regarding medicine use and health status, risks of intoxication and addiction, masked symptoms and delayed diagnoses.[46,47]

CONCLUSION

The results from this study showed that there was high prevalence of medicine use among the professors and technicians at an important public university in Brazil. Although the population studied had a high level of education, the prevalence of medicine use was similar to that of the general population in Brazil. However, it is worth emphasizing that different factors were associated with medicine use among the university professors and technicians, compared with the adult population in general, such as suicide attempts and decreased workload.

Although studies on medicine use are still very scarce, they are very important for understanding the profile of the active user population, demonstrating the role of medicines as necessary inputs for healthcare actions, rationalizing costs and improving the quality and case resolution capacity of the local healthcare system. Educational institutions should seek to understand the circumstances of their employees and should carry out pharmaceutical counseling with regard to rational use of medicines during and after the COVID-19 pandemic. In addition, studies in which it is sought to understand the effects of the pandemic on medicine use need to be continued, considering that irrational use of medicines can lead to health risks.

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The Brazilian version of the Hip Sports Activity Scale: translation and cross-cultural adaptation

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Questionnaire.
Physical activity.

ABSTRACT

BACKGROUND: The Hip Sports Activity Scale (HSAS) is a reliable and valid tool for determining the levels of sports activities among patients with femoroacetabular impingement (FAI).

OBJECTIVE: To translate and cross-culturally adapt the HSAS to the Brazilian Portuguese language.

DESIGN AND SETTING: This was a cross-sectional study conducted at the State University of Rio de Janeiro.

METHODS: The Brazilian version of the HSAS was developed following a process that comprised six steps: translation, synthesis, back-translation, review by committee, pretesting and submission of documentation to the developers. The translation phase involved three independent bilingual translators whose mother language was Brazilian Portuguese. The back-translation phase involved three independent translators whose mother language was English. In order to verify comprehension of the questionnaire, 30 undergraduate students in physical education (65% men), with mean age 23.2 years (standard deviation = 6.8), participated in the pre-testing phase.

RESULTS: During the translation step, some terms and expressions were changed to obtain cultural equivalence to the original HSAS. In the pre-testing phase, each item of the scale showed a comprehension level of 100%.

CONCLUSION: The HSAS was translated from English to the Brazilian Portuguese language and adapted to Brazilian culture. The HSAS validation is ongoing.

INTRODUCTION

There is growing evidence that femoroacetabular impingement (FAI) plays an important role in the mechanical etiology of the development of hip arthrosis. This abnormal contact between the acetabulum and the femoral neck during hip mobilization, especially during flexion and internal rotation, limits the range of motion.[1,4] Impact can occur in patients who subject their hip to extreme ranges of motion, which can cause compression of the non-spherical extension of the supraphysiological head.[5]

Individuals with FAI complain mainly of chronic pain, with insidious onset, long duration and progressive worsening.[6] Physical exercise generally causes exacerbations. In addition to sports activities, activities of daily living can also be associated with pain: for example, climbing stairs, sitting after a prolonged lying session, moving in bed and getting in and out of a car. The typical patient is a young adult, usually practicing sports that involve hip flexion. Pain can be constant, or intermittent at rest, and can interfere with sleep.[1-7]

Sports activities that require vigorous and repetitive flexion and internal hip rotation, such as ice hockey or football, are often associated with symptomatic FAI. In addition to these, martial arts such as kickboxing, taekwondo and kung-fu, and also speed athletics and hurdles, can be mentioned.

In this context, use of instruments to assess various aspects of health among individuals with different clinical conditions, in the form of questionnaires and scales, has proved to be very promising, based on patients' perceptions of their health status.[8,9]

The Hip Sports Activity Scale (HSAS) is a reliable and valid tool for determining the levels of sports activities among patients who suffer femoroacetabular impingement. The original article was published by Naal et al. in 2013.[10] Their research group has developed and validated a sports activity scale for patients with a diagnosis of femoroacetabular impingement, in English and German. The HSAS is composed of nine different levels of physical activity. It has nine items

scored from 0 to 8, such that 0 represents sedentary individuals and 8 represents high-performance athletes, with no subscales. It has been widely used in English-speaking countries.

Many instruments have been developed in the English language.[11,12] For them to be used in populations with different languages and cultures, it is necessary to follow a set of steps for their translation, cultural adaptation and validation, in order to ensure that the new instrument maintains the characteristics of the original version.[13,14]

OBJECTIVE

The aim of this study was to translate the HSAS from English to the Brazilian Portuguese language and to cross-culturally adapt it to Brazilian culture. Our hypothesis was that the translation to Brazilian Portuguese and the cultural adaptation for use in Brazil would be feasible and acceptable.

METHODS

Type of study

This was a cross-sectional study of quantitative and qualitative nature on the translation and cross-cultural adaptation of a questionnaire, using data obtained between December 2014 and June 2015.

This study was approved by the ethics committee of our institution (number 998.832; date: March 15, 2015) and all subjects signed an informed consent statement. Dr. Florian D. Naal (the first author of the HSAS) gave permission for us to translate and cross-culturally adapt the HSAS to the Brazilian Portuguese language.

Translation and cross-cultural adaptation

To translate and adapt the HSAS, the guidelines suggested by Guillemin et al.[13] and reviewed by Beaton et al.[14] were followed. The process comprised six steps: translation, synthesis, back-translation, review by committee, pretesting and submission of documentation to the developers (**Figure 1**).

Translation (into the Brazilian Portuguese language)

The original English version of the HSAS was translated from English to Brazilian Portuguese by three independent translators (two physiotherapists and one orthopedist) with experience of hip treatment. They were informed about the purpose of the study. Three different Brazilian Portuguese translations were produced: T1, T2 and T3.

Synthesis (of translations produced into the Brazilian Portuguese language)

A multidisciplinary committee composed of two physiotherapists, three orthopedists and two physical educators was formed to evaluate these three initial Brazilian Portuguese translations (T1, T2

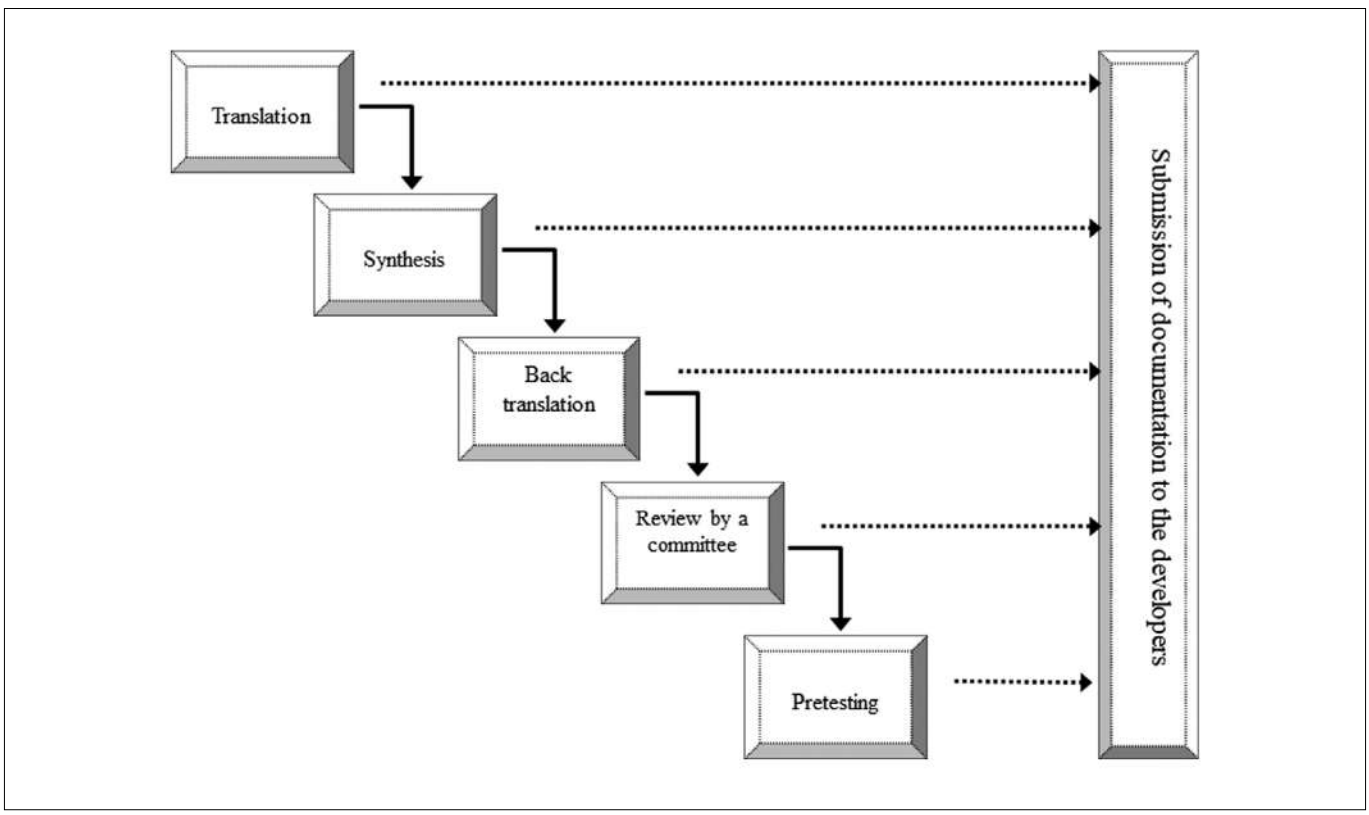

Figure 1. Steps of translation and cross-cultural adaptation according to the guidelines of Guillemin et al. and Beaton et al.: translation, synthesis, back-translation, review by a committee, pretesting and submission of documentation to the developers.[13,14]

and T3) that were produced in the translation step. Possible distortions and their applicability were analyzed. A synthesis (S1) of these three Brazilian Portuguese translations was produced.

Back-translation (into the English language)

This Brazilian Portuguese synthesis (S1) was then back-translated into English by three independent translators who were unaware of the purpose of the translation. Three different back-translations into English were produced: BT1, BT2 and BT3.

Review by a committee (revised translation into the Brazilian Portuguese language)

The multidisciplinary committee that had been formed for back-translation reviewed these three back-translations into English (BT1, BT2 and BT3), in comparison with the original HSAS in English, and a revised translation into the Brazilian Portuguese language (RT) was developed. During this step, this committee verified the semantic, idiomatic, cultural and conceptual equivalences, in order to carry out the process of cultural adaptation for Brazil.

Pretesting (cultural equivalence)

The objective of this step was to assess situations, issues or terms that were not well understood. Thirty undergraduate students of physical education gave responses to the revised translation (RT) that had been produced in the review by the committee. No instructions to indicate whether there was an unknown term or sport, or to suggest sports that were not present on the scale, were given to the participants. We found that there were no questions with an incomprehension rate of more than 15%, and the students did not consider any of the questions to be not applicable. Based on these results, this revised translation (RT) was considered to be the final translation of HSAS.

Submission of documentation to the developers

The last step of the adaptation process was to send all the reports and forms to the developers of the translated version of the instrument.

RESULTS

The sociodemographic characteristics of the 30 participants are shown in **Table 1**. Sixty-five percent of the volunteers were male, aged between 18 and 45 years, and 100% had completed high school education.

Table 2 shows the changes made through verifying the semantic, idiomatic, cultural and conceptual equivalences, in order to carry out the cultural adaptation of the HSAS for use in Brazil.

After these changes had been made by the multidisciplinary committee (at the step of review by a committee), the revised translation into Brazilian Portuguese language (RT) was produced.

In the pretesting, thirty volunteers, undergraduate students of physical education, gave responses to the RT. The results showed that there were no questions with an incomprehension rate of more than 15%, and the students did not consider any of the questions to be not applicable. From this result, our assessment was that the RT of the HSAS was well understood. Thus, the RT was considered to be the final translation of the HSAS, i.e. the HSAS-Brazil.

The original HSAS and the HSAS-Brazil adaptations are shown in **Box 1**. The HSAS-Brazil scale is available for download in **Annex 1**.

DISCUSSION

The HSAS was translated into the Brazilian Portuguese language and was cross-culturally adapted into Brazilian culture, thus confirming our hypothesis that adaptation of this scale for use in Brazil was indeed feasible and acceptable.

Guillemin et al.[13] and Beaton et al.[14] suggested in their guidelines that at least two translations of the original questionnaire or scale into the target language should be produced. In our study, we chose to perform three translations into Brazilian Portuguese language (T1, T2 and T3) and, consequently, three back-translations into English (BT1, BT2 and BT3) were produced. In the cross-cultural adaptations of the Harris Hip Score (HHS),[15] the International Knee Documentation Committee (IKDC),[16] the Nonarthritic Hip Score (NAHS)[17] and the Hip Outcome Score (HOS)[18] questionnaires, only two translations and two back-translations were performed for each of them. We believe that these three translations

Table 1. Sociodemographic data on the thirty volunteers for pretesting

Volunteers for pretesting		
Gender	Female	20
	Male	10
Age (years)	Mean (standard deviation)	23.2 (6.8)
Marital status	Married	2
	Single	28
Education	High school not completed	0
	High school completed	30

Table 2. Modifications made to the Hip Sports Activity Scale (HSAS) within the cross-cultural adaptation for Brazil

Original HSAS	Modified to
Ice hockey and field hockey	Hockey
Snowboarding	Wakeboarding
Skiing	Surfing
Lacrosse	Removed
Cross-country skiing/Biathlon	
Cricket	
Racketball	
Badminton	

Box 1. The original Hip Sports Activity Scale (HSAS) and the Brazilian version (HSAS-Brazil)

Hip Sports Activity Scale (HSAS – English version)	**Escala de Atividade Esportiva do Quadril (HSAS-Brasil)**
Please mark in the following list your current highest level of sports or recreational activity.	**Por favor, marque na lista a seguir o mais alto nível de atividade esportiva ou recreacional atual que você consegue realizar.**
8. Competitive Sports ***(elite level)*** Soccer, Ice hockey, Field hockey, American football/Rugby, Martial arts, Tennis, Track-and-field, Indoor sports*, Beach-Volleyball, Lacrosse, Baseball/Softball	**8. Esportes de Competição** ***(nível elite)*** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol
7. Competitive Sports ***(elite level)*** Downhill skiing, Snowboarding **Competitive Sports** ***(minor leagues/collegiate)*** Soccer, Ice hockey, Field hockey, American football /Rugby, Martial arts, Tennis, Track-and-field, Indoor sports*, Beach-Volleyball, Lacrosse, Baseball/Softball	**7. Esportes de Competição** ***(nível elite)*** Surfe, Wakeboard **Esportes de Competição** ***(ligas menores/estudantil)*** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol
6. Competitive Sports ***(elite level)*** Golf, Bicycle racing, Mountain biking, Swimming, Rowing, Cross-country skiing/Biathlon, Horseback riding, Cricket **Competitive Sports** ***(minor leagues/collegiate)*** Downhill skiing, Snowboarding	**6. Esportes de Competição** ***(nível elite)*** Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo **Esportes de Competição** ***(ligas menores/estudantil)*** Surfe, Wakeboard
5. Competitive Sports ***(minor leagues/collegiate)*** Golf, Bicycle racing, Mountain biking, Swimming, Rowing, Cross-country skiing/Biathlon, Horseback riding, Cricket **Recreational Sports** Soccer, Ice hockey, Field hockey, American football/Rugby, Martial arts, Track-and-field, Beach-Volleyball, Lacrosse	**5. Esportes de Competição** ***(ligas menores/estudantil)*** Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo **Esportes Recreativos** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Vôlei de praia
4. Recreational Sports Tennis, Downhill skiing, Snowboarding, Indoor sports*, Baseball/Softball	**4. Esportes Recreativos** Tênis, Surfe, Wakeboard, Esportes de quadra*, Beisebol/Softbol
3. Recreational Sports Aerobics, Jogging, Lower extremity weight-training, Horseback riding, Cricket	**3. Esportes Recreativos** Ginástica aeróbica, Corrida, Musculação para membros inferiores, Hipismo
2. Recreational Sports *Golf, Bicycle racing, Mountain biking, Swimming, Rowing, Cross-country skiing/Biathlon, Dancing, Inline skating*	*2. Esportes Recreativos* *Golfe, Ciclismo, Mountain bike, Natação, Remo, Dança, Patinação*
1. Recreational Sports Swimming, Cycling, Hiking, Nordic walking (quick walking with ski-poles)	**1. Esportes Recreativos** Natação, Andar de bicicleta, Caminhada em trilhas, Caminhada em alta velocidade.
0. No Recreational or Competitive Sports	**0. Nenhum Esporte Recreativo ou de Competição**
***Indoor Sports:** Basketball, Squash, Racketball, Handball, Badminton, Volleyball **Please indicate your preferred sport:** _____.	***Esportes de Quadra:** Basquete, Squash, Handebol, Vôlei **Por favor, indique seu esporte preferido:** _____.

and three back-translations carried out by our group helped to produce a more careful and refined version of the HSAS-Brazil.

Questionnaires and scales developed in a foreign language need a careful cross-cultural adaptation process in order to allow them to be used in another sociocultural reality.[13] The aim of the cross-cultural adaptation is to ensure consistency in content validity between the versions of the questionnaire (original language and target language). Subtle differences in life habits between different cultures can make an item on a questionnaire or scale more or less difficult to understand, thus changing the psychometric and statistical properties of the instrument.[14] In our study, we decided to change the structure of the original instrument as little as possible: the changes made were extremely necessary for the process of adapting the HSAS to Brazilian culture.

"Ice hockey" and "field hockey" were considered to be "hockey" without discrimination between ice hockey and field hockey, since Brazilians do not usually practice ice hockey. As Brazilians are not used to "Nordic walking", it was switched to "walking at high speed". "Downhill skiing" and "snowboarding" were replaced by "surfing" and "wakeboarding", water sports that are relatively

popular in Brazil and because the skiing body movement is similar to that performed in surfing. In the cultural adaptation of the IKDC questionnaire, Metsavaht et al.[16] also changed "skiing" to "surfing" because of the popularity of this sport in Brazil and the similarity of the stress applied to the knees while practicing these two sports activities.

"Cross-country skiing" and "cricket" were suppressed as they are not practiced in Brazil and because it was not possible to find an equivalent sport for them. "Biathlon" was also suppressed because it is included in cycling and swimming. "Badminton" was suppressed because it is not popular in Brazil; and, lastly, "racketball" was also suppressed because Brazilians seem to consider that this is the same as "squash".

These changes were approved by the main author of the HSAS and these adaptations for the Brazilian version (HSAS-Brazil) are shown in **Box 1**.

In the pretesting, thirty volunteers who were undergraduate students of physical education gave responses to the revised HSAS translation into Portuguese (RT), so that we could assess comprehension of the scale and the semantic, idiomatic, cultural and conceptual equivalences. It was observed that other cultural adaptation studies also applied pretesting to a similar number of patients. Oliveira et al.[18] applied pretesting of the HOS questionnaire to 30 patients with hip pain without arthrosis. Guimarães et al.[15] administered pretesting of the HHS questionnaire to 30 patients with hip disorders. Del Castillo et al.[17] performed pretesting of the NAHS questionnaire among 10 patients with hip pain and 20 healthy adults without hip pain.

One limitation of this study may have been the fact that the group of individuals who underwent the pretesting did not correspond to the target population of the scale, i.e. patients suffering from femoroacetabular impingement. However, for most questionnaires, the translations were not culturally adapted among individuals in their target population.[13] Another limitation may have been the fact that the pretesting group was formed by undergraduate students, which does not reflect the general level of education of the Brazilian population. According to the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE), half of all Brazilians have only attended school up to completion of elementary school.[19]

The strength of this study was its use of this tool to determine the levels of physical and sports activity, which is essential for evaluating younger patients, who tend to be physically very active. Their level of physical activity and participation in sports activities is an important prognostic factor. In addition, the pre-existing level may be directly related to the expectations desired by the patient. In this way, the HSAS contributes to filling the gap that existed among the questionnaires and scales for assessing the physically active population that suffers from femoroacetabular impingement.

CONCLUSION

The Hip Sports Activity Scale was translated into the Brazilian Portuguese language and adapted to Brazilian culture. Our hypothesis that use of this scale in the Brazilian Portuguese language and Brazilian culture would be feasible and acceptable was found to be true. The validation process on the Hip Sports Activity Scale in Brazil is ongoing.

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Annex 1. The Brazilian version of the Hip Sports Activity Scale, HSAS-Brasil (Escala de Atividade Esportiva do Quadril).

ESCALA DE ATIVIDADE ESPORTIVA DO QUADRIL (HSAS-BRASIL) **Por favor, marque na lista a seguir o mais alto nível de atividade esportiva ou recreacional atual que você consegue realizar.**
8. Esportes de Competição *(nível elite)* Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol.
7. Esportes de Competição *(nível elite)* Surfe, Wakeboard. **Esportes de Competição *(ligas menores/estudantil)*** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol.
6. Esportes de Competição *(nível elite)* Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo. **Esportes de Competição *(ligas menores/estudantil)*** Surfe, Wakeboard.
5. Esportes de Competição *(ligas menores/estudantil)* Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo. **Esportes Recreativos** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Vôlei de praia.
4. Esportes Recreativos Tênis, Surfe, Wakeboard, Esportes de quadra*, Beisebol/Softbol.
3. Esportes Recreativos Ginástica aeróbica, Corrida, Musculação para membros inferiores, Hipismo.
2. Esportes Recreativos Golfe, Ciclismo, Mountain bike, Natação, Remo, Dança, Patinação.
1. Esportes Recreativos Natação, Andar de bicicleta, Caminhada em trilhas, Caminhada em alta velocidade.
0. Nenhum Esporte Recreativo ou de Competição
***Esportes de Quadra:** Basquete, Squash, Handebol, Vôlei. **Por favor, indique seu esporte preferido:_____.**

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Temporal trend analysis of hospitalizations and in-hospital deaths due to female breast cancer in the state of Alagoas from 2009 to 2019: a cross-sectional study

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Breast neoplasms.
Epidemiology.
Hospitalization.
Public health.

AUTHORS' KEY WORDS:
Health.
Breast cancer.
Analysis.

ABSTRACT

BACKGROUND: Breast cancer is a common neoplasm in women worldwide. Its varying patterns of incidence and clinical prognosis in Brazil make it an important and complex public health problem that needs to be solved.

OBJECTIVES: To analyze the temporal dynamics of hospital admissions and deaths due to female breast cancer in the state of Alagoas, Brazil, from 2009 to 2019.

DESIGN AND SETTING: Cross-sectional study including secondary data from hospital admissions and deaths due to female breast cancer in Alagoas.

METHODS: A joinpoint regression model was constructed for temporal analysis of hospital admissions and deaths due to female breast cancer in Alagoas, over this period. The hospital information system of the Department of Informatics of the National Health System was used.

RESULTS: There were 5,801 hospitalizations and 633 hospital deaths due to neoplasm in Alagoas over the period. The age group from 50 to 59 years old stood out, corresponding to 28.1% of hospitalizations and 31.1% of registered deaths. An increasing trend in the rate of hospital admissions was observed (average annual percentage change, AAPC = 14.0; P-value < 0.001), from 14.9/100,000 inhabitants in 2009 to 53.6 in 2019. There was a growth trend in the in-hospital mortality rate (AAPC = 19.8; P-value < 0.001), from 6.3% in 2009 to 11.0% in 2019.

CONCLUSION: The results indicated an increasing trend of hospital admissions and mortality rates in the state of Alagoas, with a higher percentage of hospitalizations and deaths in the 50-59 age group.

INTRODUCTION

Breast cancer is the most common malignant neoplasm among women in most parts of the world. In 2018, the estimated number of new cases diagnosed was 2.1 million, and there were 627,000 deaths due to this disease. In this context, Latin America and the Caribbean are gaining prominence among the places with the highest average incidence rates, with rates of 40 cases per 100,000 women.[1]

A similar scenario is observed in Brazil, in which approximately 59,700 new cases of female breast cancer were registered in 2018. This corresponds to an incidence rate of 56.3 cases per 100,000 women. Disregarding non-melanoma skin tumors, breast cancer corresponds to 29.5% of all malignant tumors estimated for Brazilian women.[2] For this reason, breast cancer is an important and complex public health problem that needs to be solved, given its varying patterns of incidence and clinical evolution.[3,4]

In Brazil, there are differences in the incidence of breast cancer between the country's geographical regions: 73.1/100,000 in the south, 69.5/100,000 in the southeast, 52.0/100,000 in the center-west, 40.4/100,000 in the northeast and 19.2/100,000 in the north.[3] It is likely that the higher rates that are observed in the southeastern and southern regions may be influenced by the higher levels of oncological care infrastructure and disease diagnosis rates in these regions, considering that they have 66% of the chemotherapy rooms and 72% of the radiotherapy equipment.[5] In addition, risk factors such as smoking are seen more frequently in the populations of these regions.[6]

Although the northeastern region ranks fourth in incidence rates, the projections point to a higher growth rate than in other regions.[5] It is the second region in absolute numbers of hospital admissions for female breast cancer, with 14,512 cases (21.3%) in 2019, and has the same position in relation to the number of deaths due to female breast cancer, accounting for 3,807 deaths (21.6%) in 2018.[5,7] In 2020, 13,190 new cases of breast cancer are expected in the northeast, with an estimated risk of 44.29 cases per 100,000 women.[8]

In the state of Alagoas, there were 620 new cases of breast cancer among women in the year 2020, with a crude incidence rate of 35.2 per 100,000 inhabitants.[9] According to projections and indicators for 2030, among the states of the northeastern region, Alagoas is expected to present the fourth largest growth in the mortality rate and to have the third largest increase in this rate.[10]

OBJECTIVE

The aim of this study was to analyze the dynamics of hospital admissions and deaths due to female breast cancer in the state of Alagoas over the period from 2009 to 2019.

METHODS

Study design, population and period

This was a cross-sectional study on hospital admissions and deaths due to malignant female breast cancer in the state of Alagoas, over the period from 2009 to 2019. In this study, the year 2020 was not included, considering the possible influence of the coronavirus disease-19 (COVID-19) pandemic on the numbers of hospitalizations and deaths.

Study setting

This study was carried out in the state of Alagoas, which is located in the northeastern region of Brazil. This state had an estimated population of 3.36 million inhabitants in 2020, among whom the female resident population accounted for 51.5% (n = 1,646,684), with the following age distribution: < 20 years (38.2%, n = 629,638); 20-29 years (17.8%, n = 294,415); 30-39 years (14.8%, n = 244,117); 40-49 years (11.5%, n = 189.799); 50-59 years (8.1%, n = 133.660); 60-69 years (2.1%, n = 85.424); 70-79 years (2.8%, n = 46.754); and 80 years and over (1.3%, n = 22,867).[11] The state presents a human development index (HDI) of 0.631, which is lower than the national average (HDI 0.699). Its per capita income is R$ 731.0 and 47.2% of the population live in poverty or extreme poverty.[11]

For this study, the 102 municipalities in the state of Alagoas were classified as geographic units for spatial analysis. Among these municipalities that were analyzed, those with the 10 highest rates of hospital admissions and in-hospital mortality were selected to form the results from the present study.

Variables, data source and data collection

The following variables were evaluated: age group (< 20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years); number of hospitalizations; hospital deaths per residence, hospitalization rate per 100,000 inhabitants; and in-hospital mortality rate (%). The following criteria were considered with regard to data collection: Alagoas as a unit of the federation; female gender; periods of hospitalization between 2009 and 2019 and International Classification of Diseases 10th edition (ICD-10) code C50, which refers to malignant breast neoplasm.

Data on hospital admissions and deaths were obtained from the hospital information system of the Department of Informatics of the National Health System (DATASUS). Population data relating to the female population according to municipality were obtained from the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE), based on information from the 2010 census and inter-census projections for the other years of the time series. In-hospital mortality data were obtained directly from the DATASUS platform. The following equation was used to calculate the hospitalization rate: [(No. of hospital admissions (2009-2019) due to female breast cancer in the place)/(female population in the place and period)] x 100,000.

Statistical analyses

A joinpoint regression model was constructed for temporal analysis. This model checks whether a line with several segments (with several joinpoints) is more suitable for explaining the temporal evolution of the data, compared with a straight line or a line with fewer segments.[12] The trends were classified as stationary, increasing or decreasing, according to the slope of the regression line. In addition, the annual percentage variation (APC) and the average annual percentage variation (AAPC) were calculated, with 95% confidence intervals (95% CI). The statistical significance level was set at 5%. The trends were defined as follows: i) increasing, when the APC or AAPC was significantly positive; ii) decreasing, when the APC or AAPC was significantly negative; or iii) stationary, when there was no significance in these variations. For this analysis, the Joinpoint Regression software, version 4.5.0.1, was used (National Cancer Institute, Bethesda, Maryland, United States). The QGis software, version 2.8.7 (Open Source Geospatial Foundation [OS Geo], Beaverton, Oregon, United States), was used to make choropleth maps for trend analysis.

Ethical issues

This research was approved by the Research Ethics Committee of the Universidade Federal de Alagoas, through opinion report no. 3.775,018, on December 16, 2019.

RESULTS

Between 2009 and 2019, 5,801 hospital admissions were reported in the state of Alagoas (accumulated hospitalization rate for the period equal to 35.2/100,000 inhabitants). In the temporal analysis on hospitalization numbers, using the joinpoint regression model, an increasing trend was observed in the state (AAPC = 14.0; 95% CI = 12.3 to 15.8; P-value < 0.001), for which the rate went from 14.9/100,000 inhabitants (n = 239) in 2009 to 53.6 per 100,000 (n = 863) in 2019 (**Figure 1A**).

A total of 633 hospital deaths were recorded and the in-hospital mortality rate for the period was 11.7%. Regarding the time trend analysis, Alagoas showed a growth trend for female breast cancer (AAPC = 5.0; 95% CI = 0.5 to 9.7; P-value < 0.001), increasing from 6.3% (n = 15) in 2009 to 11.0% (n = 95) in 2019, with temporal inflection in 2012, after which stationary behavior was observed (**Figure 1B**).

Analysis on hospital admissions

Regarding the age groups of hospitalizations, 28.1% of the cases (n = 1,627) were among women between 50 and 59 years old, and the lowest percentage was among women under 20 years old (0.8%, n = 47). Among women under 20 years old, there was a declining trend (AAPC = -13.6; 95% CI = - 17.7 to -9.2; P-value < 0.001), whereas for those between 20 and 29 years old there was

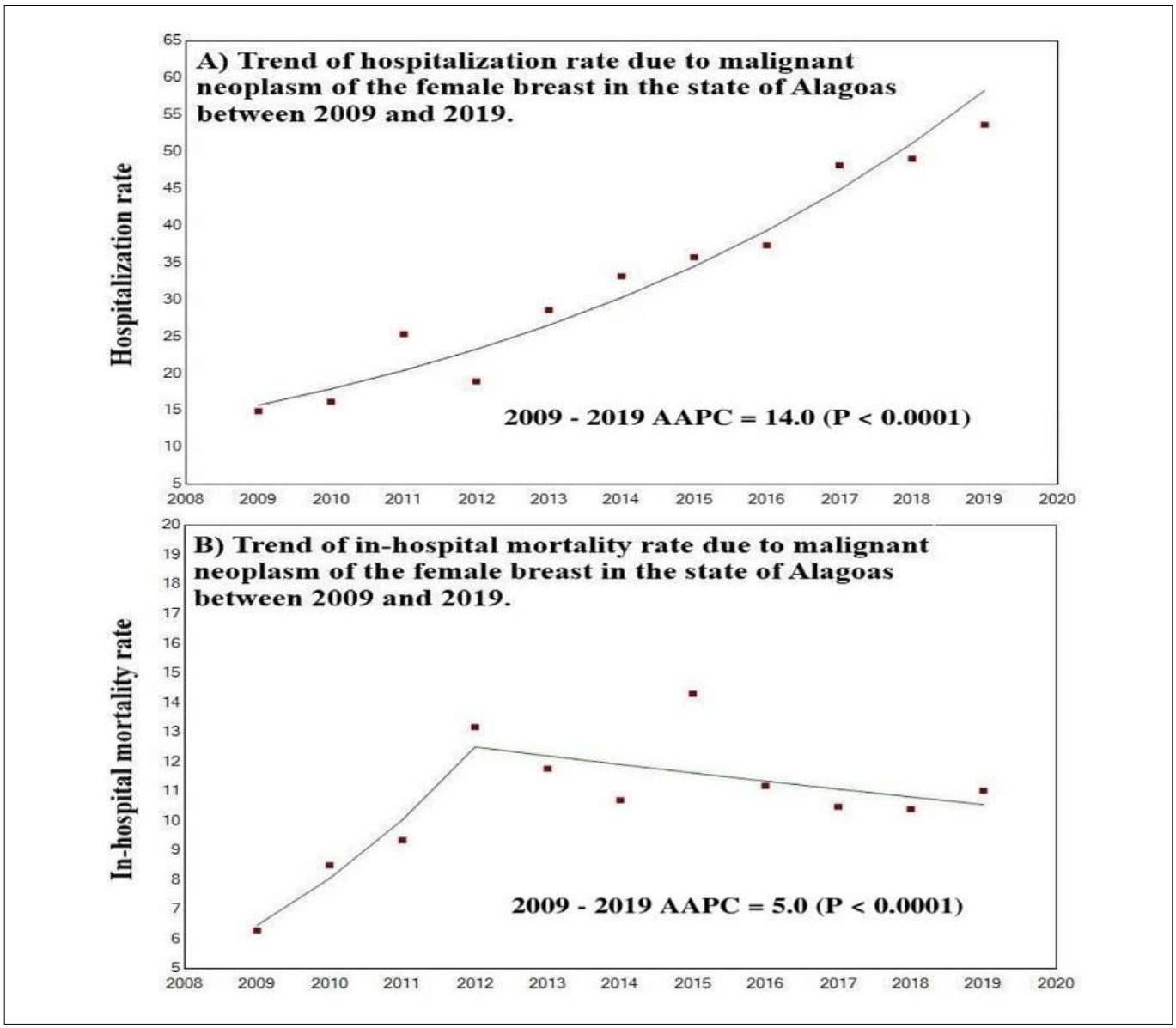

Figure 1. Temporal trend of hospitalization and in-hospital mortality rates due to female breast cancer in the state of Alagoas from 2009 to 2019. Brazil, 2021.

a tendency towards stability (AAPC = 4.7; 95% CI = - 1.6 to 11.3; p-value = 0.1) and for the other age groups (30-39, 40-49, 50-59, 60-69, 70-79 and ≥ 80 years) there was a growth trend, especially among those between 70 and 79 years old (AAPC = 19.0; 95% CI = 15.4 to 22.8; P-value < 0.001) (**Table 1A**).

We observed that most hospitalizations due to breast cancer (60.2%) occurred in 10 of the 102 municipalities of Alagoas, especially in Maceió (n = 2,440), Arapiraca (n = 737) and Palmeira dos Índios (n = 162); and, in relation to the average rate over the period, in Arapiraca (65.7), Major Isidoro (49.9) and Maceió (49.3). Among these municipalities, eight presented an increasing trend, especially the municipality of Olho d'Água Grande (AAPC = 211.4; 95% CI = 105.1 to 372.8; P-value < 0.001). Barra de Santo Antônio and São Miguel dos Milagres showed parallel stationary temporal behavior (**Table 1B**).

Among all the 102 municipalities in Alagoas, there was an increasing trend of hospitalizations in 39.2% (n = 40), particularly in Monteirópolis (AAPC = 212.8; 95% CI = 124.2 to 336.3; P-value < 0.001), Belo Monte (AAPC = 212.2; 95% CI = 212.2 to 212.2; P-value < 0.001) and Olho d'Água Grande (AAPC = 211.4; 95% CI = 105, 1 to 372.8; P-value < 0.001), which provided the three largest percentage changes over the period (**Figure 2A**).

Four municipalities (3.9%) showed decreasing trends of hospitalizations. These were Olivença (AAPC = -50.6; 95% CI = - 70.5 to

Table 1. Temporal trend of hospitalizations due to malignant neoplasm of the female breast in the state of Alagoas and in the 10 municipalities with the highest rates of hospitalizations over the period from 2009 to 2019 and according to the age group. Brazil, 2021

A) Temporal trend of hospitalizations due to malignant neoplasm of the female breast according to age group											
			Trend 1			**Trend 2**			**Total period**		
Age group	**Number of hospitalizations (%)**	**Hospitalization rate over the period/100,000 inhabitants**	**Period**	**APC**	**95% CI**	**Period**	**APC**	**95% CI**	**AAPC**	**95% CI**	**P-value**
< 20 years	47 (0.8)	0.7	-	-	-	-	-	-	-13.6*	[-17.7 to -9.2]	< 0.001
20-29 years	117 (2.0)	4.0	-	-	-	-	-	-	4.7	[-1.6 to 11.3]	0.1
30-39 years	694 (12.0)	28.4	-	-		-	-	-	11.6*	[7.5 to 15.8]	< 0.001
40-49 years	1509 (26.0)	79.5	-	-	-	-	-	-	14.3*	[11.6 to 17.0]	< 0.001
50-59 years	1627 (28.1)	121.7	-	-	-	-	-	-	15.7*	[13.2 to 18.4]	< 0.001
60-69 years	1062 (18.3)	124.3	-	-	-	-	-	-	13.6*	[11.2 to 16.1]	< 0.001
70-79 years	551 (9.5)	117.8	-	-	-	-	-	-	19.0*	[15.4 to 22.8]	< 0.001
≥ 80 years	194 (3.3)	84.8	-	-	-	-	-	-	17.7*	[13.4 to 22.1]	< 0.001
B) Temporal trend of hospitalizations due to malignant neoplasm of the female breast in the state and in the 10 municipalities of Alagoas that presented the highest rates of this variable											
			Trend 1			**Trend 2**			**Total period**		
State/ Municipality	**Number of hospitalizations (%)**	**Hospitalization rate over the period/100,000 inhabitants**	**Period**	**APC**	**95% CI**	**Period**	**APC**	**95% CI**	**AAPC**	**95% CI**	**P-value**
State of Alagoas	5801 (100)	36.1	-	-	-	-	-	-	14.0*	[12.3 to 15.8]	< 0.001
Arapiraca	737 (12.7)	65.7	-	-	-	-	-	-	13.3*	[10.6 to 16.1]	< 0.001
Major Isidoro	48 (0.8)	49.9	-	-	-	-	-	-	15.8*	[6.2 to 26.2]	< 0.001
Maceió	2444 (42.1)	49.3	-	-	-	-	-	-	12.7*	[9.8 to 15.6]	< 0.001
Jaramataia	13 (0.2)	47.2	-	-	-	-	-	-	137.7*	[44.4 to 291.3]	< 0.001
Barra de São Miguel	17 (0.3)	44.6	-	-	-	-	-	-	160.7*	[32.2 to 413.9]	< 0.001
São Miguel dos Milagres	16 (0.3)	44.4	-	-	-	-	-	-	-15.8	[-59.3 to 74.4]	0.6
Olho d'Água Grande	11 (0.2)	44.1	-	-	-	-	-	-	211.4*	[105.1 to 372.8]	< 0.001
Palmeira dos Índios	162 (2.8)	44.0	2009-2011	128.3	[-22.9 to 576.1]	2011-2019	4.4	[-0.9 to 9.9]	22.1*	[2.3 to 45.7]	< 0.001
Barra de Santo Antônio	31 (0.5)	43.3	-	-	-	-	-	-	42.2	[-0.1 to 102.4]	0.1
Paulo Jacinto	16 (0.3)	42.2	-	-	-	-	-	-	151.0*	[31.3 to 379.9]	< 0.001

No joinpoint was observed in this indicator; *Statistically significant P < 0.05. APC = annual percentage change; CI = confidence interval; AAPC: average annual percentage change.

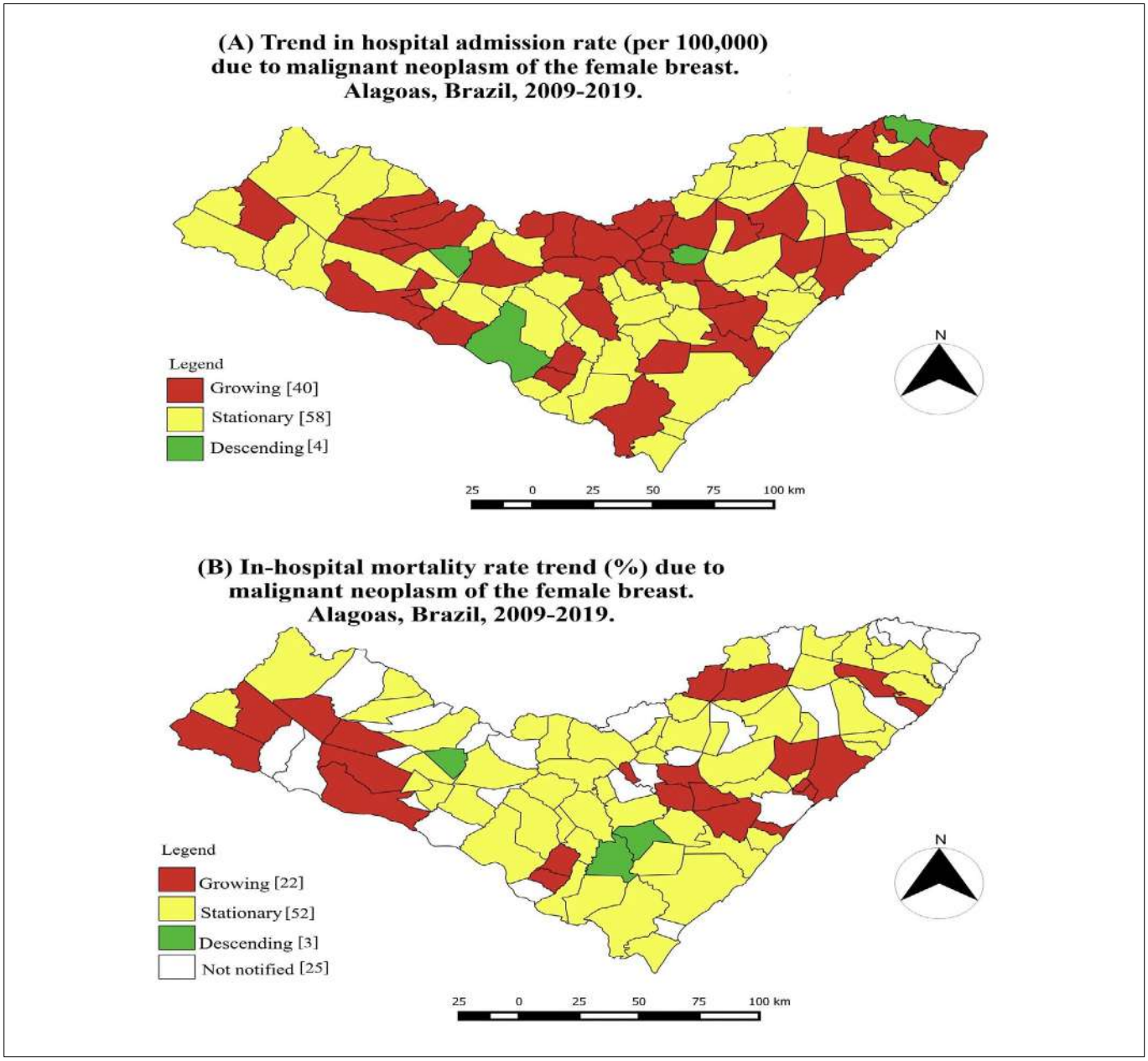

Figure 2. Distribution of the trends in hospital admission rate (per 100,000 inhabitants) and in-hospital mortality rate (%) due to female breast cancer in the municipalities of the state of Alagoas in the period from 2009 to 2019. Brazil, 2021.

-17.3; P-value < 0.001), Jacuípe (AAPC = -43.2; 95% CI = - 57.2 to -24.7; P-value < 0.001), Pindoba (AAPC = -25.8; 95% CI = - 25.8 to -25.8; P-value < 0.001) and Traipu (AAPC = -17.6; 95% CI = -28.6 to -5.0; P-value < 0.001), which are located, respectively, in the metropolitan areas of Médio Sertão, Zona da Mata, Vale do Paraíba and Agreste (**Figure 2A**).

In-hospital mortality analysis

Regarding age groups, 31.1% of hospital deaths (n = 197) occurred among women between 50 and 59 years old. Among people under 20 years old, no deaths were recorded. In the age groups of 20-29, 40-49, 50-59, 60-69 and 70-79 years, there was a tendency towards stability. The age group from 30 to 39 years old showed a growth trend between 2009 and 2011, and from 2011 onwards, it showed a pattern of stability. In considering the complete time series, growth was observed (AAPC = 58.9; 95% CI = 12.1 to 125.2; P-value < 0.001) (**Table 2A**).

In the age group from 40 to 49 years, there was a temporal inflection in 2012, going from a growth trend (AAPC = 29.5; 95% CI = 6.1 to 58.0; P-value < 0.001) to a trend of decline (AAPC = -4.6;

Table 2. Temporal trend of in-hospital mortality due to malignant neoplasm of the female breast in the state of Alagoas and in the 10 municipalities with the highest rates of this variable in the period from 2009 to 2019 and according to the age group. Brazil, 2021

A) Temporal trend of in-hospital mortality due to malignant neoplasm of the female breast according to age group														
			Trend 1			Trend 2			Trend 3			Total Period		
Age group	Number of hospital deaths (%)	In-hospital mortality rate over the period (%)	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	AAPC	95% CI	P-value
> 20 years	0													
20-29 years	8 (1.3)	6.1	-	-	-	-	-	-	-	-	-	40.4	[-35.9 to 207.6]	0.4
30-39 years	59 (9.3)	9.8	2009-2011	1204.9*	[57.5 to 10712.6]	2011-2019	-6.2	[-17.5 to 6.8]	-	-	-	58.9*	[12.1 to 125.2]	< 0.001
40-49 years	138 (21.8)	10.8	2009-2012	29.5*	[6.1 to 58.0]	2012-2019	-4.6*	[-8.8 to -0.3]	-	-	-	4.5	[-1.0 to 10.3]	0.1
50-59 years	197 (31.1)	14.6	-	-	-	-	-	-	-	-	-	1.7	[-2.4 to 6.0]	0.4
60-69 years	126 (19.9)	13.7	-	-	-	-	-	-	-	-	-	4.9	[-1.5 to 11.8]	0.1
70-79 years	70 (11.1)	16.0	-	-	-	-	-	-	-	-	-	-3.2	[-7.8 to 1.6]	0.2
≥ 80 years	35 (5.5)	17.7	2009-2011	9522.3	[-52.1 to 1930910.6]	2011-2019	0.5	[-26.4 to 37.3]	-	-	-	150.2*	[4.6 to 498.8]	< 0.001
B) Temporal trend of in-hospital mortality due to malignant neoplasm of the female breast in the state and in the 10 municipalities that presented the highest rates of this variable														
			Trend 1			Trend 2			Trend 3			Total Period		
State/ Municipality	Number of hospital deaths (%)	In-hospital mortality rate over the period (%)	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	AAPC	95% CI	P-value
State of Alagoas	633 (100)	11.7	2009-2012	24.6*	[5.7 to 46.8]	2012-2019	-2.4	[-5.7 to 1.1]	-	-	-	5.0*	[0.5 to 9.7]	< 0.001
Porto Calvo	6 (0.9)	29.3	-	-	-	-	-	-	-	-	-	48.3	[-26.7 to 200.1]	0.2
Igreja Nova	3 (0.5)	25.0	-	-	-	-	-	-	-	-	-	-8.4	[-57.8 to 98.7]	0.8
Cajueiro	4 (0.6)	22.1	-	-	-	-	-	-	-	-	-	37.9	[-25.8 to 156.0]	0.3
Pilar	10 (1.6)	21.7	2009-2011	11940.0	[-94.7 to 27301204.7]	2011-2016	25.1	[-72.1 to 462.1]	2016-2019	-95.9*	[-99.7 to -33.6]	11.9	[-65.5 to 262.9]	0.9
Lagoa da Canoa	5 (0.8)	21.7	-	-	-	-	-	-	-	-	-	-38.7	[-71.5 to 31.9]	0.2
Jequiá da Praia	2 (0.3)	20.0	-	-	-	-	-	-	-	-	-	0.0	[-44.6 to 80.4]	1.0
Colônia Leopoldina	2 (0.3)	20.0	-	-	-	-	-	-	-	-	-	0.0	[-46.6 to 87.3]	1.0
Estrela de Alagoas	4 (0.6)	18.7	-	-	-	-	-	-	-	-	-	-7.4	[-47.9 to 64.7]	0.8
Batalha	3 (0.5)	17.5	-	-	-	-	-	-	-	-	-	-4.1	[-59.0 to 124.3]	0.9
Atalaia	9 (1.4)	16.5	-	-	-	-	-	-	-	-	-	34.8	[-39.0 to 198.0]	0.4

No joinpoint was observed in this indicator; *Statistically significant P < 0.05. APC = annual percentage change; CI = confidence interval; AAPC: average annual percentage change.

95% CI = - 8.8 to -0.3; P-value < 0.001). The age group ≥ 80 years showed a linear growth trend (AAPC = 150.2; 95% CI = 4.6 to 498.8; P-value < 0.001) (**Table 2A**).

In addition, 28.6% (n = 22) of the 77 municipalities showed an increasing trend, particularly Pão de Açúcar (AAPC = 325.6; 95% CI = 325.6 to 325.6; P-value < 0.001), Inhapi (AAPC = 244.1; 95% CI = 101.6 to 487.2; P-value < 0.001) and Belém (AAPC = 150.8; 95% CI = 69.7 to 270.7; P-value < 0.001). There was a decreasing trend in 3.9% (n = 3) of the municipalities: these were Junqueiro (AAPC = -44.9; 95% CI = - 68.8 to -2.7; P-value < 0.001), São Sebastião (AAPC = -40.6; 95% CI = - 56.5 to -18.8; P-value = 0.2) and Olivença (AAPC = -37.0; 95% CI = - 59.0 to -3.0; P-value < 0.001). The first two of these are located in the metropolitan region of Agreste and the last in Médio Sertão (**Figure 2B**).

A total of 77 municipalities registered deaths. The municipalities with the highest numbers of deaths were Maceió (n = 282; 11.8%), Arapiraca (n = 71; 12.3%) and Rio Largo (n = 23; 14.0%). The ten municipalities with the highest rates accounted for only 7.5% (n = 48) of total deaths, and all these municipalities presented stationary behavior (**Table 2B**).

DISCUSSION

This study identified the temporal trend of mortality (per 100,000 inhabitants) and in-hospital mortality rate (%) due to female breast cancer in the state of Alagoas. Within these rates, variations between the municipalities of the state were observed. In 2019, data from Brazil, regarding the trend of breast cancer incidence rates according to age groups, showed that the highest rates started from 70 years old, while there was a decreasing trend for the 40 to 49-year age group and stability for the 20 to 39 and 50 to 69-year age groups.[13] Those results are in line with ours, since the values were similar to those found in the present study. In Alagoas, age groups over 30 years old showed an upward trend, especially the group between 70 and 79 years old. The higher rates for age groups of 70 years and over were consistent with what has been observed worldwide, given that the risk of developing cancer increases with advancing age.[14]

It is well known that the aging process is the main risk factor for breast cancer. Thus, this has become one of the biggest challenges in public health. In this physiological process, the decline of individuals' immune system and dysregulation of the neuroendocrine system make their organisms more vulnerable to infections and other pathological processes.[15,16] In addition, accumulation of mutations in the DNA of cells over individuals' lives is the reason why cancer occurs mostly in the elderly.[16] This could explain the higher rates of both hospital admissions and deaths due to breast cancer among women from the perimenopause onwards.

Another plausible explanation for the greater numbers of findings of cancer among older people is that there is a tendency to perform tests according to advancement of age. Thus, older people are vulnerable to discovery of cancers at more advanced stages. This consequently makes them subject to more radical surgical treatments, which reduces the opportunity for cure and increases the chances of complications and longer hospital stay,[17] thereby facilitating progression to death.

In addition to these factors, another physiological factor that may predispose women to breast cancer is the changes that they undergo during puberty. This phase of life involves increases in the serum levels of estrogen and prolactin, which have major effects on the mammary epithelium. In a survey conducted in the city of Cuiabá, Mato Grosso, Brazil, among 19 women, it was observed that 47.4% of them presented menarche in the age group between 10 and 13 years old, at an average age of 13.31. It was therefore suggested that early menarche and onset of a regular ovulatory cycle would increase the risk of breast cancer, since estrogen levels are higher during the normal luteal phase, and the cumulative estrogen exposure index is higher.[18,19]

Regarding in-hospital mortality, in 2012 there was an interruption of the growth trend in Alagoas and the age group of 40-49 years shifted from an increasing trend to a declining trend. It is likely that the implementation of the *Consensus for Breast Cancer Control,* prepared by the Brazilian Health Ministry in 2004 may have influenced this result.[20] This document recommends that clinical examination of the breasts should be performed annually from the age of 40 years onwards and that mammographic screening should be performed every two years from 50 to 69 years of age. Among high-risk women, annual clinical and mammographic examinations are recommended from the age of 35 years onwards. Thus, if diagnosis and treatment are performed early, the prognosis is considered good, with reduced mortality. In this scenario, the result is decreased mortality rates.[20]

Although the state capital of Alagoas (Maceió) had the highest number of hospital deaths due to breast cancer among women, it had a lower in-hospital mortality rate than other municipalities in inland areas. Among the state capitals of the northeastern region of Brazil, mammography coverage estimates have ranged from 64.3% to 84.4%.[21] In municipalities away from the state capitals, mortality due to breast cancer has increased in all regions since the 1990s.[22] It is possible that among women in non-metropolitan regions, access to mammography is lower than among residents in the state capitals. This was shown in a study conducted in 2015, in which living in an urban area increased the likelihood of undergoing a mammographic examination by 10.97 percentage points[23] and therefore increased the likelihood of early detection of cancer.

One possible reason for this disparity may arise from differences in women's exposure to risk factors and diagnostic practices. It is noteworthy that breast cancer tends to be diagnosed at more advanced stages in less developed regions[24] in which access to the

healthcare system is lower. Moreover, it is known that mortality rates show a correlation with access to healthcare services and the quality of care that is offered to women with breast cancer.[13] In a study published in 2017, it was seen that a proportion of the preventable deaths from breast cancer was correlated with unequal access to treatment between the rich and needy populations, and that this disparity is quite common in developing countries, such as Brazil.[25]

Another study also showed that the highest mortality rates were found in municipalities with more than 500,000 inhabitants and in those with populations of up to 5,000 inhabitants.[26] These findings corroborate what was found in our analyses when we addressed the smaller municipalities. The municipalities that presented high rates of in-hospital mortality, according to the 2010 census, had small populations. It can be suggested that in these places there is a greater possibility of shorter reach of preventive actions, as well as a lack of infrastructure, which can hinder the diagnosis and early treatment of the disease. This would form a possible explanation for the findings. In large cities, however, the high mortality rate may reflect the fact that women with breast cancer may move to large centers in search of better treatments, along with urbanization and possible changes in reproductive patterns.

Therefore, the need to promote broader access to cancer diagnoses in Brazil can be stressed, with special attention to women with lower socioeconomic status. In particular, attention is required for women residing in inland municipalities in Alagoas, which is the scenario of the present study. It has been noted that there is uneven distribution of the numbers of mammography devices in the state of Alagoas, in which more than 93.3% (n = 14) are concentrated in the two most populous municipalities: Maceió, with 53.3% (n = 8), and Arapiraca (40.0%, n = 6).[27]

Over time, the number of hospital admissions in the state of Alagoas due to breast cancer has grown. This trend corroborates studies that analyzed the increased incidence and mortality due to this type of cancer in Brazil.[13,28] In addition, there were increases in the rate of hospital admissions over the period, in 41.2% (n = 42) of the 102 municipalities in the state. This gave rise to a broad sample for regional characterization of this category of cancer. In the panorama of hospitalizations in the state, the rates of hospital admissions were concentrated among patients who were residents of 10 municipalities and among these, three cities (Arapiraca, Maceió and Palmeira dos Índios) stood out. These three cities had the highest numbers of hospital admission records. It can be inferred that, given that these are the most populous cities in the state,[11] there is a greater concentration of provision of hospital resources. This relationship is similar to what was seen in a study carried out in Bahia on hospitalizations due to malignant breast cancer.[29] It can also be deduced that some women who had been admitted to hospitals in these more populous cities stayed in these locations and provided addresses in these cities as their home address.

It needs to be mentioned that this study had some limitations that should be taken into account: i) the secondary data on hospital admissions reflected the hospital flow, and so it is possible that the same person was hospitalized more than once and, consequently, the number of admissions may have exceeded the number of people hospitalized; ii) cancer patients may not need hospitalization and, therefore, the number of hospitalizations may have been underestimated in relation to the total number of people with cancer in our population; iii) the scarcity of studies in this area may have made comparative analysis difficult; and iv) the database used only took public hospitals into consideration.

CONCLUSION

There was a higher percentage of hospital admissions and deaths due to breast cancer in the state of Alagoas among women aged 50 to 59 years, considering the period from 2009 to 2019. Over this period, according to age group, all age ranges showed an increasing trend for hospitalizations, with the exception of women under 20 years old, for whom hospitalization decreased, and those between 20 and 29 years, whose rate remained stable. Regarding in-hospital mortality, all ranges showed a stable pattern, with the exception of 30 to 39 and ≥ 80 years, which increased.

There were growing trends of hospital admissions and in-hospital mortality in the state. Among the different localities in Alagoas, most of them showed a stationary trend, followed by an increasing trend in both hospitalization and mortality rates.

In this context, knowing the profile of hospital admissions due to breast cancer makes it possible to understand the temporal panorama with more reliability and with its local specificities. Thus, this promotes regional indicators that provide data for actions aimed at this portion of the population. In addition, it is possible to measure the quality and equity of access to these oncology services and to identify the areas of greater social vulnerability.

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Epidemiological data on HIV-infected patients and the importance of education regarding the infection rate. An analytical cross-sectional study

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ABSTRACT

BACKGROUND: Sexually transmitted diseases (STIs) are an important public health problem in all countries. Knowledge of their relationship with the various socioeconomic levels is necessary for an understanding of their epidemiology and behavior in society.

OBJECTIVE: To investigate the epidemiology of human immunodeficiency virus (HIV)-positive patients and to correlate education with history of sexually transmitted diseases, especially for syphilis.

DESIGN AND SETTING: Analytical cross-sectional study carried out in the city of Juiz de Fora, Minas Gerais, Brazil.

METHODS: The medical records of HIV/acquired immunodeficiency syndrome (AIDS) patients who started antiretroviral therapy (ART) between January 2010 and July 2018 were assessed. These patients were attended at the specialized assistance service for HIV/AIDS) of the Department of Sexually Transmitted Diseases (STD/AIDS) of the city of Juiz de Fora. In total, 335 patients were selected.

RESULTS: In our sample, 73.13% were male; 57.36% were aged between 25 and 45 years and 24.23% were over 45 years of age. Regarding sexual orientation, 61.78% were homosexual. Regarding education, 52.88% had "unskilled education", while 47.12% had "qualified education". Analysis on the relationship between schooling and syphilis, a positive relationship between qualified schooling and syphilis was observed: odds ratio = 3.588; 95% confidence interval: 1.090-11.808.

CONCLUSION: Homosexual male patients are most affected by HIV. Furthermore, this disease is not limited only to individuals with low education. Syphilis should be suspected in all individuals.

INTRODUCTION

Sexually transmitted infections (STIs) are a public health problem and affect the lives of people around the world. This situation is associated with high rates of transmission, often explained by the view that people are not well informed about the transmission of these diseases or ignore the mandatory precautionary measures for safe sex. Individuals infected with any STI are five to ten times more likely than non-infected individuals to acquire or transmit the human immunodeficiency virus (HIV) through sexual contact.[1] Many asymptomatic or undiagnosed individuals transmit HIV, syphilis and hepatitis B and C, either sexually or through contact with contaminated blood, as in the transmission of hepatitis C.[2]

In Brazil and worldwide, HIV infection persists and is often associated with other STIs. Co-infection with HIV and syphilis, for example, has synergistic action and increases the transmissibility of HIV.[3] According to the Brazilian Ministry of Health, syphilis cases have increased mainly among people with "qualified" education level. This also represents a major problem and risk with regard to the transmissibility of HIV.[4]

OBJECTIVE

The objectives of this study were to outline the epidemiological data on HIV-positive patients, and to correlate these patients' education with occurrence of other STIs, such as syphilis, in Juiz de Fora, Minas Gerais.

METHODS

Design, ethical aspects and procedures

This was an analytical cross-sectional study. The medical records of HIV/acquired immunodeficiency syndrome (AIDS) patients who started ART between January 2010 and July 2018 were assessed. These patients were attended at the specialized assistance service (SAE) of the Department of Sexually Transmitted Diseases (STD/AIDS) of the city of Juiz de Fora. The survey took place between July 2019 and December 2019. The research was started after obtaining approval from the Research Ethics Committee of the Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (SUPREMA), under opinion report number 2.722.176, dated June 19, 2018. The criteria of trust and privacy were guaranteed to the participants, in accordance with Resolution 466/2012 of the National Council for Research Ethics (CONEP), which deals with research involving human beings.

Participants

The participants in this study were HIV/AIDS patients who were treated at the SAE. The inclusion criteria were that the patients needed to: 1) be attended at the SAE of the Department of Sexually Transmitted Diseases (STD/AIDS) of the city of Juiz de Fora; 2) be a carrier of the HIV/AIDS virus, as confirmed through laboratory tests. The exclusion criterion were that patients were not selected if the medical records were poorly written or had non-conformities that could generate confusion bias, such as illegible handwriting.

For this study, the medical records were separated into three groups: group A, patients who started ART with dolutegravir (DTG), with immediate adherence; group B, patients who started ART without DTG, with adherence in 45 days; and group C, patients who started ART without scheduled adherence and with different treatment schedules. In the end, the study sample comprised 335 participants.

Data analysis

The information provided was transcribed and tabulated using the Windows Excel software 2013 (Microsoft Corporation, Redmond, Washington, United States). The data on these spreadsheets was then transferred to the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (released 2015) (IBM Corp., Armonk, New York, United States), in which a statistical analysis was performed. The mean values and standard deviations for numerical variables were calculated. The statistical significance level established was $P < 0.05$.

Adjusted analysis

We constructed a logistic regression model to determine the interaction between schooling and sexually transmitted infections. First, statistical comparisons were made between schooling and other variables using the Wilcoxon signed-rank test for continuous data and Fisher's exact test, two-sided for nominal variables. Then, the variables that were significantly correlated at $P > 0.05$ (age, sex and syphilis) were included in the logistic regression model. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. The logistic regression was performed using the R Core Team software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

This study evaluated 335 patients with HIV. The epidemiological characteristics of these patients are shown in **Table 1**.

Among these 335 HIV-positive patients, 82 (24.48%) were female, 245 (73.13%) were male and 8 (2.39%) were transgender. In terms of age, the sample was divided into three parts: less than 25 years, from 25 to 45 years and more than 45 years, with the purpose of separating the sample population into three age ranges. There were 60 patients (18.40%) aged less than or equal to 24 years; 187 patients (57.36%) aged between 25 and 45 years and 79 patients (24.23%) over 45 years. The maximum age was 76 years, the minimum was 14 and the average was 36.43 (standard deviation, SD: 13.081). There were nine participants whose age was not identified.

Regarding sexual orientation, 225 patients were evaluated. Among these, 18 patients claimed to be bisexual (8.0%), 68 patients claimed to be heterosexual (30.22%) and 139 patients claimed to be homosexual (61.78%).

Regarding educational level, 278 patients provided this information. Among these: 72 (25.9%) had been educated as far as incomplete elementary school; 31 (11.5%) as far as completed elementary school; 44 (15.83%) as far as incomplete high school; 70 (25.18%) as far as completed high school; 31 (11.15%) as far as incomplete higher education; and 30 (10.79%) as far as completed higher education. This information can be seen in the graph of **Figure 1**.

In the first visits, rapid tests for syphilis and hepatitis B and C serological tests were performed (**Table 2**). The test for syphilis was done on 95 patients, among whom 48 were reactive (50.53%); the test for hepatitis B virus (HBV) was done of 48 patients, with one reactive case (2.08%); and the test for hepatitis C virus (HCV) was done on 54 patients, among whom none were reactive.

In order to investigate correlations between educational level and sexually transmitted infections, an odds ratio (OR) analysis was performed through logistic regression. The individuals analyzed were separated into two groups: the first was named "qualified education" and was composed of individuals who had reached the levels of completed high school or incomplete or completed higher education; the second was named "unskilled education" and was composed of individuals who had reached the levels of incomplete or completed elementary school or incomplete high school.

Table 1. Epidemiological data on human immunodeficiency virus-positive patients

Sample epidemiology					Frequency	Percentage
Sex	Female				82	24.48%
	Male				245	73.13%
	Transgender				8	2.39%
Total					**335**	**100.00%**
Age (years)	Average				36.43	SD: 13.081
	Maximum				76	
	Minimum				14	
	< 25				60	18.40%
	25-45				187	57.36%
	> 45				79	24.23%
Total					326	100.00%
		F	**M**	**T**		
Sexual orientation	Bisexual	0%	5%	95%	18	8.00%
	Heterosexual	47%	0%	53%	68	30.22%
	Homosexual	94.3%	5%	0.7%	139	61.78%
Total					**225**	**100.00%**
Partner serological status	Unknown				106	60.23%
	HIV-				15	8.52%
	HIV+				55	31.25%
Total					**176**	**100.00%**
Previous STIs	No				44	50%
	Yes				44	50%
Total					**88**	**100%**
Hepatitis B vaccination	No				6	1.79%
	Yes				1	0.30%
	Without knowledge				328	97.91%
Total					**335**	**100.00%**
Education	Complete elementary education				31	11.15%
	Incomplete elementary school				72	25.90%
	Complete high school				70	25.18%
	Incomplete high school				44	15.83%
	Complete higher education				30	10.79%
	Incomplete higher education				31	11.15%
Total					**278**	**100.00%**

SD = standard deviation; STIs = sexually transmitted infections; F = female; M = male; T = transgender.

Given that skilled education is age and sex-dependent, a logistic regression analysis was performed, with adjustments for these variables (**Table 3**). The difference between qualified and unskilled education was found to be nonsignificant in this adjusted model (P = 0.675), as was age (P = 0.581). However, being male (OR 3.9; P = 0.055) and being positive for syphilis (3.588; P = 0.035) were significantly correlated with qualified education.

DISCUSSION

Between 2007 and June 2019, 300,496 cases of HIV infection in Brazil were reported in the country's notifiable diseases information system (SINAN), of which 136,902 cases (45.6%) were in the southeastern region. During this period, a total of 207,207 cases (69.0%) were reported among men and 93,220 cases (31.0%) among women. The sex ratio for the year 2018 was 2.6 (M:F), i.e. 26 men for every ten women.[5] In the sample studied, a ratio of 2.98 (M:F) was observed, i.e. close to 30 men for every 10 women. We separated transgender individuals from these proportions, in order to ascertain the prevalence of this population in the sample.

Over the same period, regarding age groups, it was observed that most cases of HIV infection were in the range from 20 to 34 years of age, which accounted for 52.7% of the cases. Among the cases in which the educational level was informed, most of these individuals had completed high school, which represented 20.7% of the total. In another study, 12.1% of the cases had reached an incomplete schooling level between the 5th and 8th grades.[5] In our sample, a similar number of individuals in this same age group was seen, and 57.36% of them were between 25 and 45 years old, thus showing higher prevalence in the generations of the 1980s and 1990s. In addition, 44.12% had completed high school, which

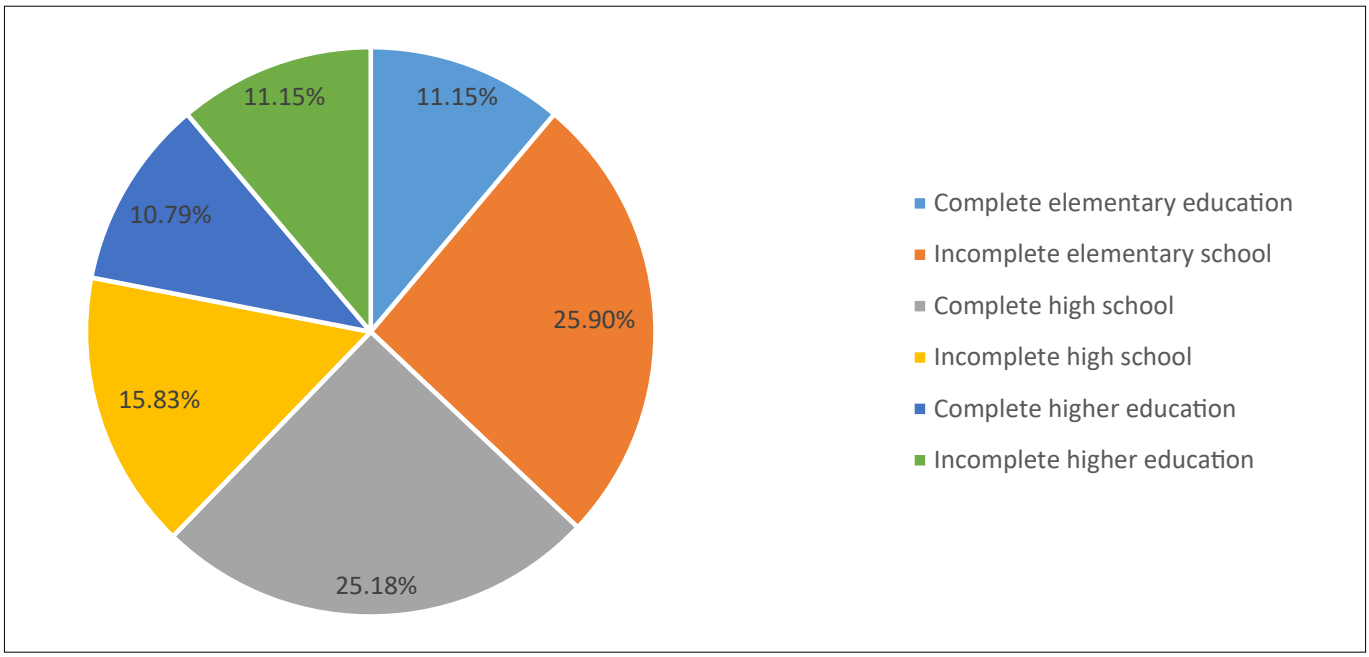

Figure 1. Graph representing the schooling of the sample studied.

Table 2. Rapid test for communicable diseases

Rapid test						
Result	**Syphilis**	**Percentage**	**HBV**	**Percentage**	**HCV**	**Percentage**
Reactive	48	50.53%	1	2.08%	0	0
Non-reactive	47	49.47%	47	97.92%	54	100.00%
Total	**95**	**100.00%**	**48**	**100.00%**	**54**	**100.00%**

HBV = hepatitis B virus; HCV = hepatitis C virus.

shows that some patients with STIs now have qualified education levels, i.e. that STIs are not just prevalent among individuals with less school education.

In addition, among men, over the period observed, it was found in another study that 51.3% of the cases were due to homosexual or bisexual exposure, while 31.4% were heterosexual.[5] In our sample, 61.78% of those infected were homosexuals, and 94.3% of them were male. Among women, it has been noted that 86.5% of the cases fall into the category of heterosexual exposure in Brazil.[5] In the sample of our study, 53% of the heterosexuals were female and about 95% of the bisexuals were female. This situation demonstrates that the population most affected is still that of individuals with homosexual sexual orientation and is concentrated more in the male sex, while in the heterosexual group there is a tendency towards equality between the groups, i.e. in this group the female and male sexes have similar distributions.

This situation is similar to what has been seen in the United States. Homosexual and bisexual men together form a group that corresponded to 86% of new infections in the United States and its dependent territories in 2017. Homosexual exposure among men corresponded to 79% of the infections diagnosed that year, with or without an association with the use of injectable drugs, i.e. a proportion considerably higher than the 51.3% seen in Brazil.[6] However, regarding American women, 76% became infected through heterosexual exposure and another group of 21%, through injecting drugs.[6]

HIV affects approximately 35 million people worldwide, and approximately 8.6% of them are co-infected with HBV.[7] The rates of HIV/HBV co-infection vary according to the origin of the

Table 3. Logistic regression results

Variable		Standard deviation	Odds ratio	P-value
Schooling	Qualified		Reference	0.675
	Unskilled	1.180	0.610 (0.060-6.164)	
Age		0.023	0.987 (0.943-1.033)	0.581
Sex	Female		Reference	0.055
	Male	0.719	3.961 (0.967-16.220)	
Syphilis	Non-reactive		Reference	0.035
	Reactive	0.607	3.588 (1.090-11.808)	

population studied and the geographical location.[8,9] In a group of 297 patients evaluated at the Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Brazil, the prevalence of hepatitis B markers was significantly associated with HIV infection, in comparison with the prevalence observed in the general population of the same geographical area.[10] Out of the 48 patients analyzed in our study, only one had positive HBV serological tests. In addition, the prevalence of HIV/HCV co-infection was low in the group analyzed here, and this was also observed in studies in Recife and Pará.[11,12] In a hospital in Porto Alegre, Brazil, anti-HCV was observed in 126 out of 330 cases (38.2%).[13] This situation confirms the idea that the prevalence of these associations depends on the geographical location.

In 2018, 158,051 cases of acquired syphilis were reported to SINAN. This condition has been subject to compulsory notification since 2010. Its detection rate increased from 34.1 to 75.8 cases per 100,000 inhabitants between 2015 and 2018. In 2018, among the cases in which the education level was reported, 39.5% of these individuals had reached at least high school education.[4]

In the group analyzed here, a positive correlation with individuals with higher education levels was observed: these individuals were more likely to have contracted syphilis than individuals with lower education. The main limitation to this finding was the number of individuals from whom the rapid test results were notified (92 patients). Nonetheless, this relationship is extremely important from a public health point of view, given that it may indicate that campaigns to prevent these diseases are not being effective, since individuals with higher socioeducational levels do not follow preventive measures. It is worth mentioning that the population studied consisted of individuals with HIV and, therefore, presented higher risk of severe forms.

Education is associated with STIs, as observed in a previous survey conducted in São Paulo.[14] An association between past STIs and lower levels of schooling has been described in the literature.[15] However, because of the limitation of the size of the population studied, we were unable to add data from other STIs to the logistic regression analysis, such as hepatitis B and C.

CONCLUSION

Our analysis shows that HIV is still a prevalent disease in society, and is more prevalent among males and homosexuals. It is similarly distributed across all educational levels; i.e. individuals with qualified education have a prevalence similar to that of individuals with unskilled education. This demonstrates that this public health problem transcends socioeducational levels.

In addition, syphilis is an emerging problem in the context of public health, and it should receive special attention for the entire population. Its incidence is not restricted mainly to less-favored socioeducational groups.

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Cohort study on 20 years' experience of bilateral video-assisted thoracic sympathectomy (VATS) for treatment of hyperhidrosis in 2431 patients

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ABSTRACT

BACKGROUND: Primary hyperhidrosis is a condition characterized by excessive sweating, inconsistent with the needs for thermoregulation.

OBJECTIVE: To assess the effectiveness and the change in the quality of life of patients undergoing bilateral VATS (video-assisted thoracoscopic sympathectomy) for treatment of hyperhidrosis, in a large case series.

DESIGN AND SETTING: Cohort study conducted in a tertiary hospital specializing in hyperhidrosis located in São Paulo, Brazil.

METHODS: A total of 2,431 patients who underwent surgery consisting of bilateral video-assisted thoracoscopic sympathectomy between January 2000 and February 2017 were retrospectively assessed in an outpatient clinic specializing in hyperhidrosis. The patients underwent clinical and quality of life assessments on two occasions: firstly, prior to surgery, and subsequently, one month after the operation. The presence or absence of compensatory hyperhidrosis (CH) and general satisfaction after the first postoperative month were also evaluated.

RESULTS: All the patients operated had poor or very poor quality of life before surgery. In the postoperative period, an improvement in the quality of life was observed in more than 90% of the patients. Only 10.7% of the patients did not present CH, and severe CH occurred in 22.1% of the patients in this sample.

CONCLUSIONS: Bilateral VATS is a therapeutic method that decreases the degree of sweating more than 90% of patients with palmar and axillary hyperhidrosis. It improves the quality of life for more than 90% of the patients, at the expense of development of CH in approximately 90% of the patients, but not intensely.

INTRODUCTION

Primary hyperhidrosis (PH) is a condition characterized by excessive sweating that is inconsistent with thermoregulation needs. It has a large impact on patients' quality of life and affects their personal and professional relationships.[1,2] In the majority of cases, PH manifests in childhood and adolescence and persists throughout life. The typical clinical presentation is limited to the palms of the hands, the plantar region of the foot and/or the axilla, and it is symmetrical. It can also affect the head and face and often occurs in two or more regions of the body. The pathophysiology of PH is not fully understood, but it is known to result from stimulation of the sympathetic nervous system in its regulatory center. PH affects approximately 2.8% of the population, and there is a positive family history in 12.5% to 56.5% of the patients.[3] Patients generally seek medical care later in life, and more frequently at a more financially secure age. Thus, young people end up suffering for many years before being able to receive the current well-known medical treatment.[4,5]

The initial treatment for patients with PH, until 2010, was sympathectomy. Thereafter, we began to use oxybutynin chloride as the first-line treatment. In patients for whom no adequate response to medication is attained, video-assisted thoracoscopic sympathectomy (VATS) becomes the treatment of choice.

VATS is considered to be the gold standard for the definitive treatment of hyperhidrosis. It provides excellent clinical results (reduced sweating at specific sites) and leads to a significant improvement in quality of life. These positive results are, among other causes, based on factors that are known to influence the effectiveness of sympathectomy among patients with hyperhidrosis,[1] such as body mass index, resection level,[6,7] preoperative quality of life[8] and the number of resected ganglia.[9]

OBJECTIVE

The objective of this study was to assess the effectiveness of the treatment and the change in the quality of life of patients undergoing VATS in a large case series (2,431 patients).

METHODS

A total of 2,431 patients who underwent bilateral video-assisted thoracoscopic sympathectomy between January 2000 and February 2017 were retrospectively assessed in an outpatient clinic specializing in hyperhidrosis. This study was approved by the research ethics committee of our institution (protocol number: 1.133.255; date: June 30, 2015).

All patients treated under our care since 2000 have been routinely evaluated through regular completion of a specific medical record that includes demographic data and description of all sites of hyperhidrosis and the quantitative intensity of hyperhidrosis complaints at each site, using a questionnaire (HDSS). This is a specific quality-of-life questionnaire that was standardized by Amir et al. and translated into English by Campos et al. The quantitative degree of improvement at each point after treatment is assessed using this specific questionnaire.[10,11]

Regarding the surgical technique, in general terms, the surgery is performed with the patient in a semi-Fowler's position at 45° to the floor. Two small incisions of approximately 1.0 cm are made in each hemithorax. The pleural cavity is accessed through an incision that is made in the fourth intercostal space, on the anterior axillary line. Through this, a 5 mm and 30° video optic is introduced. The second incision is made in the second intercostal space, on the middle axillary line, for insertion of an endoscopic scalpel. After identification of the sympathetic chain, the ganglion is isolated, always starting from the medial costal pleura, following the lateral costal pleura and ending with complete dissection of the sympathetic chain and the ganglion.

The sympathetic chain is resected on the respective costal arches. At the end of this step, the sympathetic chain segment located between the corresponding costal arches, including the target ganglion, is electrocauterized. During the sympathectomy, all patients are kept temporarily in apnea or low-flow ventilation. At the end of the surgery, the residual pneumothorax is aspirated through a nasogastric tube (no. 16) and pulmonary expansion is monitored via the video optic. The incisions are closed with intradermal sutures.

Anatomically, sympathectomy performed on the right side of the chest is slightly more laborious than on the left side owing to the greater number of large-caliber veins on the thoracic sympathetic chain and its more superior branches. This forces the surgeon to be more careful in the dissection.

Patients are usually extubated without difficulty in the operating room. After awakening from anesthesia, they are sent for anesthetic recovery and then to their room. To ensure complete pulmonary reexpansion, chest radiographs are routinely performed shortly after the surgery.

The patients underwent clinical and quality of life assessments on two occasions: firstly, prior to surgery, and subsequently, one month after the operation. All the evaluations were done by the primary investigator. The primary endpoints in the study were the following:

1. The patients' quality of life at the first visit prior to surgery.
2. The improvement in quality of life after surgery, the clinical improvement in sweating, the presence or absence of compensatory hyperhidrosis (CH) and general satisfaction after the first postoperative month.

To measuring the degree of satisfaction, we used the quality-of-life protocol described by Amir et al., which was translated to English by Campos et al.[10-12] Before the surgical treatment, the patients completed quality-of-life assessments without physician involvement. This protocol consists of 20 questions divided into four domains (functional-social, personal, emotional and special conditions). Five response levels are described in tables, from which only one response is allowed for each question. The patients were classified into five different levels of satisfaction, calculated as the summed total score from the protocol, ranging from 20 to 100. When the sum was greater than 84, the quality of life was considered very poor; from 69 to 83, poor; from 52 to 68, good; from 36 to 51, very good and from 20 to 35, excellent.

The improvement in quality of life after surgery was evaluated using the same protocol, and the patients were classified into five different levels of improvement, calculated as the total score from the protocol. For scores greater than 84, the quality of life was considered much worse after the surgical treatment; from 69 to 83, a little worse; from 52 to 68, equal; from 36 to 51, a little better; and from 20 to 35, much better.

The clinical improvement in sweating after treatment was defined on a quantitative scale ranging from 0 to 10, in which 0 represented no improvement and 10 represented absence of sweat, or anhidrosis, for each site of previous hyperhidrosis, based on the patients' own assessments. From this score regarding the patients' main complaint, the clinical improvement was graded as follows: null, 0-4; moderate, 5-7; or good, 8-10.

The degree of patient satisfaction after surgery was quantified using a questionnaire with four options for patients to describe their general satisfaction with surgery outcomes. The patients' general satisfaction was considered to be excellent if they were 100% satisfied with the surgery outcome one month after surgery, good if they were 90% satisfied, fair if they were 75% satisfied or low if they were less than 50% satisfied.

The patients' reports, with confirmation through physical examination, were used to analyze the incidence of CH. The severity of CH was graded as severe or non-severe. CH was considered to be severe if it was visible and embarrassing, and required more than one change of clothes during the day. CH was considered to be non-severe if it was visible and embarrassing but not enough to require a change of clothes, or if it was visible and embarrassing only sometimes (e.g. in hot weather and during exercise), or if it was present but did not bother the patient.

RESULTS

The demographic data, main site of hyperhidrosis and the level of VATS resection in the group are presented in **Table 1**. The prevalence was higher among females. The mean age of the group was 24.7 years and the mean body mass index was 21.7 kg/m^2. The main sites of hyperhidrosis were palmar and axillary. Resection of a single G3 ganglion was the most frequent procedure, followed by resection of a G4 ganglion.

The assessment of quality of life before surgery and the improvement in quality of life after surgery among the patients are shown in **Table 2**. It should be noted that all the patients operated under our care had poor or very poor quality of life before surgery. In the postoperative period, an improvement in the quality of life was observed in more than 90% of the patients.

A review of the clinical improvement at the main site of sweating after surgery is presented in **Table 3**. At the palmar and axillary sites that were the main site of hyperhidrosis, more than 90% of the patients in this study reported major clinical improvement. The rate of improvement was lower (80.6%) in cases in which the cranial-facial region was the main site.

An analysis on the prevalence and intensity of CH is presented in **Table 4**. Only 10.7% of the patients did not present CH, and severe CH occurred in 22.1% of the patients in this sample.

An analysis on the degree of satisfaction among the patients after surgery in both groups is shown in **Table 5**. More than 90% of the patients reported having high satisfaction with the surgery.

A correlation between the technique used and presence of compensatory hyperhidrosis is shown in **Table 6**. Ablation at lower levels (especially G4) resulted in a lesser degree of compensatory hyperhidrosis ($P < 0.00001$).

Table 1. Demographic and technical data

Variable		Patients (n = 2431)	
Sex (n %)	Female	1,618	67.4%
	Male	783	32.6%
Age (years)	Mean/SD	24.7	7.57
BMI (kg/m^2)	Mean/SD	21.7	2.80
Main site (n %)	Palmar	1,546	64.4%
	Axillary	785	32.7%
	Plantar	29	1.2%
	Cranial-facial	42	1.7%
Technique (n %)	G2	100	4.2%
	G2/G3	365	15.2%
	G2/G3/G4	1	0.0%
	G3	838	35.0%
	G3/G4	264	11.0%
	G4	828	34.5%
	G4/G5	0	0.0%

BMI = body mass index; SD = standard deviation; G = ganglion.

Table 2. Reported pre and postoperative quality of life over the age range of the patients

		Patient group n = 2,431
Preoperative QoL [n (%)]	Excellent	0
	Very good	0
	Good	0
	Poor	630 (28.0%)
	Very poor	1617 (72.0%)
Postoperative QoL [n (%)]	Much better	1,566 (78.6%)
	A little better	321 (16.1%)
	Equal	76 (3.8%)
	A little worse	19 (0.9%)
	Much worse	10 (0.5%)

QoL = quality of life.

Table 3. Analysis on clinical improvement after surgery, at the main site of hyperhidrosis (palmar, axillary or cranial-facial)

Main site of PH	Degree of clinical improvement	Patients n = 2431
Palmar n = 1,552	High	1,465 (94.4%)
	Moderate	75 (4.8%)
	Null	12 (0.8%)
Axillary n = 765	High	692 (90.5%)
	Moderate	59 (7.7%)
	Null	14 (1.8%)
Cranial-facial n = 36	High	29 (80.6%)
	Moderate	6 (16.7%)
	Null	1 (2.8%)

PH = primary hyperhidrosis.

Table 4. Prevalence of compensatory hyperhidrosis and its intensity

		Patients n = 2,362
Compensatory hyperhidrosis	Absent	251 (10.7%)
	Non-severe	1,588 (67.2%)
	Severe	523 (22.1%)

DISCUSSION

Primary hyperhidrosis is a disease that significantly affects the population, and in particular the younger population. These patients seek medical evaluations and treatments to achieve a general improvement in their quality of life.[13]

Currently in our practice, we start treatment with oxybutynin hydrochloride in all patients.[14-16] This medication was proven to be effective as an initial therapy in a randomized, placebo-controlled trial by Wolosker et al., in 2012. Positive results were obtained over both the short and the long term, while the quality of life remained unchanged in situations of treatment failure.[17] In such cases, surgical treatment was considered.[16,18]

Epidemiological evaluation of PH has revealed that there is high demand for care from young adults. It has been demonstrated that the prevalence of primary hyperhidrosis in the general population is equal between sexes.[19,20] However, there is greater demand for treatment from females, which is due, among other reasons, to greater concern for esthetics in this group.[20,21] This was shown in our previous study in which 67.4% of the patients were female.[22]

In our practice, we only operate on patients with a body mass index (BMI) lower than 25, since greater prevalence of severe CH has been observed among patients with a BMI greater than 25 who underwent the operation.[23] This is why the mean BMI was 21.7 kg/m^2 in the sample of our previous study.[22]

Regarding the distribution of the main hyperhidrosis sites, palmar hyperhidrosis was more frequent in the study group.[24] This is usually associated with significant worsening of quality of life, given that it leads to limitations in manual activities. These data from patients who underwent operations were also observed in an epidemiological study conducted by our group in 2017.[13] That study also showed that axillary hyperhidrosis[25] was the second most frequent site, followed by cranial-facial and plantar sites.[26,27]

Table 5. Degree of satisfaction after the surgery

		Patients n = 2,330
Degree of postoperative satisfaction [n (%)]	100%	1586 (68.1%)
	90%	543 (23.3%)
	75%	170 (5.9%)
	< 50%	31 (1.3%)

In our sample, the best results were in relation to the palmar and axillary sites. More than 90% of the patients in this study reported achieving major clinical improvement. This corroborates the indication for sympathectomy.

It has been demonstrated that the higher the level of VATS ganglion resection is, the greater the incidence of severe compensatory hyperhidrosis will be. The incidence of severe CH will also be greater if more than one ganglion level is resected in the same surgery.[6,28,29] In addition, with higher resections, we observed higher incidence of Horner's syndrome. Thus, we avoided extended resections in our group and gave preference to G4 or G3 ganglion sympathectomies, as demonstrated in this study, in which these were the most frequent. Earlier in our practice, resection was performed at G2 for palmar hyperhidrosis. Later on, we saved G2 in order to reduce complications. More recently, we have demonstrated that simple resection of G4 leads to therapeutic success similar to that observed with G3 resection but with a lower CH rate and maintenance of satisfaction indices with the procedure.[30] Thus, we have shown that more inferior resections are equally effective and result in a lower possibility of side effects. The prevalence of severe compensatory hyperhidrosis was 22.1% in our sample, which was compatible with findings already reported in the literature.[31-33]

Success in surgical treatment of patients has been found to be independent of age,[34] even in patients for whom there was previous clinical treatment failure.[35] More than 95% of the patients reach moderate to high clinical improvement at the main site of hyperhidrosis.

Weng et al. retrospectively reviewed 506 patients with palmar hyperhidrosis who were treated with either R4 or R4+5, in order to evaluate the long-term results regarding postoperative moist hands (PMH) after sympathectomy.[36] PMH occurred in over half of the patients after sympathectomy, but most of these patients were satisfied with the surgical results. Only six patients (1.3%) were dissatisfied because of frequent PMH. Those findings are consistent with our data, which showed improved quality of life in most patients. Thus, we also believe the main objective of treatment should be to improve the patient's quality of life.

Several tools are available for assessing quality of life among hyperhidrosis patients. Wade et al. studied a wide diversity of tools.[37] Twenty-two quality-of-life tools were identified. The most

Table 6. Correlation of technique with compensatory hyperhidrosis

Technique	Compensatory hyperhidrosis				Total	P*
	Absent	Mild	Moderate	Severe		
G4	126 (15.2%)	331 (39.9%)	249 (30%)	122 (14.7%)	**828**	
G3 G4	29 (10.9%)	62 (23.4%)	96 (36.3%)	77 (29.1%)	**264**	
G3	107 (12.7%)	271 (32.3%)	310 (36.9%)	150 (17.9%)	**838**	< 0.00001
G2 G3	42 (11.5%)	53 (14.5%)	140 (38.3%)	130 (35.6%)	**365**	
G2	7 (7%)	20 (20%)	36 (36%)	37 (37%)	**100**	

*Chi-square test; G = ganglion.

commonly used tools were the Hyperhidrosis Disease Severity Scale, the Dermatology Quality of Life Index and the Hyperhidrosis Quality-of-Life Questionnaire.

All the patients operated under our care presented poor or very poor quality of life and were preoperatively counselled regarding the risk of surgical failure and the incidence of severe compensatory hyperhidrosis after VATS. During the postoperative period, we observed improvement in the quality of life in more than 90% of the patients, and the degree of satisfaction was considered excellent or good in more than 90% of this sample. In addition, there was significant clinical improvement (greater than 90%) when the main site of hyperhidrosis was the hands or axilla. These findings reflect the patients' expectations before and after the procedure, and demonstrate that VATS is a therapeutic method that can have a marked positive impact on the lives of patients with PH who seek treatment.

CONCLUSIONS

Bilateral VATS is a therapeutic method that decreases the degree of sweating in more than 90% of the patients with palmar and axillary hyperhidrosis. It improves the quality of life of more than 90% of the patients, at the expense of development of CH in approximately 90% of patients, but not intensely.

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Hospitalization, mortality and public healthcare expenditure in Brazil during the COVID-19 crisis: vulnerabilities in the spotlight

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ABSTRACT

BACKGROUND: Multiple opinion-based communications have highlighted the actions of the Brazilian government during the pandemic. Nevertheless, none have appraised public data to identify factors associated with worsening of the healthcare system.

OBJECTIVE: To analyze and collate data from public health and treasury information systems in order to understand the escalating process of weakening of Brazilian healthcare and welfare since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

DESIGN AND SETTING: Secondary data study conducted using multiple public databases administered by the Brazilian federal government.

METHODS: We processed information from multiple national databases and appraised health and economic-related data.

RESULTS: Based on our analyses, there were substantial reductions in inpatient hospital admissions and in the numbers of patients seeking primary care services, along with a decrease in immunization coverage. Moreover, we observed a considerable decline in government transfers to hospital services (reduction of 82.0%) and a diminution of public outlays in several healthcare-related subfunctions ("hospital and outpatient care", "primary care", "prophylactic and therapeutic support" and "epidemiological surveillance"). We observed an increase in the overall mortality rate over the period analyzed, especially regarding all group-based diseases. Notably, there were remarkable differences among geographic, racial, gender and other parameters, thus revealing the impact of vulnerabilities on COVID-19 outcomes.

CONCLUSION: This assessment of documentation of public expenditure and the shrinkage of investment in sensitive areas of the healthcare system in Brazil emphasized areas that still require collective attention in order to guarantee national welfare.

INTRODUCTION

Ever since 2020 began, governments worldwide have been implementing community, economic and health-related policies to tackle the hurdles resulting from the COVID-19 pandemic.[1,2] These have included financial support packages to encourage investment and maintenance of local business, expanded and strengthened public healthcare and reasonable financial relief programs to socioeconomically vulnerable individuals.[3-6] However, going against the global trends of continuous health and socioeconomic support to families and individuals experiencing any coronavirus-related impact, recent Brazilian government decisions have negatively affected millions of lives, particularly in impoverished macroregions.[7-10]

Over the last months, several reports in the popular media and editorials have reported on the anti-science discourse and anti-life decisions taken by the Brazilian government leader.[11-15] These decisions included cessation or reduction of the "*Emergency Benefit*". This has raised poverty and has forcibly led vulnerable individuals to suspend their social distancing measures. Moreover, divisive rhetoric that has exacerbated economic inequality and the caregiving crisis in Brazil has been disseminated.[16,17]

Nevertheless, to the extent of our knowledge, no previous reports have combined financial and health-related data from multiple public datasets to analyze the potential effects of decision-makers' measures on general health. Thus, this study outlines, evaluates and combines data from public

health and treasury information systems in order to understand the escalating process of weakening of the Brazilian healthcare system and worsening of welfare since the onset of the pandemic.

OBJECTIVE

To analyze and collate data from public health and treasury information systems in order to understand the escalating process of weakening of Brazilian healthcare and welfare since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

METHODS

We designed and conducted this study through secondary data that originated from the Information Technology Department of the Brazilian National Health System (DATASUS), the health information system for primary healthcare (SISAB) and the Brazilian public expenditure portal (a platform dedicated to making public all expenditures of the federal government).[18-20] DATASUS is an online interface governed by the Secretariat for Strategic and Participative Management of the Ministry of Health.[18] It contains multiple information about procedures performed at primary, secondary and tertiary healthcare facilities.[18] Additionally, SISAB is a strategy created by the Department of Family Health that has the aim of expanding information management and process automation, thereby improving conditions and improving work processes.[19]

We extracted information about the numbers of hospital admission authorizations, total cost of admissions, mortality rate and amounts of the federal government transfers. The data were stratified according to geographic region, race, type of medical care (elective or emergency), level of complexity and chapter of the International Classification of Diseases, 10th edition (ICD-10).

We defined four health indicators as relevant primary healthcare performance measurements, in order to monitor the healthcare actions and services offered to society within the primary care level: 1. Mean percentage of diabetic individuals for whom measurements of glycated hemoglobin (HbA1c) were requested; 2. Mean percentage of hypertensive individuals for whom blood pressure levels were measured each semester; 3. Mean proportion of pregnant females who attended at least six prenatal consultations, among which the first consultation occurred no later than the 20th gestational week; and 4. Immunization coverage rate. We also examined public healthcare-related expenditure by assessing the overall amounts paid in specific subareas/subfunctions (hospital and outpatient assistance, primary care, therapeutic and prophylactic support, general administrative tasks, epidemiological surveillance and others). Descriptive analysis was performed, and the variance over the period analyzed was calculated. The data were stored and processed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States).

All quantitative data from 2020 were compared with baseline data from 2019. All monetary-related variables were deflated in accordance with the Expanded Consumer Price Index (IPCA), based on the 2019 values.[21] One United States (US) dollar was equivalent to 5.32 Brazilian reais on May 25, 2020.

RESULTS

Overall, there was a reduction in the number of inpatient hospital authorizations in 2020, compared with 2019 (mean decrease of 13.7%, ranging from 11.4% to 15.6%; **Table 1** and **Figure 1**). The reduction was more pronounced in the northeastern and southern regions (-15.6% and -15.1%, respectively) and among white and indigenous individuals (-15.1% and -16.1%, respectively). Interestingly, black individuals were a racial group with a disproportionately large decrease in inpatient hospital authorizations (-3.4%), compared with other racial groups. Additionally, elective medical hospitalizations showed a substantial decline from 2019 to 2020 (-34.3%) with increases in the total cost of hospitalizations (+3.4%) and the all-cause mortality rate (+30.6%).

Considering each chapter of the ICD-10, most groups showed a decrease in the number of inpatient hospital authorizations, except with regard to chapter I (infectious and parasitic diseases) and chapter XVI (disorders of the perinatal period). Nevertheless, as can be seen in **Figure 1**, the decrease in hospital admissions was not followed by any reduction in the specific-cause mortality rate (except with regard to chapters XVI, VII and XV). Additionally, there was an increase in deaths due to infectious and parasitic diseases (approximately 40.0%).

Regarding monetary variables, general hospitalization costs increased in most Brazilian macroregions, except in the southern region (-1.1%). In addition, hospitalization costs declined among individuals of indigenous origin (-0.8%), elective medical hospitalizations (-21.9%) and high-complexity care procedures (-12.5%). Regarding the general value of the federal complement of hospital services approved over the period analyzed, a substantial decrease in the amount transferred was noticed from 2019 to 2020 (-82.0%). Based on the public expenditure analysis (**Table 2**), the federal government spent nearly R$ 114 billion (9.5% of total federal expenditure) on healthcare in 2019. Of that, the subfunction "hospital and outpatient care" accounted for nearly R$ 57 billion, "primary care" about R$ 26 billion, "prophylactic and therapeutic support" about R$ 10 billion and "general administration" about R$ 7 billion. The full-year federal expenditure report for the fiscal year 2020 showed that there was an increase in the federal government's direct outlays on healthcare (approximately R$ 150 billion, corresponding to 9.4% of total federal expenditure), particularly for the subfunction "general administration" (relative increase of 24.2%). Nevertheless, significant reductions in public expenditure in several healthcare-related subfunctions were noticed, including for "hospital and outpatient care" (relative reduction of 13.6%), "primary

Table 1. Differences in hospitalization parameters, associated costs, all-cause mortality rates and federal complement for hospital services between 2019 and 2020, in the Brazilian National Health System

	Inpatient hospital admissions	Total cost (approved value of production)	Mortality rate	Federal complement for hospital services
	Δ % difference from 2019 to 2020			
Total	**-13.7**	**3.4%**	**30.6**	**-81.9%**
Geographic area				
North	-11.9	6.6%	44.6	-40.7%
Northeast	-15.6	2.2%	33.2	-85.3%
Southeast	-12.6	5.5%	29.0	-85.3%
South	-15.1	-1.1%	25.7	-85.0%
Center-West	-11.4	7.6%	32.8	-64.7%
According to race				
White	-15.1	0.8%	27.2	-83.9%
Black	-3.4	17.4%	35.5	-83.4%
"Pardo" (mixed)	-12.3	3.8%	30.3	-81.4%
Asian	-6.8	15.8%	36.2	-86.4%
Indigenous	-16.1	-0.8%	49.7	-81.9%
According to gender				
Male	-13.1	6.7%	32.5	-83.2%
Female	-14.2	0.07%	27.8	-81.0%
Type of medical care				
Elective	-34.3	-21.9%	83.6	-81.9%
Emergency and urgent	-8.0	12.7%	21.9	-
Level of complexity				
Medium	-13.5	10.7%	31.4	-80.7%
High	-16.6	-12.5%	14.3	-87.8%

Δ = difference between data from 2019 and 2020, in percentages. Data were obtained from the Department of Informatics of the Brazilian National Health System/Hospital Information System (*Departamento de Informática do Sistema Único de Saúde do Brasil/Sistema de Informações Hospitalares*, DATASUS-SIH).

care" (relative reduction of 5.9%), "prophylactic and therapeutic support" (relative reduction of 2.0%) and "epidemiological surveillance" (relative reduction of 1.1%).

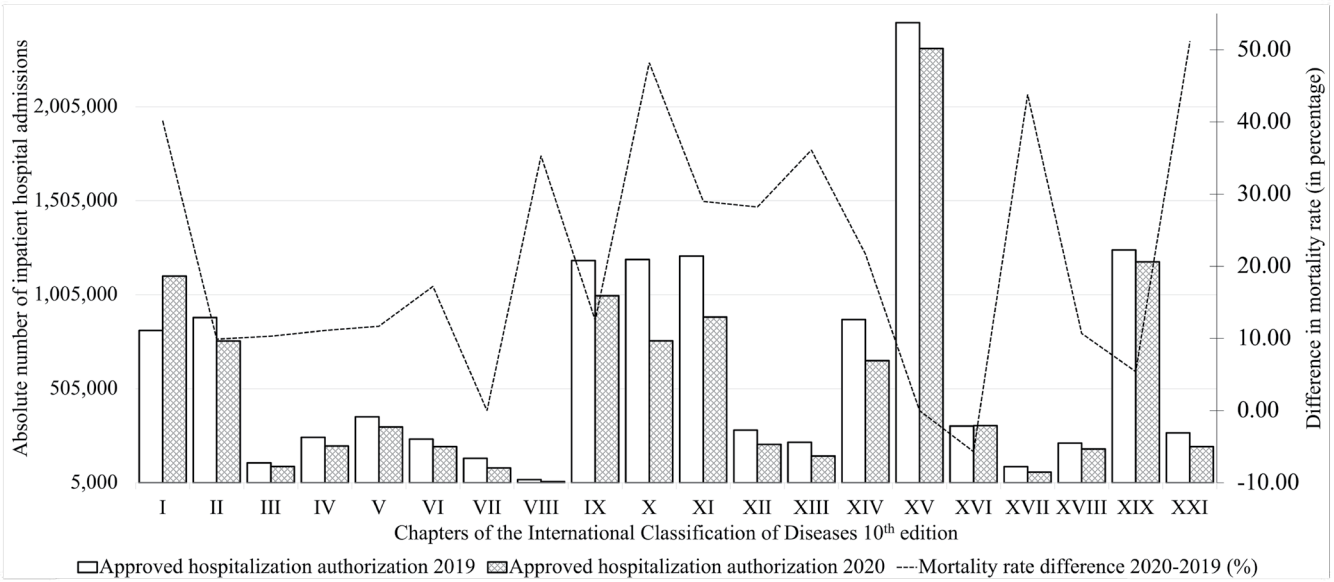
The all-cause mortality rate increased among all the major parameters analyzed (**Figure 1**). The greatest differences in all-cause mortality rate were observed in the northern region (+44.6%), among indigenous and male individuals (+49.7% and +32.5%, respectively), in elective medical procedures (+83.6%) and in medium-complexity care (+45.9%).

Among primary care performance variables, four main parameters were analyzed. Overall, the mean percentage of diabetic individuals for whom glycated hemoglobin (HbA1c) measurements were requested rose by 3.0% (5.3% in 2019 to 8.3% in 2020). Similarly, the mean percentage of hypertensive individuals for whom blood pressure levels were measured in each semester increased slightly from 2019 (3.0%) to 2020 (3.3%). Furthermore, an increase of 3.0% in the mean proportion of pregnant females who attended at least six prenatal consultations among which the first consultation occurred no later than the 20th gestational week was observed over the period analyzed. However, immunization coverage dropped from 73.4% in 2019 to 66.6% in 2020.

DISCUSSION

This study demonstrates that although there has been an overall increase in the transfer of funds to the healthcare system in Brazil since the onset of the pandemic, no immediate improvement in national health-related variables has been noticed. We observed contrasting reductions in the numbers of inpatient hospital authorizations in relation to different geographic, racial and gender-related features. Remarkably, there was an unequal decline in hospital admissions among black individuals. Immunization coverage was the only primary care performance benchmark that declined from 2019 to 2020. A significant reduction in hospital admissions was observed with regard to most chapters of the ICD-10, except for infectious and parasitic diseases and disorders of the perinatal period, but this was not strictly associated with the decrease in the specific-cause mortality rate. Considering the abovementioned parameters, recent political decisions may have impacted Brazil over the course of the coronavirus pandemic, with regard to national welfare.

Our results have implications for policymakers and medical professionals, given that most individuals in situations of poverty were significantly more affected by the pandemic. Our findings



*Chapter XX of ICD-10 was excluded due to lack of data

Chapter I (Certain Infectious and Parasitic Diseases), Chapter II (Neoplasms), Chapter III (Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism), Chapter IV (Endocrine, nutritional and metabolic diseases), Chapter V (Mental and behavioral disorders), Chapter VI (Diseases of the nervous system), Chapter VII (Diseases of the eye and adnexa), Chapter VIII (Diseases of the ear and mastoid process), Chapter IX (Diseases of the circulatory system), Chapter X (Diseases of the respiratory system), Chapter XI (Diseases of the digestive system), Chapter XII (Diseases of the skin and subcutaneous tissue), Chapter XIII (Diseases of the musculoskeletal system and connective tissue), Chapter XIV (Diseases of the genitourinary system), Chapter XV (Pregnancy, childbirth and the puerperium), Chapter XVI (Certain conditions originating in the perinatal period), Chapter XVII (Congenital malformations, deformations and chromosomal abnormalities), Chapter XVIII (Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified), Chapter XIX (Injury, poisoning and certain other consequences of external causes), and Chapter XXI (Factors influencing health status and contact with health services).

Figure 1. Absolute numbers of inpatient hospital admissions in Brazil, according to the chapters of the International Classification of Diseases 10th edition (ICD-10)*, and the percentage difference in the mortality rate between the years 2019 and 2020.

Table 2. Brazilian federal government public expenditure on health between 2019 and 2020

Subarea/subfunction	Expenditure in million reais (%)		Difference in million reais (relative % difference from 2019 to 2020)
	2019	2020	
Hospital and outpatient care	57,017.14 (49.9)	54,585.73 (36.2)	-2,431.41 (-4.2)
Primary care	26,404.33 (23.1)	25,813.42 (17.1)	-590.91 (-2.2)
Prophylactic and therapeutic support	10,968.56 (9.6)	11,365.96 (7.5)	397.40 (+3.6)
General administration	7,959.63 (6.9)	47,013.74 (31.2)	39,054.11 (+490.6)
Epidemiological surveillance	6,266.46 (5.4)	6,091.47 (4.0)	-174.99 (-2.7)
Others	5,565.96 (4.8)	5,592.95 (3.7)	26.99 (+0.04)
Total	**114,182.11 (100)**	**150,463.29 (100)**	**36,281.18 (+31.7)**

Difference refers to the row data from 2019 and 2020. The relative difference is expressed as a percentage and is calculated as follows: [difference from 2019 to 2020)/2019]. Data were obtained from DATASUS–SIH, SISAB and the Brazilian public expenditure portal. Values are expressed per R$ 1,000,000. US$ 1.00 = R$ 5.32 on May 25, 2021.

suggest that vulnerable populations (including indigenous and black individuals) and people living in socioeconomically vulnerable settings (such as in the Northeast and North of Brazil) may have been negatively overwhelmed by the pandemic, potentially because these populations have historically had inadequate access to care, generally have precarious work conditions, with informal employment that often cannot be accommodated to remote work. Similar results have been reported from several cohorts and worldwide cross-sectional studies.[22–25] The study by Rocha et al. demonstrated the correlation between socioeconomic

vulnerability and the disorderly spread of the disease and mortality in Brazil.[22]

Furthermore, according to Garg et al., among COVID-19 deaths registered in New York City for which race and ethnicity data were obtainable, mortality rates were considerably higher among black or African-American populations (92.3 deaths per 100,000 individuals) and among Hispanic or Latino individuals (45.2 deaths per 100,000 individuals).[25] Likewise, based on data from the Mexican Ministry of Health, Ibarra-Nava et al. identified that the proportion of deaths caused by COVID-19 among indigenous communities was higher than in non-indigenous populations (16.5% versus 11.1%, respectively).[24] Even though recent studies have emphasized the late impact of the pandemic among socioeconomically susceptible individuals, there is still a need for additional studies addressing the effects of the pandemic among groups, in order to prevent and limit the spread of coronavirus among people who are at greater risk of poorer outcomes.

The mean 13.7% reduction in inpatient hospital admissions was accompanied by a lower number of hospitalizations for elective medical procedures (mean reduction of 34.3%) and an increase in the all-cause mortality rate (30.6%). Similar findings have been reported in the literature, including among developed countries such as Italy, Spain, the United States and the United Kingdom.[26-29] For instance, in the United States, cardiac catheterization due to laboratory ST-segment elevation myocardial infarction activation was reduced by 38.0%, and this was similar to results found in Spain (40.0% reduction).

Regarding oncology services, a recent systematic review showed that interruption of cancer treatment at any stage was reported by up to 77.5% of the patients enrolled at the services included in the surveys, and that this was usually associated with reduced service availability.[30] In general, the reasons for this reduction in services may involve interruption of clinical and surgical procedures, including those with diagnostic purposes, and a representative decrease in transplantation activities. This ultimately implies an increasing accumulation of patients with chronic conditions but without care, which would be in addition to the historical repressed demand for elective surgeries. This situation may be exceedingly harmful, and is aggravated by the reduction of 81.9% in federal complementation of resources destined for hospitalizations. Thus, we reiterate and advocate that there is a need to maintain access to healthcare, particularly for patients with comorbidities, in order to decrease morbidity and mortality among this considerable proportion of the whole population.

We found that there had been considerable reductions in public expenditure in relation to important subfunctions of the Ministry of Health (hospital and outpatient care, primary care, prophylactic and therapeutic support and epidemiological surveillance). Together, the target for the strategy for reductions in federal government outlays totaled more than R$ 3.1 billion. Nevertheless, federal transfers within the "general administrative" subfunction have increased nearly fivefold, which represents an unprecedented rise since 2016. This specific governmental subfunction coordinates the management and maintenance of other government bodies, including federal employees and unit administration payments, and does not necessarily correlate with improvement of the overall healthcare system. Contrariwise, in nations with better-coordinated pandemic governance arrangements, including improvement of outpatient services, social supportive policies and primary care, the investment in areas specifically oriented towards healthcare have increased during the pandemic.[31-34]

We observed that there was a high excess mortality rate in undeveloped and socially vulnerable areas, and also among indigenous, Asian and black individuals. Our mortality results were similar to those reported for Asian, European, South and North American and African countries.[35-39] For instance, in a study conducted in the United States, in which 3,135 counties from different datasets were enrolled, individuals living in "poor housing conditions" had a 50.0% higher risk of contracting SARS-CoV-2 and a 42.0% higher risk of dying because of the viral infection. Correspondingly, in Stockholm, Sweden, an excess mortality rate was noticed among people living in socioeconomically deprived areas (excess mortality rate ranging from 162% to 178%). Interestingly, our results showed that an increase in hospitalization costs is unlikely to translate into a reduced mortality rate. Therefore, governmental officials need to understand that the achievement of highly impactful healthcare outcomes is often not purely associated with the quantity of resources available but, rather, with how the system is reorganized.

The mean 6.8% reduction in the vaccination coverage was the only primary care indicator that demonstrated significant variation, over the period analyzed. However, the performance of all three additional parameters was classified as insufficient (< 20% of the target population had comorbidity-specific check-ups over the period). This result suggests that further actions are required in order to strengthen the primary care system and related activities, and to establish a more efficient healthcare policy, so as to prevent the development and worsening of most diseases.

CONCLUSION

The scenario described here highlights how healthcare inequalities have become more pronounced during the COVID-19 pandemic due to underfunding of the healthcare system and social policies in general, as well as due to the dynamic of the pandemic, which has increased historical vulnerabilities. At times, the actions and, at times, inaction of the Brazilian government have gone against worldwide evidence about the importance of continuous primary healthcare systems, health surveillance and social protection programs. These are critical for improving

equity and access, healthcare performance and health outcomes, and for identifying public health emergencies, particularly during crises like the ongoing pandemic.

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Knowledge of and adherence to standard precautions in a hemodialysis unit: a cross-sectional study

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ABSTRACT

BACKGROUND: Standard precautions (SPs) are recommended safety measures for healthcare professionals to follow, with a view to preventing healthcare-related infections (HCRIs) and for their own protection. Inadequate adherence to these measures can lead to occurrences of occupational accidents and HCRIs.

OBJECTIVES: To ascertain the knowledge of and adherence to SP measures among the nursing staff of a hemodialysis service and the relationship of these variables to occurrences of work accidents with biological material.

DESIGN AND SETTING: Descriptive cross-sectional and correlational study with a quantitative approach developed in a hemodialysis clinic in Minas Gerais.

METHODS: Data were collected through sociodemographic questionnaires and questionnaires on knowledge of and adherence to SPs.

RESULTS: 29 professionals participated in the study. It is noteworthy that all of them had already participated in training related to SPs. However, no relationship was identified between knowledge of (15.17 points) and adherence to (71.86 points) SPs. In addition, inferential analysis showed that there was a relationship between suffering a work accident with biological material and the sociodemographic data and knowledge of and adherence to standard precautions.

CONCLUSION: Knowledge of the SPs that had been established did not mean mastery of the subject. Despite positive results regarding adherence, factors requiring improvement were observed. It was possible to infer the characteristics that gave rise to greater risk of occurrences of accidents at work. Thus, this study showed the importance of assessing knowledge of and adherence to SP, in order to optimize and direct continuing education towards resolving occupational exposure.

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), standard precautions (SPs) are essential safety measures for healthcare with a view to protecting the client against healthcare-related infections (HCRIs), and for professional protection against occupational exposure to potentially contaminated biological material (PCBM).[1]

This set of SP measures is composed of the following: hand hygiene before and after contact with patients or areas adjacent to them; use of personal protective equipment (PPE), including glasses, mask, apron and procedure gloves; correct handling and disposal of sharps; and vaccination against hepatitis B.[2,3]

It is known that low adherence to SPs contributes to growing numbers of occupational accidents in healthcare services.[3] Professionals who do not make adequate use of PPE and who handle sharps are exposed to occupational risks. In this context, the nursing professionals of hemodialysis services can be highlighted, given that they handle sharp devices and potentially contaminated equipment on a daily basis.[4,5]

It is important to consider that chronic renal patients who are undergoing renal replacement therapy (RRT) are in a vulnerable condition. They are subjected to invasive procedures every week, which are performed in a hospital environment, where pathogens and multidrug-resistant agents are present.[6] Studies have demonstrated occurrences of infection among patients on RRT,[7,8] thus highlighting the prevalence of infections caused by resistant microorganisms among patients on dialysis and awaiting kidney transplantation.[9]

In view of the complexity of the hemodialysis service and the vulnerability of patients subject to RRT, the nursing team at these services takes on an important role of responsibility for care, in order to ensure patient safety and their own safety through adherence to SP.

However, studies have revealed low adherence to SP among nursing professionals[10,11] and have identified factors that determine inadequate adherence. Recklessness, shortage of materials in hospital units,[12] insufficient knowledge and work overload have been highlighted.[13]

In view of the above, we perceived that there was a gap in the literature. In particular, there seemed to be a need to assess the knowledge of and adherence to SP among the nursing team working on hemodialysis, considering that these variables are directly related to occurrences of HCRIs, occupational accidents with exposure to PCBM and the quality and safety of healthcare.

OBJECTIVE

The aim of this study was to ascertain the knowledge and adherence of the nursing staff of a hemodialysis unit with regard to SP measures and correlate these variables with occurrences of occupational accidents with PCBM.

METHODS

This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative.[14] It was a descriptive quantitative cross-sectional and correlational study performed at a hemodialysis clinic in the city of Uberlândia, Minas Gerais, Brazil. This is a private clinic accredited to the Brazilian National Health System (Sistema Unico de Saúde, SUS) that performs an average of 3,500 hemodialysis sessions per month.

A non-probabilistic or convenience sample was used. All the nursing professionals at the institution who had worked there for more than six months with a minimum workload of 20 hours a week were eligible for inclusion in the study, provided that they were not on vacation, maternity leave or sick leave at the time of data collection.

Professionals whose work exclusively involved administrative activities were excluded. In addition, those who were participating in training related to safety measures at the time of data collection were also excluded, as this training would possibly overvalue their knowledge about SP.

Data collection and statistical analysis

Data were collected using self-administered questionnaires: one seeking sociodemographic data and variables relating to occurrences of occupational accidents with PCBM; a questionnaire to assess knowledge of SP (Standard Precautions Knowledge Questionnaire, SPKQ);[15] and another questionnaire to measure adherence to SPs (Standard Precautions Adherence Questionnaire, SPAQ).[16]

The SPKQ had previously been validated for Brazilian realities. It contains 20 questions relating to healthcare professionals' knowledge of SP, and has proved to be stable due to its reliability according to the intraclass correlation coefficient, which was calculated as 0.91, and its satisfactory agreement with the mean kappa index.[15]

The SPAQ is another instrument that has been translated and validated for use in Brazil.[16] It is composed of 20 questions relating to adherence to SP, in a Likert-type format, ranging from 1 to 4 points for each question.

For data compilation, double entry was used independently, in order to eliminate possible mistakes. The data were analyzed by means of the R software, version 3.6.3, and the R Studio software, version 1.2.5001 (Integrated Development for R; RStudio, PBC, Boston, MA, United States).

Descriptive statistical techniques were used for presentation of the numerical data. Categorical data were expressed in terms of frequencies (absolute and relative). To identify the relationship between occurrences of accidents with PCBM and the other variables studied, bivariate analysis was performed using Fisher's exact test. Simple and multiple linear regression models were used to identify the relationship of the scores obtained in the SPAQ and the SPKQ with occurrences of accidents with PCBM. The significance level was taken to be alpha < 0.05.

Ethical issues

This study was approved by our institution's ethics committee for research on human beings, under CAAE number 09987318.7.0000.5152, dated July 17, 2019. Confidentiality and anonymity for the participants was ensured, in accordance with resolution no. 466/2012 of the National Health Council.

RESULTS

Twenty-nine nursing professionals participated in the study who were active in the outpatient dialysis service of our institution participated in this study. These comprised 24 nursing technicians (82.75%) and five nurses (17.24%); 79.31% were female; the participants' mean age was 39.1 years; their mean length of professional experience was 13.0 years; and their mean length of experience of dialysis was 11.9 years (**Table 1**).

Regarding participation in training relating to SPs, 29 (100%) responded that they had had some training: 26 (89.65%) underwent this in 2019 and the majority (55.17%) received their training from the institution's Internal Accident Prevention Commission (IAPC). It was noteworthy that 26 (89.65%) of the nursing staff surveyed expressed a desire to receive training and updates on SP measures.

Table 1. Distribution of the nursing staff according to gender, age, education level, accidents with sharps, accidents with potentially contaminated biological material, participation in training, vaccination status against hepatitis B and knowledge of vaccine response, at a hemodialysis clinic in the city of Uberlândia, Minas Gerais, Brazil, 2020 (n = 29)

Variables	n	%
Participants' gender		
Male	6	20.69
Female	23	79.31
Age (years)		
20 to 30	5	17.24
30 to 40	10	34.48
40 to 50	10	34.48
50 to 60	2	6.89
> 60	1	3.44
Education level reached		
Completed high school	19	65.51
Undergraduate at university/college	4	13.79
Graduated from university/college	1	3.44
Specialization	5	17.24
Work accidents with PCBM		
No	16	55.17
Yes	13	44.82
Accidents with PCBM consisting of unhealthy skin or mucus, involving contact with potentially contaminated blood or body fluids		
No	19	65.51
Yes	10	34.48
How many times have you had an accident with PCBM consisting of unhealthy skin or mucus, involving contact with potentially contaminated body fluids?		
None	18	62.06
Once	3	10.34
Twice	2	6.89
Four times	2	6.89
Several (more than four)	3	10.34
Missing response	1	3.44
Accidents at work with biological material by means of sharps or exposure to mucous membranes or unhealthy skin in the last 12 months (last year)		
No	24	82.75
Yes	5	17.24
Participation in training on standard precautions offered by the employing institution		
Yes	29	100.00
Schedule for complete hepatitis B vaccination (3 doses)		
Yes	29	100.00
Underwent a medical examination to detect antibodies for hepatitis B		
No	1	3.44
Yes	28	96.55
Examination result regarding antibodies for hepatitis B		
Positive	14	48.27
Negative	8	27.58
I don't know	3	10.34
Missing response	4	13.79

n = absolute number; % = percentage; PCBM = potentially contaminated biological material.

When asked about changing devices for disposing of sharps when they reached two-thirds of their capacity, 21 (72.41%) reported that the device was changed when it reached its maximum recommended capacity, while eight (27.58%) reported that they did not do this replacement.

In analyzing the responses to the SPKQ, the average knowledge of SPs was 15.17 points; the maximum score was 18 and the minimum was 5 points. With regard to adherence to SPs (SPAQ), the mean score was 71.86 points, the maximum was 80 and the minimum was 45 points. The relationship between knowledge of and adherence to PP was calculated by means of Kendall's correlation between the scores. A weak correlation of 0.221 (P = 0.126) was noted, which showed that there was no relationship between knowledge of and adherence to SPs in the sample studied.

The majority of the participants correctly judged each item in the SPKQ questionnaire. It was noteworthy that 79.31% said that they knew what SPs were. However, 82.75% considered question 3 (Q3) to be true, which states that SPs have the main objective of protecting the healthcare team, thereby devaluing patient safety. In addition, more than 41% of the professionals surveyed judged Q18 to be incorrect or did not know how to judge Q18: "When providing nursing care to patients with hepatitis C or human immunodeficiency virus (HIV), it is necessary to adopt only the SP measures" (**Table 2**).

Regarding adherence to SP, it was highlighted that 6.89% of the nursing professionals performed hand hygiene before providing assistance to patients only rarely or sometimes. In procedures with the possibility of contact with urine or feces, 100% of the participants reported always wearing gloves. However, in procedures with the possibility of contact with unhealthy skin, adherence to use of this equipment decreased (82.75%). Regarding the use of goggles and a mask, 79.31% stated that they always used this equipment. However, only 48.27% use the respiratory etiquette when coughing or sneezing (**Table 3**).

In correlating occurrences of biological accidents with PCBM and other variables, significance at the 5% level was identified through Fisher's exact test. There were associations with the following response variables: suffering an occupational accident with PCBM (P < 0.001); suffering a work accident with PCBM through needlestick or exposure to mucous membranes or unhealthy skin over the last 12 months (P = 0.036); the frequency with which occupational accidents with PCBM were notified (P <0.001); results from examinations for antibodies to hepatitis B post-vaccination (P = 0.021); responses to question 1 (Q1) of the SPKQ, "Do you know what the standard precautions (SP) measures are?" (P = 0.002); responses to Q6 of the SPKQ, "Since the use of gloves can prevent hand contamination, it is not necessary to clean your hands after removing the gloves" (P < 0.001); responses to Q18 of the SPKQ, "When providing nursing care to patients with hepatitis

Table 2. Descriptive analysis on knowledge of standard precautions in a nursing team at a hemodialysis clinic in the city of Uberlândia, Minas Gerais, Brazil, 2020 (N = 29)

Knowledge of standard precautions	True/yes	False/no	I don't know
Q1 - Do you know what standard precaution measures are?	23 (79.31)	0 (0.0)	5 (17.24)
Q2 – Standard precautions should only be applied to patients diagnosed with infection or patients who are in the incubation period for a given infection.	4 (13.79)	20 (68.96)	3 (10.34)
Q3 - The main objective of adhering to standard precaution measures is to protect the healthcare team.	24 (82.75)	2 (6.89)	3 (10.34)
Q5 - Hand hygiene should be performed when providing care to different patients.	26 (89.65)	2 (6.89)	0 (0)
Q16 - Symptomatic respiratory patients (coughing, sneezing, etc.) must be kept at least one meter away from other patients in the ward.	22 (75.86)	2 (6.89)	4 (13.79)

Table 3. Descriptive analysis on adherence to standard precautions in a nursing team at a hemodialysis clinic in the city of Uberlândia, Minas Gerais, Brazil, 2020 (n = 29)

Adherence to standard precautions	N	R	S	O	A
Q1 - I perform hand hygiene before assisting the patient.	0 (0)	1 (3.44)	1 (3.44)	7 (24.13)	20 (68.96)
Q14 - I use a protective mask when there is the possibility of contact with splashes of blood, body fluids, secretions or excretions.	0 (0)	0 (0)	1 (3.44)	3 (10.34)	23 (79.31)
Q15 - I wear goggles when there is a possibility of contact with splashes of blood, body fluids, secretions or excretions.	0 (0)	1 (3.44)	4 (13.79)	1 (3.44)	23 (79.31)
Q18 - I do not recap used needles.	5 (17.24)	4 (13.79)	3 (10.34)	5 (17.24)	10 (34.48)
Q20 - When coughing or sneezing, I use a disposable handkerchief to cover my mouth and nose, and then I dispose of it and sanitize my hands.	1 (3.44)	2 (6.89)	7 (24.13)	5 (17.24)	14 (48.27)

N = never; R = rarely; S = sometimes; O = often; A = always.

C or HIV, it is necessary to adopt only the standard precaution measures" (P = 0.004); responses to Q20 of the SPAQ, "When I cough or sneeze, I use a disposable handkerchief to cover my mouth and nose, then I dispose of it and clean my hands" (P = 0.049).

Univariate analysis was carried out on responses to the indicator of suffering an accident with PCBM. All the variables of the SPKQ and SPAQ were used as covariates. Variables with significance at 10% in univariate analysis were then subjected to multivariate analysis.

In making multivariate adjustments using the significant variables, the variables in the final multivariate model that explained suffering an accident with PCBM with a significance level of 5% were the following: occurrence of a work accident with potentially contaminated sharps (standard deviation, SD: ± 1.409; confidence interval, CI: [0.935; 6,867]; P = 0.019); and identifying question 18 of the SPKQ as false, i.e. "When providing nursing care to patients with hepatitis C or HIV, it is necessary to adopt only standard precaution measures" (SD: ± 1.297; CI: [0.566; 6.054]; P = 0.028).

Thus, the odds ratio (OR) between occurrence of work accidents with potentially contaminated sharps and the variable "If you suffered a work accident with potentially contaminated sharps", showed that nursing professionals who reported having already suffered this type of accident were 27 times more likely to have accidents in this way than were those who had not suffered a work accident with sharps (OR: 27.51; CI: [2.546; 959.731]; P = 0.019). In addition, those who believed that the sentence in question SPKQ-18 was false ("When providing nursing care to patients with hepatitis C or HIV, it is necessary to adopt only standard precaution measures") were 17 times more likely to suffer an accident through working with PCBM than were those who believed that the sentence was true or did not know whether they believed the sentence (OR: 17.27; CI: [1.761; 425.760]; P = 0.028).

DISCUSSION

After recruiting nursing professionals and applying the questionnaires, the sociodemographic description and the relationship between occurrences of occupational accidents and other variables studied were assessed.

There was a predominance of professionals at technical level, which can be explained by the provisions of Ordinance No. 389/14, which determines that in hemodialysis services, one nursing technician is required for every four patients and one nurse per shift is required for every 35 patients.[17] Thus, it is inferred that the demand for professionals at technical level will always be greater than the demand for nurses.

In a previous study, it was observed that 61.7% of the population of nursing professionals was up to 40 years old.[18] This corroborates our results, in which the average age was found to be 39.1 years. The prevalence of young adult professionals explains the average of 13 years of professional experience.

Another result presented by 100% (29) of the professionals was that they had all participated in training provided by the employing institution within the last 12 months, with a SP approach. Their responses to Q1 of the SPKQ ("Do you know what standard precautions measures are?") may have been determined by this fact, given the impact of continuing education in healthcare services, with a view to expanding knowledge and preparing the team for work activities,[2,12,19] especially those with active methodology and protagonism of the subject.[15] However, even so, it was observed that 17.24% of the professionals stated that they did not have any knowledge about SPs.

Although 79.31% of the sample claimed to know about SPs, the antagonistic result stood out, in which 82.75% responded that Q3 of the SPKQ was true ("Adherence to standard precaution measures has the main objective of protecting the healthcare team"), which incorrectly presents the main objective of SPs. A similar result was observed in a study in which 67.5% of the nurses believed that the main objective of SPs was to protect the healthcare team, while ignoring the protection provided for patients that was involved in adherence to SPs.[12]

On the other hand, a study carried out in São Paulo showed results that were contrary to those of previous studies, in which 87.6% of the participating nurses disagreed with the statement contained in Q3 of the SPKQ.[15] This result was also described in another recent study, in which 72% of the participants strongly disagreed with the objective of the SPs that is presented in that question.[20]

The participants in our study showed positive results regarding the SPAQ questions that investigate the frequency of hand hygiene at different times or situations, namely: Q1 - before providing assistance to the patient; Q2 - before performing aseptic techniques; and Q3 - after exposure to potentially contaminated body fluids. This result demonstrates the coherence and ability of the professionals to recognize the moments when hand hygiene is essential. However, even though these results were satisfactory, it is important to highlight that for Q1 of the SPAQ, 6.89% of the participants presented an incoherent response to the recommendations. On the other hand, this was not repeated in Q3 of the same instrument. This suggests that nursing professionals are concerned with sanitizing their hands in order to minimize the risk of contamination when exposing themselves to potentially contaminated fluids, but give less value to the importance of this act before providing nursing care, which thus represents an important risk to patients' safety.[21]

From a study developed in a hemodialysis unit, it was pointed out that nursing professionals had low adherence to hand hygiene, and that they performed this technique only in 16.6% out of 1090 opportunities.[22] Although hand hygiene is frequently discussed, educational interventions remain one of the important alternatives for raising professionals' awareness of this.[23,24]

There was significant divergence in the responses to the assertion in Q18 of the SPKQ ("When providing nursing care to patients with hepatitis C or HIV, it is necessary to adopt only the standard precaution measures"). Among the professionals surveyed, 38% judged that this assertion was incorrect and 3% did not know how to judge it. This was in contrast to their self-reported knowledge of SP and drew attention to the fact that the hemodialysis unit studied serves patients who are seropositive for HIV and hepatitis B and C. This result was similarly observed in two other studies: in one, only 85% judged the same statement to be correct;[12] while in another study, 76.8% marked this statement as true.[15] In addition, this finding highlights the existence of stigma in caring for patients who are known to be positive for these viruses. This attitude puts nursing professionals in a situation of greater occupational risk, due to their unnecessary (excessive) and inappropriate use of PPE.

The relationship between occurrences of accidents with PCBM and the SPKQ variables shows the impact of knowledge of SPs on the prevalence of occupational accidents, since accidents with PCBM are usually associated with nonuse or inappropriate use of PPE and non-adherence to SPs.[25,26] This can be shown by the result in which 80% of the professionals who suffered accidents with PCBM did not believing that just adopting SPs was enough for care directed to patients with hepatitis C or HIV.

The risk of accidents with potentially contaminated sharps was 27.51 times greater among professionals who had already had an accident. This corroborated a result observed in another study, in which 46.6% of the sample reported having already been exposed to PCBM and 63.5% of these individuals claimed to have been injured more than once.[26]

The importance of training in terms of biosafety practices can be emphasized: not only at work, but also in professional training, as a strategy for minimizing the impacts of lack of knowledge,[27] since occupational accidents with PCBM may be associated with lack of knowledge or low participation in training activities.[26] In addition, our findings contribute to directing institutional managers' attention towards professionals who are at greater risk of suffering new accidents at work with PCBM. Our findings emphasize training measures for promoting a better institutional safety climate and, thus, for also promoting health safety (for both patients and professionals) in the institution.

Although the average scores obtained from the questionnaires (SPAQ = 15.17 and SPKQ = 89.82) were positive, the deficits in

knowledge of and adherence to SPs become significant in view of the vulnerability of users of the renal replacement therapy service and the possible consequences for workers, such as occupational accidents and their associated morbidity, in addition to possible losses for the institution.[3]

In another study, it was concluded that knowledge of SPs did not necessarily mean adherence to these measures.[12] This corroborates what was observed in our sample, since only a weak correlation was identified between these two variables.

It is worth mentioning that the present study was carried out in a single center, which limited the population for composition of the sample. It can therefore be suggested that further studies should be conducted, with participation of several dialysis services, in order to confirm and generalize the findings from the present study, for nursing professionals working in these services.

CONCLUSION

Although the institution evaluated in this study had provided training on SPs within the last 12 months, the professionals surveyed showed significant inconsistencies in their knowledge of SPs. We can highlight their inappropriate perception of insecurity regarding use of SPs to care for people with viral conditions such as HIV and hepatitis C.

Regarding adherence to SP, although the overall result was positive, there were reports of non-adherence to hand hygiene before performing nursing care, insufficient adherence to respiratory etiquette and inadequate needle recapping. This occurrences demonstrate that there is a need for improvements in adherence to these measures among the nursing professionals surveyed.

Furthermore, this study highlights the importance of training healthcare teams to provide them with better knowledge of and adherence to SP. It provides a stimulus for undertaking other studies in order to expand the understanding of this problem among healthcare professionals who are exposed to potentially contaminated biological material in their work practice, especially with regard to professionals working in dialysis services, given their daily exposure.

Lastly, the relationship between occurrences of accidents with potentially contaminated sharps and lack of knowledge of SPs corroborates data from the literature. This highlights the importance of evidence-based practice in order to optimize health safety, both for professionals and for patients.

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Impact of the COVID-19 pandemic on compulsory notification of meningitis during the first wave of the pandemic in Brazil: an ecological study using P-score

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ABSTRACT

BACKGROUND: Meningitis is listed as one of the diseases requiring compulsory notification in Brazil. It can affect all age groups and also has no seasonality. Cases can be recorded in all months of the year and in all states of Brazil. Despite its importance, the obligation of immediate notification may have been compromised by the coronavirus disease 2019 (COVID-19) pandemic.

OBJECTIVE: To analyze the immediate impact of the COVID-19 pandemic on compulsory notifications of meningitis in Brazil and its states during the first wave of the pandemic.

DESIGN AND SETTING: This was an ecological study involving all confirmed cases of meningitis in Brazil, in its regions and in its states.

METHODS: Data for the months from 2015 to 2020 were obtained from the database of the Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação, SINAN), in the Department of Informatics of the National Health System (Departamento de Informática do Sistema Único de Saúde, DATASUS). The P-score was used to obtain the percentage change in the numbers of cases reported in 2020.

RESULTS: A 45.7% reduction in notifications of meningitis in Brazil was observed. Regarding the regions and the states, with the exception of Roraima, all of them showed a negative P-score, with decreasing curves each month.

CONCLUSION: The pandemic caused a negative impact on meningitis notifications in Brazil.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was recorded for the first time in Brazil on February 26, 2020. Just over a year later, on June 11, 2021, this country ranked third in the absolute number of disease records (17.2 million cases) and second in the number of deaths (482,000), with incidence of 8190.0/100,000 inhabitants, mortality of 229.4/100,000 and case fatality rate of 2.8%.[1]

Due to the pandemic, the Brazilian healthcare system directed its efforts to combating COVID-19, through adjusting the healthcare network (opening of temporary hospitals and expansion of numbers of infirmary beds and intensive care units, for example), as well as through implementation of non-pharmacological measures to reduce the intensity of disease transmission, such as restricting urban mobility and changes to healthcare services, i.e. reduced hours and numbers of daily appointments.[2] These measures, although necessary, impacted the diagnosis and management of other endemic diseases in this country, as already observed in investigations involving leprosy[3] and tuberculosis.[4] This went against the measures that would be necessary for control and monitoring of these diseases,[5] which thus received less attention. Consequently, there were delays in diagnosing these diseases, due to the pandemic.[6]

In accordance with Consolidation Ordinance No. 4/GM/MS, of September 28, 2017, meningitis is listed as one of the diseases requiring compulsory notification, given that it is a public health problem.[7] It is considered endemic in Brazil, can affect all age groups and also has no seasonality. Cases can be recorded in all months of the year and in all states of Brazil.[8] Despite its importance, the obligation of immediate notification may have been compromised by the COVID-19 pandemic.

In order to analyze the impact of the pandemic on different health problems, tools to quantify this impact have been developed, among which the P-score[9] stands out. Although this was developed to assess excess mortality during the pandemic, it can also identify underrecording of health events. Moreover, this was the first national study to use P-scores to analyze the impact of the pandemic.

OBJECTIVE

In the light of the above context, the aim of this study was to analyze the immediate impact of the COVID-19 pandemic on compulsory notifications of meningitis in Brazil and its states during the first wave of the pandemic.

METHODS

This was an ecological study involving all confirmed cases of meningitis in Brazil, in its regions and states, from 2015 to 2020 The period 2015 to 2019 was used to obtain the expected values of the events analyzed (pre-pandemic period) and the year 2020 was used for comparison purposes (pandemic period). Data were collected in relation to the general population and in relation to children under 15 years of age. The records were obtained from the Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação, SINAN), of the Department of Informatics of the National Health System (Departamento de Informática do Sistema Único de Saúde, DATASUS).

For analysis, an adaptation of the P-score was applied,[9] considering the following equation:

$$P-score = \frac{No.\,of\ meningitis\ cases\ in\ 2020\ (January-August) - Expected\ meningitis\ case\ numbers\ in\ 2020}{Expected\ meningitis\ case\ numbers\ in\ 2020\ (January-August)} x100$$

The expected value for the event was calculated considering the average of the past five years, prior to the occurrence of the COVID-19 pandemic (i.e. from 2015 to 2019), as recommended.[9] The results were expressed as percentages, such that positive values indicated excess numbers of cases, and negative values indicated decreased numbers of cases.

This study did not require any adjudication from a research ethics committee, since it used data from the public domain.

RESULTS

From January to August 2020, 4,712 cases of meningitis were reported nationwide in the general population. For this same year, according to the calculation of mean values, 10,634 notifications were expected nationwide, thus resulting in a P-score of -45.7%. Considering only meningitis notifications among children under 15 years of age, 2,101 cases (44.6%) were recorded in 2020, while 5,343 notifications were expected nationally, thus giving rise to P-score of -60.7% for this group (**Figures 1** and **2**).

The southeastern region of Brazil had the highest number of notifications (2,446 registered cases; 51.9%). Out of this total, 1,131 notifications were from children under 15 years old (46.2%). In the southeastern region, in both groups, the P-score was negative, since 5,658 records were expected in the general group and 3,081 notifications in the under-15 group (P-scores of -56.8% and -63.3%, respectively). In addition, all other regions also showed negative P-scores in both groups, with declines of less than -50% (**Figures 1** and **2**).

The P-score curve showed a continuous drop in monthly notifications, in both groups, in all regions of the country after the beginning of the pandemic. In the first two months of 2020, before the arrival of COVID-19 in Brazil, there were also reductions in case notifications: -18% in January and -28.1% in February in the general group; -64% and -17% in the under-15 group. From March on, after confirmation of the first case of COVID-19 in Brazil, the drops were more pronounced, both nationally and regionally. The largest reductions were observed in August, just after the peak of the first pandemic wave, which was in June/July (-78% in the general group and -81.8% in the group with children under 15 years of age) (**Figure 2**).

Regarding the states, with the exception of Roraima, in the north of the country, which showed a positive P-score (22.8% in the general population and 57.9% in the group with children under 15 years of age), the other states showed declines in the numbers of notifications, especially Rondônia (no records in SINAN in 2020; P-score -100.0%) and Espírito Santo (three records in January 2020, among which one was in a child under 15 years of age; P-scores of -97.6% for the general population and -98.4% for children under 15 years of age). The state of Sergipe showed the smallest discrepancy between observed and expected values in the general population group (P-score of -14.4%) and Rio Grande do Norte was the state with values closest to what was expected for the group of children under 15 years old (P-score of -24.4%) (**Figure 1**).

DISCUSSION

The negative effects of the pandemic on making diagnoses of other diseases have been reported worldwide.[3,4,6,10] In Brazil, concerning only meningitis, the significant decrease in the number of compulsory notifications in 2020 does not seem to have occurred as a result of lower incidence of this disease during the pandemic period of COVID-19. As has been observed in relation to other diseases, this decrease in the number of records may be indicative of a reduction in the number of diagnoses made, or of operational losses that the pandemic has caused to the meningitis surveillance programs, in view of the guidelines provided by national and international healthcare organizations.[3,4]

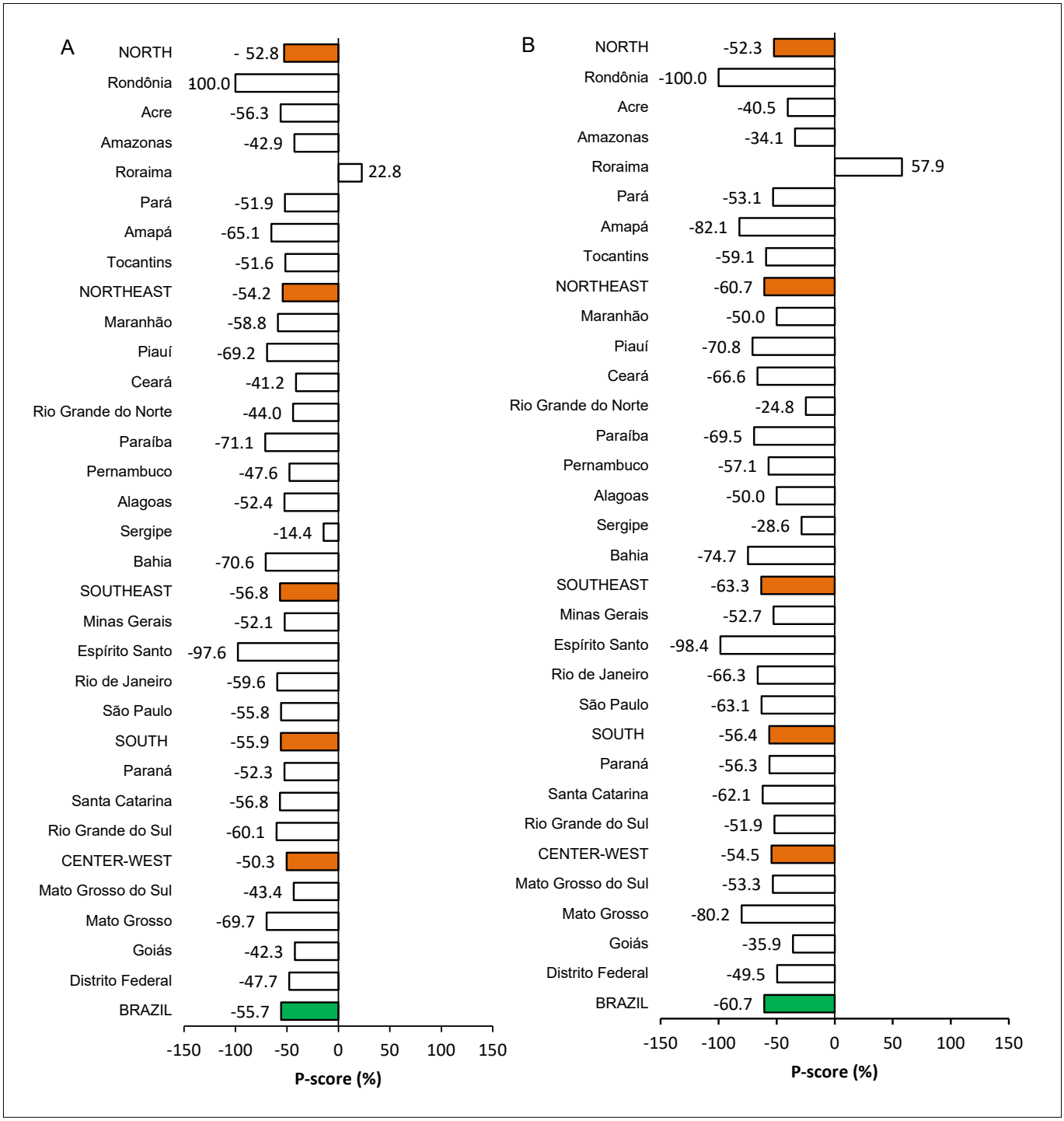

Figure 1. P-scores from reporting of meningitis (A) in the general population and (B) among children under 15 years of age. Brazil, regions and states. 2020.

Non-pharmacological measures to reduce transmission of COVID-19 may have influenced the chain of meningitis transmission in Brazil. The lower exposure engendered through isolation and social distancing actions during this period is one of the hypotheses for the drop in the rates, although we believe that this alone would not have the capacity to result in such a decline. Additionally, the pandemic caused changes to the routine of outpatient settings, including reductions in the numbers of consultations and absence of healthcare professionals infected by the virus, which would also have contributed to slowing down the number of

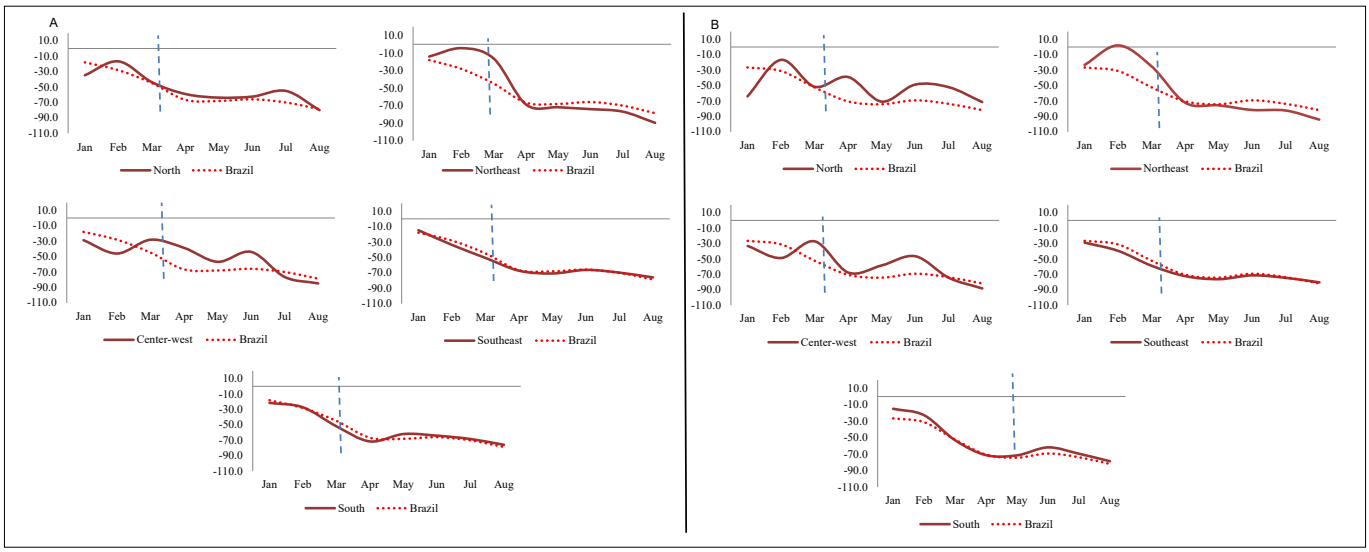

Figure 2. P-score curves from reporting of meningitis in the general population (A) and among children under 15 years of age (B). Brazil and regions; 2020.

diagnoses made.[4,11] On the other hand, fear made the population afraid to attend hospitals and healthcare centers, with a consequent impact on notifications of many diseases, including meningitis.

It is noticeable that the instability caused by the pandemic hampered and still interferes with normalization of the healthcare network and data supplied to healthcare information systems. Timely feeding of data from the National Health System (Sistema Único de Saúde, SUS) into its databases is very important for enabling analysis and monitoring of the health conditions of the Brazilian population. If this does not take place, it could lead to increases in hidden prevalence and maintenance of the transmission chains of many diseases.[3] Furthermore, the records in these systems make it possible to evaluate the impacts resulting from ongoing government projects, such as interventions and vaccination campaigns, as well as guiding the development of new healthcare policies.[12]

This study had limitations, among which its use of secondary data stands out. The quality of such data is influenced by the capacity of the local surveillance system. In addition, we can highlight the impact of the pandemic on the process of notification, typing, investigation and closure of cases.

CONCLUSIONS

The pandemic caused by COVID-19 had a negative impact on reports of meningitis in Brazil in 2020, with a sharp and constant drop throughout all the months studied. Additionally, an inverse correlation was observed between cases of COVID-19 and reported cases of meningitis, especially in August, after the first peak of the pandemic in Brazil. This impact should be seen as a warning sign for political and healthcare authorities, and it highlights the need for improvements in healthcare and surveillance services, such as adoption and/or strengthening of strategies for ensuring diagnoses and mandatory notifications while the pandemic persists.

Furthermore, it is essential and urgent to investigate how COVID-19 can influence the prognosis of patients with meningitis, considering that there are no studies that address this aspect, and that this information can help prevent occurrences of the disease.

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Telementored ultrasonography: a narrative review

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KEY WORDS (MeSH terms):
Ultrasonography.
Teleradiology.
Telemedicine.
Remote consultation.

AUTHORS' KEY WORDS:
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Telesonography.
Telementoring.

ABSTRACT

BACKGROUND: Teleradiology consists of electronic transmission of radiological images from one location to another, including between countries, for interpretation and/or consultation. It is one of the most successful applications of telemedicine. Combining this methodology with ultrasound (called telesonography) can accelerate the process of making diagnoses. Despite this rationale, the quality of the evidence about the effectiveness and accuracy of teleradiology remains unknown.

OBJECTIVE: To review the literature on the evidence that exists regarding use of telemedicine for ultrasound in situations of synchronous transmission.

DESIGN AND SETTING: Narrative review conducted within the evidence-based health program at a federal university in São Paulo (SP), Brazil.

METHODS: A search of the literature was carried out in April 2020, in the online databases MEDLINE, EMBASE, Cochrane Library, Tripdatabase, CINAHL and LILACS, for original publications in all languages. The reference lists of the studies included and the main reviews on the subject were also evaluated.

RESULTS: We included ten studies that assessed procedures performed by different healthcare professionals, always with a doctor experienced in ultrasound as a distant mentor. Among these, only one study assessed disease diagnoses in relation to real patients.

CONCLUSIONS: Despite the promising position of telesonography within telemedicine, no studies with reasonable methodological quality have yet been conducted to demonstrate its effectiveness.

INTRODUCTION

Ultrasonography (US) is a portable and sensitive noninvasive method that does not use ionizing radiation and which is easily available in places where traditional imaging methods are expensive or unavailable.[1-5]

High levels of individual skill in US are difficult to achieve, as the only reference for location and orientation of the image plane for the organ under investigation is the image of this organ on the monitor. There is no positioning feedback to show the examiner how far an image plane deviates from the true axial or cross-sectional plane of a target organ.[6] Consequently, even experienced examiners may make mistakes regarding image plane positioning.[6]

More and more medical schools, mainly in Europe, have incorporated US training in their curriculum, especially in the discipline of medical emergencies.[7-9] US requires not only theoretical and anatomical knowledge (which can be acquired through distant-learning methods) but also visual, sensory and motor perceptual skills, along with the ability to integrate ultrasound findings into real-time clinical contexts, as part of decision-making processes.[7,8]

Telemedicine consists of use of telecommunications technologies to communicate and facilitate health-related services between two remote parties. It is typically used in healthcare between provider and patient or between two healthcare providers.[5,10-12] It can serve as a vehicle to enable provision of high-quality, cost-effective, convenient and efficient healthcare for patients while providing access to healthcare services from virtually any location.[5,10,13,14]

Telemedicine can improve the quality of care provided, through complementing the services available or providing care that otherwise would not be available because of time, distance or resource limitations.[10,13,15] This forms a potential solution for scarcities of medical resources in remote regions.[16-19] Low-cost telemedicine technologies can enable rural doctors to access expert support, remote procedure guidance and real-time training opportunities, which may result in

reduced transportation costs and improved patient outcomes.[2,13,19-21] The specialties that use it most often are the following:[16,18,22-25]

- Anesthesiology.
- Cardiology.
- Dermatology.
- Emergency.
- Internal medicine.
- Neurology.
- Obstetrics.
- Pathology.
- Radiology.

Teleradiology consists of electronic transmission of radiological images from one location to another, including between countries, for interpretation and/or consultation. It is one of the most successful and well-structured applications of telemedicine. It has the following objectives:[22,24,25]

- To provide radiological consultations for medical services that do not have local radiological support.
- To facilitate radiological interpretations in on-call situations.
- To provide availability of evaluation and interpretation of radiological images in emergency and non-emergency situations.
- To provide consultative and interpretive radiology services.
- To provide supervision of remote imaging studies.
- To provide support for radiological subspecialties.
- To improve radiological education.
- To promote efficiency and improve the quality of reports.

The only radiologists who need to be on-site are the practical subspecialists for ultrasound and angiography and the interventional radiologist.[22] Other radiologists can perform their work remotely.[22] The importance of this becomes clear when it is considered that two-thirds of the world's population does not have access to imaging examinations.[26]

Tele-ultrasonography, also known as remotely supported ultrasound, teleultrasound, telesonography or telementoring, combines use of ultrasound with telemedicine, thereby allowing interpretation by external specialists. The telesonography process can be conducted in two ways:[26,27]

1. With synchronous transmission, in which the examiner and the specialist are linked through a real-time connection.
2. With asynchronous transmission, in which the images are acquired by an ultrasound operator and later transmitted to a specialist for review.

The advantage of using teleultrasound is that the process of making diagnoses is accelerated. In the case of elective examinations in places with difficult access, use of teleultrasound hastens patients' return to the primary medical facility, thus improving the continuity of their treatment.[26,28]

OBJECTIVES

The aim of this study was to review the literature on the evidence that exists regarding use of telemedicine to perform US in situations of synchronous transmission.

METHODS

For this review, a search of the literature, for original publications, was carried out in April 2020. The following online databases were investigated: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), Cochrane Library, Tripdatabase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Latin American and Caribbean Health Sciences Literature (Literatura Latino-Americana e do Caribe em Ciências da Saúde, LILACS). The following Medical Subject Headings (MeSH) terms were used: ultrasonography; teleradiology; telemedicine; remote consultation. The reference lists of studies included and those of the main reviews on the subject were also evaluated. Manual searches were also performed on the reference lists. The full search strategy is presented in **Table 1**.

Studies that evaluated teleultrasound in relation to detection of diseases or the quality of ultrasound images, or to make comparisons with the usual ultrasound procedures were included, independent of the study design. All the studies analyzed in this review had an experienced physician as a distant mentor and were published between 2010 and April 2020. There was no language restriction, and no exclusion due to the population size. There was no funding for this study.

RESULTS

Given the scarcity of good-quality studies on this topic, we included 10 studies that analyzed procedures performed by different healthcare professionals, always with a physician with experience of ultrasound as a distant mentor. Among the studies selected, one was used a prospective cohort;[29] three were cross-sectional[1,30,31] (but one of these was non-comparative[30]); four were randomized clinical trials;[2,6,32,33] one was an observational prospective study;[4] and one was a prospective randomized crossover study.[34]

Regarding the individuals evaluated, one study evaluated emergency medicine residents with one to two years of previous experience with ultrasound,[4] and two studies evaluated medical students.[2,6] The other seven studies, conducted in Canada, South Korea, the United States and Haiti, evaluated non-medical professionals:[1,29–34] six studies on other healthcare professionals[1,29-31,33,34] (including sonographers and nurses) and one study on firefighters.[32] All of these ten studies featured a trained and experienced physician as a distant assessor.

In a randomized clinical trial by Hurst et al.,[33] 30 sonographers with no previous experience were evaluated. These were divided

Table 1. Search strategy according to the corresponding database

Database	Search strategy	Filter	Results
MEDLINE (Medical literature analysis and retrieval system online)	#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] #3: "Telemedicine"[mesh] or (mobile health) or (health, mobile) or (health) or (telehealth) or (ehealth) #4: "Remote consultation"[mesh] or (consultation, remote) or (teleconsultation) or (teleconsultations) #5: #1 And #2 or #3 or #4	Since 2010 Free full text Comparative study Controlled clinical trial Randomized clinical trial Observational study	6,841
Cochrane library	#1: "Ultrasonography"[mesh] #2: "Teleradiology"[mesh] #3: "Telemedicine"[mesh] #4: "Remote consultation"[mesh] #5: #1 And #2 or #3 or #4	Since 2010	2,722
EMBASE (Excerpta Medica database)	#1: 'Echography'/exp or 'diagnostic ultrasonic examination' or 'diagnostic ultrasonic imaging' or 'diagnostic ultrasonic method' or 'diagnostic ultrasound' or 'doptone' or 'duplex echography' or 'echogram' or 'echographic evaluation' or 'echography' or 'echoscopy' or 'echosound' or 'high resolution echography' or 'scanning, ultrasonic' or 'sonogram' or 'sonographic examination' or 'sonographic screening' or 'sonography' or 'ultrasonic detection' or 'ultrasonic diagnosis' or 'ultrasonic echo' or 'ultrasonic examination' or 'ultrasonic scanning' or 'ultrasonic scintillation' or 'ultrasonogram' or 'ultrasonographic examination' or 'ultrasonographic screening' or 'ultrasonography' or 'ultrasound diagnosis' or 'ultrasound scanning' #2: 'Teleradiology'/exp or 'tele-radiology' or 'teleradiology' #3: 'Telemedicine'/exp or 'tele medicine' or 'telemedicine' #4: 'Teleconsultation'/exp or 'remote consultation' or 'tele-consultation' or 'teleconsultation' or 'telephone consultation') #5: #1 And #2 or #3 or #4	Since 2010 Diagnosis Prospective study Diagnostic test accuracy study Observational study Cohort analysis Cross-sectional study Comparative study Controlled clinical trial	39
TRIPDATABASE	#1: "Ultrasonography" #2: "Teleradiology" #3: "Telemedicine" #4: "Remote consultation" #5: #1 And #2 or #3 or #4	Since 2010	08
CINAHL (Cumulative index to nursing and allied health literature)	#1: "Ultrasonography" #2: "Teleradiology" #3: "Telemedicine" #4: "Remote consultation" #5: #1 And #2 or #3 or #4	Since 2010	229
LILACS (Latin American and Caribbean health sciences literature)	#1: Mh:"ultrassonografia" or (ultrasonografía) or (ultrasonography) or (échographie)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$) #2: Mh:"telerradiologia" or (teleradiology) or (telerradiología) or (téléradiologie) or (mh:e05.920.700$) 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$)	Since 2010 Diagnostic imaging Prospective study Diagnostic study Observational study Controlled clinical trial	04

Continue…

Table 1. Continuation

Database	Search strategy	Filter	Results
LILACS (Latin American and Caribbean health sciences literature)	#3: Mh:"telemedicina" or (telemedicine) or (telemedicina) or (télémédecine) or (ciber saúde) or (ciber-saúde) or (cibersaúde) or (disque saúde da mulher) or (medicina 2.0) Or (saúde 2.0) Or (saúde conectada) or (saúde digital) or (saúde eletrônica) or (saúde móvel) or (saúde onipresente) or (saúde pervasiva) or (saúde ubíqua) or (serviço de telemedicina) or (serviço de telessaúde) or (serviços de telemedicina) or (serviços de telessaúde) or (serviços de e-saúde) or (serviços de esaúde) or (serviços em telemedicina) or (tele-serviços em saúde) or (teleassistência) or (telecuidado) or (telecura) or (telessaúde) or (telesserviços de saúde) or (telesserviços em saúde) or (telesserviços na saúde) or (e-saúde) or (esaúde) or (msaúde) or (usaúde) 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$) Or (mh:sp2.031.332$) #4: Mh: "consulta remota" or (remote consultation) or (consulta remota) or (consultation à distance) or (consulta à distância) or (consultadoria remota) or (consultadoria à distância) or (consultoria remota) or (consultoria à distância) or (teleconsulta) or (teleconsulta assíncrona) or (teleconsulta clínica) or (teleconsulta eletiva) or (teleconsulta síncrona) or (teleconsulta urgente) or (teleconsulta para discussão de casos clínicos) or (teleconsultadoria) or (teleconsultadoria assíncrona) or (teleconsultadoria clínica) or (teleconsultadoria eletiva) or (teleconsultadoria síncrona) or (teleconsultadorias) or (teleconsultas) or (teleconsultoria) or (teleconsultoria assíncrona) or (teleconsultoria clínica) or (teleconsultoria eletiva) or (teleconsultoria síncrona) or (teleconsultoria em urgências) or (teleconsultorias) or (l01.178.847.652.550$) Or (n04.452.758.849.550$) Or (n04.590.374.800.550$) Or (sp2.021.167.010.090.010$) Or (sp2.031.332.010$) #5: #1 And #2 or #3 or #4		

into three groups: 10 who had had a computer class (two-minute videos); 10 who had had a computer class (two-minute videos) plus telementoring; and 10 who had only had telementoring. The quality of images in Focused Assessment with Sonography in Trauma (FAST*)* examinations was evaluated. In the end, Hurst et al.[33] concluded that the groups with telementoring obtained better-quality images.

In a prospective randomized study by Smith et al.,[2] the effectiveness of point-of-care teleultrasound systems consisting of multiple fixed cameras, smartphones and live ultrasound images with real-time audio was evaluated, among 36 medical students from years one to three of their course and among paramedics. The different systems showed similar results, but the smartphones took longer to guide the examination, despite not showing statistical significance. In a second step, the 36 participants were divided into two telementoring groups: one group received telementoring alone, while the other group watched a video before the procedure, which was also carried out with telementoring. These two groups did not present any significant difference regarding their US performance.

Kirkpatrick et al.[32] conducted a randomized prospective study to evaluate the accuracy of the diagnosis of free liquid in the abdominal cavity, using mannequins, among 101 firefighters with no previous experience with ultrasound, divided into two groups: 53 with telementoring and 48 without telementoring. In the end, the group with telementoring presented diagnostic accuracy of 98.1% while the group without telementoring obtained 95.8%.

In a prospective randomized crossover study by Lee et al.,[34] 30 novice sonographers were evaluated with regard to assessing the cecal appendix in actors (patients simulating appendicitis), who were divided into two groups: face-to-face and distant mentoring. Among 90 examinations, the appendix was detected within 10 minutes in 82 cases with an onsite expert's guidance, while in 8 cases it took more than ten minutes of examination to detect the appendix. Among 90 examinations conducted with guidance from a remote expert, 79 appendixes were detected. In 10 cases, the appendix was only detected after more than ten minutes of examination. In one case in the group guided by a remote expert, a failure occurred: the remote expert misinterpreted the terminal ileum as the appendix.

Sheehan et al.[6] conducted a prospective randomized study in which they evaluated 20 second-year medical students without previous experience with ultrasound. These were divided into two groups that had verbal assistance, but only one received visual guidance (software for expert visual guidance). These authors evaluated the quality of abdominal images and found that the group that received visual guidance produced images of better quality.

In a prospective observational study by Kim et al.,[4] conducted in South Korea, 12 emergency residents with one to two years of experience with ultrasound were evaluated. These residents performed ultrasound examinations and then, after having completed them, performed the procedure again, this time with telementoring from an experienced doctor. After this procedure, the mentor doctor performed the procedure in person. Residents did not identify the appendix without telementoring, in nine of the 115 ultrasounds performed, but always identified it in the case of appendicitis. With the telementored aid, the appendix was not identified in only two patients. With the onsite analysis, the appendix was identified in all patients. It was concluded that ultrasound with telementoring between an inexperienced doctor and an experienced doctor as a mentor can be used effectively to diagnose acute pediatric appendicitis in an emergency clinical setting, since the results when the specialist provided assistance at a distance were similar to those when the specialist acted in person.

In a cross-sectional study by Levine et al.,[31] 11 non-medical healthcare workers who had had a theoretical class of 20 minutes and who received assistance at a distance from a doctor while performing ultrasonography were evaluated. The quality of the images was the main outcome. At the end of the study, 91% of the images obtained with the aid of mentoring doctor acting at a distance presented good quality.

Choo et al.[30] conducted a non-comparative cross-sectional study in which telementoring in echocardiography was evaluated on a simulator, among 33 intensive care nurses without any previous training. With the aid of a mentor, identification of cardiac pathological conditions (anterior myocardial infarction, cardiac tamponade, dilated cardiomyopathy and ventricular fibrillation) became possible in 32 out of 33 examinations.

In a prospective cohort study, Douglas et al.[29] evaluated 16 non-medical healthcare professionals who had had previous classes on how ultrasound works: 11 through e-learning and five through in-person classes. These professionals' comfort in performing ultrasound examinations on the internal jugular vein, apex and base of the lungs, cardiac sub-xiphoid view and urinary bladder was evaluated. The authors concluded that, regardless of the teaching group and with the aid of tele-teaching by a doctor, these non-medical healthcare professionals felt comfortable performing ultrasound.

In a cross-sectional study, Robertson et al.[1] evaluated the application of telementoring to point-of-care ultrasonography in Haiti. Nine non-doctors performed the procedure while using Facetime. They had had a previous 20-minute training session on basic US techniques. The authors evaluated the quality of the images obtained at five anatomical sites: right internal jugular vein, bilateral lung apices, lung bases, heart (subxiphoid view) and bladder; the distant physician reported that 90% of the images were of adequate quality.

A summary of all the studies is presented in **Table 2**.

DISCUSSION

Out of the ten studies analyzed, only one[4] actually analyzed diagnoses of diseases in patients with the advent of telementoring in ultrasound. It was concluded that mentoring by an experienced physician improved resident physicians' capacity to diagnose appendicitis. Choo et al.[30] and Kirkpatrick et al.[32] analyzed telementoring among non-medical professionals on a simulator, and obtained favorable results through telementoring, while Douglas et al.[29] noticed that non-medical healthcare professionals were comfortable with mentoring received from a specialist doctor at a distance. Hurst et al.,[33] Levine et al.[31] and Robertson et al.[1] evaluated the quality of the images produced by non-medical healthcare workers and found sufficient quality for diagnostic evaluation by a specialist doctor. Lee et al.[34] compared face-to-face mentoring and distant mentoring with regard to defining the location of the cecal appendix, and showed that there was no difference between these types of mentoring. Sheehan et al.[6] concluded that visual aids for mentoring presented results that were superior to those from telementoring alone. Smith et al.[2] analyzed different types of telementoring and concluded that there was no difference in their effectiveness.

Jensen et al.[35] reported that there was good acceptance of telemonitoring for emergency use among medical residents, in relation to point-of-care ultrasonography, despite recognizing a slight improvement in the ultrasound technique over the course of the four months of study. This finding was shared by the mentor doctors, who had more than five years of experience in ultrasound.

Due to advances in technology, innovative techniques can be applied to help perform ultrasound scans, especially in relation to critically ill patients.[36-39] These advances include wireless image transmission in the emergency department, and corresponding software that allows remote review and delivery of written feedback from ultrasound specialists via email.[36,37,40,41]

Integration of telemedicine with ultrasonography allows individuals who have no experience with ultrasound to obtain and transmit US images to specialists, i.e. trained and experienced professionals who are located remotely, for them to provide interpretations, especially with regard to targeted and point-of-care

Table 2. Summary of the studies analyzed

Study	Study design	Participants	Country	Objective	Results
Choo et al.[30]	Non-comparative cross-sectional.	33 Intensive care nurses with no training.	Canada	To identify cardiac pathological conditions using echocardiography in a simulator.	The mentor was able to identify cardiac pathological conditions in 32 out of 33 examinations.
Douglas et al.[29]	Prospective cohort.	16 Non-medical healthcare professionals who had previously had classes on how ultrasound works.	United States	To analyze the comfort of non-medical healthcare professionals for performing ultrasound examinations on the internal jugular vein, apices and bases of the lungs, cardiac sub-xiphoid view and urinary bladder, on a healthy volunteer.	The professionals, regardless of the teaching group and with the aid of teleteaching by a doctor, felt comfortable performing ultrasound examinations.
Hurst et al.[33]	Randomized clinical trial.	30 Sonographers with no previous experience with ultrasound.	United States	To evaluate the quality of the images in the focused assessment with sonography in trauma examination, in a healthy volunteer.	The groups that received telementoring provided images with better quality.
Kim et al.[4]	Prospective observational.	12 Emergency residents with one to two years of experience with ultrasound.	South Korea	To analyze the diagnosis of acute pediatric appendicitis in patients.	Ultrasound with telementoring between an inexperienced doctor and an experienced doctor as a mentor can be effectively used to diagnose acute pediatric appendicitis in an emergency clinic.
Kirkpatrick et al.[32]	Randomized clinical trial.	101 Firefighters with no previous experience with ultrasound.	Canada	To identify free liquid in the abdominal cavity in mannequins, comparing telementoring and no telementoring.	The group with telementoring presented diagnostic accuracy of 98.1%, While the group without telementoring obtained 95.8%.
Lee et al.[34]	Prospective randomized crossover.	30 Novice sonographers.	South Korea	To identify the cecal appendix in actors, comparing the guidance from a remote experts with that of an onsite expert.	The difference between the remote expert's guidance group and the onsite expert's group was not significant.
Levine et al.[31]	Cross-sectional.	11 Non-medical healthcare workers who had had a theoretical class of 20 minutes.	United States	To evaluate the quality of images from bedside ultrasound among patients.	91% Of the images had good quality, as assessed by a doctor at a distance.
Robertson et al.[1]	Cross-sectional.	9 Non-physician healthcare workers with 20 minutes of training on basic ultrasound techniques.	United States and Haiti	To evaluate the quality of the images from point-of-care ultrasound on a volunteer.	The distant physician found that 90% of the images were of adequate quality.
Sheehan et al.[6]	Randomized clinical trial.	20 Second-year medical students without previous experience with ultrasound.	United States	To compare verbal and verbal plus visual guidance in identifying the abdominal aorta and right kidney through ultrasound on patients and normal volunteers.	The group that received visual guidance produced images of better quality.
Smith et al.[2]	Randomized clinical trial.	36 Medical students from the first three years of their course and paramedics. All of them were inexperienced in ultrasound.	Canada	To compare different types of telemedicine in ultrasound examinations on the right upper quadrant, on a volunteer.	The different types of telemedicine showed similar results. The group that watched the video did the examination faster than did the group that just received mentoring.

assessments.[2,29-31,33,42,43] Point-of-care ultrasound is a valuable tool that improves the diagnostic potential regarding management of critical patients, especially in resource-constrained environments.[1,35,44] This situation has already occurred not only with regard to healthcare workers being instructed at a distance (doctors with no experience in ultrasound, nurses and students in the field of healthcare); but also among non-healthcare workers, such as astronauts on the space station, in order to diagnose thrombosis of the internal jugular vein.[31,45]

However, there are barriers to the application of this technique. Distant instructors usually complain about the background noise at the examination location. To solve this problem, some of the alternatives possible include:[46]

- Minimizing the number of people in the examination room.
- Use of rooms with better sound insulation.
- Use of headphones.

Jensen et al.[35] pointed out that there is a need for a good internet connection and equipment, both for capturing the images and for receiving the images, in order to prevent delays in image transmission (especially in movement, as in cardiac evaluations). This is also needed for receiving the distant physician's instructions. Lack of a good internet connection would hinder real-time image assessment, which is an essential feature in emergencies.

Another observation mentioned by the resident physicians in the present study was in relation to the limitations on communication between the mentor-physician and the patient, considering that the mentor is in contact with the resident physician through a headset. Nonetheless, however, both the distant physician and the resident physicians preferred the headset to the speakerphone. Added to this, there was difficulty in communication, mainly reported by the distant physician, in relation to limitations on the total movement of the probe device in the resident's hand, in order to obtain the proper image, which was considered by the residents to be an advantage.

In a systematic review by Marsh-Feiley et al., which showed that a significant proportion of the studies evaluated presented low methodological quality, telesonography was assessed as viable for use in emergency medicine. It has also been shown to have diagnostic power comparable to conventional face-to-face ultrasound. Although the potential benefits have been described, particularly in the context of low-resource environments, they have not been adequately demonstrated in practice, and more robust evidence is required before implementation.[27] This conclusion, from that review, was similar to what was found in a systematic review by Britton et al., in which low-quality evidence suggested that ultrasound images acquired in environments with limited resources and transmitted using a telemedicine platform to a specialist interpreter had satisfactory quality and value for diagnosis and treatment.[26]

It is noteworthy that in both of the two existing systematic reviews on telementoring in ultrasonography, the studies included presented low methodological quality. Moreover, in all of those studies, there was always a specialist doctor at a distance, as a mentor. For this reason, there is a lack of comparative "head-to-head" studies, in relation to the traditional method of performing ultrasound with telementoring.

Use of smartphones

It has been speculated that use of new telemedicine and telepresence technologies could potentially eliminate the need for specialists to attend patients face-to-face, thus evincing the usefulness of these technologies for isolated regions and developing countries.[2,37,46] Most of the benefits from use of smartphones that have been reported have come from very "visual" specialties, in which this tool for easy iconographic communication is probably more relevant than for "less visual" medical specialties.[2,47] It should nevertheless be taken into account that, today, smartphones are practically omnipresent.[2,48]

Some apps, like WhatsApp, provides immediate interaction among educators and learners, thus providing opportunities to discuss clinical cases and take part in the management performed by residents.[47] Clavier et al. hypothesized that WhatsApp could have an impact equivalent to that of the practice of exchange groups in clinical thinking.[47] Likewise, FaceTime can also be applied for teaching and tele-teaching,[1,16] including for invasive procedures using ultrasound, such as anesthesia.[16]

Cost savings

Rural physicians often need to travel to the main centers to obtain medical knowledge and practice.[37,49] In a reverse manner, trained physicians from those main centers need to go to teach in remote regions.[2,37,50] Both practices are time-consuming and expensive.[2,37,50] Telementoring offers an economical option for remote environments or for locations with limited resources.[1,2,37,49]

CONCLUSION

Although telesonography, whether done in "real-time" or not, shows promise within the field of telemedicine, through bringing specialists with a high degree of expertise to remote regions, and assisting in obtaining images and diagnosis, there are still no studies of reasonable methodological quality for demonstrating its efficiency.

Studies with greater methodological rigor, and preferably large-scale randomized clinical trials that evaluate the diagnostic accuracy of the methodology, using multiple telementoring alternatives, along with easily accessible tools and comparisons with the traditional methodology for the procedure, are still necessary in order to reach definitive conclusions.

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What do Cochrane systematic reviews say about congenital vascular anomalies and hemangiomas? A narrative review

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ABSTRACT

BACKGROUND: Congenital vascular anomalies and hemangiomas (CVAH) such as infantile hemangiomas, port-wine stains and brain arteriovenous malformations (AVMs) impair patients' lives and may require treatment if complications occur. However, a great variety of treatments for those conditions exist and the best interventions remain under discussion.

OBJECTIVE: To summarize Cochrane systematic review (SR) evidence on treatments for CVAH.

DESIGN AND SETTING: Review of SRs conducted in the Division of Vascular and Endovascular Surgery of Universidade Federal de São Paulo, Brazil.

METHODS: A broad search was conducted on March 9, 2021, in the Cochrane Database of Systematic Reviews to retrieve any Cochrane SRs that assessed treatments for CVAH. The key characteristics and results of all SRs included were summarized and discussed.

RESULTS: A total of three SRs fulfilled the inclusion criteria and were presented as a qualitative synthesis. One SR reported a significant clinical reduction of skin redness by at least 20%, with more pain, among 103 participants with port-wine stains. One SR reported that propranolol improved the likelihood of clearance 13 to 16-fold among 312 children with hemangiomas. One SR reported that the relative risk of death or dependence was 2.53 times greater in the intervention arm than with conservative management, among 218 participants with brain AVMs.

CONCLUSION: Cochrane reviews suggest that treatment of port-wine stains with pulsed-dye laser improves redness; propranolol remains the best option for infantile hemangiomas; and conservative management seems to be superior to surgical intervention for treating brain AVMs.

INTRODUCTION

Vascular anomalies are characterized by a disorder in blood vessels, either in structure or growth, and can affect arteries, veins and lymphatic vessels. These lesions are usually detected in children and account for 20%-30% of pediatric soft-tissue tumors. According to the International Society for the Study of Vascular Anomalies (ISSVA), vascular anomalies can be divided into tumors and vascular malformations.[1-3]

Vascular malformations are complex lesions that do not regress or disappear spontaneously and are subclassified as simple or combined. The combined lesions are further divided into 'of major named vessels' or 'associated with other anomalies'.[1-4] These condition affect 1.5% of the general population and have a wide variety of clinical presentations, such as disfiguration, coagulopathy (bleeding or thrombosis), organic or musculoskeletal dysfunction and pain, along with variation in the evolution of the clinical condition over time. Because of this heterogeneity, in terms of both origin and clinical status and evolution, there are several treatment options, requiring multidisciplinary follow-up to reduce the impact on quality of life.[5-7]

In contrast, vascular tumors are characterized by high rates of vascular cell proliferation. They are classified as benign, locally aggressive or borderline, or malignant.[2,8] Hemangiomas are benign-subtype tumors than can be divided into infantile or congenital types.[2] Despite the ISSVA nomenclature, both of these types of tumor are congenital. They have been described as proliferations of endothelial cells and growths of new vessels (angiogenesis) that usually flourish in the first weeks of life and tend to start to regress over time.[4,6,9] Infantile hemangiomas are the most common soft-tissue tumor of infancy and occur in nearly 5% of the population.[10,11] As hemangiomas tend to regress in childhood or during puberty, many tumors do not require

treatment. However, infantile hemangiomas may need treatment when they follow a course that involves some complications, such as functional impairment, potential disfigurement or ulceration.[5]

In summary, vascular anomalies are a set of complex and heterogeneous pathological conditions, with regard to both their clinical presentation and their natural course. Because these lesions are usually located in visible areas, there are considerable chances that not only will systemic alterations appear, but also they will have great potential for psychosocial involvement in both the patient's life and also the lives of the whole family. In fact, a multidisciplinary team is needed for treating these anomalies, and the treatment should be aimed towards better management of symptoms and complications, considering that the healing of these injuries is difficult and that resurgence of lesions occurs frequently. Hence, evidence concerning congenital vascular anomalies and hemangiomas is needed in order to improve the understanding of these diseases and the benefits of different types of treatment.

OBJECTIVE

The aim of this review was to identify and summarize the evidence from Cochrane systematic reviews (SRs) regarding congenital vascular anomalies and hemangiomas, in order to establish better clinical decision-making.

METHODS

Design and setting

This was a review of Cochrane SRs conducted in the Division of Vascular and Endovascular Surgery, Universidade Federal de São Paulo, Brazil.

Inclusion criteria

Types of participants

The participants included children and adults (both males and females) who had been diagnosed with congenital vascular anomalies or hemangiomas, without any restrictions regarding the site affected.

Types of interventions

We considered SRs that assessed any pharmacological intervention (e.g. beta-blocker agents) or non-pharmacological intervention (e.g. transdermal laser) for treating congenital vascular anomalies or hemangiomas. The focus of the studies included was to analyze different types of interventions for treating congenital vascular anomalies and hemangiomas, and the respective improvements. The main types of treatment referred to were pulsed-dye laser therapy, oral propranolol, oral prednisolone and conservative management.

Types of outcomes

We did not predefine the outcomes of interest. Rather, we considered all outcomes as reported in the SRs included.

Types of studies

All Cochrane SRs published thus far, about congenital vascular anomalies or hemangiomas, without restrictions regarding date of publication, were included. Withdrawn or outdated versions of SRs and protocols for SRs were considered not relevant.

Search for reviews

We conducted a systematic search in the Cochrane Database of Systematic Reviews on March 9, 2021. We used the following MeSH terms and related variants in the titles, abstracts and keywords: "Vascular malformations", "Lymphatic abnormalities" and "Hemangioma". The detailed search strategy is presented in **Table 1**.

Selection of reviews

Two researchers (HJGN and LCUN) independently evaluated the titles and abstracts to analyze whether the SRs fulfilled the inclusion criteria. Any disagreement was resolved by consulting other authors (DABK, RLGF, JCCBS and JEA). A total of three reviews fulfilled the inclusion criteria. The SRs were selected and summarized by two authors (HJGN and DABK) using previously developed forms to extract data from SRs, which had already been used in previous narrative reviews with this purpose.[5] We extracted the following study characteristics:

- Participants: N randomized, N lost to follow-up/withdrawn, N analyzed, N of interest, mean age, age range, gender, condition of interest, inclusion criteria and exclusion criteria.
- Interventions: intervention and comparison characteristics, level of experience of the person carrying out the procedure, concomitant medications and medications excluded.

Table 1. Search strategy and results from the Cochrane Database of Systematic Reviews

Lines	Search terms	Number of records
#1	MeSH descriptor: [Vascular Malformations] explode all trees	301
#2	MeSH descriptor: [Lymphatic Abnormalities] explode all trees	20
#3	(Lymphatic Abnormalit*) or (vascular malformation*)	597
#4	MeSH descriptor: [Hemangioma] explode all trees	171
#5	Hemangioma* or (Hemangioma* Intramuscular) or (Hemangioma* Histiocytoid) or Angioma or Chorioangioma* or Chorangioma*	473
#6	#1 #2 or #3 or #4 or #5	1041
#7	Cochrane reviews of intervention	156

- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Study methods: primary study design, number of primary studies and location, study setting and date of study.

Presentation of results

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

Ethics

No ethics committee approval was necessary since this was not a primary study and we did not deal directly with patients.

RESULTS

Search results

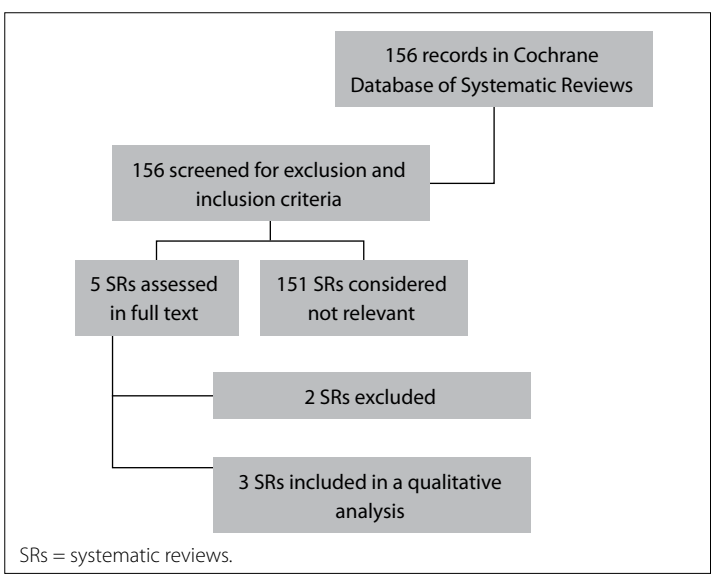
Our search strategy retrieved 156 references and, after screening the titles and abstracts, five SRs were preselected. After assessing the full texts, three reviews were found to fulfill the criteria for inclusion and were assessed in a qualitative synthesis (**Figure 1**).

Reviews included

The latest versions of all the SRs included were published between 2011 and 2019.[13-15] Details regarding the characteristics of interventions, comparisons, outcomes and certainty of evidence are presented in **Table 2**.

Lasers or light sources for treating port-wine stains[13]

The aim of this SR was to study participant satisfaction with treatment of port-wine stains by means of laser and light sources, and the clinical efficacy and adverse events of this treatment. Five randomized clinical trials (RCTs) were identified, involving a total of 103 participants. The interventions and outcomes varied among the primary studies and therefore, could not be combined for numerical analysis.



SRs = systematic reviews.

Figure 1. Study flow diagram.

Main findings

All of the primary studies described the participants' level of satisfaction at less than six months after treatments with the pulsed-dye laser, intense pulsed light and Nd:YAG laser, and reported that the participants' satisfaction was good or excellent, with regard to the degree of improvement attained.

Participant preference was analyzed in three of the five studies included, and most of the participants preferred pulsed-dye laser over intense pulsed light. The participants also preferred treatment with pulsed-dye laser in association with cooling, over treatment solely with pulsed-dye laser.

There was a significant clinical change of at least 20% in all the SRs regarding reduction of skin redness. All the studies determined the level of reduction in redness at one to three months after the final treatment. All five trials used the pulsed-dye laser, and, depending upon the setting, this resulted in more than 25% reduction in redness. The results reported were achieved after one to three sessions for up to six months postoperatively, in 50% to 100% of the participants. Adverse effects were considered in terms of their cosmetic aspect and were determined as either permanent or lasting longer than six months.

Complications

Few studies described short-term adverse effects occurring only in the first two weeks. Two primary studies reported that treatment with pulsed-dye laser alone was more painful than with pulsed-dye laser combined with cryogenic cooling. Three trials reported pigmentary complications in 3%-24% of the participants, such that the highest percentage occurred among Chinese participants with darker skin types. One case of scarring of the skin caused by high-dose laser was also reported. The trials included reported short-term side-effects such as pain, crusting and blistering in the first two weeks after the intervention.

Conclusion

Treatment of port-wine stains with pulsed-dye laser has clinical benefits, especially in relation to improvement of redness. However, it was not possible to compare the different types of treatments due to the small number of SRs involved in the studies and the absence of certainty regarding the evidence available, as determined through using validated tools like the 'Grading of Recommendations, Assessment, Development and Evaluation' (GRADE).

Interventions for infantile hemangiomas of the skin[14]

This SR focused on assessing the effects of interventions for managing infantile hemangiomas in children. Twenty-eight primary

Table 2. Characteristics of interventions, comparisons, participants and main findings and the certainty of the evidence, as evaluated by means of the grading of recommendations, assessment, development and evaluation (GRADE) system

Review (primary studies, participants)	Interventions	Outcomes	Participants	Main findings	GRADE
Faurschou et al.[13] (5 RCTs; 103 participants)	**Pulsed-dye laser and intense pulsed light**	Participant preference	Adults and children with port-wine stains	• Most patients preferred pulsed-dye laser over intense pulsed light	•N.A.
	Pulsed-dye laser in association with cooling and pulsed dye laser alone	Participant preference	Adults and children with port-wine stains	• Most patients preferred pulsed-dye laser in association with cooling, rather than pulsed-dye laser alone	•N.A.
	Pulsed-dye laser and wait-and-see (active monitoring)	Clearance	Children with port-wine stains	• There was no statistically relevant difference between these two approaches	•N.A.
		Skin atrophy		• 3.5 times more frequent with pulsed-dye laser	•N.A.
		Hypopigmentation		• 3.0 times more frequent with pulsed-dye laser	•N.A.
		Aesthetic appearance		• There was no statistically relevant difference between these two approaches	•N.A.
Novoa et al[14] (28 RCTs; 1728 participants)	**Placebo and propranolol**	Clearance	Children with hemangiomas of the skin	• The likelihood of clearance after propranolol 1 mg/kg/day was 13.48 times greater than after placebo • The likelihood of clearance after propranolol 3 mg/kg/day was 16.6 times greater than after placebo	• Moderate
		Adverse events		• There was no difference between these two approaches	• Low
		Redness improvement, proportion of parents who considered that their children still had a problem, proportion of children who considered that they still had a problem, esthetic appearance and requirement for surgical correction		• There were no studies reporting this outcome	• N.A.
	Topical timolol and placebo	Clearance and subjective measurement of improvement	Children with hemangiomas of the skin	• There were no studies reporting this outcome	• N.A.
		Adverse events (bradycardia)		• There was no difference between these two approaches	• Low
		Volume reduction		• The likelihood of volume reduction after topical timolol maleate was 5.21 greater than with placebo	• Moderate
		Other measurements of resolution, as assessed by a clinician, at any follow-up: no redness		• The likelihood of no redness after topical timolol maleate was 8.11 times greater than with placebo	• Low
	Topical bleomycin and placebo	Shrinkage of lesions	Children with hemangiomas of the skin	• The shrinkage of lesions after bleomycin was 21 times greater than with placebo	•N.A.
	Nd:YAG in association with oral propranolol versus Nd:YAG alone	Clearance and superficial scars	Children with hemangiomas of the skin	• There was no clear difference between these two approaches	•N.A.

Continues...

Table 2. Continuation

Review (primary studies, participants)	Interventions	Outcomes	Participants	Main findings	GRADE
Novoa et al[14] (28 RCTs; 1728 participants)	**Nd:YAG in association with oral propranolol versus oral propranolol alone**	Clearance	Children with hemangiomas of the skin	• The likelihood of clearance after Nd:YAG + oral propranolol was 8.44 times greater than with propranolol alone	•N.A.
		Superficial scars		• There was no clear difference between these two approaches	•N.A.
		Improvement ≥ 95%		• The likelihood was 2.83 times greater with Nd:YAG + oral propranolol than with oral propranolol alone	•N.A.
	Propranolol and prednisolone	Risk of complications	Children with hemangiomas of the skin	• The risk of complications after oral propranolol was 78% lower than after oral prednisolone	•N.A.
		Size reduction		• No clear difference was found	•N.A.
	Oral propranolol + oral prednisolone versus oral propranolol alone	Risk of adverse events	Children with hemangiomas of the skin	• The risk of adverse events after oral propranolol was 70% lower than with dual therapy	•N.A.
	Oral propranolol + oral prednisolone versus oral prednisolone alone	Adverse events	Children with hemangiomas of the skin	• No clear difference was found between these two types of treatment	•N.A.
		Size reduction		• There was no significant difference between dual therapy and oral prednisolone	•N.A.
	Oral propranolol versus topical timolol	Clearance and subjective measurement of improvement	Children with hemangiomas of the skin	• There were no studies reporting this outcome	• N.A.
		Adverse events (general adverse events)		• The risk was 7 times higher among participants randomized for propranolol	• Very low
		Other measurements of resolution, as assessed by a clinician, at any follow-up: no redness		• There was no statistically relevant difference between these two approaches	• Low
Zuurbier et al.[15] (One RCT; 226 participants)	**Intervention and conservative management for treating brain arteriovenous malformations**	Risk of death or dependence	Adults with brain arteriovenous malformations	• 2.53 times greater for patients randomized for intervention	• Moderate
		Symptomatic intracranial hemorrhage		• The risk was 6.75 times higher for participants who underwent to intervention	• Moderate
		Epilepsy		• There was no statistically relevant difference between them	• Moderate

N.A. = not available; Nd:YAG = neodymium-doped yttrium aluminum garnet laser; RCTs = randomized controlled trials.

studies were included, with a total of 1728 participants, in which 12 different kinds of interventions were analyzed. The most commonly used interventions were beta blockers, lasers, steroids, surgery and other types of treatment such as bleomycin and imiquimod. The primary outcomes analyzed were clearance (proportion of children with lesions completely cleared) and subjective measurements of improvement and adverse events secondary to each intervention over the short and long terms. The secondary outcomes were other measurements of resolution (i.e. surface area, lesion volume and lesion redness), the proportions of the parents and children who considered that the participant still had a problem, esthetic appearance and requirement for surgical correction. The quality of the evidence relating to the primary and secondary outcomes was assessed using the GRADE system.

Main findings and complications

Twenty-one studies used a two-arm design, six studies used a three-arm design and a single study used a four-arm, parallel group design. The numbers of children in the studies ranged from 12 to 460. Most of the studies had a greater number of females than males and the maximum age at enrollment at the beginning of the trial ranged from 14 weeks to five years. The median

time taken for treatment was 24 weeks and the follow-up period ranged from seven days to 72 months.

The first comparison between pulsed-dye laser and the wait-and-see approach (active monitoring) included 143 children from two different trials. One study proved that there was no difference in terms of clearance, in comparing these two different approaches, with a risk ratio (RR) = 0.94 and 95% confidence interval (CI) = 0.62-1.42. Two different trials provided information about adverse events. In one of them, it was concluded that skin atrophy and hypopigmentation after pulsed-dye laser were more frequent, with RR = 3.46 (95% CI = 1.36-8.77) and RR = 3.05 (95% CI = 1.57-5.93), respectively. One study analyzed the proportion of parents who considered that their children still had a problem after treatment, during the follow-up period, and no clear difference was found in comparing pulsed-dye laser and the wait-and-see approach (RR = 1.24; 95% CI = 0.56-2.78). Regarding esthetic appearance after treatment, it was reported in one study that there was a better cosmetic outcome in seven children out of 11 after pulsed-dye laser therapy and in four out of 11 in the wait-and-see group, but that there was no statistically significant difference (RR = 1.75; 95% CI = 0.71-4.31).

The second comparison between placebo and propranolol treatments included information from three trials (312 children). One trial proved that the risk of clearance after administration of propranolol, 1 mg/kg/day, was 13.48 times greater than after placebo (RR = 13.48; 95% CI = 3.41-53.30). The likelihood of clearance after administration of propranolol, 3 mg/kg/day, was 16.6 times greater than after placebo (RR = 16.61; 95% CI = 4.22-65.34). In terms of adverse events, there was no significant difference between use of oral propranolol and placebo, at any doses. Also, there were no differences between these two different approaches, with regard to redness improvement, the proportion of parents who considered that their children still had a problem, the proportion of children who considered that they still had a problem, esthetic appearance or requirement for surgical correction.

Comparison of topical timolol and placebo treatments proved that there was no significant difference between them, with regard to clearance, subjective measurements of improvement or adverse events. One study demonstrated that volume reduction after use of topical timolol maleate was 5.21 times greater than after placebo (RR = 5.21; 95% CI = 1.28-21.21).

On the other hand, the analysis of topical bleomycin and placebo included one trial with 30 children. This trial suggested that most of the children treated with bleomycin reached clearance of lesions and shrinkage of lesions after use of bleomycin at a rate 21 times greater than through use of placebo (RR = 21.00; 95% CI = 1.34-328.86).

The analysis on neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in association with oral propranolol versus Nd:YAG alone included two trials with a total of 107 children. The duration of treatment and follow-up was six months. There was no clear difference between these two types of treatment in terms of clearance and superficial scars. One of the studies proved that Nd:YAG laser + oral propranolol was 8.5 times more likely to show an improvement of at least 95%, compared with Nd:YAG laser alone.

On the other hand, comparison of Nd:YAG in association with oral propranolol versus oral propranolol alone proved that the likelihood of clearance after use of Nd:YAG laser + oral propranolol was 8.44 times greater than through use of propranolol alone (RR = 8.44; 95% CI = 1.14-62.66). There was no clear difference in terms of superficial scars (RR = 0.60; 95% CI = 0.05-7.63). Attainment of an improvement greater than or equal to 95% was 2.83 times more likely with Nd:YAG laser + oral propranolol than with oral propranolol alone (RR = 2.83; 95% CI = 1.42-5.67).

The comparison between propranolol and prednisolone included information from two trials, with a total of 39 children. These trials did not include any information regarding clearance and subjective measurement. One of the studies suggested that the risk of complications after use of oral propranolol was 78% lower than after use of oral prednisolone (RR = 0.22; 95% CI = 0.06-0.78). Neither of these studies found any clear differences in terms of size reduction, in comparing these two types of interventions.

The analyses on oral propranolol + oral prednisolone versus oral propranolol alone demonstrated that the risk of adverse events after use of oral propranolol was 70% lower than when dual therapy was used (RR = 0.30; 95% CI = 0.10-0.91; I^2 = 0%), with no clear benefit regarding size reduction. However, the analysis on oral propranolol + oral prednisolone versus oral prednisolone alone demonstrated that there were no clear differences, in terms of adverse events, between these two types of treatment. Also, there was no significant difference between dual therapy and oral prednisolone, regarding size reduction.

Conclusion

Propranolol remains the standard treatment for infantile hemangiomas and is probably beneficial, in terms of clearance and reduction of hemangioma volume, compared with placebo.

Interventions for treating brain arteriovenous malformations in adults[15]

The objective of this review was to determine the effectiveness and safety of different interventions, alone or in combination, for treating brain AVMs in adults, compared against each other, or with conservative management, in RCTs. The primary outcome was death or dependence due to any cause. The secondary outcomes included symptomatic intracranial hemorrhage, epilepsy,

symptomatic radiation necrosis and quality of life. Only one study fulfilled the inclusion criteria for this review.

Main findings

The primary and secondary outcomes were available for 218 participants. During the first year, the relative risk of death or dependence for participants randomized to interventional treatment was 2.53 greater than for participants randomized to conservative management (RR = 2.53; 95% CI = 1.28-4.98). The total number of participants with symptomatic intracranial hemorrhage was also higher in the group with intervention (RR = 6.75; 95% CI = 2.07-21.96).

In terms of epilepsy, comparison between the study arm that underwent the intervention and the arm that was treated with conservative management demonstrated a RR of 1.14 (95% CI = 0.63-2.06).

Conclusion

Although the quality of evidence of this study was considered moderate, conservative management was superior to intervention with regard to functional outcome and symptomatic intracranial hemorrhage, over one year after randomization.

DISCUSSION

Overall, there is a great variety of treatments for congenital vascular abnormalities and infantile hemangiomas and yet there is no consensus about which one is better.[5,6,8,11] Each technique has its benefits and risks and the type of treatment should be based not only on the characteristics of the lesion, but also on the participant's profile.

The first review described in this study suggested that treatment of port-wine stains with pulsed-dye laser improves the redness of these lesions. Pulsed-dye laser is considered to be the gold-standard treatment for port-wine stains,[16] but the response to this treatment varies according to the patient's age, lesion location, the frequency used and the intervals between sessions.[17] Some studies have suggested that port-wine stains located proximally to the limbs tend to have better results than those that are distal to the limbs, from treatment with pulsed-dye laser.[18] The SR described above included a small number of studies and, therefore, it was not possible to properly analyze these factors or compare different types of treatment.

The second SR compared a number of types of treatment and suggested that propranolol remains the standard treatment for infantile hemangiomas and is probably beneficial in terms of clearance and reduction of hemangioma volume. Although this review suggested that there were no significant differences in terms of improvement and adverse events, in comparing the use of propranolol at 1 mg/kg/day and 3 mg/kg/day with use of placebo, some reports in the literature have suggested that there is higher incidence of adverse events related to propranolol when it is administered at higher doses.[19] Perhaps the number of participants included was not enough to compare the effects of propranolol at different doses.

Regarding treatment of brain AVMs, our study suggested that conservative management was superior to intervention. However, there is no consensus about this. There is evidence from different studies suggesting that conservative management may be associated with worse outcomes.[20-21]

The major limitation of this review was the small number of SRs included. There were also the facts that a great variety of treatments were presented and different comparisons were made between small numbers of participants. The results may have been influenced by the ages of the participants, locations of lesions and individual characteristics of each participant. These matters were not stratified in some of the analyses.

Nonetheless, our study had intrinsic value with regard to providing information about different types of treatment and their benefits and complications, especially considering the small number of SRs published thus far in the literature. This may help physicians to improve clinical care and medical treatment.

CONCLUSION

Despite the controversies in the literature regarding the treatment of congenital vascular abnormalities and hemangiomas, Cochrane SRs suggest that treatment of port-wine stains with pulsed-dye laser improves redness; propranolol remains the best option for infantile hemangiomas; and conservative management seems to be superior to surgical intervention for treating brain AVMs.

Additional evidence is needed to better understand the different types of treatments and their benefits and complications, along with the clinical results after a long period of follow-up.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

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

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

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

Editorial policy

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

São Paulo Medical Journal accepts manuscripts previously deposited in a trusted preprint server.

São Paulo Medical Journal supports Open Science practices. It invites reviewers to join Open Peer Review practices through acceptance that their identities can be revealed to the authors of articles. However, this is purely an invitation: reviewers may also continue to provide their input anonymously.

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

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

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

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

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

Conflicts of interest

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

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

Acknowledgements and funding

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

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

Authorship

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

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

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

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the

reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

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São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

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

The Journal's peer review policy and procedures

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

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

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

Articles will be rejected without peer review if:

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

After peer review

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

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

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

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

Submission

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

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

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

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

Covering letter

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

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

General guidelines for original articles

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

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

Trial and systematic review registration policy

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

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

Sample size

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

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

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

Abbreviations, acronyms and products

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

Interventions

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

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

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

Supplementary material

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

Short communications

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

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

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

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

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

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
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10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
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12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

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

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
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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.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

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

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

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

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

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

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

Figures and tables

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

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

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

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

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

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

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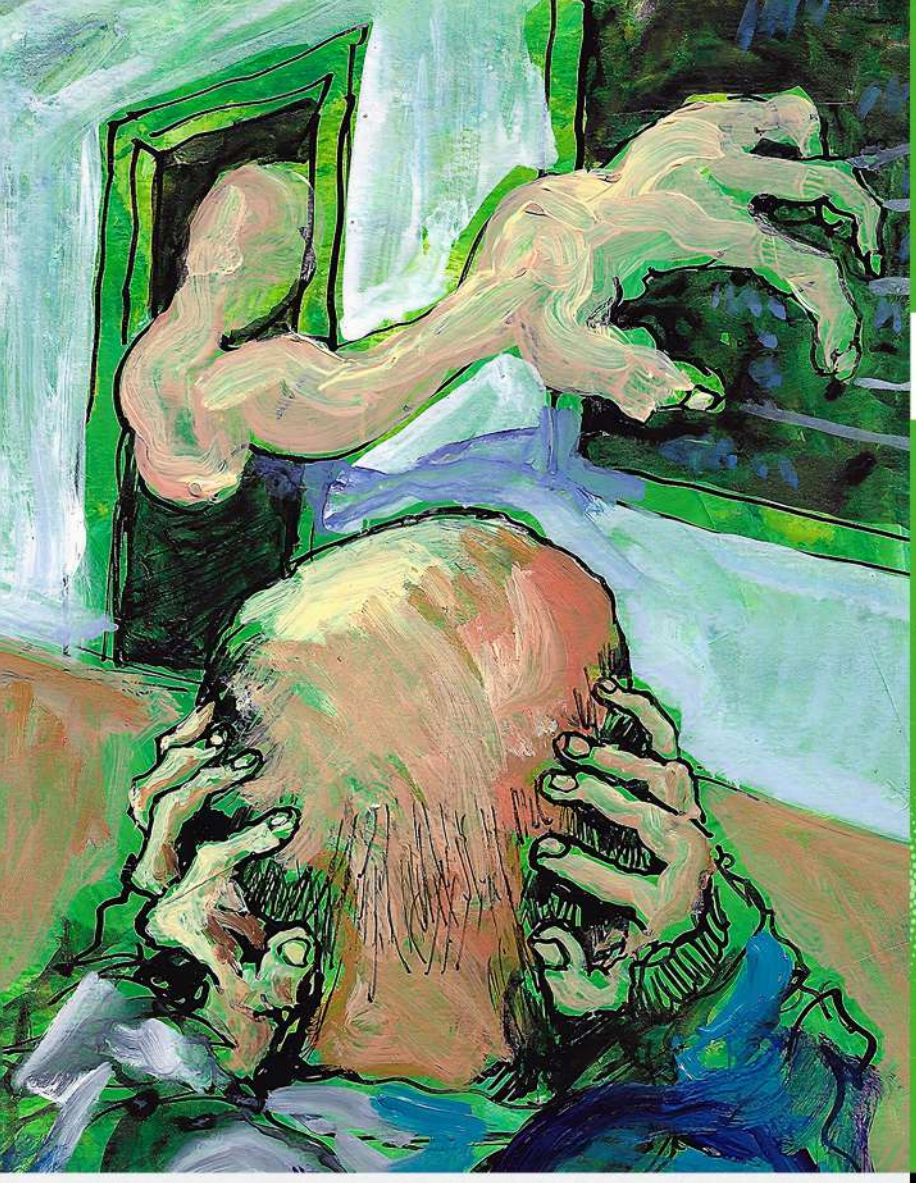

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