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INDEX

Editorial

Original article

Letter to the editor

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Beyond the burden of cardiovascular and cancer mortality among adults: mental health as a cause of death

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In a previous editorial in this Journal this year, I addressed the temporal trends of the risk of death due to the most critical causes among Brazilians aged 45 to 64 years: circulatory disorders and neoplasms.[1] The aim was to make comparisons with the patterns of heart disease and cancer deaths in the United States.[2] The results were that cardiovascular diseases showed reductions in age-adjusted rates from 2000 to 2010 for men (-1.8% per year) and women (-2.2% per year). Over the same period, the death rates due to cancer stagnated for men and climbed for women (0.6% per year), mainly due to smoking-related neoplasm.[1]

One point of interest in this regard is to verify the pattern of mortality beyond cardiovascular diseases and cancer from 2000 to 2017 for the age stratum of 45-64 years. Four years ago, one report astonished public health managers and epidemiologists through showing that among white men aged 45-54 years, there were increases in the risk of death due to drug and alcohol poisoning, cirrhosis and suicide.[3]

To test the trends of death due to non-cancer and non-cardiovascular disease causes in Brazil, I firstly used the Tenth Revision of the International Classification of Diseases (ICD-10) to calculate which causes of deaths according to sex showed absolute increases in the numbers of events. From this, I identified in the Brazilian DATASUS system (http://datasus.saude.gov.br), 10 underlying causes of death with absolute increases over this period: viral hepatitis (ICD-10: B15-B19); HIV-related disorders (ICD-10: B20-B24); diabetes (ICD-10: E10-E14); mental disorders due to psychoactive drugs (ICD-10: F10-F19); chronic obstructive pulmonary disorder (ICD-10: J40-J47); cirrhosis due to alcoholic beverages (ICD-10: K70); renal disorders (ICD-10: N17-N19); road accidents (ICD-10: V01-V99); homicide (ICD-10: X85-Y09); and suicide (ICD-10: X60-X84). Secondly, I applied Poisson regression to test whether the death rates trends of these ten causes reached statistical significance.

For one group of causes (viral hepatitis, diabetes and chronic obstructive pulmonary disorder), despite the rise in the absolute number of cases, there were significant reductions per year in the mortality rates. For two other causes (road accidents and homicides), the risk of death did not change materially during this period.

On the other hand, five conditions showed significantly increased risks of mortality: HIV-related disorders, mental disorders due to psychoactive drugs (women), cirrhosis due to chronic alcoholic beverage intake (men), renal disorders and suicide. **Table 1** shows that from 2000 to 2017,

Table 1. Proportional mortality (PM), annual percentage change (APC) and 95% confidence interval (95% CI) for five causes of death in Brazil with increasing trends, among people aged 45-64 years over the period from 2000 to 2017

Cause of death	Men		Women	
	PM 2000-17	APC (95% CI)	PM 2000-17	APC (95% CI)
HIV	1.1% to 1.6%	1.3 (0.9 to 1.8)	0.7% to 1.3%	2.3 (1.6 to 3.0)
Drug abuse	1.5% to 2.1%	1.0 (-0.0 to 1.9)	0.3% to 0.7%	3.1 (1.8 to 4.4)
Cirrhosis	1.9% to 2.8%	0.9 (0.4 to 1.4)	0.4% to 0.6%	0.8 (-0.1 to 1.8)
Renal disorders	1.3% to 1.9%	1.4 (0.9 to 1.9)	1.6% to 2.6%	1.9 (1.3 to 2.5)
Suicide	1.0% to 1.5%	0.7 (0.2 to 1.2)	0.4% to 0.7%	2.0 (1.5 to 2.6)

Note: the numbers of deaths and populations were obtained from the Brazilian public health system DATASUS, 2019, and the annual percentage change was obtained by applying Poisson regression, available through the Joinpoint regression software 4.7.0.0 (https://surveillance.cancer.gov/joinpoint/; downloaded in February 2019).

these five causes together accounted for an increasing proportion of all-cause deaths, from 6.7% to 10% (men) and from 3.4% to 5.9% (women). The pace of the increase in death rates for men was high for HIV-related disorders, use of psychoactive drugs, suicide and renal diseases.

The increase in deaths caused by renal diseases can be better understood through the increase in the incidence of end-stage kidney failure.[4] Deaths relating to HIV can be explained partially as due to prolongation of the lifespan of the generation with high incidence of the infection who began to receive highly active antiretroviral therapy HAART (in the early 1990s), among whom there are now higher mortality rates among older men; and partially because of HIV cases among intravenous drug users.[5]

The combination of greater risk of death due to use of psychoactive drugs, suicide, cirrhosis due to alcohol intake and a proportion of human immunodeficiency virus (HIV) cases relating to intravenous drug indicates the existence of a cluster of mental health problems. This situation in Brazil is therefore relatively similar to what has been described in the United States as deaths due to overdoses of illicit drugs, cirrhosis and suicide.[6]

If these trends are real, as has been proven in the United States, and given that I do not have any means to refute that this is also valid in Brazil, then epidemiologists, anthropologists and social scientists face a big challenge in trying to decipher what is going on in our society.

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The effect of bispectral index monitoring on cognitive performance following sedation for outpatient colonoscopy: a randomized controlled trial

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KEY WORDS:
Consciousness monitors.
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Conscious sedation.
Colonoscopy.

ABSTRACT

BACKGROUND: Bispectral index (BIS) monitoring can positively affect cognitive performance through decreasing the use of sedative agents. We aimed to evaluate the effect of BIS monitoring on early cognitive performance among patients undergoing sedation for colonoscopy.

DESIGN AND SETTING: Randomized, controlled trial in a university hospital.

METHODS: 100 patients were randomized into two groups. In the monitored group (n = 50), the depth of anesthesia was monitored using the BIS, and BIS scores were maintained between 60 and 80. In the usual care group (n = 50), BIS monitoring was not performed. To determine the patients' baseline cognitive performance levels, the mini-mental state examination (MMSE), Trieger dot test (TDT) and clock drawing test (CDT) were used. The patients' post-procedure cognitive performance levels were determined when they were classified as ready for discharge.

RESULTS: The total volume (mg) of propofol used [median (range) IQR] in the sedation procedure was lower in the monitored group [100 (50-200) 100-140] than in the usual care group [150 (75-200) 100-200] ($P < 0.001$). The discharge scores [mean (SD)] using MMSE and CDT were higher in the monitored group [26 (3) and 3 (1), respectively] than in the usual care group [23 (3) and 2 (1), respectively] ($P = 0.002$ and $P = 0.002$, respectively). The discharge scores using TDT [mean (SD)] were lower in the monitored group [11 (7)] than in the usual care group [15 (11)] ($P = 0.033$).

CONCLUSION: BIS monitoring among sedated patients was associated with lower propofol use and smaller decline in cognitive performance.

CLINICAL TRIAL REGISTRATION: This trial was registered in the Australian New Zealand Clinical Trial Registry (ACTRN12617000134325).

INTRODUCTION

Colonoscopy is one of the most commonly performed procedures worldwide. However, it frequently results in pain and discomfort in patients undergoing the procedure. Cooperation from the patient is crucial for obtaining clear endoscopic images. Effective sedation ensures that the patient can tolerate the procedure and cooperate well, in addition to facilitating recovery, all of which increase the satisfaction of both the patient and the endoscopist. Sedation has the aim of facilitating endoscopy, but it may also prolong hospitalization and result in cognitive impairments that can affect daily activities.[1]

Postoperative cognitive dysfunction (POCD) is a relatively common entity that can adversely affect recovery and discharge after outpatient procedures.[2] A review of the literature has indicated that the incidence of POCD ranges from 7% to 60%, depending on the patient group and type of procedure.[3] Postoperative cognitive problems can be evaluated in terms of several categories, and previous studies have suggested different diagnoses and classifications.[4,5] POCD can be diagnosed based on the changes noted in psychomotor test scores, e.g. using the digit-symbol-substitution test (DSST), Trieger dot test (TDT) or mini-mental state examination (MMSE), in comparison with the pre-procedural values.[6] POCD also affects a wide range of cognitive functions, including memory, attention, orientation and concentration, and these effects may persist for months after operations, in certain patients.[7]

The mechanism underlying POCD is still unclear. It is a challenge to establish a definitive conclusion regarding the mechanism underlying this condition, given the differences between

patient populations, the tools used for diagnosing it and the variations between analyses of cognitive test results in the literature.[4] However, old age, low levels of education and low preoperative cognitive reserves have been implicated as risk factors for the development of postoperative cognitive dysfunction.[4,5,8,9]

A bispectral index (BIS) monitor is commonly used to assess depth of sedation when administering sedative, hypnotic or anesthetic agents during surgical and medical procedures.[10] Monitoring the level of sedation by means of safe objective methods such as BIS monitoring makes it possible to use lower amounts of sedative agents.[11] Previous studies on the use of BIS for sedation monitoring during colonoscopy mostly focused on decreasing the amount of sedative agent administered and the recovery time required, and on assessing the patient's or endoscopist's satisfaction.[12-16]

The influence of depth of anesthesia on postoperative impairment of cognitive function among surgical patients has already been investigated through BIS monitoring.[17] Various medications have been compared in studies assessing postoperative impairment of cognitive function subsequent to procedures such as colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP).[1,18] However, no previous study has evaluated the effects of BIS monitoring on early cognitive performance after outpatient procedures such as colonoscopy and ERCP.

The reduction in consumption of anesthetic agent achieved through BIS monitoring has been shown to result in improvement in the early recovery profile.[19-21] However, it is still unclear whether the lower dose of anesthetic agents administered with the aid of BIS monitoring reduces the risk of postoperative cognitive dysfunction.

OBJECTIVE

We conducted a randomized controlled trial to evaluate the effect of BIS monitoring on early cognitive performance among patients undergoing sedation for colonoscopy. The primary aim was to evaluate cognitive performance and the secondary aims were to evaluate the effect of BIS monitoring on total propofol use, duration of sedation and patient satisfaction.

METHODS

Ethics

We declare that implementation of this study was endorsed by the Internal Review Board (Ethics Committee) of Meram School of Medicine, Necmettin Erbakan University, under the date and approval number 04/12/2015/2015/366. Furthermore, informed written consent was obtained from all patients between January 30, 2017, and January 15, 2018. This study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12617000134325).

Trial design and setting

This was a parallel, randomized controlled trial conducted at Konya Training and Research Hospital, Health Sciences University, Konya, Turkey.

Participants

Patients between the ages of 18 and 70 years, who presented American Society of Anesthesiologists (ASA) physical status I-III and had been scheduled to undergo planned colonoscopy, were studied.

Patients with inadequate comprehension of Turkish, mini-mental state examination score ≤ 23, significant cardiorespiratory instability (ASA IV–V), prior administration of intravenous fluid, allergies to eggs, beans or latex, previous history of alcohol or sedative overdose, previous history of adverse events associated with propofol, sleep apnea or recent history of central nervous system (CNS) abnormalities (e.g. stroke) were excluded. Also, patients who refused sedation during colonoscopy, who were hospitalized or who were pregnant or lactating were excluded from the study.

The participants who were recruited, and who met the inclusion criteria, were consecutive individuals who underwent colonoscopy at the same unit, between January 30, 2017, and January 15, 2018. The fasting periods implemented were in accordance with ASA guidelines. All patients underwent colonoscopy preparation following the standard procedure of the endoscopy unit.

Randomization and blinding

Patients were randomized, by using computer-generated block randomization (http://www.randomization.com), into two groups (1:1 allocation ratio). One anesthetist controlled the randomization table and another anesthesiology professional performed sedation, and this latter was blinded for allocation.

All sedation procedures were performed by an anesthesiologist (BŞ) who was blinded to the pre-procedure steps. Colonoscopy commenced when the anesthesiologist decided that the depth of sedation was adequate.

All endoscopy procedures were performed blindly in relation to this study, by one of three endoscopists, each of whom had performed more than 500 endoscopies before participating in this study.

Interventions

In the monitored group (n = 50), the depth of anesthesia was monitored by means of the BIS (BIS Monitor, Aspect 2000 XP, USA) and BIS scores were maintained between 60-80. In the usual care group (n = 50), BIS monitoring was not performed.

The depth of sedation was calculated by measuring cerebral electric activity via an electroencephalogram (EEG). The BIS algorithm processed the frontal EEG and converted the signal to a

waveform on the BIS monitor. The monitor calculated the data received by the two to four sensors and displayed this information as numerical values from 0 to 100 with a 10 to 30-second delay. Each numerical range correlated with a different degree of sedation: 100 to 90, awake and responding appropriately to verbal stimulation; 80 to 70, light to moderate sedation; 70 to 60, deep sedation; 60 to 40, general anesthesia; less than 40, deep hypnotic state; less than 20, burst suppression; and 0, totally suppressed EEG (flat line).[10] The BIS measurement times in the present study were as follows: t_0: at baseline; t_1: immediately after induction; t_2: at the beginning of colonoscopy; t_3: at the 5th minute of colonoscopy; and t_4: at the end of colonoscopy.

A 20-gauge intravenous catheter was inserted in the right forearm when the patient arrived in the endoscopy room. Supplemental oxygen (4 l/min) was administered through a nasal cannula. In addition to routine monitoring (consisting of use of a pulse oximeter, three-lead electrocardiogram (ECG) and non-invasive blood pressure cuff), BIS monitoring (BIS Monitor, Aspect 2000 XP, USA) was applied to the patients in the monitored group. After baseline measurements (hemodynamic profiles and BIS values) had been obtained, the patient was placed in the left lateral position.

Two milligrams of midazolam were administered intravenously. Next, an initial intravenous dose of propofol (0.3-0.5 mg/kg of body weight) was administered, followed by repeated 10-20 mg doses. In the monitored group, this was done until BIS values of 60-80 were reached or the patient expressed discomfort. In the usual care group, this was done until the patient's sedation level was more than a score of 4 on the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S)[22] or the patient expressed discomfort. No other medications, including analgesics, were used in the present study.

Outcomes

To determine the baseline levels of the patients' cognitive performance, the MMSE,[23] TDT[24] and clock drawing test (CDT)[25] were performed on the day of the procedure, after admission to the endoscopy unit. The MMSE evaluates orientation, registration, attention, calculation, recall, language and praxis (cutoff < 23, for abnormal).[23] This test was used to quantitatively assess psychomotor activity.[24] The TDT score represents the total number of dots that are not connected, with a total score of 70 points. The TDT scores and TDT deviations were normalized to baseline scores and deviations for each patient. The CDT is a simple neuropsychometric instrument that can easily be applied to assess several neuropsychiatric functions (scores from 0 to 5; cutoff: 3 points).[25]

Age, gender, ASA physical status, body mass index (BMI), total propofol dose, duration of sedation, patient satisfaction and MOAA/S on arrival at the post-anesthesia care unit (PACU) were recorded. Furthermore, heart rate (HR), mean blood pressure (MBP), oxygen saturation (SpO_2) and BIS values (at baseline, immediately after induction, at the beginning of colonoscopy, at the 5th minute of colonoscopy, at the end of colonoscopy and at discharge from the post-anesthesia care unit) were recorded. We also recorded any complications associated with sedation (i.e. oxygen saturation < 90%, blood pressure < 90/50 mmHg or HR < 50 bpm).

The patients were classified as ready for hospital discharge in accordance with the Chung criteria.[26] Within these criteria, they were considered fit for discharge home when their score was ≥ 9 out of a total of 10. At this point, the patients' satisfaction was evaluated (as dissatisfied, neutral or satisfied). In addition, post-procedural cognitive performance was assessed using the MMSE, TDT and CDT. The baseline and the post-procedural cognitive performance were assessed by another anesthesiologist (MSU), who was blinded to the BIS that had been used.

Sample size

The sample size calculation was based on a prior pilot study with 16 patients (unpublished data). The primary outcome variable was the mini-mental state examination test score at discharge. The mean and standard deviation (SD) of the discharge MMSE test scores of the two groups were taken to be 25.30 (SD 3.83) and 23.30 (SD 2.98), as determined based on the preliminary study on 16 patients. It was calculated that, for a 25% difference between the groups, with a significance level of 0.05 and a power of 80%, 48 subjects would be required. Thus, 50 subjects were included, to cope with possible drop-outs.

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences 15.0 software (SPSS Institute, Chicago, IL, USA). Continuous data were tested for normality. Normally distributed data were summarized using the mean and standard deviation and were compared using unpaired two-tailed t tests. Skewed data were summarized using the median with the range and interquartile range (IQR) and were compared using Wilcoxon's rank sum test. Categorical data were summarized using the number and percentage (%) and were compared using the chi-square (X^2) test or Fisher's exact test. Paired data were compared using paired two-tailed t tests or signed-rank tests. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 100 patients were enrolled in the study, and all patients completed the investigation. **Figure 1** shows the Consolidated Standards Of Reporting Trials (CONSORT) flow chart detailing

patient recruitment. Data analysis was performed on the two groups. No patient was withdrawn from the study after induction of sedation, and no complication developed.

The patients' demographic data are summarized in **Table 1**. There were no significant differences between the groups regarding age, gender, ASA physical status or BMI.

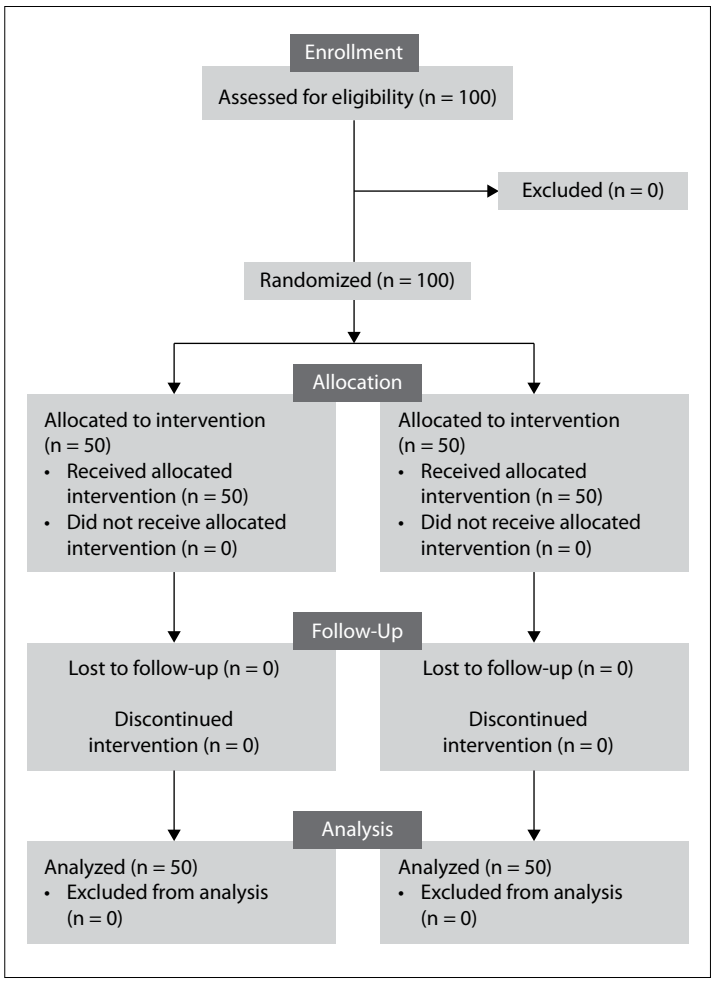


Figure 1. CONSORT flowchart detailing patient recruitment.

Table 1. Patients' characteristics

	Monitored group (n = 50)	Usual care group (n = 50)	P
Age (years), mean (SD)	47 (13)	48 (14)	0.722*
Gender (male/female)	31/19	28 / 22	0.462#
ASA physical status, number (%)			
I	29 (58)	30 (60)	0.763#
II	21 (42)	20 (40)	
BMI (kg/m²), median (range) [IQR]	27 (16-36) [24-31]	26 (15-36) [21-29]	0.143$

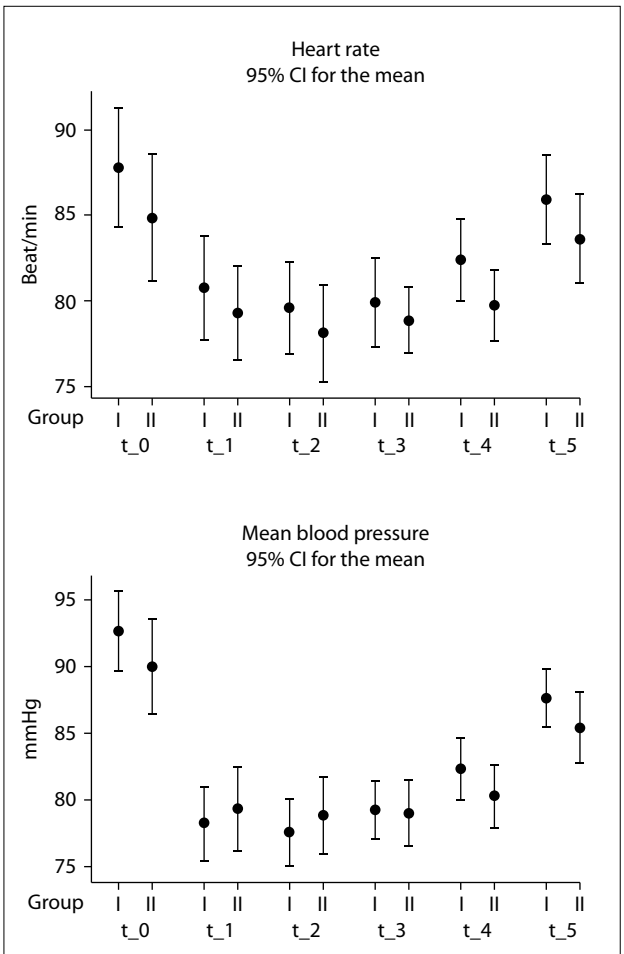
*Unpaired two-tailed t tests; #χ^2 test; $Wilcoxon's rank sum test.
SD = standard deviation; ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range.

The changes in HR and MBP can be seen in **Figure 2**. The measurements of hemodynamic parameters (HR and MBP) were statistically similar between the groups at all measurement times.

Sedation, procedure and recovery characteristics are summarized in **Table 2**. There were no significant differences in the duration of sedation or in the patients' satisfaction between the groups. The total amount of propofol used in the sedation procedure was statistically significantly lower in the monitored group than in the usual care group ($P < 0.001$).

The changes in BIS values in the monitored group BIS are summarized in **Table 3**.

The patients' cognitive function test results at baseline and discharge are summarized in **Table 4**. There were no significant differences between the groups regarding the baseline values of the



Group I: monitored group; Group II: usual care group; CI: confidence interval. t_0: at baseline; t_1: immediately after induction; t_2: at the beginning of colonoscopy; t_3: at the 5th minute of colonoscopy; t_4: at the end of colonoscopy; t_5: at discharge from post-anesthesia care unit. Paired two-tailed t tests were used.

Figure 2. Changes to heart rate and mean blood pressure.

cognitive function test results (MMSE, TDT and CDT). The discharge values of the MMSE and CDT were statistically significantly higher in the monitored group than in the usual care group (P = 0.002 and P = 0.002, respectively). Moreover, the discharge values of the TDT were statistically significantly lower in the monitored group than in the usual care group (P = 0.033).

Table 2. Sedation, procedure and recovery characteristics

	Monitored group (n = 50)	Usual care group (n = 50)	P
Total propofol dose (mg), median (range) [IQR]	100 (50-200) [100-140]	150 (75-200) [100-200]	< 0.001$
Duration of sedation (min), median (range) [IQR]	16 (10-25) [15-20]	16 (11-22) [12-20]	0.197$
MOAA/S on arrival at PACU, median (range) [IQR]	3 (2-4) [3-4]	4 (2-4) [3-4]	0.001$
Patients' satisfaction, number (%)			
Dissatisfied	3 (6)	5 (10)	
Neutral	10 (20)	10 (20)	0.260#
Satisfied	37 (74)	35 (70)	

IQR = interquartile range; MOAA/S = Modified Observer's Assessment of Alertness/Sedation scale; PACU = post-anesthesia care unit. #: χ^2 test, $: Wilcoxon's rank sum test.

Table 3. Changes to bispectral index (BIS) values in monitored group

Time	BIS values*
t_0	97 (92-98) [96-98]
t_1	66 (55-78) [61-72]
t_2	65 (58-77) [62-70]
t_3	71 (59-80) [68-74]
t_4	78 (68-86) [75-81]

*Values are expressed as median (range) [interquartile range, IQR]. t_0: at baseline; t_1: immediately after induction; t_2: at the beginning of colonoscopy; t_3: at the 5th minute of colonoscopy; t_4: at the end of colonoscopy.

Table 4. Cognitive performance tests on the patients at baseline and discharge

	Monitored group (n = 50)	Usual care group (n = 50)	P*
MMSE, mean (SD)			
Baseline	27 (3)	26 (2)	0.113
Discharge	26 (3)	23 (3)	0.002
TDT, mean (SD)			
Baseline	8 (6)	7 (5)	0.057
Discharge	11 (7)	15 (11)	0.033
CDT, mean (SD)			
Baseline	3 (1)	3(1)	0.584
Discharge	3 (1)	2 (1)	0.002

*Unpaired two-tailed t tests. MMSE = mini-mental state examination test; SD = standard deviation; TDT = Trieger dot test; CDT = clock drawing test.

DISCUSSION

The current study demonstrated that BIS monitoring of patients subjected to sedation for colonoscopy was associated with diminished use of propofol and better scores in post-procedure cognitive performance tests than what was observed among patients who were not monitored.

Postoperative cognitive function disorder is a common neurological complication seen after surgery, anesthesia and sedation. It is characterized by impairments in recent memory, concentration, language comprehension and social integration.[27] The effect of anesthetic depth on postoperative cognitive dysfunction among surgical patients has already been investigated using BIS monitoring,[17] and various medications have been compared in studies assessing POCD subsequent to procedures such as colonoscopy and ERCP.[1,18] However, no previous study has evaluated the effects of BIS monitoring on early cognitive performance after outpatient procedures such as colonoscopy and ERCP.

To reduce the amount of sedative agents administered to patients, sedation depth can be monitored using objective and reliable methods such as BIS monitoring. BIS, obtained through use of a conventional electroencephalogram, is independent of the type of hypnotic medications and individual patient characteristics. However, some agents such as ketamine and opioids are not suitable for BIS monitoring.[11] Previous publications on the use of BIS for monitoring sedation during colonoscopy mostly focused on decreasing the amount of sedative agents administered, or on assessing recovery time or patients' or endoscopists' satisfaction.[12-16]

It has been demonstrated that intraoperative BIS monitoring facilitates the titration of anesthetic agents. Thus, it has the potential to decrease the use of anesthetic agents.[28-30] BIS monitoring has also been shown to enable improvement in the early recovery profile through reducing the use of anesthetic agents.[19,20] However, it is unclear whether the reduced dose of anesthetic agents achieved through the use of BIS monitoring decreases the risk of POCD.

In sedated patients, BIS monitoring has been shown to result in decreased propofol use, shortening of the duration of awakening and reduction in the number of adverse events.[21] The decrease in the amount of sedative agents used during colonoscopy procedures that were accompanied with BIS monitoring, as previously reported in the literature, were confirmed through the present study as well. In the present study, the amount of propofol used during the procedure was significantly lower in the group that underwent BIS monitoring than in the group without BIS intervention. Post-procedure cognitive performance was significantly better in the monitored group, possibly due to reduced use of sedative agents.

Although it has been reported in several studies that BIS monitoring reduced the use of propofol in sedated patients, contrary results have also been demonstrated in some other studies.[16,31] Unlike in our study, Imagawa et al.[13] reported that BIS monitoring

did not reduce the use of propofol during sedation, but that it improved patient satisfaction scores. Similar to our findings, Yu et al. did not find any effect from BIS monitoring on patient satisfaction scores.[16]

Although studies have evaluated the effects of general anesthesia accompanied by BIS monitoring on cognitive dysfunction, no previous study has investigated early cognitive performance among patients sedated under the guidance of BIS monitoring.[32,33] In a previous study that included geriatric patients, use of intraoperative BIS monitoring was associated with decreased incidence of postoperative delirium, but no decrease in the rate of POCD was noted.[32] Another study among geriatric patients demonstrated that intraoperative use of BIS monitoring decreased the rates of both postoperative delirium and cognitive dysfunction.[33]

In this study, the period between the termination of the procedure and the second application of cognitive tests was not recorded, and this was one limitation of the study. The second limitation of this study was the absence of longer follow-up to assess cognition several days after the procedure.

CONCLUSION

The results from our study suggest that BIS monitoring during colonoscopy in sedated patients gives rise to in a decrease in the amount of propofol used during the procedure and that it possibly precludes cognitive performance decline. In addition, the lower MOAA/S values on arrival at the PACU that were detected in the group sedated under the guidance of BIS monitoring can be considered to be a consequence of the decrease in the propofol dose used during the procedure.

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Prevalence of arterial hypertension in Brazilian adults and its associated factors and activity limitations: a cross-sectional study

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ABSTRACT

BACKGROUND: Hypertension is a serious global public health problem that affects a large part of the Brazilian adult population and can cause limitations and losses of quality of life.

OBJECTIVE: The objective of this study was to analyze the association of hypertension and its correlated limitations, with sociodemographic and epidemiological factors.

DESIGN AND SETTING: Cross-sectional study analyzing information on 44,271 adults (30 years or older) from the Brazilian National Health Survey of 2013.

METHODS: The prevalence of hypertension and the degree of limitation of the patients' activities associated with hypertension, according to sociodemographic characteristics, anthropometric measurements and lifestyles, were calculated for both sexes. To analyze the strength of association, bivariate and multivariate Poisson regression were used.

RESULTS: Hypertension was the most prevalent risk factor among Brazilian adults aged 30 years or older (40.7%). It was strongly associated with the aging process (prevalence ratio, PR 3.51), obesity (PR 1.73), heart disease (PR 1.67) and stroke (PR 1.86). Furthermore, limitations associated with hypertension were more prevalent among those with comorbidities from noncommunicable diseases relating to hypertension complications (stroke PR 1.47; heart disease PR 1.69) and with incomplete elementary education (PR 1.19).

CONCLUSIONS: This study showed sociodemographic inequality in the prevalence of hypertension, especially in the population with some degree of limitation associated with hypertension. It showed that improvements in access to primary care services for controlling hypertension at its initial stages are essential in order to avoid comorbidities of greater severity and limitations and losses of quality of life, especially among socially disadvantaged people.

INTRODUCTION

According to a World Health Organization (WHO) report,[1] noncommunicable diseases (NCDs) were responsible for 38 million deaths in 2012, thus accounting for 70% of deaths worldwide. Hypertension is considered to be an intermediate risk factor, given its substantial impact on the burden of cardiovascular diseases.[2,3] WHO has estimated that, in 2008, around 12.8% of the deaths resulted from hypertension.[4] Moreover, it has been estimated that around 40% of the adult population worldwide aged 24 years or older has hypertension, and that this proportion is in even higher in low and middle-income countries in which living conditions are worse and the healthcare systems are fragile.[5]

The relationship between hypertension and both cardiovascular and cerebrovascular diseases is well known, stable and independent of other risk factors.[6] Arterial hypertension is recognized as a major public health problem that contributes greatly to increased burdens of cardiopathies, stroke, renal failure and disability.[2]

Hypertension is an important risk factor among the Brazilian adult population. According to PNAD 2008 data, nearly 14% of Brazilians aged 18 years or over self-reported having a diagnosis of hypertension.[7] This proportion has increased over more recent years. In 2013, the prevalence of self-reported hypertension in the same population was 32.3%, with a sharp increase among adults aged 30 years and over.[8]

Hypertension has complex and multifactorial characteristics, and it combines hereditary and genetic factors with socioeconomic, environmental and lifestyle factors. Knowing the risk factors

associated with hypertension, along with the magnitudes of the associations, is fundamental for making it possible to reduce hypertension and the morbidity and mortality caused by other NCDs.

OBJECTIVE

The objective of the present study was to analyze the association of hypertension and the limitations associated with this, with sociodemographic and epidemiological factors, among the Brazilian adult population aged 30 years or over.

METHODS

Study design, sampling and ethics

This cross-sectional study analyzed the prevalence of hypertension and the degree of limitation of the patients' activities associated with hypertension, according to information from the Brazilian National Health Survey (Pesquisa Nacional de Saúde, PNS) of 2013. PNS 2013 was a household survey on the Brazilian population according to major regions, states and state capitals, using a representative sample design. The foremost objective of this survey was to characterize the health situation of the Brazilian population and its lifestyles, and to collect information about its healthcare and access to and utilization of healthcare services.

The PNS had a complex sampling design. Three-stage cluster sampling (census tracts, households and individuals) was used, with stratification of the primary sampling units (PSUs) and random selection in each stratum. Census tracts or sets of sectors composed the PSUs; households were the units of the second stage; and residents aged 18 years or older defined the third-stage unit.[9] The PNS fieldwork was carried out from August 2013 to February 2014, in 6,069 selected census tracts, with visits to 81,254 homes. Among these, 69,994 homes were found to be occupied, 64,348 household interviews were conducted and 60,202 individual interviews were completed. In this study, we restricted the data analysis to adults aged 30 years and older (44,271 individuals).

This study was approved by the National Commission for Research Ethics (Comissão Nacional de Ética em Pesquisa, CONEP) in June 2013 (No. 328,159).[10]

Study outcomes and explanatory variables

The hypertension definition used was that subjects were classified as hypertensive when their final systolic blood pressure (average of three measurements) was greater than or equal to 140 mmHg and/or their final diastolic blood pressure was greater than or equal to 90 mmHg and/or they self-reported having used antihypertensive medication in the last two weeks. The methods of assessment and the definition of hypertension were based upon the recommendation of the evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8).[6]

The limitations associated with hypertension were defined as including only the individuals with a self-reported diagnosis of hypertension with some degree of limitation (responses 2 to 4), based on the following question: "In general, to what extent does hypertension or some complication of hypertension limit your usual activities (such as working, studying, doing household chores, etc.)? 1. none; 2. a little; 3. greatly; or 4. very greatly".

The sociodemographic characteristics used in the analysis were: sex (male or female); age group (30 to 39 years, 40 to 49 years, 50 to 59 years or 60 years or over); race/color (white, black or brown/mixed); and educational level (elementary education incomplete; elementary education completed or high school education incomplete; or high school education completed or more).

The following anthropometric variables, both classified according to WHO recommendations, were considered in the analysis: body mass index (BMI) (< 25 kg/m², 25-29 kg/m² or ≥ 30 kg/m²); and waist circumference (WC) (women: < 80 cm normal; 80-87.9 cm enlarged; or ≥ 88 cm substantially enlarged; and men: < 94 cm normal; 94-101.9 cm enlarged; or ≥ 102 cm substantially enlarged).[10]

We also considered variables representing lifestyles: smoking (current smoker, former smoker or nonsmoker); recommended daily consumption of fruit and vegetables on five or more days per week (yes or no); and recommended physical activity in leisure time greater than or equal to 150 minutes per week (yes or no).

The health situation characteristics assessed included the following variables regarding health status and access to healthcare services: self-rated health (good/very good; or fair/poor/very poor); chest pain when walking (yes or no); self-reported diagnosis of some heart disease (yes or no); self-reported stroke (yes or no); self-reported diabetes (yes or no); depression based on the Patient Health Questionnaire-9 (PHQ-9)[11] (yes or no) and at least one medical consultation in the last 12 months (yes or no).

To ensure the quality of information and control for potential bias, we trained the interviewers; experienced researchers prepared an operational manual for interviewers; and the anthropometric and blood pressure measurements followed international protocols. A pilot test was conducted in March 2013 and fieldwork coordination was carried out by the Brazilian Institute for Geography and Statistics (IBGE).[10]

Statistical analysis

To study the association between hypertension and sociodemographic characteristics, lifestyle factors and health status, we estimated the hypertension prevalence ratio (PR) and 95% confidence intervals (95% CI), using Poisson regression models. The outcome was the presence of hypertension and the

independent variables were the following: sex, age group, race/skin color, educational level, BMI, WC, smoking, adequate consumption of fruits and vegetables, being physically active, self-rated health, chest pain when walking, heart disease, stroke, diabetes, depression based on PHQ-9 and at least one medical consultation in the last year.

The statistical analysis was done separately for four groups of variables: sociodemographic characteristics; anthropometric measurements; lifestyles; and health situation. For each group of variables, we calculated the crude prevalence ratio. Then, we calculated the adjusted prevalence ratio according to sex and age (model 1) and according to all other covariates (model 2).

The data were analyzed using the Stata software, version 11.0, through the survey module, which incorporates the effects of complex samples.

RESULTS

In 2013, the prevalence of hypertension in the Brazilian population aged 30 years or older was 40.7%. The prevalence of hypertension was seen to increase with age: while the prevalence was only 18.8% in the age group from 30 to 39 years, the rate reached 66% in the age group of 60 years or older. People with lower educational level and of black race/color had higher prevalence of hypertension (**Table 1**).

The results presented in **Table 1** show that the higher the BMI was, the larger the prevalence of hypertension also was, reaching 54.2% among obese individuals (those with BMI greater than or equal to 30 kg/m^2). The same results were found for WC: among people with substantially enlarged WC, the prevalence of hypertension was 52.4%. Regarding the habit of smoking, former smokers and current smokers showed higher prevalence of hypertension than nonsmokers did. The prevalence of hypertension was higher among physically inactive individuals.

With regard to health situation (**Table 1**), the prevalence of hypertension among people with fair/poor self-reported health was higher (52.1%). People with other NCDs also showed high prevalence rates: 65.5% among those with heart diseases, 74.4% among those who had had a stroke, 73.2% among those with diabetes and 47.4% among people with depression.

Analysis on the presence of limitations associated with hypertension (**Table 1**) showed that 69.2% of the hypertensive individuals did not have any limitations associated with the disease. Women reported limitations associated with hypertension more frequently than did men: 34.0% and 26.1%, respectively. Elderly people reported limitations associated with hypertension to a higher degree than did individuals aged 30-39 years. Significant differences in the prevalence of limitations associated with hypertension were found according to educational level: the lower the degree of education was, the higher the percentage of people with some limitations was. The prevalence of these limitations ranged from 19.1% to 37.4%. White people (27.6%) reported lower limitations than did black people (36.1%) or brown/mixed-race people (33.8%).

People with high BMI and high WC presented slightly lower proportions of limitations. There was also no statistical difference in the limitations associated with hypertension levels according to smoking status. On the other hand, people with adequate consumption of fruits and vegetables had lower limitations (72.5% had no limitations associated with hypertension) and most of the physically active individuals with hypertension reported that they did not have any limitations associated with the disease (79.3%).

Limitations associated with hypertension were more common among individuals with worse health status. Among those with fair/poor self-reported health, 39.9% reported having some limitations. More than half (52.3%) of those who reported having chest pain when walking also reported some limitations. Among people with other NCDs, the prevalence of limitations associated with hypertension was also high: 48.1% for another heart disease; 44.1% for stroke; 40.3% for diabetes; and 51.8% for depression based on PHQ-9. Among individuals who had had at least one medical consultation in the last 12 months, 31.9% reported having some limitations associated with hypertension (**Table 1**).

Table 2 shows the association analysis for sociodemographic characteristics in relation to hypertension and the limitations associated with hypertension. Greater age was strongly associated with greater hypertension, such that the prevalence ratio (PR) among elderly people (≥ 60 years) was three times higher than that of the youngest age group (30-39 years). Lower educational levels were also associated with higher prevalence of hypertension, in all the regression models considered, especially for individuals with incomplete elementary school in comparison with those with completed high school or more (PR 1.19; 95% CI 1.14-1.25). Black individuals showed higher prevalence of hypertension in all models, in comparison with white individuals.

Regarding the presence of limitations associated with hypertension, the variables associated were sex, educational level and race/color. Women showed higher prevalence of limitations associated with hypertension in all regression models. The lowest level of schooling (incomplete elementary school) was strongly associated with the presence of limitations associated with hypertension. Not being white was also significantly associated (**Table 2**).

The results presented in **Table 3** show that high BMI or WC were significantly associated with hypertension in all the models analyzed. Among people with substantially enlarged WC, the PR was 1.91 (95% CI 1.18-2.02) in the bivariate analysis and 1.53 (95% CI 1.43-1.64) in the multivariate analysis. Both the crude analysis and model 1 (adjusted according to sex and age) showed that physically inactive people had higher prevalence of hypertension, but the association was not significant in the multivariate model.

Table 1. Prevalence of hypertension and some degree of limitation associated with this among adults aged 30 years or older, according to sociodemographic, anthropometric, lifestyle and health status characteristics (n = 44,271)

	n	%	Hypertension		Some degree of limitation[1]	
			Prevalence ratio	95% CI	Prevalence ratio	95% CI
Total	44,271	100.0	40.7	(39.8-41.5)	30.8	(29.3-32.4)
Sociodemographic characteristics						
Age						
30 to 39	12,811	28.9	18.8	(17.7-20.0)	28.3	(24.3-32.7)
40 to 49	10,851	24.5	33.1	(31.5-34.6)	28.1	(24.9-31.6)
50 to 59	9,742	22.0	49.6	(47.7-51.4)	30.5	(27.7-33.4)
60 or older	10,866	24.5	66.0	(64.5-67.6)	32.8	(30.6-35.0)
Sex						
Male	20,575	46.5	41.0	(39.8-42.3)	26.1	(24.0-28.4)
Female	23,696	53.5	40.3	(39.3-41.4)	34.0	(32.0-36.0)
Education level						
High school education or over	17,966	40.6	31.4	(30.1-32.6)	19.1	(16.9-21.5)
Elementary education completed/high school education incomplete	5,655	12.8	37.6	(35.4-39.9)	29.0	(25.0-33.3)
Elementary education incomplete	20,649	46.6	49.6	(48.4-50.8)	37.4	(35.4-39.5)
Race/color						
White	21,629	48.9	41.2	(40.0-42.5)	27.6	(25.6-29.7)
Black	4,189	9.5	45.0	(42.4-47.6)	36.1	(31.4-41.2)
Brown/mixed	17,861	40.3	39.1	(37.9-40.3)	33.8	(31.4-36.3)
Anthropometric and lifestyle characteristics						
Body mass index						
< 25 kg/m^2	16,232	36.7	31.3	(30.1-32.6)	32.0	(29.2-34.9)
25-29 kg/m^2	17,447	39.5	41.1	(39.8-42.5)	30.3	(28.0-32.7)
≥ 30 kg/m^2	10,509	23.8	54.2	(52.5-55.9)	30.7	(28.1-33.5)
Waist circumference[2]						
Normal	14,371	32.5	27.4	(26.1-28.7)	32.9	(29.5-36.4)
Enlarged	9,908	22.4	36.2	(34.6-37.8)	29.1	(26.0-32.3)
Substantially enlarged	19,991	45.2	52.4	(51.1-53.7)	30.8	(28.9-32.7)
Smoking						
Smoker	7,077	16.0	40.2	(38.0-42.4)	31.8	(28.1-35.7)
Former smoker	9,292	21.0	51.4	(49.7-53.1)	31.5	(28.8-34.3)
Nonsmoker	27,902	63.0	37.2	(36.2-38.3)	30.3	(28.3-32.3)
Recommended consumption of fruit and vegetables						
No	30,762	69.5	40.8	(39.8-41.8)	32.3	(30.4-34.2)
Yes	13,509	30.5	40.4	(39.8-41.8)	27.5	(24.9-30.3)
Physical activity during free time						
No	36,094	81.5	42.1	(41.2-43.0)	32.7	(31.1-34.4)
Yes	8,176	18.5	34.5	(32.7-36.2)	20.7	(17.8-24.1)
Health situation characteristics						
Self-rated health						
Good/very good	26,791	60.5	33.2	(32.1-34.2)	17.4	(15.4-19.6)
Fair/poor/very poor	17,479	39.5	52.1	(50.8-53.4)	39.9	(37.9-41.9)
Chest pain when walking						
No	38,486	86.9	38.8	(37.9-39.7)	24.8	(23.3-26.4)
Yes	5,784	13.1	53.1	(50.9-55.4)	52.3	(48.8-55.8)
Some heart disease						
No	41,892	94.6	39.3	(40.1-40.7)	28.4	(26.8-30.1)
Yes	2,378	5.4	65.5	(61.7-69.1)	48.1	(43.4-52.8)
Stroke						
No	43,370	98.0	40.0	(39.1-40.8)	30.1	(28.5-31.7)
Yes	901	2.0	74.4	(69.4-78.8)	44.1	(37.6-50.9)
Diabetes						
No	36,729	90.9	38.4	(37.5-39.3)	28.3	(26.6-30.0)
Yes	3,656	9.1	73.2	(70.6-75.8)	40.3	(36.7-44.0)
Depression (PHQ-9 scale)						
No	39,465	89.1	39.8	(39.0-40.7)	26.7	(25.1-28.4)
Yes	4,806	10.9	47.4	(44.9-50.0)	51.8	(48.2-55.3)
Medical appointment within the last 12 months						
No	10,095	23.0	32.0	(30.4-33.7)	20.9	(17.5-24.7)
Yes	33,887	77.0	43.3	(42.3-44.3)	31.9	(30.3-33.6)

1) Self-reported hypertension; 2) Female (normal: < 80 cm; enlarged: 80-87.9 cm; substantially enlarged: ≥ 88 cm); Male (normal: < 94 cm; enlarged: 94-101.9 cm; substantially enlarged: ≥ 102 cm). Source: National Health Survey, 2013.[9] CI = confidence interval; PHQ-9 = Patient Health Questionnaire-9.

Hypertension did not show any association with consumption of fruits and vegetables or with smoking in any of the models. However, the probability of being hypertensive was higher among former smokers.

Regarding some reported limitations associated with hypertension (**Table 3**), neither BMI nor smoking habits showed any association with the outcome. On the other hand, physical inactivity during leisure time was strongly associated with the limitations linked with hypertension. in all the analysis models, with PR ranging from 1.58 (95% CI 1.35-1.84) in the bivariate model to 1.38 (95% CI 1.19-1.61) in model 2. Individuals with enlarged WC had slightly lower prevalence of limitations associated with hypertension in the multivariate models 1 and 2.

Table 4 shows the PR (crude and adjusted) for the association of health status with hypertension and the limitations associated with hypertension. The disease most strongly associated with hypertension was diabetes, with PR ranging from 1.91 (95% CI 1.83-1.99) in the bivariate model to 1.31 (95% CI 1.25-1.36) in multivariate model 2. Other indicators that also showed significantly higher prevalence of hypertension were the following: fair/poor/very poor self-reported health; stroke; chest pain when walking; some heart disease; and medical consultation within the last year. Depression was associated with hypertension in the bivariate model and in model 1.

Regarding the analysis on the association between health status and some limitations associated with hypertension, we

Table 2. Results from Poisson regression models in which hypertension and some degree of limitation associated with this were the outcomes and sociodemographic characteristics were the covariates, among adults aged 30 years or older (n = 44,271)

Hypertension	Unadjusted model			Model 1[1]			Model 2[2]		
	PR	95% CI	P-value	PR	95% CI	P-value	PR	95% CI	P-value
Age									
30-39	1			1			1		
40-49	1.76	(1.63-1.89)	< 0.001	1.76	(1.63-1.89)	< 0.001	1.72	(1.60-1.85)	< 0.001
50-59	2.64	(2.45-2.83)	< 0.001	2.64	(2.45-2.83)	< 0.001	2.54	(2.36-2.73)	< 0.001
60+	3.51	(3.29-3.75)	< 0.001	3.52	(3.29-3.76)	< 0.001	3.29	(3.07-3.53)	< 0.001
Sex									
Female	1			1			1		
Male	1.02	(0.98-1.06)	0.398	1.04	(1.00-1.08)	0.024	1.04	(1.00-1.08)	0.036
Education level									
High school education or over	1			1			1		
Elementary education completed/high school education incomplete	1.20	(1.11-1.29)	< 0.001	1.12	(1.04-1.20)	0.002	1.11	(1.04-1.20)	0.003
Elementary education incomplete	1.58	(1.50-1.65)	< 0.001	1.19	(1.14-1.25)	< 0.001	1.19	(1.14-1.25)	< 0.001
Race/color									
White	1			1			1		
Black	1.09	(1.02-1.16)	0.008	1.12	(1.05-1.19)	< 0.001	1.09	(1.02-1.16)	0.007
Brown/mixed	0.95	(0.91-0.99)	0.014	1.02	(0.98-1.06)	0.351	0.99	(0.94-1.03)	0.565
Some degree of limitation[3]	**Unadjusted model**			**Model 1[1]**			**Model 2[2]**		
	PR	95% CI	P-value	PR	95% CI	P-value	PR	95% CI	P-value
Age									
30-39	1			1			1		
40-49	0.99	(0.83-1.18)	0.937	0.99	(0.83-1.18)	0.907	0.94	(0.79-1.11)	0.458
50-59	1.08	(0.91-1.28)	0.399	1.08	(0.91-1.28)	0.400	0.99	(0.84-1.18)	0.925
60+	1.16	(0.98-1.37)	0.084	1.15	(0.98-1.36)	0.095	0.96	(0.81-1.13)	0.622
Sex									
Female	1			1			1		
Male	0.77	(0.70-0.85)	< 0.001	0.77	(0.70-0.85)	< 0.001	0.81	(0.73-0.89)	< 0.001
Schooling level									
High school education or over	1			1			1		
Elementary education completed/high school education incomplete	1.50	(1.25-1.80)	< 0.001	1.50	(1.25-1.80)	< 0.001	1.47	(1.22-1.76)	< 0.001
Elementary education incomplete	1.96	(1.72-2.22)	< 0.001	1.94	(1.71-2.20)	< 0.001	1.89	(1.66-2.15)	< 0.001
Race/color									
White	1			1			1		
Black	1.31	(1.13-1.52)	< 0.001	1.31	(1.13-1.52)	< 0.001	1.23	(1.05-1.42)	0.008
Brown/mixed	1.22	(1.11-1.35)	< 0.001	1.23	(1.11-1.36)	< 0.001	1.13	(1.02-1.25)	0.016

1) Model 1 = sex and age; 2) Model 2 = all variables; 3) Self-reported hypertension. Source: National Health Survey, 2013.[9] PR = prevalence ratio; CI = confidence interval.

observed that people with fair/poor self-reported health presented PR 1.68 (95% CI 1.48-1.93) after controlling for all other variables. Likewise, for chest pain when walking, the PR was 1.59 (95% CI 1.45-1.75). For some heart disease, diabetes or stroke, the PR was approximately 1.20 in the multivariate model. Depression was strongly associated with limitations relating to hypertension, with PR ranging from 1.94 (95% CI 1.77-2.12) in the bivariate analysis to 1.33 (95% CI 1.21-1.47) in the multivariate model. Having had a medical consultation within the last year showed a significant association in the bivariate analysis and in model 1, but lost significance after controlling for all other variables (**Table 4**).

DISCUSSION

This study used blood pressure measurements to define hypertension, unlike other national studies that used self-reported diagnoses of hypertension.[12,13] However, studies based on reported morbidity are impacted by inequalities in healthcare access.[14,15] Use of blood pressure measurements allows better prevalence estimates for the outcome in the population.

Table 3. Results from Poisson regression models in which hypertension and some degree of limitation associated with this were the outcomes and anthropometric and lifestyle indicators were the covariates, among adults aged 30 years or older (n = 44,271)

Hypertension	Unadjusted model			Model 1[1]			Model 2[2]		
	PR	95% CI	P-value	PR	95% CI	P-value	PR	95% CI	P-value
Body mass index									
< 25 kg/m²	1			1			1		
25-29 kg/m²	1.31	(1.22-1.38)	< 0.001	1.28	(1.22-1.35)	< 0.001	1.09	(1.03-1.16)	0.003
≥ 30 kg/m²	1.73	(1.64-1.82)	< 0.001	1.68	(1.60-1.76)	< 0.001	1.30	(1.22-1.38)	< 0.001
Waist circumference[3]									
Normal	1			1			1		
Enlarged	1.32	(1.23-1.41)	< 0.001	1.30	(1.23-1.38)	< 0.001	1.24	(1.17-1.33)	< 0.001
Substantially enlarged	1.91	(1.81-2.02)	< 0.001	1.77	(1.67-1.86)	< 0.001	1.53	(1.43-1.64)	< 0.001
Smoking									
Nonsmoker	1			1			1		
Smoker	1.08	(1.02-1.15)	0.012	1.01	(0.95-1.08)	0.680	1.05	(0.99-1.12)	0.085
Former smoker	1.38	(1.32-1.44)	< 0.001	1.12	(1.08-1.17)	< 0.001	1.08	(1.03-1.13)	< 0.001
Recommended consumption of fruit and vegetables									
No	1			1			1		
Yes	0.99	(0.95-1.03)	0.633	0.97	(0.93-1.01)	0.121	1.00	(0.96-1.04)	0.810
Physical activity during free time									
Yes	1			1			1		
No	1.22	(1.16-1.29)	< 0.001	1.10	(1.04-1.16)	< 0.001	1.05	(1.00-1.11)	0.056
Some degree of limitation[4]	**Unadjusted model**			**Model 1[1]**			**Model 2[2]**		
	PR	95% CI	P-value	PR	95% CI	P-value	PR	95% CI	P-value
Body mass index									
< 25 kg/m²	1			1			1		
25-29 kg/m²	1.06	(0.94-1.19)	0.347	0.95	(0.85-1.07)	0,382	1,08	(0.95-1.22)	0.239
≥ 30 kg/m²	1.01	(0.90-1.33)	0.799	0.95	(0.84-1.08)	0.457	1.12	(0.96-1.30)	0.155
Waist circumference[3]									
Normal	1			1			1		
Enlarged	0.88	(0.76-1.03)	0.112	0.84	(0.73-0.98)	0.029	0.86	(0.74-1.00)	0.051
Substantially enlarged	0.94	(0.83-1.06)	0.285	0.83	(0.73-0.94)	0.004	0.80	(0.69-0.93)	0.004
Smoking									
Nonsmoker	1			1			1		
Smoker	1.05	(0.91-1.20)	0.498	1.11	(0.97-1.27)	0.133	1.02	(0.89-1.16)	0.793
Former smoker	1.04	(0.93-1.16)	0.478	1.09	(0.97-1.21)	0.134	1.05	(0.95-1.17)	0.325
Recommended consumption of fruit and vegetables									
No	1			1			1		
Yes	0.85	(0.76-0.95)	0.005	0.84	(0.76-0.94)	0.003	0.91	(0.82-1.02)	0.101
Physical activity during free time									
Yes	1			1			1		
No	1.58	(1.35-1.84)	< 0.001	1.56	(1.34-1.82)	< 0.001	1.38	(1.19-1.61)	< 0.001

1) Model 1 = sex and age; 2) Model 2 = sex, age, anthropometric and lifestyle variables; 3) Female (normal: < 80 cm; enlarged: 80-87.9 cm; substantially enlarged: ≥ 88 cm); Male (normal: < 94 cm; enlarged: 94-101.9 cm; substantially enlarged: ≥ 102 cm); 4) Self-reported hypertension. Source: National Health Survey, 2013.[9]
PR = prevalence ratio; CI = confidence interval.

Nevertheless, in the case of limitations associated with hypertension, we had to consider only those individuals who had been previously diagnosed.

The results from this study showed that the prevalence of hypertension in the Brazilian adult population aged 30 years or over is high (40.7%), and that it increases progressively with age, especially

Table 4. Results from Poisson regression models in which hypertension and some degree of limitation associated with this were the outcomes and health situation indicators were the covariates, among adults aged 30 years or older (n = 44,271)

Hypertension	Unadjusted model			Model 1[1]			Model 2[2]		
	PR	95% CI	P-value	PR	95% CI	P-value	PR	95% CI	P-value
Self-rated health									
Good/very good	1			1			1		
Fair/poor/ very poor	1.57	(1.51-1.63)	< 0.001	1.26	(1.21-1.31)	< 0.001	1.18	(1.13-1.23)	< 0.001
Chest pain when walking									
No	1			1			1		
Yes	1.37	(1.31-1.43)	< 0.001	1.25	(1.19-1.30)	< 0.001	1.16	(1.11-1.21)	< 0.001
Some heart disease									
No	1			1			1		
Yes	1.67	(1.57-1.77)	0.004	1.26	(1.19-1.34)	0.004	1.10	(1.03-1.17)	0.004
Stroke									
No	1			1			1		
Yes	1.86	(1.74-1.99)	< 0.001	1.33	(1.24-1.41)	< 0.001	1.17	(1.10-1.25)	< 0.001
Diabetes									
No	1			1			1		
Yes	1.91	(1.83-1.99)	< 0.001	1.41	(1.36-1.47)	< 0.001	1.31	(1.25-1.36)	< 0.001
Depression scale (PHQ-9 scale)									
No	1			1			1		
Yes	1.19	(1.13-1.26)	< 0.001	1.13	(1.07-1.19)	< 0.001	1.00	(0.95-1.05)	0.910
Medical appointment within the last 12 months									
No	1			1			1		
Yes	1.35	(1.28-1.43)	< 0.001	1.23	(1.16-1.29)	< 0.001	1.16	(1.10-1.23)	< 0.001
Some degree of limitation[3]	**Unadjusted model**			**Model 1[1]**			**Model 2[2]**		
	PR	**95% CI**	**P-value**	**PR**	**95% CI**	**P-value**	**PR**	**95% CI**	**P-value**
Self-rated health									
Good/very good	1			1			1		
Fair/poor/ very poor	2.29	(2.02-2.60)	< 0.001	2.25	(1.98-2.55)	< 0.001	1.68	(1.48-1.93)	< 0.001
Chest pain when walking									
No	1			1			1		
Yes	2.11	(1.93-2.29)	< 0.001	2.09	(1.92-2.28)	< 0.001	1.59	(1.45-1.75)	< 0.001
Some heart disease									
No	1			1			1		
Yes	1.69	(1.51-1.89)	< 0.001	1.69	(1.51-1.90)	< 0.001	1.23	(1.10-1.38)	< 0.001
Stroke									
No	1			1			1		
Yes	1.47	(1.25-1.72)	< 0.001	1.47	(1.26-1.72)	< 0.001	1.20	(1.04-1.40)	0.015
Diabetes									
No	1			1			1		
Yes	1.43	(1.28-1.59)	< 0.001	1.39	(1.25-1.55)	< 0.001	1.19	(1.08-1.32)	0.001
Depression (PHQ-9 scale)									
No	1			1			1		
Yes	1.94	(1.77-2.12)	< 0.001	1.90	(1.72-2.08)	< 0.001	1.33	(1.21-1.47)	< 0.001
Medical appointment within the last 12 months									
No	1			1			1		
Yes	1.53	(1.28-1.82)	< 0.001	1.45	(1.21-1.74)	< 0.001	1.22	(1.00-1.48)	0.047

1) Model 1 = sex and age; 2) Model 2 = sex, age and health situation; 3) Self-reported hypertension. Source: National Health Survey, 2013.[9] PR = prevalence ratio; CI = confidence interval; PHQ-9 = Patient Health Questionnaire-9.

among elderly individuals. The prevalence was also significantly higher among people who were nonwhite or less schooled, those with high BMI or enlarged WC, former smokers, those who were physically inactive and those who had had at least one medical consultation in the last 12 months before the survey.

Regarding comorbidities, individuals with fair/poor/very poor self-reported health, chest pain when walking, heart disease, diabetes, stroke or depression showed greater prevalence of hypertension. Regarding the limitations associated with hypertension, the prevalence was significantly higher among women, elderly people, people with lower schooling levels, nonwhites, people who were physically inactive and people consuming insufficient daily amounts of fruits and vegetables.

Male subjects presented higher prevalence of hypertension than did female subjects. This finding contrasted with the results from another study in which higher prevalence of hypertension among women was observed through use of self-reported data on diagnoses of hypertension.[13] Use of a self-reported variable of diagnosis is influenced by the degree of knowledge of the diagnosis, which, in turn, is related to access to and use of healthcare services. It is known that Brazilian women seek healthcare services more often than men do, which thus leads to underdiagnosing of hypertension among men.[16]

It has been recognized in the literature both from Brazil and from other countries that hypertension occurs most frequently at older ages. Physiological changes occur in the cardiovascular system as a normal characteristic of the aging process.[17] The increasing life expectancy and aging of the Brazilian population, as well as in the whole world, are factors that can explain the increase in the prevalence of hypertension over the last decades.[5]

The higher prevalence of hypertension among nonwhites that was found in the present study is in line with the findings from other studies on the Brazilian population.[8,13] The limitations associated with hypertension were also greater among nonwhite individuals. Some studies have pointed out genetic characteristics to explain the higher prevalence of hypertension among black people.[17] However, other factors that can be correlated with this include the accumulation of social disadvantages that have historically been found in this population group, which experiences greater socioeconomic vulnerability and lower access to healthcare services.[18]

In the present study, important socioeconomic inequalities in the distribution of hypertension were observed with regard not only to skin color, but also to educational level. Many studies have pointed out that multiple socioeconomic characteristics are associated with greater risk of hypertension, both at the individual level[19] and at the structural level.[20] It has been shown that individuals exposed to worse socioeconomic conditions are at greater risk of becoming hypertensive.[21]

The findings from the present study indicated that the lower the schooling level was, the greater the prevalence of hypertension and limitations associated with this were. Schooling level is an individual attribute that is generally imprinted on people's life cycles, thus influencing their opportunities, choices and experiences. Among adult individuals, it is a relatively stable characteristic, in comparison with younger people. It has been indicated in the scientific literature that low schooling levels heighten the exposure to risk factors for hypertension, such as improper feeding, smoking, physical inactivity during leisure time and higher levels of psychosocial stress.[18]

Both anthropometric measurements that were used in the present study to define obesity were significantly associated with higher prevalence of hypertension. It is well known that obesity is a strong predictor for cardiovascular diseases.[5] Data from the Brazilian National Health Survey showed that obesity (BMI $\geq$ 30 kg/m^2) resulted in an increase of 5.6 mmHg in systolic blood pressure and 3.1 mmHg in diastolic blood pressure among men and, respectively, 3.8 mmHg and 2.0 mmHg among women.[22]

The GBD study pointed out that smoking was responsible for 45% of the deaths associated with acute myocardial infarction and 25% of the deaths caused by cerebrovascular diseases.[23] In 2011, 21% of the deaths due to cardiovascular diseases and 18% due to stroke in Brazil were also associated with smoking habits.[24] The results from the present study showed that there was an association between formerly smoking and presenting hypertension. Since PNS was a cross-sectional study, formerly smoking represented tobacco exposure in the past, with smoking cessation greater among individuals diagnosed with hypertension.[25]

All the NCDs analyzed showed associations with hypertension, except depression. This finding corroborated results in the literature regarding the relationship between hypertension and other NCDs.[26] Comorbidities also heightened the prevalence of limitations associated with hypertension, since coexistence with other diseases can exacerbate the limiting effects.

Having had a medical consultation within the last 12 months before the survey was also associated with presence of hypertension. Greater access to healthcare services increases the opportunity to make the diagnosis, the chance of treatment and the life expectancy of individuals.[27] Nevertheless, the rate of diagnosing hypertension is still low in Brazil. A recent study that used PNS data indicated that only 43.2% of hypertensive adults had received a diagnosis of the disease. Hypertension is a silent disease, which makes early diagnosis a major challenge in primary healthcare services.[28]

One limitation of the present study was its use of a self-reported question about limitations associated with hypertension. Poor health status or depression can increase the perception of limitations in people's usual activities and may influence the frequency of negative responses to this question.

CONCLUSION

Hypertension is the most prevalent risk factor among Brazilian adults aged 30 years or over. It is strongly associated with the aging process, obesity and cardiovascular and cerebrovascular diseases. Furthermore, occurrences of limitations associated with hypertension are more prevalent among individuals with comorbidities of NCDs relating to the complications of hypertension. Therefore, it is essential to make improvements in access to primary care services for controlling hypertension at its initial stages, thus avoiding comorbidities of greater severity and limitations and losses of quality of life, especially among socially disadvantaged people.

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Incidence rates and temporal trends of cervical cancer relating to opportunistic screening in two developed metropolitan regions of Brazil: a population-based cohort study

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Uterine cervical neoplasms.
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ABSTRACT

BACKGROUND: Brazilian opportunistic screening programs for cervical cancer have limited impact. In the regions of two cities (Campinas and Curitiba) with high human development indices, consistent information from 96-97% of all cervical cancer cases managed within the public healthcare system is available.

OBJECTIVE: To estimate the incidence rate (IR) and temporal trends in these regions, covering 2001-2012.

DESIGN AND SETTING: A population-based cohort study was conducted under the assumption that all cervical cancer cases were managed in cancer referral center hospitals.

METHODS: 3,364 records (1,646 from Campinas; 1,718 from Curitiba) were analyzed to provide estimates of IR, age-standardized IR (ASR) and cervical cancer trends (shown per 100,000 women/year). Longitudinal patterns were analyzed using linear regression and shown as annual percentage change (APC); $P < 0.05$ for significance.

RESULTS: Annual IR and ASR estimates for cervical cancer ranged from 3.8 to 8.0 over 2001-2012, decreasing over more recent years, and were similar for the two regions. The age-specific IR was about 50% lower among women aged 45 years or older (IR-2001/IR-2012: Campinas = 14.8/8.0; Curitiba = 18.7/8.3; $P < 0.001$). There was an increasing APC trend in Campinas among women aged 15-24 years, and a decreasing IR trend for squamous-cell histology in both regions ($P < 0.05$).

CONCLUSION: Cervical cancer incidence estimates showed slowly decreasing trends in both regions, most evidently for women aged 45 years or older and for squamous-cell histology. These findings reflect the opportunistic nature of the population screening program, despite the comparatively high economic development level in the two regions.

INTRODUCTION

Cervical cancer remains an important burden in relation to women's health, especially in places with limited resources. The Brazilian government estimated that there would be 16,370 new cases in 2018,[1] with great regional variability. Thus, cervical cancer was placed as between the first and fourth most prevalent forms of cancer among women.[1,2]

Cervical cancer and its precursor lesions can be detected by screening. The success of population screening programs relates to their level of organization. Organized programs have defined target populations (age, screening interval and satisfactory access), predefined treatment algorithms, management teams, structures for quality assurance, surveillance systems, enough coverage and population education. Such programs have the potential to decrease cervical cancer rates by 80%.[3]

In contrast, there are opportunistic screening programs, such as the official population-screening program of the Brazilian National Health System (Sistema Único de Saúde, SUS). There is no registration system to control the screened or unscreened population and cytological tests are performed opportunistically, as a result of recommendations made during routine medical consultations, based on presence of increased risk of developing cancer, or through self-referral. The Brazilian program indicates that conventional cytological tests should be performed every three years, after two consecutive negative tests with a one-year interval between them, for women aged 25 to 64 years.[4] However, the age range and test interval recommendations are

not widely followed.[6] After several decades, the program has not achieved organized status, thus resulting in both low coverage and a lack of significant impact on mortality.[2,5]

The cities of Campinas (state of São Paulo, SP) and Curitiba (state of Paraná, PR), located respectively in the southeastern and southern regions of Brazil, are the administrative centers for two major regional areas with high human development indices, according to the World Health Organization (WHO).[7] These regions have well-established public primary care networks, but there are no controls in place to monitor population screening for cervical cancer. The system is based on primary healthcare units that are connected to a tertiary-level regional hospital cancer center, to which cases of suspected high-grade intraepithelial lesions or cervical cancer are referred.

The Brazilian population-based cancer registry system started in São Paulo in 1969 and was then expanded to other major cities that support the Brazilian National Cancer Institute (Instituto Nacional do Câncer, INCA), which has been calculating cancer incidence since 1995.[5] However, this registry system operates discontinuously and ineffectively in some places, including in the cities of Campinas, SP, and Curitiba, PR.[8-10]

These cities have regional hospitals that serve as the main reference for managing gynecological cancer among the residents of 82 municipalities in the Campinas region, covering 5.5 million people,[11] and 95 municipalities in the Curitiba region, covering 5.1 million people.[12] These two regions together represent around 5% of the Brazilian population. According to information from SUS regarding cervical cancer treatment, 97% of the cases in Campinas during the period 2010-2011 were managed at the Women's Health Hospital (WH), which is located at the University of Campinas (Universidade de Campinas, UNICAMP). In Curitiba, for the period 2008-2012, 96% of the cases were managed at the Clinics Hospital (CH) of the Federal University of Paraná (Universidade Federal do Paraná, UFPR) and at the Erasto Gaertner Cancer Center Hospital (EGH).[8-10]

Although these regional hospitals do not record all cervical cancer cases, thus making it impossible to calculate the real incidence, their data enable estimation of cervical cancer incidence and trends in the populations covered by opportunistic screening, in regions of Brazil with comparatively high economic development.

OBJECTIVE

The aim of the present study was to estimate the cervical cancer incidence rate (IR) and trends in the abovementioned Brazilian cities and their surrounding regions, for the period 2001-2012.

METHODS

Study design and setting

A population-based cohort study was conducted under the assumption that all cases of cervical cancer were managed in SUS cancer referral center hospitals. It can be expected that the vast majority of women with this neoplasia are treated at these centers. The hospitals considered were the Women's Hospital (WH), in the Campinas region, and the Clinics Hospital (CH) and Erasto Gaertner Hospital (EGH), in the Curitiba region. The information about women with cervical cancer was collected from each hospital-based cancer registry system for the period from January 2001 to December 2012.

Only cases originating in municipalities that were located in each region, as defined by the official geographical distribution (political, administrative and/or healthcare system),[11,12] and which systematically referred cases for care in the specified regional hospitals during the period 2001-2012, were considered.

Patients' records and general population

Records from 3,875 subjects were selected in accordance with the International Classification of Diseases (ICD-O) 2013 code C53.[13] The histological types considered were squamous-cell carcinoma (SCC) and equivalents, adenocarcinoma (AC) or any variant thereof and adenosquamous carcinoma (ASC);[13] 58 records with uncommon histological types that are less detectable through screening were excluded. Another 453 records relating to cases that arose from municipalities outside the official regions covered by these hospitals in Campinas and Curitiba were also excluded.[11,12] Thus, a total of 3,364 records (1,646 from the Campinas region and 1,718 from the Curitiba region) were included for analysis.

The population base upon which the incidence estimates were drawn was the Brazilian official censuses conducted in the years 2000 and 2010, and yearly projections for the interval between them. The data were available according to gender and five-year age groups for each city considered. The detailed database for each city is accessible online for public and technical consultations.[14,15]

Statistical analysis

Regional crude IRs were estimated using the number of cancer cases registered as the numerator and the female population for the same region and period as the denominator. To enable comparison between the regions studied, age-standardized incidence rates (ASRs) were obtained through a direct method, as described by the International Agency for Research on Cancer (IARC). These rates used the world standard population proposed by Segi in 1960.[16] Trend analyses were done according to year and age group, using the same 25-64 age range that is used in the official Brazilian screening program.[4] These analyses were also done according to histological type (using the WHO classification).[13] The results were reported per 100,000 women per year and were presented in terms of the annual percentage change (APC) and as percentage points (pp). Trend analysis was done by means of

linear regression using the StatsDirect statistical software (v. 3.0; StatsDirect, Cheshire, UK). Increasing or decreasing trends with P-values of less than 0.05 were considered statistically significant.

Ethics

This study followed the recommendations of the National Health Council of Brazil and was previously approved by the ethics committee of each hospital, under the following approval numbers: UNICAMP 890.837, dated November 24, 2014; UFPR 1.031.168, dated March 30, 2015; and EGH 1.486.542, dated April 11, 2018.

RESULTS

As shown in **Table 1**, the IR and ASR according to year were similar for the two regions. The ASRs for the two regions showed similar APCs with a decreasing trend, as can be seen in **Figure 1** (Campinas = -0.29 pp, P < 0.001; Curitiba = -0.26 pp, P = 0.003).

Considering age-specific IR, the Campinas region exhibited progressive and substantial decreases in IR among women aged 45 years or older, with a decreasing APC trend of 1.05 pp for cancer incidence among women aged 45-64 years (P < 0.001) and 1.25 pp among women aged 65 years or older (P = 0.002) (**Figure 2**; **Table 2**). The same pattern was observed in the Curitiba region for the age range 45-64 years, for which a decreasing APC trend of 0.95 pp was observed (P < 0.001) (**Figure 2**; **Table 2**). For IR, the Campinas region showed an increasing APC trend of 0.06 pp in the age range 15-24 years (P = 0.046), with IR of 0.44 per 100,000 women in 2001 and 1.39 per 100,000 women in 2012. This effect was very small and is not visible in **Figure 2**. The other age groups did not show any significant trend in either region (**Table 2**).

The histological type SCC presented a decreasing IR trend in both regions, with an APC of 0.17 pp in the Campinas region (P < 0.001) and 0.14 pp in the Curitiba region (P < 0.028), whereas the IRs for AC and ASC did not change over the period evaluated (**Table 2**; **Figure 3**).

DISCUSSION

The annual cervical cancer IR and ASR estimates ranged from 3.9 to 8.0 per 100,000 women per year over the period 2001-2012, but were lower over more recent years. They were similar for the two regions. Longitudinal analyses revealed a significant and slowly decreasing trend that was similar to patterns identified in previous reports about cervical cancer incidence and mortality in Brazil.[2,3]

According to official information from the Brazilian population-based cancer registry that was released in 2018, INCA has calculated that the crude IR was 9.17 and the ASR was 6.97 in Campinas for the years 2010-2011. In Curitiba, the crude IR was 13.27 and the

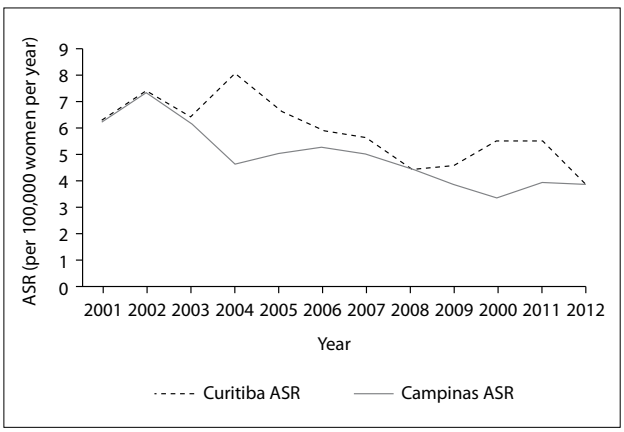


Figure 1. Estimated annual age-standardized incidence rate (ASR) for cervical cancer according to the region studied. The regions showed similar annual percentage change (APC) with decreasing trends (Campinas = 0.29 pp, P < 0.001; Curitiba = 0.26 pp, P = 0.003).

Table 1. Cervical cancer incidence rate, estimated according to year and region

	Campinas region				Curitiba region			
Year	Population (N)	Cancer (n)	IR	ASR	Population (N)	Cancer (n)	IR	ASR
2001	2,385,508	141	5.9	6.2	2,227,430	132	5.9	6.3
2002	2,428,290	178	7.3	7.3	2,265,751	157	6.9	7.4
2003	2,472,054	148	6.0	6.2	2,307,103	141	6.1	6.4
2004	2,515,664	116	4.6	4.7	2,348,361	175	7.5	8.0
2005	2,614,776	127	4.9	5.0	2,442,000	152	6.2	6.7
2006	2,665,255	144	5.4	5.3	2,489,744	140	5.6	5.9
2007	2,727,899	155	5.7	5.0	2,538,530	146	5.8	5.6
2008	2,683,221	137	5.1	4.5	2,495,481	120	4.8	4.5
2009	2,717,171	125	4.6	3.9	2,526,281	128	5.1	4.6
2010	2,738,136	115	4.2	3.4	2,467,100	157	6.4	5.5
2011	2,767,814	127	4.6	4.0	2,488,139	159	6.4	5.5
2012	2,796,449	133	4.8	3.9	2,508,543	111	4.4	3.9

IR = crude incidence rate (per 100,000 women per year); ASR = age-standardized incidence rate (per 100,000 women per year).

ASR was 10.82 for the years 2008-2012.[8-10] According to an international report from ICO (2016), referring to the year 2012, the ASR per 100,000 women was 16.3 cases for Brazil, 14.2 cases for Campinas, 15.2 cases for São Paulo and 22.1 cases for Porto Alegre (in the south of Brazil).[17] These rates were higher than the rates that we present here, and one possible explanation could be that cases from cities outside of the geographical areas of the present study, which were excluded here, were included in the incidence calculation in ICO (2016).

The slowly decreasing trends observed for IR and ASR in Campinas and Curitiba regions were similar to the IR patterns that have been reported from places that have made efforts to decrease cervical cancer rates, but without success in promoting changes to achieve organized screening programs. The classic example of a successful screening program comes from England, where, similarly to what was reported here, before 1988 the screening programs had low-impact on cervical cancer incidence. Cervical cancer rates started to change in England after implementation of strategies to organize the screening program, with IR decreasing faster, as seen from data reported in 1995, eight years after implementation of the modifications.[18] In England, there was an 8% decrease in IR each year, from 16 cases to < 10 per 100,000. The main strategy used to achieve this decrease was the "call and recall" method, which was inserted in a system to register and control the screened population.

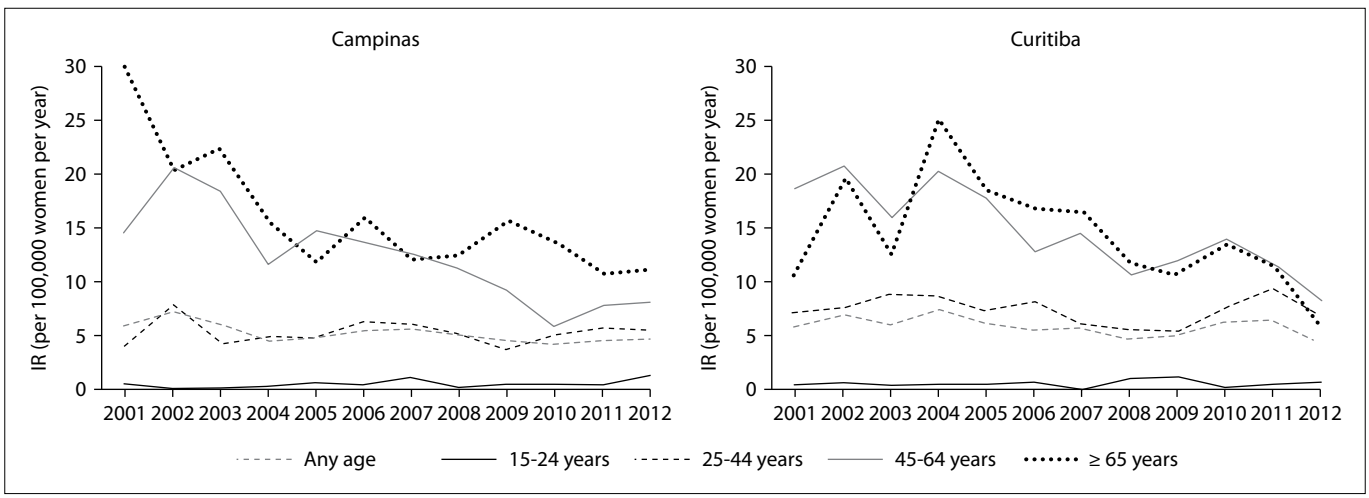


Figure 2. Annual evolution of the estimated incidence rate (IR) for cervical cancer per 100,000 women per year, according to age group and region.

Table 2. Crude cervical cancer incidence rate, estimated according to region for the years 2001, 2006 and 2012; and diagnosis trend over the period 2001 to 2012, according to age-specific group and histological type

	Incidence									
	Campinas region					Curitiba region				
	Rate according to year[a]			Trend[b]		Rate according to year[a]			Trend[b]	
	2001	2006	2012	APC	P	2001	2006	2012	APC	P
Age group[c]										
15-24 years	0.44	0.39	1.39	+0.06	0.046	0.47	0.63	0.70		0.655
25-44 years	4.10	6.15	5.59		0.962	7.17	8.07	6.71		0.507
45-64 years	14.75	13.69	8.02	-1.05	< 0.001	18.73	12.76	8.29	0.95	< 0.001
≥ 65 years	29.96	15.98	11.13	-1.25	0.002	10.79	16.76	5.84		0.744
Histological type										
SCC	4.70	4.24	3.58	-0.17	0.001	5.39	4.86	3.79	0.14	0.028
AC + ASC	1.22	1.16	1.18		0.988	0.54	0.76	0.64		0.457

[a]Incidence: number of cancer cases per 100,000 women per year.

[b]Trend for period 2001-2012 was presented as "APC" (annual percentage change in percentage points): negative value indicates decreasing trend and positive indicates increasing trend.

[c]Age group: mean incidence in age-specific population. Number of cases under 20 years/15-24 years of age: 2/25 for Campinas region and 1/27 for Curitiba region. Statistical test: simple linear regression.

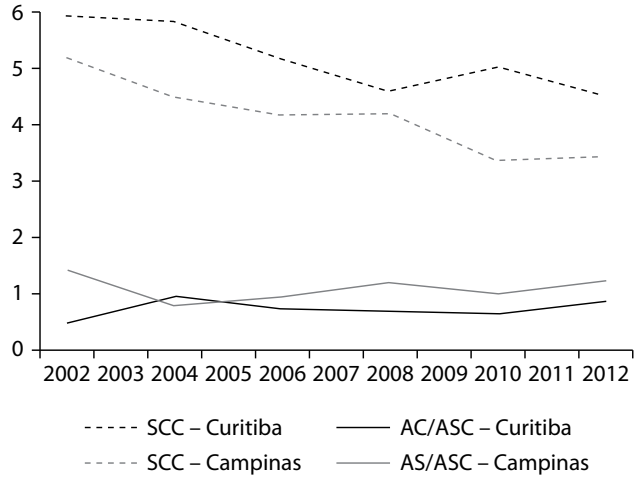
SCC = squamous-cell carcinoma; AC = adenocarcinoma; ASC = adenosquamous carcinoma.

Over the same period, the coverage of women screened increased from 42% in 1988 to 85% in 1994.[18]

Although the IR and ASR estimates of the present study may present some issues, the way in which the information originated from each region can be considered to have remained constant, which thus makes it possible to compare the longitudinal pattern of change in ASR. The ASR over the study period decreased by 35% (from 5.88 to 3.80) for the Campinas region and by 37% (from 6.96 to 4.37) for the Curitiba region. There was a clear reduction in the incidence of uterine CC over time, which was similar in the two regions studied. According to information available from INCA about ASR for the cities of São Paulo and Curitiba, comparing the period 2001-2005 with the period 2008-2012, there was a substantial decrease in ASR, as follows: São Paulo, 16.47 to 7.75 (-53%); Curitiba, 15.75 to 10.82 (-31%).[8-10,19,20]

The cancer cases registered were concentrated in the age group of 45 years or older, with higher estimated IR and an evident annual decreasing trend, which can be seen in **Figure 2** for both regions (IR-2001/IR-2012: Campinas = 14.8/8.0; Curitiba = 18.7/8.3 for the age group 45-64 years; $P < 0.001$). It could be seen that the estimated IR decreased by around 50% over the years 2001-2012. A similar pattern was seen in the Netherlands over the period 1989-1998,[21] thus showing the positive impact of organized screening, in that the number of cervical cancer cases decreased from 7.1 to 6.1 per 100,000 women per year, among which most cases were diagnosed at age 45 years or older.

As expected, the estimated IR in the 15-24 age group was very low, but the Campinas region exhibited an increasing trend, with IRs of 0.44 in 2001 and 1.39 in 2012 (per 100,000 women per year; two cases under 20 years of age and 23 cases in the 20-24 age range). There is controversy about the age at which screening should start, with some reports suggesting 18-21 years, as in United States and Australia,[22,23] and others, including Canada, England and Brazil, advising that no screening should be done before the age of 25 years.[4,24,25] In general, about 1% of all cervical cancer cases are diagnosed in women under 25 years old, and cervical cancer is considered rare before 20 years of age.[24,26]



SCC = squamous-cell carcinoma; AC = adenocarcinoma; ASC = adenosquamous carcinoma.

Figure 3. Estimated incidence rate for cervical cancer, according to histological type and region.

In addition to the positive effects regarding estimated IR and ASR that were observed for specific age groups in the present study, the estimated IR for the SCC histological type of cervical cancer decreased. This can be considered to be another positive effect, although no change was observed for glandular histology. A similar pattern was reported in the Netherlands, as one of the first changes arising from implementation of organized screening over the period 1989-1998.[21] A decreasing number of cervical cancer cases and an increasing proportion of glandular histological type can thus be considered as indications of effective screening through cytological tests. A recent report from Brazil with more than 50,000 cervical cancer cases registered over the period 2000-2009 showed an increasing proportion of glandular histological type (10% to 16%), but these are still considered modest values.[28] The proportion of glandular histological type over the period 2001-2012 was 21%-26% for the Campinas region and 8%-16% for the Curitiba region.[29]

Our study presents some limitations. For example, only cases from referral hospitals within the public healthcare system were considered for calculating the estimated IR. However, there were no significant changes to the service network or any creation of new reference services for treatment of gynecological cancer during the period studied, and these hospitals (which were the data source) remained the main services treating women with gynecological cancer. Although the IR estimates may have had some bias, the trend analysis allowed assessments of changes in cervical cancer rates relating to opportunistic screening program.

We analyzed two regions of Brazil with prominent development, high human development indices, and established primary care networks, where at least 50% of the population is treated through the public health system (SUS), but where the only screening program is of uncontrolled and opportunistic nature. Therefore, our results probably included a high proportion of women who were outside the screening program and who received their cancer diagnoses after experiencing symptoms. Another report on the same population showed that 60% of the cases were diagnosed at advanced stages of the disease.[29] This is an effect from opportunistic screening and is associated with low coverage of the target population. The number of cases of cervical cancer that were treated outside of SUS (and thus not analyzed here) can be considered minimal.

Some remarkable positive changes were observed in this study, including decreasing estimated IR among women over 45 years of age, and a decreasing trend for SCC histological type, perhaps reflecting the strong commitment by the regional healthcare system to control this cancer, albeit without organization. Although the results are slightly encouraging, these findings may give us an estimate of the best performance to be expected from opportunistic screening programs, with no tools to identify the screened and non-screened populations, similar to results reported by Costa et al.[5]

Hard work without a controlled screening program is unlikely to achieve the desired results, as shown here. Annually, SUS pays for enough Pap smears to cover 90% of the country's total target population, despite the fact that 40 to 50% of this population is treated in private care networks. In the best-case scenario, therefore, the real coverage of cytological tests is only 30%, as previously reported for the city of Campinas.[6]

Additional financial support to combat this disease has produced limited results, as a consequence of the deficient organization of screening programs.[5,27] Reaching an adequate level of organization is crucial for the future, including screening through new technologies or in vaccinated populations against HPV, and Brazil needs to promote effective changes in this process.

CONCLUSION

Estimated IR and ASR for cervical cancer in two developed regions of Brazil showed a slowly decreasing trend, which was most evident among women aged 45 years or older and among cases with SCC histological type. These finding reflects the opportunistic nature of the population screening program, despite the comparatively high level of economic development in the two regions.

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Identifying children who are susceptible to dropping out from physical activity and sport: a cross-sectional study

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ABSTRACT

BACKGROUND: Although the benefits of physical activity are clear, adherence to physical activity programs is a challenge, especially during transitional phases of life.

OBJECTIVE: We aimed to identify adolescents who were more likely to drop out from physical activity and sports participation, from childhood to adolescence.

DESIGN AND SETTING: This was a cross-sectional study on retrospective data regarding childhood activity among 803 Brazilian adolescents. The study was conducted at public schools in Londrina, Paraná, in 2011.

METHODS: Habitual physical activity, sports participation during childhood, parental physical activity, socioeconomic status and perception of social relationships were self-reported. Cardiorespiratory fitness was estimated via a 20-m shuttle-run test and somatic maturation was estimated from the age at peak height velocity.

RESULTS: Our results provided evidence that girls (physical activity: odds ratio, OR: 4.37 [95% confidence interval, CI: 1.86-10.3]; sports: OR: 2.65 [95% CI: 1.39-5.05]) and adolescents with low cardiorespiratory fitness (physical activity: OR: 1.77 [95% CI: 1.13-2.78]; sports: OR: 1.62 [95% CI: 1.15-2.26]) were more likely to drop out from active behaviors. Children with inactive mothers and inactive fathers (OR: 3.55 [95% CI: 1.12-11.3]) also showed a higher dropout rate from physical activity. Adolescents with negative perceptions of friendships (OR: 2.33 [95% CI: 1.21-4.47]) were more likely to drop out from sports.

CONCLUSIONS: Higher dropout rates from active lifestyles during childhood were observed among girls and adolescents with low cardiorespiratory fitness. Parental inactivity and negative perceptions of friendships were also potential risk factors for discontinuation of childhood physical activity and sports.

INTRODUCTION

Physical inactivity is one of the greatest causes of death worldwide.[1] It has been estimated that if the population worldwide increased its physical activity levels, global life expectancy would increase by at least one year.[1] However, the prevalence of physical inactivity is still high.[2]

Ecological approaches have proposed several levels of behavioral correlates, such as the political, social and built environments and intrapersonal characteristics.[3] In this regard, early experiences with physical activity seem to be important for adoption of active lifestyles in adulthood.[4] Additionally, among the contexts and types of physical activity, sports practices are one of the most common manifestations of active lifestyles during childhood, and this has been correlated with health in adulthood, regardless of other forms of exercise practice and daily physical activity.[5]

Although correlates of physical activity have been widely investigated in relation to static points and behavior tracking, it seems clear that active behaviors decrease during the transition from early ages.[6] Social support through parents and friends can stimulate physical activity practice among adolescents in different domains.[7,8] Moreover, intrinsic biological characteristics such as sex, biological maturation, nutritional status and cardiorespiratory fitness seem to be related to active behaviors.[8-10] However, the correlates of dropping out from physical activity and sports, from childhood to adolescence, are still not clear.

Thus, considering that maintenance of physical activity[11] and sports practice[12] are protective against the short and long-term risks of cardiovascular diseases, understanding the correlates of dropping out from these behaviors during specific periods of life could help towards targeting interventions to promote sustainable active lifestyles. Kwon et al.[13] found that adolescents with high socioeconomic status and those whose parents were active were more likely to be consistently

active. Nonetheless, investigation of a greater range of variables that influence the dropout rates from physical activity and sports practice is still lacking. Such investigations could help in identifying population subgroups that would be more likely to drop out from active behavior. These subgroups would thus become targets for physical activity interventions starting at an early age. In addition, although behavioral correlates tend to vary according to social and cultural norms, no studies aimed towards identifying such groups have been conducted in low to middle-income countries, to our knowledge.

OBJECTIVE

Thus, our aim was to analyze the psychological, biological and social correlates of dropping out from physical activity and sports practice, from childhood to adolescence, among Brazilian adolescents. Our hypothesis was that biological factors would be strongly associated with dropping out from active behaviors, and that psychological and social factors might explain part of this negative outcome.

METHODS

Ethical statement

The authors declare that they did not have any conflict of interests regarding the publication of this paper. This work was supported by the Brazilian Council for Scientific and Technological Development (CNPq/Brazil; procedural no. 15608/2011). The local ethics committee approved all the study procedures (CAAE: 0142.0.268.000-11), and these complied with the principles of the Declaration of Helsinki.

Design, sample size and participants

This was a cross-sectional study conducted in 2011 among adolescents aged between 10 and 17 years old who were enrolled in public schools in Londrina, Brazil. This city had 506,701 inhabitants, a human development index of 0.778 and a gross domestic product per capita of US$ 8,530.77.[14]

The current study formed part of a project under the title "Prevalence of metabolic syndrome and cardiovascular risk factors in adolescents in Londrina." For this project, the sample size calculation was based on the following parameters: prevalence of metabolic syndrome of 4%; α of 0.05; margin of error of two percentage points; and design effect of 2.0. This calculation indicated that at least 900 adolescents should be selected.

Recruitment of participants was performed in two stages. Initially, all the public schools in the city were categorized according to the regions of the city (north, south, east, west and center). Thereafter, two schools were randomly selected from each region. Classes within the schools chosen were then randomly selected, and all students within these classes were invited to participate in the study. Students using prescription medicines or undergoing treatment for an illness, and those who did not return the consent form with a parent's signature, were excluded from the study.

In total, 1,395 adolescents were enrolled in the study. However, given that our aim was to analyze factors associated with dropping out from sports and physical activity from childhood to adolescence, we excluded participants who were older than 17 years (n = 17), those who had not participated in regular sports during childhood (n = 383) and those for whom physical activity data were missing (n = 192).

Organized sports participation during childhood

To assess childhood sports participation, adolescents were asked (yes/no) if they had participated in supervised sports for at least one year between the ages of 7 and 10 (intraclass correlation coefficient, ICC = 0.87). As described above, participants who had not taken part in organized sports were excluded.

Physical activity and organized sports participation during adolescence

The Baecke questionnaire[15] was self-completed by the adolescents and was used as an indicator of concurrent physical activity level. This instrument contains questions relating to physical activity performed at school, during leisure time and as part of sport. The sum of all its domains constitutes the estimated habitual physical activity (through a specific score).[8] For quality control, the questionnaire was applied again to a representative portion of the sample (10%) after an interval of seven days. The ICC for this was calculated to be 0.73.

In deriving the outcomes for this investigation, participants who were in the highest quartile of habitual physical activity (all domains) during adolescence, or those who were in the highest quartile for sports participation, were considered to have been successful in maintaining their activity behaviors. The participants were thus distributed between four non-exclusive categories:

1. Maintenance of activity (sports participation during childhood and habitually active during adolescence);
2. Maintenance of sports participation (sports participation during both childhood and adolescence);
3. Dropping out from physical activity (sports participation during childhood, but habitually inactive during adolescence;
4. Dropping out from sports participation (sports participation during childhood but not during adolescence).

Self-perception of social relationships

Participants' self-perception about their relationships with friends and classmates was assessed on a four-point scale ranging from "very unsatisfied" to "very satisfied" (ICC for this question = 0.50).

Participants who were either "very unsatisfied" or "unsatisfied" were deemed to have a negative perception of their relationships with friends.

Biological variables

Somatic maturation was estimated using the peak height velocity (PHV)[16]. The "distance from PHV" (how many years left until PHV) was calculated from information on height, trunk-cephalic height and leg length. After this, PHV was subtracted from chronological age, creating the age of peak height velocity. Cardiorespiratory fitness (CRF) was assessed by means of the 20-meter shuttle-run test, as designed by Leger and Lambert.[17] This test was conducted in a multi-sports indoor court. Based on the testing time, peak VO_2 in ml/kg/min (maximal volume of oxygen consumption) was calculated in accordance with the equation proposed by Leger et al.[18] Low cardiorespiratory fitness was defined using the cutoff points of Fitnessgram.[19] Body mass index (BMI) was calculated from body weight and height, which were measured using standard procedures. The technical error of measurement for these measurements was: weight = 0.68% and height = 0.37%. BMI data were categorized using the cutoffs described by Cole et al.[20]

Parent-reported variables

The subjects' parents provided information about their own physical activity level and the socioeconomic status (SES) of the family. The adolescents handed the questionnaires to their parents and subsequently returned them to the research team. The Baecke questionnaire[15] was administered to provide an estimate of paternal and maternal physical activity. Parents who reported having at least 180 minutes/week of moderate to vigorous physical activity, over the previous nine months, were classified as "active".[5] The Brazilian Economic Classification Criteria instrument[21] was used to classify families into one of five SES groups ranging from A (highest SES) to E (lowest SES), based on family possessions and the educational level of the head of the household. For this study, groups D and E were considered indicative of low SES.

Statistical analysis

Descriptive statistics (means, standard deviations and frequencies) were used to characterize the sample. Group comparisons between participants who remained physically active or remained involved in sports versus those who dropped out were performed using the Mann-Whitney and chi-square tests. Crude and adjusted logistic regression models were specified to investigate factors associated with increased likelihood of dropping out from physical activity or sports participation. Factors showing some evidence of an association with the outcome in crude analyses ($P < 0.2$) were taken forward for inclusion in the adjusted model and were maintained if they showed $P < 0.05$ in the final model. All analyses were conducted in STATA 13.0.

RESULTS

The final sample included 803 adolescents (49.9% girls), with a mean chronological age of 12.9 ± 1.5 years. Among these subjects, 33.3% presented low socioeconomic status. In general, the adolescents who dropped out of physical activity showed lower values for age at peak height velocity and cardiorespiratory fitness. The majority of these subjects were girls, and they had inactive mothers. Likewise, the adolescents who dropped out of

Table 1. Descriptive statistics and comparison of independent variables between physical activity and sports participation "dropouts" versus "maintainers", from childhood to adolescence

	Physical activity			Sports participation		
	Dropouts (n = 536)	Maintainers (n = 267)	P	Dropouts (n = 543)	Maintainers (n = 260)	P
Sex (girls)	60% (55.3 to 63.6)	31% (25.5 to 36.5)	< 0.001	58% (54.0 to 62.3)	33% (27.3 to 38.6)	< 0.001
Chronological age (years)	13 ± 1.61	13 ± 1.46	0.661	13 ± 1.58	13 ± 1.48	0.544
Age at PHV (years)	13 ± 1.22	14 ± 1.14	< 0.001	13 ± 1.21	14 ± 1.17	< 0.001
BMI (kg/m^2)	19.8 ± 3.65	20.1 ± 1.13	0.450	19.9 ± 4.02	20.0 ± 3.96	0.549
CRF (ml/kg/min)	39.7 ± 4.71	42.1 ± 4.85	< 0.001	39.8 ± 4.68	42.1 ± 4.96	< 0.001
No sports participation	89% (86.1 to 91.4)	24% (19.9 to 30.2)	< 0.001	100% (98.3 to 100)	0% (0 to 0.9)	< 0.001
Inactive	100% (98.3 to 100)	0% (0 to 0.9)	< 0.001	22.7% (18.0 to 28.2)	87.8% (84.8 to 90.3)	< 0.001
Overweight (BMI)	23% (19.8 to 27.1)	19% (14.5 to 24.2)	0.171	23% (19.7 to 26.9)	19% (14.7 to 24.5)	0.214
Low CRF	54% (49.8 to 58.7)	42% (35.6 to 47.9)	0.001	54% (49.7 to 58.4)	41% (35.1 to 47.8)	0.001
Low SES	32% (27.4 to 36.4)	37% (30.6 to 44.2)	0.187	32% (27.9 to 36.8)	36% (29.8 to 43.5)	0.309
Inactive mother	97% (95.4 to 98.7)	92% (87.1 to 95.4)	0.003	96% (93.9 to 97.8)	95% (90.4 to 97.4)	0.447
Inactive father	94% (91.4 to 96.5)	90% (84.2 to 93.8)	0.066	93% (88.3 to 96.6)	93% (89.6 to 95.1)	0.793
Friends*	10% (7.7 to 12.8)	7% (4.9 to 11.4)	0.262	11% (8.8 to 14.1)	5% (4.7 to 13.5)	0.005

Data are presented as mean ± standard deviation or % (with 95% confidence intervals). PHV = peak height velocity; BMI = body mass index; CRF = cardiorespiratory fitness; SES = socioeconomic status; *Negative perceptions of relationships with friends.

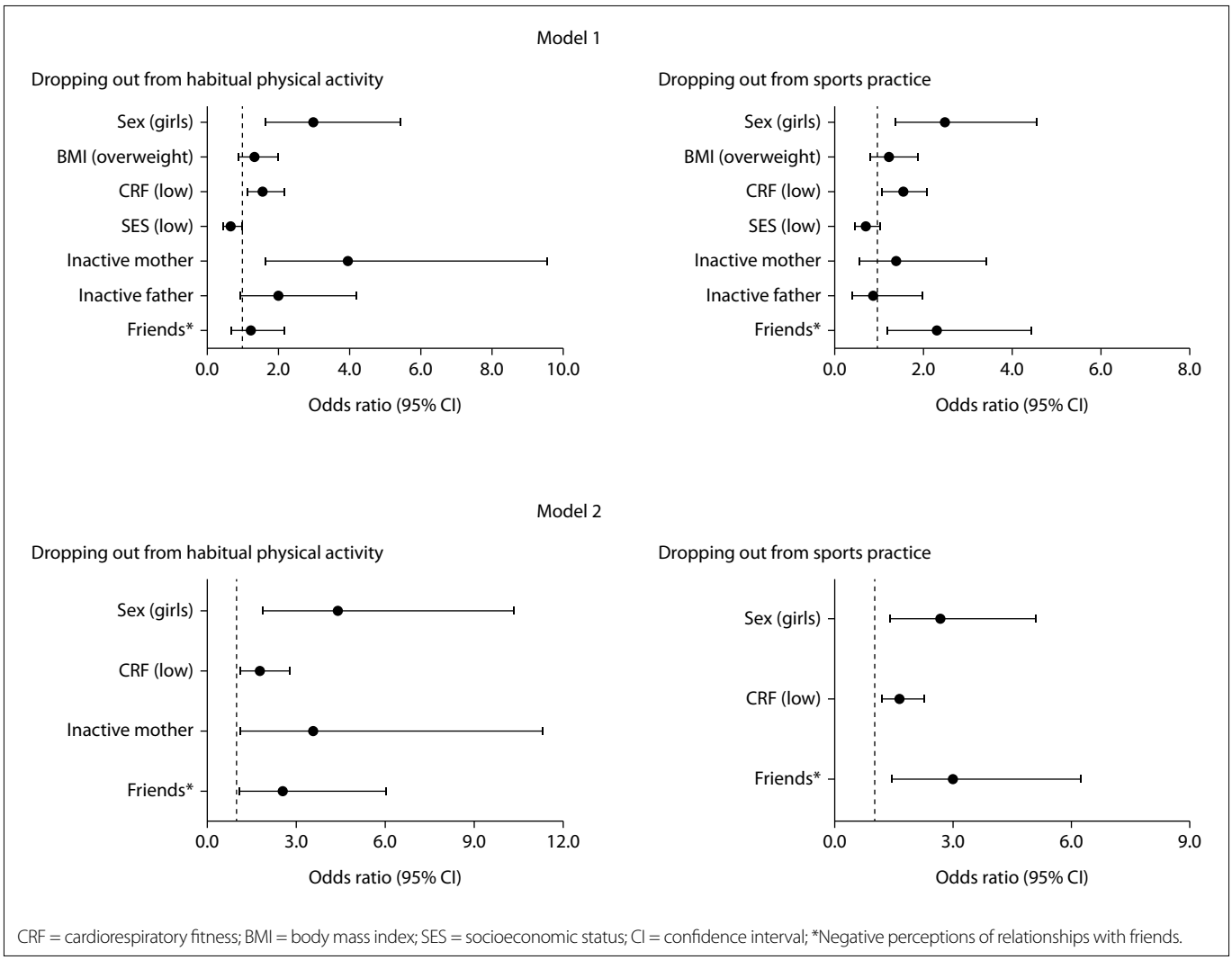
sports also presented lower values for age at peak height velocity and cardiorespiratory fitness (**Table 1**), were mostly girls and also reported negative perceptions of friendships.

Figure 1 shows the odds ratios for dropping out from physical activity and sports participation. The first (unadjusted) model showed that girls, individuals with low cardiorespiratory fitness and children with inactive mothers were more likely to drop out of physical activity. In the unadjusted model, children from low SES families were less likely to drop out from physical activity. However, in the second (adjusted) model, SES ceased to be significantly related to dropping out from physical activity. In the second model, paternal physical activity emerged as an additional factor that was associated with increased likelihood of dropping out.

Girls and any adolescents with low cardiorespiratory fitness or negative perceptions of friendships were more likely to drop out from participating in sports. The associations for dropping out from sports remained unchanged following adjustment of model 2 for the adolescents' ages and their ages at PHV.

DISCUSSION

This was a cross-sectional study that used retrospective information relating to early sports participation. Our aim was to identify adolescents who were more likely to drop out from active behaviors, from childhood to adolescence, by analyzing correlates of dropping out from physical activity and sports practice. We found that girls and any adolescents who had low cardiorespiratory fitness were more likely to drop out from both sports participation and habitual physical activity (all domains). Moreover, adolescents who had two inactive parents and who reported having negative perceptions of friendships exhibited, respectively, greater frequency of dropping out from habitual physical activity and from sports practice.



CRF = cardiorespiratory fitness; BMI = body mass index; SES = socioeconomic status; CI = confidence interval; *Negative perceptions of relationships with friends.

Figure 1. Correlates of dropping out from physical activity and sports participation, from childhood to adolescence. Model 1 = unadjusted crude associations. Model 2 = adjusted for adolescent age, age at peak height velocity and all other variables in the model.

Physical inactivity is associated with several chronic diseases and metabolic risk factors.[22] Sports participation during childhood seems to be a protective factor for cardiovascular risk in adulthood.[5] Several paths have been proposed to explain the influence of early sports participation on health in adulthood.[23] Among these, maintenance of active behaviors (sports/physical activity) at subsequent ages and their positive effects on body fat regulation, as well as more direct paths through DNA methylation,[23,24] have been highlighted. However, it seems clear that physical activity decreases over individuals' lifetimes.[6,25] Thus, although correlates of physical activity at static points have frequently been investigated,[3] less attention has been given to correlates of longitudinal changes in behavior.

In the present study, we found that girls were more likely to drop out from both physical activity and sports participation. One possible explanation for this finding may be that boys are given greater encouragement to perform physical exercise during leisure time.[10] This may be one of the reasons for the lower prevalence of physical activity among girls. It was thus expected that there would be a greater likelihood that girls would drop out. Furthermore, biological maturation is an important confounder in analyses on physical activity among girls because of differences in their intrinsic characteristics, such as increasing amounts of body fat and psychological variables.[26] However, even after adjustment for somatic maturation, we observed that girls were more likely to drop out from sports practice and habitual physical activity.

These findings indicate that social issues may have more longitudinal influence on sports participation and general physical activity than biological factors.[27] It is well established that women's social roles (e.g. the notions of being fragile or delicate, or of being housewives) are not associated with physical effort or physical activity and sports practice. Thus, during this transitional phase (adolescence), girls tend to be less encouraged by their parents and friends to be physically active. This finding extends the discussion in the current literature on the perspective of dropping out from active behaviors.

Similarly, the adolescents who presented low cardiorespiratory fitness showed greater likelihood of dropping out from both of these active behaviors. Given that physical inactivity is negatively associated with cardiorespiratory fitness,[28] adolescents who drop out from physical activity or sports practice tend to present lower values for cardiorespiratory fitness. On the other hand, adolescents with lower physical fitness also tend to adopt a less active lifestyle.[29] Because of the study design, and since we had no early information on or measurement of cardiorespiratory fitness, our findings tend to support the first hypothesis.

Interestingly, we found that inactivity among parents was associated with their offspring's dropping out from physical activity, but not from sports practice. This result may have been be due to transference of behaviors from parents to their children,[30] since inactive lifestyles among parents could influence their children to be less active (overall indicator). Thus, inactive parents can still support their offspring's sports practice.[31] However, sports practice seems to be more influenced by friends and characteristics of intrinsic motivation.[7] In this regard, our results provide support for the notion that social relationships have a role in maintenance of health-related behaviors, since we found that negative perceptions of friendships were related to dropping out from sports participation. Previous studies also demonstrated that perceptions of social relationships are correlated with leisure-time physical activity and sports practice,[7,8] especially regarding collective forms of sports activities.[32]

While low socioeconomic status is an important issue in terms of healthcare, we found that it seemed to protect against dropping out from physical activity in the crude analysis. Adolescents with lower socioeconomic status, especially in developing countries, are more active in the domains of transportation and occupation and, consequently, tend to have a more active lifestyle.[33,34] However, no association was found between socioeconomic status and dropping out from sports practice. It is important to note that our sample was relatively homogeneous regarding socioeconomic status (recruitment from public schools), which could explain the lack of significance of this variable in the final model for dropping out from physical activity. However, the parents' physical activity may have overlapped with this effect (**Figure 1**; Model 2), since socioeconomic status is an important predictor of physical activity in adulthood.[33]

The results from the present study lead to some practical applications. Firstly, special attention could be given to girls and to adolescents with low cardiorespiratory fitness. Sustainable early interventions should be conducted in these specific target groups, in order to promote adequate levels of physical fitness during adolescence.[35] Moreover, bearing in mind that physical inactivity among parents is related to adolescents' dropping out from physical activity, family-based interventions could be conducted to increase the levels of physical activity among both parents and adolescents, as well as to improve parental social support for adolescents. School-based interventions that promote good social interactions between children should also be encouraged.

Concerning our methods, this study had the limitation that only one physical activity domain during childhood (supervised sports practice) was assessed. Even though supervised sports practice is the greatest manifestation of physical activity during this phase[36] there was the potential for recall bias, caused by the retrospective design of our study. We did not take into consideration unsupervised sports participation.

Moreover, our measurement of physical activity and sports practice during adolescence was self-reported. Nonetheless, the physical activity questionnaire showed good reproducibility (ICC = 0.73). Similarly, physical activity among the participants' parents was also

self-reported, and thus could also have presented bias. The lack of reproducibility of the information in the parents' questionnaire is an important limitation.

Lastly, because of the study design (cross-sectional), we were unable to discern the temporality/causality between the variables. Nevertheless, these initial data can provide support for future longitudinal studies.

Among the strengths of this study, it was the first to evaluate correlates of dropping out from physical activity and sports practice, from childhood to adolescence, in Brazil. We can highlight the control over biological maturation in the adjusted analyses: this is an important confounding variable in physical activity studies conducted among adolescents.[9] Our study presented correlates of dropping out from physical activity and sports practice that were derived from data on more than 800 adolescents from a middle-income country of continental dimensions and distinct culture.

CONCLUSIONS

Girls and adolescents who presented low cardiorespiratory fitness were more likely to drop out from active behaviors. Parents' physical inactivity and negative perceptions of friendships among the students were, respectively, also related to increased rates of dropping out from physical activity and sports practice, from childhood to adolescence.

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Mammary adenectomy followed by immediate reconstruction for treatment of patients with early-infiltrating breast carcinoma: a cohort study

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KEY WORDS:
Breast neoplasms.
Mastectomy.
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Esthetics.

ABSTRACT

BACKGROUND: Use of mammary adenectomy for breast carcinoma treatment remains controversial.

OBJECTIVE: This study aimed to verify the oncological safety of mammary adenectomy and immediate breast reconstruction for treating selected patients with infiltrating breast carcinoma and to evaluate patients' satisfaction with the reconstructed breasts.

DESIGN AND SETTING: Cohort study conducted among patients treated at Hospital Sírio-Libanês, São Paulo, Brazil.

METHODS: This study was based on 152 selected patients (161 operated breasts) with infiltrating breast carcinoma who underwent mammary adenectomy and immediate breast reconstruction. In all patients, the diameter of the largest focus of the tumor was less than 3.0 cm, the imaging tumor-nipple distance was greater than 2.0 cm and the pathological assessment showed clear margins. The cumulative incidence of local recurrence (LR), recurrence-free survival (RFS) and overall survival (OS) curves were estimated using the Kaplan-Meier method. After at least one year of follow-up, 64 patients were asked about their satisfaction with the reconstructed breast(s).

RESULTS: At a mean follow-up time of 43.5 months, seven cases of LR (4.4%), four distant metastases (2.6%) and five deaths (3.3%) were recorded. The five-year actuarial LR-free survival, RFS and OS were 97.6%, 98.3% and 98.3%, respectively. No cases of nipple-areolar complex recurrence were reported. Forty-one patients (64%) indicated a high level of satisfaction with the reconstructed breasts.

CONCLUSIONS: Mammary adenectomy is a safe and efficacious procedure for selected patients with early-infiltrating breast carcinoma and results in a high rate of patient satisfaction with the reconstructed breasts.

INTRODUCTION

Mammary adenectomy involves resection of all gross visible glandular tissue, including tissue under the nipple, while preserving the overlying breast skin and the nipple-areolar complex (NAC).[1] It is an evolving procedure for breast cancer patients who are not considered to be candidates for breast-conserving surgery. In mastectomy, the NAC is removed because, in theory, it can harbor neoplastic cells. However, when no initial tumor is located in the central breast region, the frequency of nipple involvement is generally less than 10%. Moreover, with proper selection of patients for mammary adenectomy, NAC relapse rates may be very low.[2]

In 1980, Gentil et al. innovatively performed mammary adenectomy for breast cancer treatment.[3] Subsequently, Horiguchi et al., Benediktsson et al. and Gerber et al. compared mammary adenectomy favorably with more radical mastectomy for patients.[4-6] More recently, other authors suggested that mammary adenectomy may be valid for selected breast cancer cases.[7-11]

Preservation of the NAC is very important for women's satisfaction with their physical appearance.[12-14] Although it may be tempting for surgeons to offer mammary adenectomy, NAC-sparing surgery should still be recommended only with caution. Persistent uncertainties remain regarding patients' eligibility, the surgical approach and oncological safety.[2,11,15]

There is a paucity of high-quality studies combining all the essential elements of this procedure, such as a standardized surgical procedure, a strict patient eligibility protocol and reporting on long-term oncological outcomes. Here, we present a series of patients who we treated and followed up over a 10-year period at the Sírio-Libanês Hospital, São Paulo, Brazil.

OBJECTIVES

Our main objective was to report on the oncological safety of mammary adenectomy and immediate breast reconstruction for treating selected patients with infiltrating breast cancer. A secondary objective was to evaluate the patients' satisfaction with their reconstructed breasts.

METHODS

Design, setting and ethics

In this retrospective cohort study, clinical data from selected patients who fulfilled the institutional eligibility criteria for therapeutic mammary adenectomy and immediate breast reconstruction were collected. All patients were operated at Hospital Sírio-Libanês, in São Paulo, Brazil. The research protocol was approved by the institution's ethics committee (judgment number 10414227; February 18, 2016).

Inclusion and exclusion criteria

Patients with infiltrating breast cancer were deemed eligible if they fulfilled all of the following inclusion criteria: largest focus of the tumor with less than 3.0 cm in diameter; tumor-nipple distance greater than 2.0 cm according to physical examination and imaging methods; clinically negative axilla or axilla with movable level I-II lymph nodes (cN0-cN1); negative sentinel node biopsy (SNB); and clear surgical margins in intraoperative and definitive analyses.

Patients were excluded if at least one of the following conditions was presented: male breast cancer, clinical evidence of skin/NAC involvement, occult breast cancer, nipple discharge and more than three centers/foci of neoplasia.

Surgical technique

Two forms of mammary adenectomy were performed: one totally sparing the skin envelope and the other removing a small paddle of skin over the tumor. The surgeries were performed by experienced breast surgeons from the Philanthropic Service of the Mastology Department of the Hospital Sírio-Libanês.

The most frequent form of incision for procedures with total skin maintenance was a vertical radial incision, from the areola to the inframammary fold, going around up to 25% of the areolar circumference (to protect NAC vascularization), in the axillary direction, as shown in **Figure 1**.

The skin flaps were carefully raised using a diathermy knife. It is advisable to make this cut in the thin fascia between the subcutaneous fat and the glandular tissue. The mammary glandular corpus, with the axillary Spence tail, was removed along the pectoralis major muscle fascia. The surgeons had to leave flaps with a thickness of approximately 0.5 cm in the sub-NAC area and 0.5 to 1.0 cm in other parts of the breast (**Figure 2**). When there was superficial and peripheral neoplasia, located 2.0 cm or more from the areolar border and close to the skin (≤ 2.0 cm in depth), an elliptical skin paddle incision was made in the overlying tumor area. This incision might be extended to the areolar border (**Figures 3** and **4**).

The perforator branches deriving from the 2nd and 3rd internal thoracic vessels had to be preserved to maintain NAC irrigation. After gland removal, the nipple was inverted, and the ducts arranged inside in the central bundle were excised using a pointed-end knife.

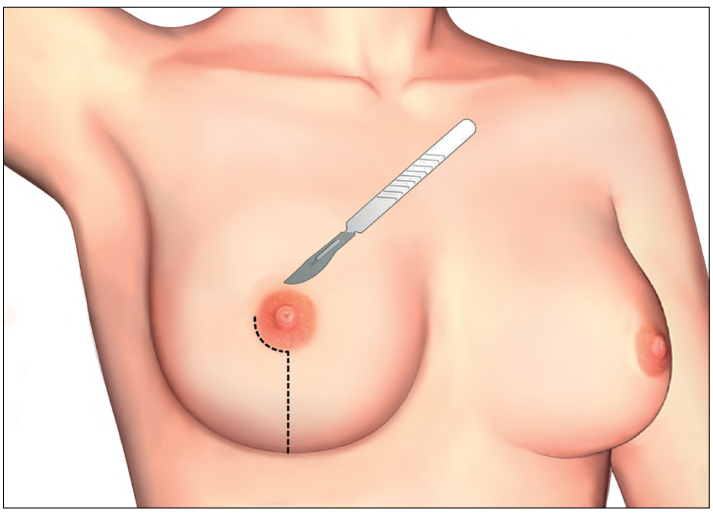

Figure 1. Most frequent incision for mammary adenectomy.

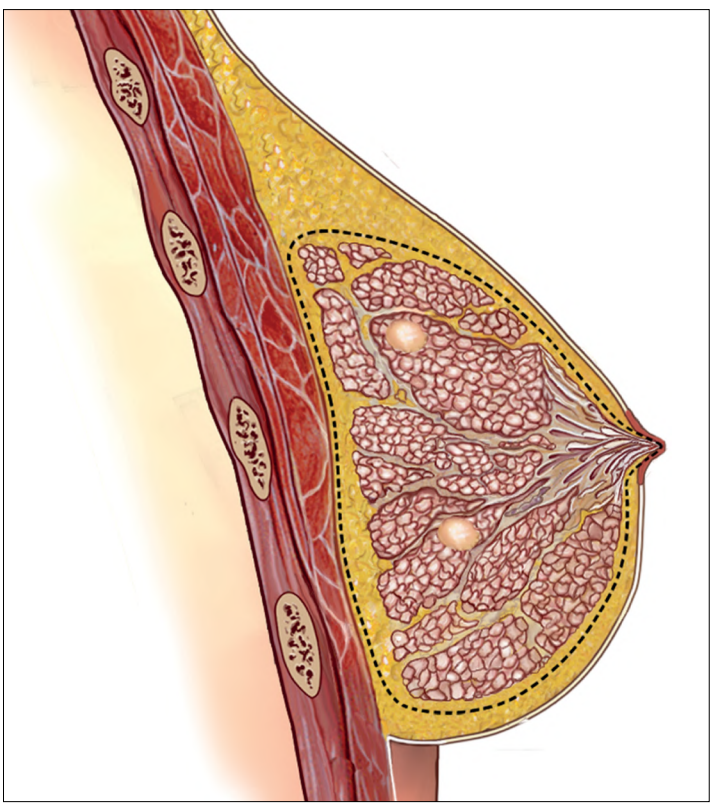

Figure 2. Scheme of the dissection plane for mammary adenectomy in a case with two tumor foci.

Surgical margins and nipple duct assessments

During the surgery, the sub-NAC margin was microscopically analyzed by means of imprint cytology and frozen sections (4-µm slices, cut at intervals of 200 µm). If the margin was negative, and remained so according to paraffinized sections, the NAC was preserved. However, if the margin was positive in any of the examinations, the NAC was removed. Nipple ducts were examined only in the definitive analysis. Positive findings indicated that NAC removal was needed, in a second-step procedure.

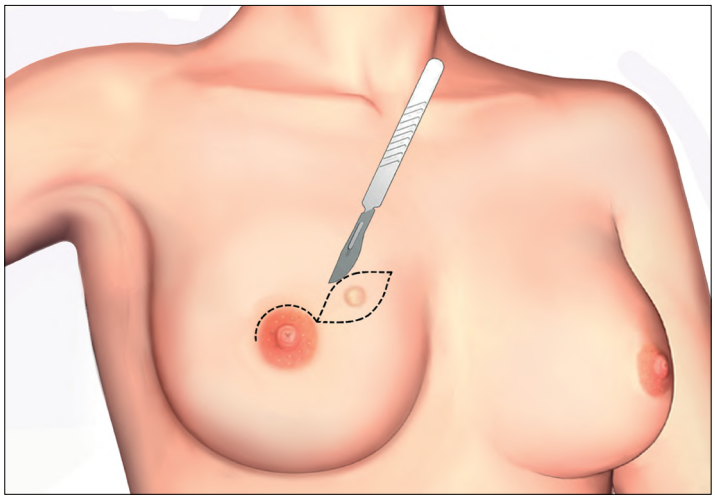

Figure 3. Incision for mammary adenectomy to remove a paddle of skin over the tumor.

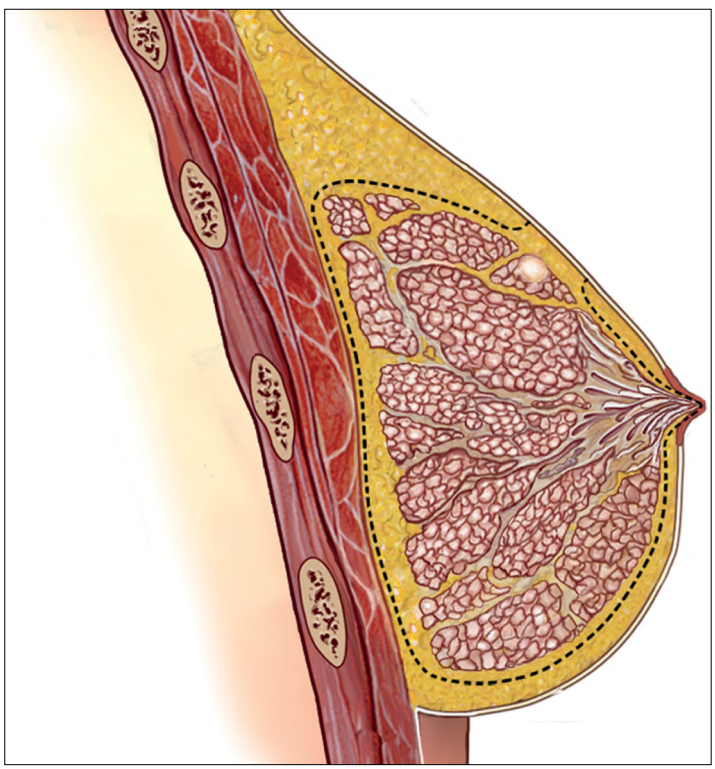

Figure 4. Scheme of the dissection in a case of mammary adenectomy with skin overlying the tumor removed.

Breast reconstruction

Permanent submuscular silicone implants (single-stage procedure) were the mainstay for breast reconstruction. Expander implants and myocutaneous flaps were occasionally used, depending on individual conditions.

Simultaneous mastopexy was performed in women with ptosis, in whom NAC was migrated and centralized in the breast mound.

Imaging control of the residual tissue and complementary radiotherapy

The remaining fat layer under the skin was evaluated by means of ultrasound or magnetic resonance imaging (MRI), three to six months after the surgery. Conventional fractioned radiotherapy (RT) for the breast/chest wall was delivered when excessive remaining tissue was detected. Supraclavicular lymph nodes were also irradiated, with or without the internal mammary chain nodes, depending on the number of lymph nodes (LNs) affected.

Adjuvant systemic therapy

Adjuvant chemotherapy and/or hormonotherapy were administered in accordance with contemporary guidelines. All patients with overexpression of human epidermal growth factor receptor-2 (HER-2) received trastuzumab.

Self-evaluation of esthetic result

At least one year after the surgery, during a consultation, some patients were asked to give their self-evaluation of their reconstructed breast(s). According to their own impression of the final breast silhouette and consistency, the women classified their degree of satisfaction as highly satisfied, satisfied, indifferent, dissatisfied or highly dissatisfied.

Data acquisition and statistical analysis

Follow-up visits were scheduled for every three months during the first year post-surgery, every six months until the fifth year and annually thereafter. A physical examination was performed during every visit, and breast ultrasonography was performed once a year.

The following oncological outcomes were determined, taking the date of the surgery as the starting date: local recurrence (LR), recurrence-free survival (RFS) and overall survival (OS). Patients alive at the time of the final analysis of the study were censored at the date of their last visit.

Descriptive and frequency analyses were performed. The cumulative incidences of LR, RFS and OS were calculated using the Kaplan-Meier method. The SPSS package version 20.0 (Chicago[11]) was used for statistical analysis.

RESULTS

Between June 2005 and September 2015, 156 patients underwent mammary adenectomy, comprising 166 breast surgeries (10 patients with bilateral tumors). Four patients (one with bilateral tumors) were lost during the follow-up and, thus, the final numbers considered for the analysis became 152 patients and 161 breasts. LR was estimated according to the number of operated breasts, whereas OS and RFS were estimated according to the number of patients.

The patients' mean age was 50.2 years (range, 27-84 years). All the patients had infiltrating carcinomas: 81.4% had carcinomas not otherwise specified (NOS); 12.4% had lobular carcinoma; and 6.2% had other subtypes. 41.5% of the population were in clinical stage I, and 58.5% were in stage II. The distribution among pathological stages was as follows: I – 49.6%; II – 39.4%; and III – 11.0%. Most of the patients did not have any lymph node (LN) involvement (66.5%), whereas 24.8% had one to three positive LNs and 8.7% had at least four.

Total skin preservation was performed in 124 breasts (77.0%) and mammary adenectomy with overlying tumor skin removal was performed in 37 breasts (22.9%). Several types of immediate breast reconstruction were used, with predominance of definitive silicone implant placement (136 cases; 84.9%).

Sixty-four women were asked about their satisfaction with the reconstructed breast(s). Seventeen (26.5%) were highly satisfied (**Figure 5**), 24 (37.5%) were satisfied, one (1.5%) was indifferent, 10 (15.6%) were dissatisfied and 12 (18.7%) were highly dissatisfied (**Figure 6**).

Overall, 56 breasts (34.8%) of 55 patients (one bilateral case) were irradiated. As systemic adjuvant treatment, 70 patients (46.0%) received both chemotherapy and endocrine therapy: 44 (28.9%) received endocrine therapy only; 36 (23.6%) received chemotherapy only; and two (1.3%) received no adjuvant treatment. Trastuzumab was given in combination with chemotherapy in 21 cases (13.8%).

Oncological outcomes

The length of follow-up was calculated from the date of the surgery until the last follow-up visit or death, whichever came first. The mean length of follow-up was 43.5 months (range, 6-126 months).

At the last data censoring, five deaths (3.3%) had been recorded, among which four (2.6%) related to breast cancer, and one (0.7%) to a non-cancer-related cause. The five-year actuarial estimate of OS was 98.3%.

The crude incidences of first unfavorable events were as follows: 4.4% (seven breasts in seven patients) with LR (one patient presented axillary relapse with associated LR); and 2.6% (four patients) with distant metastasis, among which one also had regional recurrence. There were no cases of NAC recurrence. The five-year actuarial estimate of RFS was 98.3%. The Kaplan-Meier estimates of OS and RFS are shown in **Figures 7** and **8**.

LRs, recorded according to the number of breasts operated, were observed for up to 115 months of follow-up. The five-year actuarial estimate of LR-free survival was 97.6% (**Figure 9**).

We performed a subgroup analysis on 101 patients who had at least three years' follow-up, in which the cumulative incidence of LR was 5.8% (six cases).

DISCUSSION

There are concerns about the safety of skin and NAC preservation in patients treated by means of nipple-sparing mastectomies. These concerns relate mainly to the possibility of impairment of local control, as a result of inadequate surgery that leaves behind residual cancer cells. Nevertheless, several studies with high heterogeneity of patient selection and surgical techniques, and with patients presenting indications for RT, have suggested that MA promotes acceptable oncological results.[16-19]

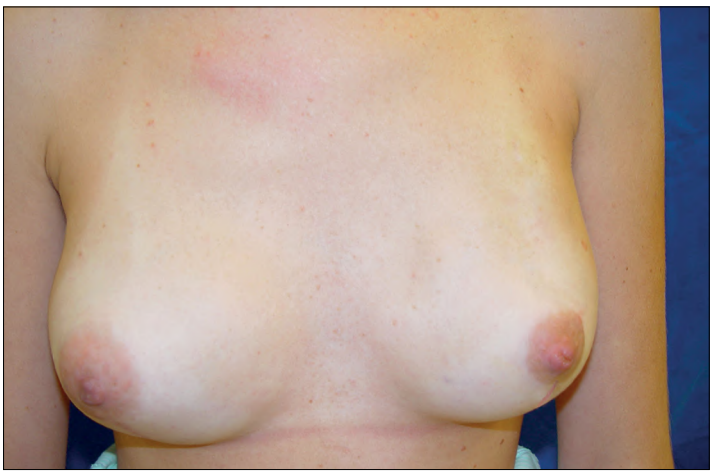

Figure 5. Case in which the patient was highly satisfied with the esthetic result 24 months after the surgery.

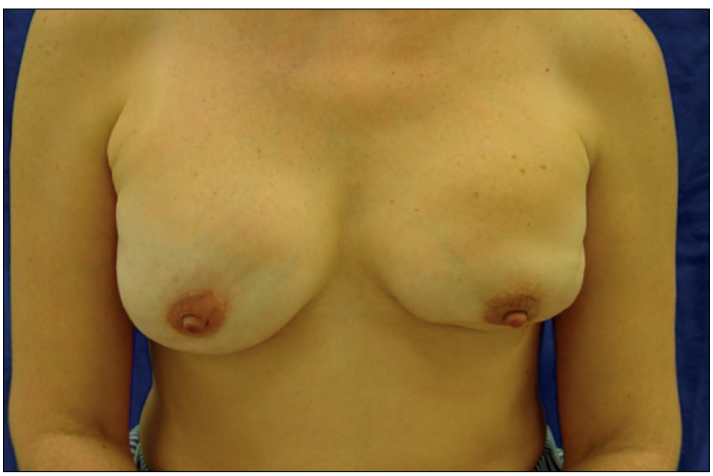

Figure 6. Case in which the patient was highly dissatisfied with the esthetic result 13 months after the surgery.

Our results add to the available literature in terms of reassuring the scientific community about the favorable outcomes among selected BC patients undergoing MA. We observed an LR rate of 4.4%, with no cases of NAC recurrence. In addition, low rates of distant recurrence and breast cancer-related deaths were reported in our cohort (2.6% for each). It is likely that the favorable oncological results obtained in this study can be attributed to proper preoperative patient selection, meticulous sub-NAC margin assessments and adequate operative technique, performed by a homogeneous group of senior breast surgeons at a major cancer reference center.

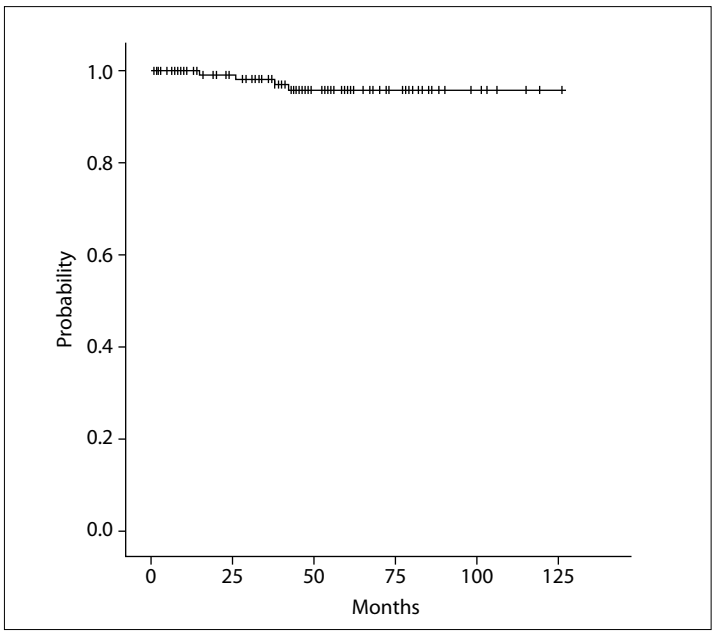

Figure 7. Kaplan-Meier estimates of recurrence-free survival.

A paradigm shift from radical surgery toward personalized procedures has evolved over the last few decades. Mammary adenectomy should be a valid alternative for women who are opting for "maximal surgery" instead of breast-conserving surgeries, especially in cases associated with one or more of the following conditions: hereditary breast cancer, young age (≤ 35), tumor multifocality/multicentricity, suspicious diffuse microcalcifications, large tumor in a very small breast, difficulty in achieving intraoperative clear margins in segmental resections or contraindication for RT.

The indication for bilateral mammary adenectomy is sometimes considered. Modern genetic sequencing that allows identification of mutations in suppressor genes of carcinogenesis has strengthened its indication for primary tumor management with concurrent contralateral prophylactic surgery, especially in young patients or in women with a family history of breast cancer. The advantages of the dual procedure derive from its psychological and quality-of-life benefits and maintenance of breast symmetry.[20] However, this group of patients at high genetic risk of bilateral disease accounts for only a small proportion of the cases. For the average patient, the perception of the risk of contralateral breast cancer is often overestimated. We believe that extensive discussion after patients have been given comprehensive information and reassurance by a multidisciplinary team is a mandatory step before any decision is made.

One essential prerequisite for sparing the NAC is a safe tumor-nipple distance. Our inclusion criteria for mammary adenectomy entailed a distance greater than 2.0 cm, measured by physical examination and imaging methods. This can aid the surgeon in selecting suitable cases for mammary adenectomy. The tumor-nipple distance measured using MRI and the intraoperative pathological margin

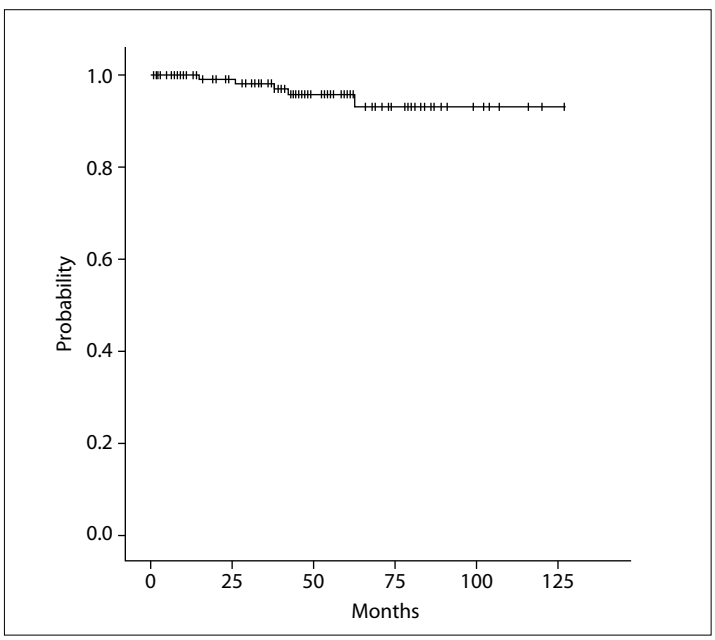

Figure 8. Kaplan-Meier estimates of overall survival.

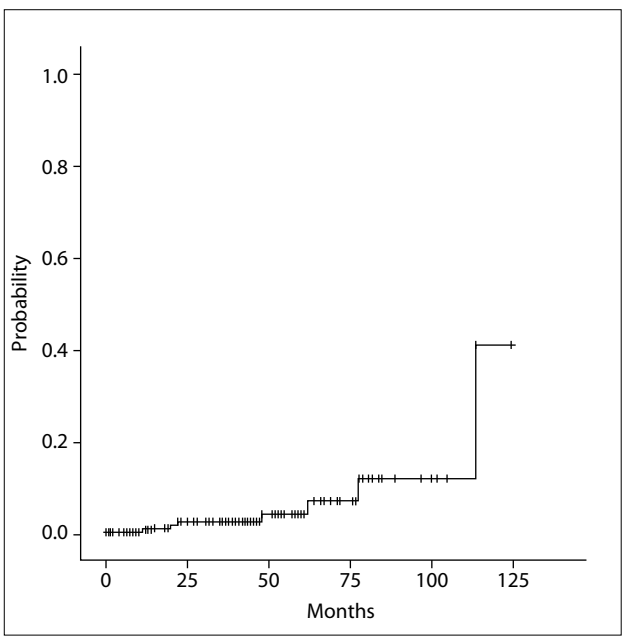

Figure 9. Incidence of local failure events.

assessment are the most accurate predictors of occult NAC involvement.[21-24]

The small ducts inside the nipple are arranged in a central bundle. This configuration enables nipple duct excision, which is deemed advisable.[25] When positive nipple ducts are found, in either the intraoperative or the postoperative report, NAC excision is required.

The most important step in the surgical approach relates to the skin flap thickness, which should be less than 5.0 mm directly under the areola and should gradually increase from 5.0 to 10.0 mm toward the gland periphery. A delicate surgical plane is usually achievable at the level of the superficial fascial layer between the subcutaneous fatty tissue and breast parenchyma.[26] Torresan et al. reported that the remnant terminal ductal-lobular units were significantly associated with skin flaps thicker than 5 mm (81.3% versus 46.2%), in specimens from skin-sparing mastectomies.[27] Since the cosmetic result are improved through preservation of a large subcutaneous tissue pad beneath the skin, one challenge faced by the surgeon is to achieve a balance between radicality and esthetics.

The role of RT among patients treated by MA is a matter of controversy. On the one hand, radiation protects the NAC and adjacent tissue against recurrence, but on the other hand, it may cause dermatitis, contour asymmetry, capsular contracture and implant extrusion.[7,28] Most likely, the majority of the patients with early-stage cancers treated by means of mammary adenectomy do not need adjuvant irradiation, except perhaps when postoperative imaging shows an excess of remaining tissue or in cases with more than three LNs affected.

Concerning the women's satisfaction with their breasts, most of our patients (64%) who responded to the satisfaction survey felt highly satisfied or satisfied. This may be considered to be a fair result, but it highlights the importance of discussing the variable of cosmetic outcomes before making the decision to opt for this surgery. Among 100 patients (117 procedures), Corso et al. found satisfaction with the breasts in 79 cases and satisfaction with the nipples in 31.[29] High expectations regarding the final cosmetic result should be discouraged.

Moreover, some complications may occur. The complications of mammary adenectomy with immediate reconstruction include flap and/or NAC necrosis, epidermolysis, implant loss, asymmetry, capsule contracture, infection and wound dehiscence. The factors that predispose towards complications are smoking, comorbidities, ptotic breast and periareolar incision.[29] In a systematic review of the literature with a pooled analysis on 12,358 procedures, Headon et al.[30] found a nipple necrosis rate of 5.9% and an overall complication rate of 22.3%. In that study, they observed that the rates of complications decreased over time, and this was attributed to improving surgeon expertise. Cutaneous hypoesthesia was very common. All these possibilities need to have been previously addressed.

Our study was not without limitations. There was no control group and the study was conducted on a relatively small number of patients. Nonetheless, despite such limitations, we were able to provide additional insights into personalized surgical treatment of breast cancer.

CONCLUSIONS

From the current analyses, we were able to conclude that mammary adenectomy preserving the NAC with a minimal amount of remaining glandular tissue, followed by immediate breast reconstruction, was a safe surgical option for selected patients presenting early-infiltration breast carcinoma. Among our patients, there was a high rate of satisfaction with the reconstructed breast(s).

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Detection of potentially pathogenic bacteria on cell phones of hospital and university-based populations in Curitiba, southern Brazil. A cross-sectional study

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KEY WORDS:
Cell phone.
Methicillin-resistant *Staphylococcus aureus.*
Enterobacteriaceae.

ABSTRACT

BACKGROUND: Cell phones have become indispensable for professional activities, including healthcare. Thus, they are possible sources of bacterial contamination. There is a scarcity of data in the literature regarding identification of risk factors for contamination of cell phones with pathogenic bacteria.

OBJECTIVE: To compare the prevalence rates of *Staphylococcus aureus (S. aureus)*, methicillin-resistant *S. aureus* (MRSA) and/or Enterobacteriaceae on cell phones belonging to hospital healthcare staff and university students in Curitiba, Paraná, Brazil, and to identify variables associated with such contamination.

DESIGN AND SETTING: Cross-sectional study conducted in a public university's referral hospital and lecture buildings in 2017.

METHODS: We sampled the surface of cell phones using the dipslide method, with Baird-Parker agar and *Escherichia coli*-coliform chromogenic (ECC) agar. We assessed the population's sociodemographic, behavioral and hygiene characteristics through interviews. Possible presence of *S. aureus* colonies was confirmed using agglutination tests, with evaluation of methicillin sensitivity. Colonies in ECC medium were counted. Stepwise logistic regression (forward $P < 0.15$) was performed to identify characteristics associated with bacterial contamination.

RESULTS: The prevalence rates of *S. aureus*, MRSA and Enterobacteriaceae were, respectively, 32%, 4% and 3%. No difference was found between the hospital and university-based populations ($P > 0.05$). The only variable associated with bacterial contamination was the use of cloth/velvet/leather phone cases (odds ratio: 2.92; 95% confidence interval: 1.08-7.91).

CONCLUSIONS: Potentially pathogenic bacteria were prevalent on the cell phones of this hospital and university population. Use of phone cases made of cloth-like material should be discouraged, especially in hospital settings.

INTRODUCTION

The number of cell phones users is estimated to be five billion, which corresponds to more than two thirds of the world's population.[1] Internet access is one of the factors responsible for the increasing number of users.[2] Over time, these devices have become indispensable not only for personal but also for professional life, since they allow efficient and quick communication, along with online searches.[3-5]

In hospitals, cell phones have also been widely used for sharing clinical information and the results from laboratory tests, diagnostic imaging and so on. In addition, several applications ("apps") with clinical utility have been developed for, but not limited to, drug dosage calculations, request codes for laboratory tests and access to scientific publications.[3,5,6] Thus, it is now impossible to dissociate the use of cell phones from healthcare assistance, especially in hospital settings. However, over the last decade, it has been pointed out in the literature that they might be considered to be a source of bacterial contamination, both in hospital and in community settings.[7,8]

Studies have shown that the skin colonizer *Staphylococcus aureus (S. aureus)* is the most frequent pathogenic bacterial species isolated from cell phones. Additionally, they have shown that methicillin-resistant *Staphylococcus aureus* (MRSA) may be found among the isolates.[4,5] The pathogenic potential of MRSA is unquestionable, especially with regard to nosocomial infections. Moreover, although cell phone contamination caused by members of the family Enterobacteriaceae

is less frequent than contamination due to MRSA, it is not rare. Species such as *Klebsiella pneumoniae* and *Escherichia coli* have been reported as contaminants of these devices and are undoubtedly important infectious agents.[4,9,10]

Although studies aiming to detect bacterial contamination of cell phones have already been conducted in several countries, they mostly focused on microbiological findings. Thus, those studies did not provide any information regarding the characteristics of the population that were associated with detection of pathogenic bacteria on these devices.[5,10-12] Additionally, to the best of our knowledge, there are no studies in the scientific literature showing information regarding cell phone contamination in Brazilian hospitals.

OBJECTIVE

Our aim was to compare the prevalence and loads of *S. aureus* (including MRSA) and Enterobacteriaceae on the cell phones belonging to healthcare professionals at a referral hospital with those on phones belonging to university students, in Curitiba, Paraná, Brazil. Additionally, we aimed to test associations between population characteristics and such contamination.

METHODS

Study design, ethics and sampling

This study was approved by the Ethics Committee of the Federal University of Paraná (Universidade Federal do Paraná, UFPR), under the number 1.858.500, on December 9, 2016. From January to September 2017, we cross-sectionally screened the cell phones of 300 participants, who were recruited in equal numbers (n = 150) in two enrollment settings.

One of the enrollment centers was the Hospital das Clínicas (Clinics Hospital, HC) of UFPR, which is a referral hospital in Curitiba, state of Paraná, Brazil. At HC-UFPR we enrolled multidisciplinary healthcare professionals who were attending the postgraduate course "Multiprofessional Integrated Residency Program of the HC/UFPR". This is a two-year specialization course that is taken by physicians, nurses, physiotherapists, dentists and psychologists, among others, who have close contact with hospital patients during their activities for obtaining their specialization degree. The participants were approached by the research team during their coffee or lunch break.

The second enrollment center was the Biological Sciences Sector (BSS) of UFPR, in Curitiba, Brazil. University students were approached in classroom halls while waiting for their next lecture. They were taking undergraduate health-related courses (medicine, biomedical sciences, physiotherapy, nursing and dentistry) at BSS-UFPR. Some of the students may also have been attending HC-UFPR for lectures and/or extracurricular activities. These participants did not see patients by themselves and were not performing any type of procedure at inpatient or outpatient clinics, since they were only accompanying local medical staff as part of their extracurricular activities. Among the undergraduates of the medicine course, none of them had started their internship at the time of enrollment.

Approaches to participants and sample collection

Three members of the research team (ASJ, GCB and TF) visited each enrollment center once a week and included similar numbers of participants per visit. When approaching potential participants, we explained the objectives of the study. Upon giving agreement to participate, these individuals signed a consent statement. None of the participants approached refused to participate. Before any sampling procedure was conducted, the participants individually answered a structured questionnaire. The questions sought information about their habits regarding the places where they used the phone (including the bathroom and bedroom), frequency of cleansing their hands and phone and the cleansing products used, among other information.

Only the participants themselves held their devices during the sampling procedure, in order to avoid contamination with the researchers' skin microbiota. Samples were obtained by allowing contact between the whole surface of the device and the two sides of the commercial dipslide Nutrilab P (Laborclin, Pinhais, Paraná, Brazil), which was coated with Baird-Parker agar and *Escherichia coli*-coliform chromogenic agar (ECC) on each face.

Sample analysis

The samples were transported to the laboratory within two hours after collection and were immediately incubated at 37 °C for 48 hours. In the presence of any growth, colonies on both faces of Nutrilab P were counted and recorded according to their morphology. The numbers of similar colonies retrieved in each medium were divided by the dipslide medium area (= 8.5 cm^2) to obtain the number of colony-forming units (CFU) per cm^2.

We considered that areas of black or gray color surrounded by a lipase halo on Baird-Parker agar were potentially colonies of *S. aureus*. To make a positive identification of *S. aureus*, these strains were tested for catalase production and confirmed using the latex agglutination-based test StaphclinLatex (Laborclin, Pinhais, Paraná, Brazil), in accordance with the manufacturer's instructions.

We further tested *S. aureus* isolates for cefoxitin susceptibility by means of disk diffusion, as standardized by the Clinical and Laboratory Standards Institute (CLSI), 2015.[13] When the cefoxitin inhibition zone diameter was < 22 mm, the strains were identified as MRSA.[14] We also identified all colony types counted on ECC agar at species level using the phenotypic tests provided through the enteroBacterias kit (Laborclin, Pinhais, Paraná, Brazil), in accordance with the manufacturer's instructions.

Statistical analysis

In the data analyses, variables regarding cell phone use and hygiene habits were compared between participants from the two enrollment settings using the Mann-Whitney nonparametric test and chi-square test for, respectively, continuous and categorical variables. The number of positive cultures and the number of colonies grown were compared using, respectively, the chi-square and Mann-Whitney tests, also according to the enrollment setting.

Additionally, univariate logistic regression models were constructed to assess any associations between the variables and the presence of any cell phone contamination (by *S. aureus* and/or Enterobacteriaceae). Crude and enrollment setting-adjusted odds ratios (OR) were estimated, along with their corresponding 95% confidence intervals (CI). Lastly, multivariable logistic regression analysis was carried out using a forward stepwise model selection process (variables retained at P-values ≤ 0.15), to identify variables independently associated with contamination.

All the statistical analyses were performed using Stata (Statacorp LLC, College Station, TX), considering P-values < 0.05 to be significant.

RESULTS

The median age of the 300 participants was 23 years, and most of them were female (n = 236; 78.7%) (**Table 1**). All the information on the participants' behavioral characteristics and hygiene habits that was acquired through interviews is shown in **Table 1**.

Nearly all the participants (94.3%) reported that they used their cell phones in all rooms of the house, including in bed. Furthermore, the data stratified according to enrollment setting in **Table 1** shows

Table 1. Sociodemographic data, behavioral characteristics and hygiene habits of the study participants: overall and according to enrolment setting

	Overall (n = 300)	BSS-UFPR (n = 150)	HC-UFPR (n = 150)	P-value
Age (years), median (min-max)	23 (17-74)	20 (17-39)	27.5 (21-74)	< 0.0001
Gender				
Male	64 (21.3%)	41 (27.3%)	23 (15.3%)	0.01
Female	236 (78.7%)	109 (72.7%)	127 (84.7%)	
Places in which cell phone was used				
In all rooms of the house	283 (94.3%)	141 (94.0%)	142 (94.7%)	0.80
In bed	283 (94.3%)	146 (97.3%)	137 (91.3%)	0.03
Water and soap available in all bathrooms used	102 (34.0%)	25 (16.7%)	77 (51.3%)	< 0.0001
Regular use of hand sanitizer (gel with alcohol)	209 (69.7%)	75 (50.0%)	133 (88.7%)	< 0.0001
Daily use of facial cream/sunscreen/foundation	210 (70.0%)	95 (63.3%)	115 (76.7%)	0.01
Day(s) at hospital facilities, per week				
None	83 (27.7%)	82 (54.7%)	1 (0.7%)	
1 day	44 (14.7%)	42 (28.0%)	2 (1.3%)	< 0.0001
2 or more days	173 (57.7%)	26 (17.3%)	147 (98.0%)	
Hospital settings regularly entered[a]				
None	113 (37.3%)	113 (75.3%)	0 (0.0%)	--
Outpatient clinics	107 (35.7%)	20 (13.3%)	87 (58.0%)	< 0.0001
Inpatient clinics	130 (43.3%)	18 (12.0%)	112 (74.7%)	< 0.0001
Operation rooms	47 (15.7%)	0 (0.0%)	47 (31.3%)	--
Intensive care units	25 (8.3%)	0 (0.0%)	25 (16.7%)	--
Other[b]	56 (18.7%)	12 (8.0%)	44 (29.3%)	< 0.0001
Frequency of cell phone cleansing				
Never	164 (54.7%)	105 (70.0%)	59 (39.3%)	
At least once	136 (45.4%)	45 (30.0%)	91 (60.7%)	
Daily	26 (8.7%)	5 (3.3%)	21 (14.0%)	< 0.0001[c]
Weekly	65 (21.7%)	21 (14.0%)	44 (29.3%)	
Monthly	45 (15.0%)	19 (12.7%)	26 (17.3%)	
Products used for cell phone cleansing				
None	164 (54.7%)	105 (70.0%)	59 (39.3%)	
Yes, using alcohol (gel or a 70% [v/v] solution)	104 (34.7%)	33 (22.0%)	71 (47.7%)	< 0.0001
Yes, using other products (soap, wipes, cloth or paper)	32 (10.6%)	12 (8.0%)	20 (13.3%)	
Material of the phone case				
None	74(24.7%)	38 (25.3%)	36 (24.0%)	
Plastic/silicone/rubber	209 (69.7%)	106 (70.7%)	103 (68.7%)	0.46
Cloth/velvet/leather	17 (5.7%)	6 (4.0%)	11 (7.3%)	

BSS = Biological Sciences Sector; UFPR = Universidade Federal do Paraná; min-max = minimum-maximum; HC = Hospital of Clinics; -- Not calculated; [a]Sum may be greater than 100%, because the participants mostly entered more than one hospital setting; [b]Laboratories, administrative offices, pharmacy and others; [c]Comparison between "never" and "at least once" categories.

that a significantly higher proportion of the participants enrolled at the university hospital (HC-UFPR) reported having access to bathrooms equipped with water and soap for hand washing at all times (51.3%) and making regular use of hand sanitizer (gel with alcohol) (88.7%).

Regarding cell phone cleansing habits, 70% of the students at BSS reported that they had never cleaned their device. This proportion was significantly lower among the participants enrolled at the hospital (39.3%). The most common product used for phone cleansing was alcohol solution (gels or liquid). At both enrollment sites, nearly 70% of the participants used phone cases made of smooth materials such as plastic, silicone or rubber, while approximately 5% used a cloth-like case (including cloth, velvet or leather materials).

The prevalence rates of contamination according to the enrolment setting are displayed in **Table 2**. The overall positivity for *S. aureus* was 32% and did not differ between enrollment sites. Among the 46 cases of *S. aureus* isolated from the students' phones, 5 (3.3%) were methicillin-resistant. The proportion of MRSA among the isolates from the hospital population was higher (n = 8; 5.3%) but did not reach statistical significance. The positivity rate for Enterobacteriaceae in the hospital population was twice the rate among the students, but did not differ statistically (**Table 2**). Regarding the comparison between the numbers of colonies yielded from the two study groups, no difference was observed in relation to any of the microorganisms.

Table 3 shows the results from association tests between positive cultures for *S. aureus* and/or Enterobacteriaceae and the characteristics assessed in the study population. Three different association analyses were performed: crude, adjusted for enrollment setting and multivariable. All of them showed very similar results. None of the variables tested were associated with colonization with *S. aureus* and/or Enterobacteriaceae except for the use of phone cases made of cloth-like material (cloth, velvet or leather).

Table 2. Comparison of frequency and number of CFU of *Staphylococcus aureus* and Enterobacteriaceae isolated from participants' cell phones, between enrollment sites

	BSS/UFPR (n = 150)	HC/UFPR (n = 150)	P-value
Staphylococcus aureus			
Positivity n (%)	46 (30.7%)	51 (34.0%)	0.54[a]
CFU/cm², median (min-max)	0.6 (0.1-8.8)	0.7 (0.1-14.1)	0.95[b]
MRSA			
Positivity n (%)	5 (3.3%)	8 (5.3%)	0.57[c]
CFU/cm², median (min-max)	0.6 (0.2-2.4)	0.9 (0.1-2.0)	0.83[b]
Enterobacteriaceae			
Positivity n (%)	3 (2.0%)	6 (4.0%)	0.50[c]
CFU/cm², median (min-max)	0.5 (0.1-0.5)	0.1 (0.1-0.4)	0.22[b]
***Staphylococcus aureus* and/or Enterobacteriaceae**			
Positivity n (%)	49 (32.7%)	54 (36.0%)	0.54[a]
CFU/cm², median (min-max)	0.6 (0.1-8.8)	0.6 (0.1-14.1)	0.74[b]

CFU = colony-forming units; UFRP = Universidade Federal do Paraná; min-max = minimum-maximum; SBS = Biological Sciences Sector; HC = Clinics Hospital; MRSA = methicillin-resistant *Staphylococcus aureus* (resistant if zone diameter < 22 mm in cefoxitin disk test); v/v = volume/volume.
[a]Chi-square test; [b]Mann-Whitney test; [c]Fisher exact test.

Table 3. Odds ratio and 95% confidence interval for the association of positivity in cultures for *Staphylococcus aureus* and/or Enterobacteriaceae with sociodemographic, behavioral and hygiene habits

	Crude	Enrollment setting-adjusted	Multivariable
Age	1.00 (0.99-1.03)	1.01 (0.98-1.03)	--
Gender			
Male	1.00	1.00	
Female	0.63 (0.34-1.17)	0.64 (0.34-1.19)	--
Sees patients on regular basis[a]			
No	1.00	1.00	
Yes	1.15 (0.71-1.86)	1.09 (0.59-2.00)	--
Cell phone use in all rooms at home			
No	1.00	1.00	
Yes	0.57 (0.21-1.52)	0.56 (0.21-1.51)	--
Water and soap available in all bathrooms used at work/study facilities			
No	1.00	1.00	
Yes	1.38 (0.84-2.27)	1.36 (0.79-2.32)	--
Regular use of hand sanitizer (gel with alcohol)			
No	1.00	1.00	
Yes	1.11 (0.66-1.88)	1.05 (0.59-1.87)	--
Day(s) at hospital facilities, per week[b]			
None or 1 day	1.00	1.00	
2 or more days	1.10 (0.70-1.79)	0.92 (0.40-2.16)	--
Daily phone cleansing			
No	1.00	1.00	
Yes	0.68 (0.28-1.68)	0.64 (0.25-1.60)	--
Phone cleansing with alcohol			
No	1.00	1.00	
Yes	1.02 (0.62-1.68)	0.98 (0.58-1.64)	--
Cloth/velvet/leather phone case			
No	1.00	1.00	1.00
Yes	2.92 (1.08-7.91)	2.87 (1.06-7.80)	2.92 (1.08-7.91)
Daily use of facial cream/sunscreen/foundation			
No	1.00	1.00	
Yes	1.23 (0.72-2.09)	1.21 (0.71-2.06)	--

-- variables not retained in the multivariable analysis (P-value > 0.10); [a]intensive care units and in and outpatient clinics; [b]at least for 2 hours excluding lecture rooms.

DISCUSSION

Despite the constant use of cell phones in many daily activities of healthcare personnel, there is still no consensus regarding the best approach for cleansing frequency, products or techniques. Nonetheless, studies have consistently shown that cell phones can be a source of contamination in hospital environments and that decontamination practices conducted on these devices to decrease their bacterial load may also reduce the cross-contamination risk.[7,8] Our data showed that the contamination rates were very similar to the prevalence of *S. aureus* carriage in individuals' oral and nasal mucosae. We could have hypothesized that healthcare professionals may present even higher prevalence but, on the other hand, they were seen to be more inclined to take decontamination measures in relation to their cell phones and no such difference was noted.[13]

Another factor that could have contributed towards the similar contamination rates observed in the two groups was that most of the participants enrolled at HC/UFPR reported that they made regular use of hand sanitizers. The findings from a previous study corroborate this idea, since that study showed that the microbiota of the hands is the main source of contamination of cell phones.[6] Hand sanitizer was also the most common product used for cell phone cleansing among the participants (104 out of 136; 76.4%) (data not shown). The efficacy of this product for reducing the microbial load on these devices has been acknowledged and has been recommended.[14]

Despite the notable rate of bacterial contamination of cell phones among the university students in our study (33%), this rate was lower than what has been reported in the literature. A study by Tagoe et al. found 100% prevalence of bacterial contamination on the cell phones of students in Ghana, while Zakai et al. showed 96% prevalence on the devices of students in Saudi Arabia.[8,15] The contamination rate among healthcare professionals in our study (36%) was also lower than what has been reported in the literature, which has ranged from 74% to 91% in similar populations.[10,16] The main reason for these discrepancies between our data and the reports in the literature is that we used two selective culture media, while the other studies were based on culturing in nutritionally enriched media, such as brain heart infusion, blood sheep agar and others.

Studies in the literature have mostly reported that the prevalence of bacterial contamination on students' cell phones is higher than the prevalence on the devices of healthcare professionals.[8,10,14,17] In part, this could be due to the more frequent decontamination procedures performed by hospital workers. However, those studies were performed either among students or among hospital staff and did not make comparisons between the two populations. Akinyemi et al. did compare the two populations and showed that the contamination rate of students' cell phones was twice that of the devices belonging to healthcare workers.[7] On the other hand, a study by Pal et al. agreed with our contamination rate by showing that it was greater among hospital staff than among students.[6] It is worth mentioning that in our study, although 37 students (24.7%) did enter the hospital environment on a regular basis, they did not see patients by themselves because they were only undertaking extracurricular activities.

As expected, among the pathogenic bacterial species assessed in this study, the most prevalent of them was *S. aureus*. This result is similar to findings reported in the literature: a study by Rana et al. showed that *S. aureus* was the most prevalent species, not only on the cell phones of healthcare professionals, but also on those of the non-healthcare professionals.[4] The positivity rate for MRSA found in our study was lower than what was previously reported on the cell phones of inpatients and both healthcare and non-healthcare professionals in Egypt and India.[4,5] Regarding the species belonging to the Enterobacteriaceae family that were also assessed in our study, the positivity rates of 2% and 4% on the devices of students and healthcare professionals, respectively, were similar to those found in the literature. Studies by Pal et al. and Heyba et al. found, respectively, positivity rates of 6% and 7% on the cell phones of hospital staff members.[6,10] One of the reasons for the lower prevalence of Gram-negative bacteria on cell phones may be their low tolerance towards desiccation and consequent reduced viability on the surface of cell phones.

The majority of our population (75%) used protective phone cases on their devices. According to a study by Tiwari et al., cell phones with protective cases show higher contamination rates than do those without cases, but they did not specify the types of materials used in the cases.[14]

Therefore, we now add to the literature the information that use of protective cases made of cloth-like material is independently associated with contamination of cell phones with potentially pathogenic bacteria. Hence, we suggest that the use of such covers should be discouraged, especially among healthcare staff and, even more importantly, those working in intensive care units or other clinics with especially critical patients. We also propose that this information should be addressed through guidelines regarding healthcare settings.

CONCLUSION

The prevalence rates of MRSA and Enterobacteriaceae contamination on cell phones were found to be similar in community and hospital-based populations. The use of phone cases made of cloth, velvet or leather was independently associated with contamination. Therefore, the use of this type of case should be discouraged, especially in healthcare settings. Further studies are needed, including assessment of a wider range of variables with greater sample sizes. Such studies will better contribute towards knowledge of the behavioral or hygiene characteristics of populations that might increase the risk of contamination. Such knowledge would make it possible to develop important prophylactic strategies and ensure safe use of cell phones.

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Procalcitonin levels among patients with fever secondary to severe intracerebral infection. A cross-sectional study

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C-reactive protein.

ABSTRACT

BACKGROUND: Making the differential diagnosis between central fever and infectious fever is critically important among intracerebral hemorrhage patients followed up in intensive care units (ICUs). Serum procalcitonin (PCT) has been found to be a promising biomarker for the initial diagnosis of infection, even before culturing results.

OBJECTIVES: To investigate the relationship between PCT and both fever etiologies and C-reactive protein (CRP) levels among critically ill patients with suspected intracerebral hemorrhage.

DESIGN AND SETTING: Cross-sectional study in a public university hospital in Elazig, Turkey.

METHODS: ICU patients diagnosed with intracerebral hemorrhage and normal procalcitonin levels were included in this study. From clinical assessments and cultures, they were classified as presenting either infectious or central fever. The sensitivity and specificity of PCT and CRP for predicting infection were calculated using a receiver operating characteristic (ROC) curve.

RESULTS: There were 98 ICU patients with diagnoses of intracerebral hemorrhage. The median (interquartile range) PCT levels of patients with infectious and central fever were 4 (0.9-11) and 0.1 (0.1-0.4) ng/ml, respectively, with a statistically significant intergroup difference ($P < 0.001$). The areas under the ROC curve for predicting infectious or central fever PCT and CRP were 0.958 ($P < 0.001$) and 0.816 ($P < 0.001$), respectively. A statistically significant positive correlation was detected between PCT and CRP levels in patients with infectious fever (rho: 0.461; $P = 0.003$), but not in patients with central fever.

CONCLUSIONS: PCT can possibly be used as a biomarker to differentiate between infectious and central fever among ICU patients.

INTRODUCTION

In intensive care units (ICUs), delay in diagnosis and treatment increases mortality rates. Serious infections among ICU patients most commonly consist of respiratory tract infections, followed by urinary system infections, wound site infections and primary bacteremia.[1,2]

Fever in patients hospitalized in ICUs is an important indicator of infection. Despite new treatment alternatives, the infection-related mortality rate remains high. Likewise, clinical findings of fever remain frequent. Moreover, routine laboratory tests are not specific and sometimes may mislead clinicians. Lack of early-phase and specific markers for diagnosing infection cause delays in treatment and unnecessary use of antibiotics.[3] Early diagnosis and appropriate antibiotherapy decrease infection-related morbidity and mortality.[4]

Assessment of clinical and laboratory findings constitutes an ideal method for diagnosing infection. Growth of an infectious agent through culturing provides the most important laboratory evidence. However, this method is time-consuming. While awaiting the results from culturing, other diagnostic laboratory parameters such as the levels of procalcitonin (PCT), C-reactive protein (CRP), leukocytes, neutrophils and erythrocyte sedimentation rate (ESR) have been used. Over recent years, serum PCT has been found to be an important and promising biomarker for making the initial diagnosis of infection.[5]

The incidence of fever in ICUs is 23%.[6] Nearly 50% of these cases relate to noninfectious etiologies. The noninfectious causes of fever include bleeding, atelectasis, drug effects, venous thromboembolism and blood transfusion reactions.[7]

Another noninfectious type of fever seen in ICUs is central fever in patients diagnosed with intracerebral hemorrhage.[6] Central fever has been defined as emergence of fever in patients with intracerebral

hemorrhage without any focus of infection.[8] Any disequilibrium in central thermomodulation relating to neurological damage may cause hyperthermia.[9] In animal models, direct trauma applied to the preoptic nucleus of the hypothalamus has been observed to induce development of hyperthermia within two minutes.[10] Central fever, which is a frequent complication seen in patients with intracerebral hemorrhage, has been seen in 72% of the patients diagnosed with subarachnoid hemorrhage, 37% of traumatic cerebral injuries and 32-37% of patients with a diagnosis of primary intracranial hemorrhage.[6]

If central fever seen in patients with intracerebral hemorrhage can be distinguished from manifestations of systemic inflammatory response syndrome (SIRS) due to infection, this will prevent use of inappropriate antibiotherapy and enable initiation of antibiotherapy that is effective for infection-related SIRS.[7]

Infectious and noninfectious causes of fever emerging in patients who have been hospitalized in an ICU need to be identified, and treatment should be rapidly instituted. Many studies have demonstrated that PCT levels do not change or only slightly increase in cases of noninfectious inflammation, surgical trauma, uncomplicated infection, autoimmune disease or neoplastic disease. Therefore, PCT can be used as a reliable biomarker for differentiating between bacterial and non-bacterial inflammatory processes.[11-14]

A significant correlation exists between increased PCT levels and greater severity of infection. Plasma PCT concentrations of between 0.5 and 2 ng/ml are deemed to be mildly elevated levels and are interpreted as local infection. PCT levels above 10 ng/ml are considered to be increased levels. PCT levels of up to 100 ng/ml are considered to be very high levels. Very high levels of PCT are seen in severe bacterial infections and in the hyperinflammatory phase of sepsis. In nonbacterial or nonparasitic diseases, PCT levels are generally below 2 ng/ml. In severe bacterial infections and sepsis, plasma PCT concentrations range between 2 ng/ml and 1,000 ng/ml.[15]

OBJECTIVES

The aim of the present study was to investigate the relationship between PCT levels and both fever etiology and CRP levels among critically ill patients with intracerebral hemorrhage. Early determination of the etiology of their fever would enable rational use of antibiotics. Furthermore, through diagnosing infections at an early stage, morbidity and mortality would be prevented and there would also be economic gains.

METHODS

Study design and ethics

This cross-sectional study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the local institutional review board (date: August 2, 2016; decision number: 155682).

Setting and participants

Febrile patients admitted to Firat University Hospital ICU with a diagnosis of intracerebral hemorrhage (subarachnoid hemorrhage, traumatic subarachnoid hemorrhage, subdural hematoma or primary intracerebral hemorrhage) and normal procalcitonin levels (initially) between January 2015 and January 2017 were included in this study. Patients with symptoms of infection or histories of chronic rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, familial Mediterranean fever, etc.) were excluded from the study.

Outcome evaluations

Hemogram, ESR, biochemical tests, CRP levels and PCT levels were evaluated at baseline and then routinely every day, and the results were recorded. Procalcitonin values on the day of development of findings were recorded in relation to patients who developed signs and symptoms of infection.

Endotracheal aspirate cultures were obtained from patients connected to mechanical ventilation. Aspirator tip, urine and deep wound site cultures were obtained from patients who were not connected to mechanical ventilation. Cerebrospinal fluid cultures were obtained from operated patients with indwelling drains. The results from these cultures were all evaluated.

Infectious fever was defined as fever suggestively related to an infection, through evaluation of the patient's clinical state and laboratory data by a specialist. The types of infections were classified according to the source of the infection, as blood stream, urinary, respiratory system or wound site infections.

Blood stream infection was defined as a situation in which a known pathogen isolated from one or more blood cultures was not associated with infection from another site or from growth of skin flora, in blood cultures obtained at two or more different time points. In catheterized patients, the following were defined as catheter-related blood stream infection: growth of the same microorganism both in semiquantitative peripheral blood cultures (> 15 colony-forming units/catheter segment) and in quantitative peripheral blood cultures (> 10^3 colony-forming units/catheter segment); bacterial growth rate of > 5/1 in simultaneously obtained central venous catheter blood and peripheral blood cultures; or detection of bacterial growth at least two hours earlier in a blood culture obtained from a catheter, relative to a simultaneously obtained peripheral blood culture.

Urinary tract infection (UTI) was defined as one of the following: bacterial growth of > 10^5 colony-forming units/ml or growth of at most two different bacteria in urine cultures; nitrite or leukocyte esterase positivity in complete urinalysis; or pyuria in a patient with one of the symptoms of fever, pollakiuria, dysuria or suprapubic tenderness.

The diagnosis of respiratory system infection was established based on a newly developed infiltration detected on chest X-ray, alteration to the patient's respiratory function of the patient (increased ventilation support or oxygen requirement), increased purulence of aspirated secretion and positivity of sputum culture.

Presence of a wound site, purulent discharge, local pain and tenderness, local warmth, redness, swelling and bacterial growth in aseptically collected discharges or tissue cultures favored the presence of wound site infection. Patients in whom infection was detected in multiple foci were included in a multiple infection group.

Central fever in patients with a diagnosis of intracerebral hemorrhage was evaluated based on clinical, laboratory and culture results and was defined as absence of any infection.

The clinical progression of the patients, including their ICU stay, discharge and death, was also recorded on forms.

Statistical analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences v22 (SPSS, Inc., Chicago, IL, USA). The sample size was decided in accordance with a power analysis (significance level of $P < 0.05$; power analysis 80%). Descriptive statistics, including frequencies and percentages for categorical variables and the mean (± standard deviation) and median (with interquartile range, IQR) for continuous variables, were used to describe the baseline demographic data and clinical characteristics.

The variables were investigated using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether or not they were normally distributed. The Mann-Whitney U test was applied to compare continuous variables. To determine the correlation between two continuous variables, Spearman's rank correlation analysis was used for asymmetrical variables.

The data distribution was not normal, and for this reason, nonparametric analytical methods (Mann-Whitney and Spearman) were used. The cutoff values of PCT, CRP and ESR for predicting infectious fever were determined by means of a receiver operating characteristic (ROC) analysis. ROC curves were generated by plotting the relationship between true positivity (sensitivity) and false positivity (1-specificity) at various cutoff points of the tests. P-values < 0.05 were considered to be statistically significant in all analyses.

RESULTS

A total of 98 patients were admitted to the ICU with a diagnosis of intracerebral hemorrhage. Among these patients, eight (8.16%) had abnormal procalcitonin levels, one (1.02%) had a history of rheumatic disease and 16 (16.32%) were afebrile on the day of admission. Therefore, all these patients were excluded from the study. Forty-five male patients (61.6%) and 28 female patients (38.4%) with a mean age of 55.59 ± 16.04 years (range, 22-87 years) were included in this study (total of 73 patients). They presented the following conditions: subarachnoid hemorrhage (n = 42; 57.5%), subdural hematoma (n = 15; 20.5%), traumatic subarachnoid hemorrhage (n = 12; 16.4%) and primary intracerebral hemorrhage (n = 4; 5.5%).

Among these 73 patients who were assessed, 39 (53.4%) presented infectious fever and 34 (46.6%) had central fever. The foci of infection were investigated. There were 22 cases of single-site infection, which most frequently consisted of respiratory tract infection (n = 17), followed by urinary tract infection (n = 3). The other 17 patients with infectious fever presented multiple infections.

The median PCT value among the 39 febrile patients with intracerebral hemorrhage who were diagnosed as presenting infectious fever was 4 ng/ml (IQR, 0.9-11). In the central fever group (n = 34), the median PCT was 0.1 ng/ml (0.1-0.4) ($P < 0.001$). PCT values were investigated according to the foci of infection, and the highest PCT values were found in patients with multiple infections: 5.0 ng/ml (2.7-27) (**Table 1**).

Multiple infections were investigated according to their foci of infection, as concomitant infections. These included secondary blood stream infections (total n = 15), pneumonia (n = 9; 52.4%), urinary system infections (n = 4; 23.53%) and wound site infections (n = 2; 11.76%). In one patient (5.88%), pneumonia and wound site infection were detected, and in another patient (5.88%), pneumonia and urinary tract infection.

The median PCT levels according to foci of multiple infections were 5.01 ng/ml (min-max, 0.1-200) in cases of blood stream infection plus pneumonia; 5.5 ng/ml (3.5-19) in cases of blood stream infection concomitant to urinary system infection; 5.01 ng/ml (5-12) in cases of blood stream infection plus wound site infection; 32.5 ng/ml in a patient with pneumonia plus urinary system infection; and 0.4 ng/ml in another patient with pneumonia plus wound site infection.

The median hospital stay among all the patients was 21 days (IQR, 13-47.5). For 36 patients with PCT > 0.5 ng/ml, it was 30 days

Table 1. Median procalcitonin (PCT) levels (ng/ml) of cases with infectious fever, according to focus of infection

Group	n (%)	PCT median (interquartile range)
Multiple infection sites	17 (43.6)	5.0 (2.7-27.0)
Single infection site	22 (56.4)	3.4 (0.8-6.8)
Pneumonia	17 (43.6)	4.3 (1.5-8.5)
Urinary tract infection	3 (7.6)	0.7 (0.5-0.8)
Wound site infection	1 (2.6)	1
Primary blood stream infection	1 (2.6)	0.8
Total	**39 (100)**	**4 (0.9-11)**

(min-max, 5-210); while for those with PCT < 0.5 ng/ml, it was 20 days (min-max, 7-150). In parallel with longer hospital stays, increases in mean serum PCT levels were seen. However, no statistically significant differences were detected (P = 0.051).

The median PCT level of patients who died (n = 28; 38.36%) was 5 ng/ml (IQR, 0.8-18.5). This was significantly higher than that of discharged patients (n = 45; 61.64%), for whom the PCT level was 0.2 ng/ml (IQR, 0.1-0.6) (P < 0.001).

The median CRP level among the patients with infectious fever was 167 mg/l (IQR, 138-201); while the median CRP level of the cases with central fever was 72.5 mg/l (IQR, 16.25-137.7).

A statistically significant positive correlation was detected between PCT and CRP levels in patients with infectious fever (rho: 0.461; P = 0.003) (**Figure 1**). However, in cases with central fever, no significant correlation was detected between PCT and CRP levels (rho: 0.239; P = 0.173). In both groups, there were no statistically significant correlations between PCT levels, ESR, blood leukocyte levels and polymorphonuclear leukocyte (PMNL) percentages.

The median white blood cell count, neutrophil count, erythrocyte sedimentation rate, CRP level and PCT level of the cases are presented in **Table 2**. A statistically significant difference was detected between the infectious fever and central fever groups regarding PCT level, ESR and CRP level.

To evaluate the sensitivity and specificity of these three biomarkers, ROC curves were calculated. The ROC analysis showed that PCT was a good marker for distinguishing infectious fever patients, with an area under the curve (AUC) of 0.958 (95% confidence interval: 0.912-1.000; P < 0.001). CRP was found to have an AUC of 0.816 (95% confidence interval: 0.714-0.917; P < 0.001). The ESR was found to have an AUC of 0.748 (95% confidence interval: 0.633-0.863; P < 0.001). The sensitivity and specificity of PCT, CRP and ESR for diagnosing infectious fever in cases of intracerebral hemorrhage are presented in **Table 3**. ROC curves comparing PCT, CRP and ESR with regard to predicting the diagnosis of infectious fever in cases of intracerebral hemorrhage are shown in **Figure 2**.

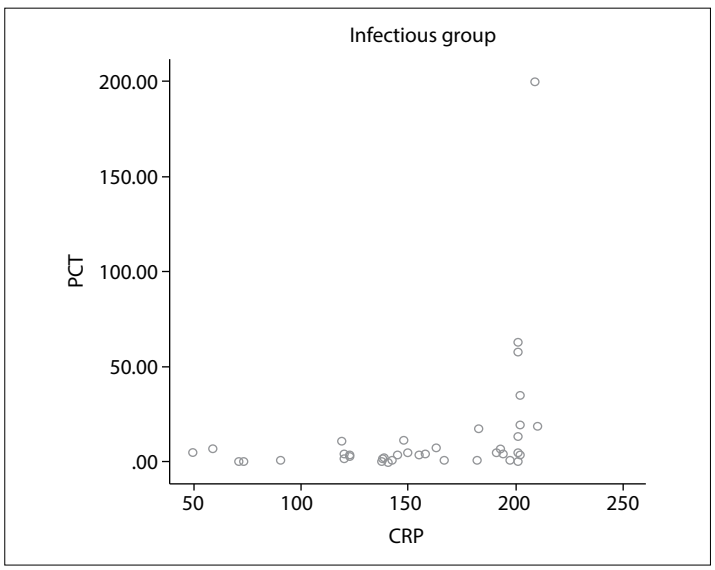

Figure 1. Correlation between procalcitonin (PCT) and C-reactive protein (CRP) levels in cases with infectious fever.

Table 2. Laboratory parameter results from the infectious fever and central fever groups, expressed as median (interquartile range)

	Infectious fever (n = 39)	Central fever (n = 34)	P
Blood leukocyte count (10^3/μl)	11200 (7550-13500)	10625 (6545-12125)	0.278
Blood PMNL percentage (10^3/μl)	80 (76-87)	79 (66-84)	0.121
Erythrocyte sedimentation rate (mm/h)	90 (65-105)	55 (30-77)	< 0.001
C- reactive protein (mg/l)	167 (138-201)	72 (16-137)	< 0.001
Procalcitonin (ng/ml)	4 (0.9-11)	0.1 (0.1-0.4)	< 0.001

PMNL = polymorphonuclear leukocyte.

Table 3. Sensitivity and specificity of procalcitonin (PCT), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) for diagnosing infectious fever in cases of intracerebral hemorrhage

	PCT	CRP	ESR
Cutoff	0.35 (ng/ml)	119.5 (mg/l)	56.5 (mm/h)
Sensitivity	94.87	84.62	87.18
Specificity	73.58	64.71	50.0
Positive predictive value	80.43	73.33	66.67
Negative predictive value	92.59	78.57	77.27
Area under the curve	0.958	0.816	0.748
P-values	< 0.001	< 0.001	< 0.001

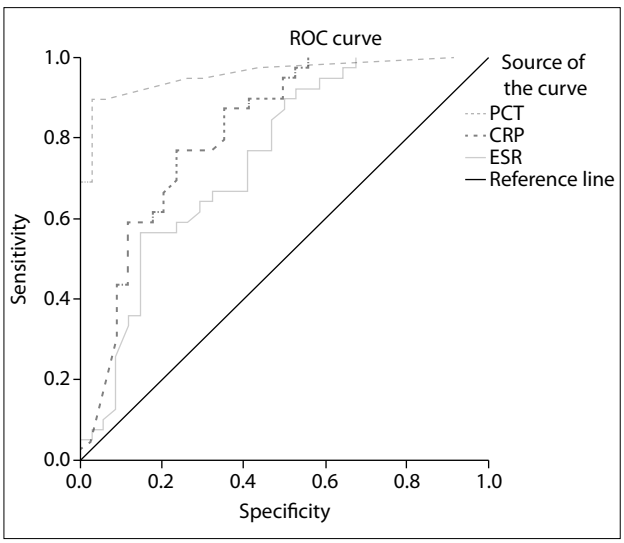

Figure 2. Receiver operating characteristic (ROC) curves for procalcitonin (PCT), C-reactive protein and erythrocyte sedimentation rate (ESR), for predicting diagnoses of infectious fever in cases of intracerebral hemorrhage.

DISCUSSION

Recently, the information available about use of PCT as a biomarker in ICUs has been increasing. In the literature, most PCT-related studies have focused on PCT levels relating to the diagnosis of sepsis. The objectives of investigating PCT levels have been to detect possible bacterial infection in order to reveal the severity of SIRS, discern the progression of infection towards sepsis, observe the response of sepsis to treatment and predict the prognosis.[16]

It has been demonstrated that PCT levels enable reliable differentiation of sepsis from SIRS.[17] In both human and animal models, increased levels of PCT production have been demonstrated in situations of bacterial infection.[18] PCT levels markedly increase when bacterial infection is present; while in situations of localized or viral infections, PCT levels remain normal or increase slightly. Festic et al. conducted a study on patients who were followed up in ICUs with a diagnosis of subarachnoid hemorrhage. They evaluated PCT levels at all foci of infection and noted that PCT had high specificity but low sensitivity for predicting infection. However, when UTIs were considered to be minor infections and were excluded from the analysis, it was then observed that PCT levels presented increased specificity and sensitivity in relation to infection.[19]

Halvarson et al. conducted a study on 73 patients with diagnoses of spontaneous subarachnoid hemorrhage, subdural hematoma, traumatic subarachnoid hemorrhage or primary intracerebral hemorrhage who had been hospitalized and were being followed up in the ICU of a neurology department. These authors investigated the specificity of PCT levels for differentiating between infectious and central fevers. The patients were classified according to their foci of infection, as patients with pneumonia, urinary tract infection, infection of the bloodstream, encephalitis, sinusitis, enterocolitis or multiple infections.[20] PCT levels were compared between patients with infectious and central fevers, and increased PCT levels in cases of intracerebral hemorrhage were not found to be specific for the diagnosis of infectious fever. In their study, localized infections, such as sinusitis and enterocolitis, were frequently encountered; however, in our study, higher incidence of secondary bloodstream infections was encountered, which may have been the reason for the relatively higher PCT levels.

A relatively small-scale study in which PCT was investigated as a biomarker of infection was unable to provide adequate and significant information on this issue.[21] In another study, PCT levels were compared between patient groups with sterile meningeal inflammation in Neuro-Behcet's disease and with bacterial meningitis, and no statistically significant difference was found.[22] The differences that have arisen between various studies may have been due to the diverse effects of different types of infection on the production of PCT. Larger-scale studies need to be conducted on this issue.

Several investigations have been performed concerning the use of CRP and PCT levels for diagnosing and following up cases of infection in patients. In most studies, PCT has been reported to be superior to CRP for differentiating between sepsis and SIRS. However, some other studies have not indicated any superiority of PCT.[23-27] PCT has been found to be 7% more sensitive and 23% more specific than CRP for establishing the diagnosis of bacterial infection.[28,29] In another study, it was reported that both PCT and CRP could be used in making the diagnosis of infection, but that PCT was superior for determining the prognosis.[30]

Ugarte et al. followed up 190 adult ICU patients and diagnosed the presence of hospital-acquired infection in 111 patients. They compared the patients with and without infection and observed that there were statistically significantly higher PCT and CRP levels in patients with infection.[31] In their study, the best cutoff values for PCT and CRP were 0.6 ng/ml and 7.9 mg/dl, respectively. According to their study, PCT is not a better marker of infection than CRP, among critically ill patients.

In our patients, a statistically significant positive correlation was detected between the PCT and CRP levels in cases with infectious fever. However, this significant correlation was not detected in the central fever group (rho: 0.239; P = 0.173). CRP is classified as an acute-phase reactant, which means that its levels will rise in response to inflammation. A variety of conditions could commonly cause increases in the levels of CRP and other inflammatory markers.

The limitations of the present study included its characteristics of being a single-site study with only a small number of patients. Multi-site studies would enable acquisition of more accurate information.

CONCLUSIONS

Differentiation between infectious and noninfectious etiologies of fever that emerges in patients who have been diagnosed with intracerebral hemorrhage, along with early institution of treatment, makes it possible to institute appropriate antibiotic therapy in patients with infection and prevent unnecessary use of antibiotics in patients with central fever. This adds importance to the guiding role of serum PCT levels in making the diagnosis and prognosis of infection. In this population, serum PCT levels can help physicians to correctly diagnose and use antibiotics. Our study demonstrated that PCT levels can be used to differentiate between infectious and central fevers in patients with intracerebral hemorrhage, with high specificity and predictive values for infection. However, studies with larger numbers of patients need to be conducted in relation to this issue.

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Projection of new thresholds for hypertension to outpatient clinic patients and impact of risk factors: a cross-sectional study

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ABSTRACT

BACKGROUND: The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on hypertension management recommend new stage 1 hypertension thresholds (130-139/80-89 mmHg) for starting antihypertensive treatment.

OBJECTIVE: To analyze the impact of the 2017 ACC/AHA guidelines on patients' diagnoses within daily practice, in comparison with management using the 2018 European hypertension guidelines, regarding the new thresholds.

DESIGN AND SETTING: Cross-sectional study conducted in a hypertension outpatient clinic at a tertiary-level public hospital.

METHODS: The diagnosis of hypertension was defined separately using each guideline. The participants were patients who were attending the hypertension clinic, who were evaluated using the thresholds of two guidelines, based on cardiovascular risk factors, including age, gender, smoking status, diabetes mellitus, dyslipidemia, obesity, osteoporosis, chronic renal failure and family history of hypertension.

RESULTS: After adapting the guidelines to the blood pressure values of our sample, 74.5% (n = 277) of the patients were diagnosed as hypertensive according to the blood pressure classification of the European Society of Cardiology (ESC) guidelines published in 2018, while 91.1% (n = 339) of the patients were hypertensive according to the new 2017 ACC/AHA guidelines. Multivariate regression analysis revealed that the significant demographic and cardiovascular risk factors associated with hypertension, based on the 2018 European Society of Hypertension (ESH)/ESC guidelines, were age (odds ratio, OR: 1.027; 95% confidence interval, CI: 1.001-1.054; P = 0.042), obesity (OR: 4.534; 95% CI: 1.830-11.237; P = 0.001) and family history of hypertension (OR: 2.199; 95% CI: 1.252-3.862; P = 0.006).

CONCLUSIONS: The factors associated with the definition of hypertension may vary through changing the threshold values.

INTRODUCTION

Hypertension is one of the leading public health problems in both developed and developing countries. Studies have shown that cardiovascular morbidity and mortality are closely related to systolic and diastolic blood pressure. Up-to-date guidelines are needed in order to achieve the targets that have been accepted as international standards for diagnosing and treating hypertension. Although the guidelines are not decisive in themselves alone, they assist physicians in the approach that they take towards hypertension.[1]

In 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) released new guidelines for prevention, detection, evaluation and management of hypertension in adults. The new guidelines lower the threshold for the diagnosis of hypertension and target blood pressure levels of 130/80 mmHg in the general population. The new classification will add a large number of patients who will now be diagnosed as hypertensive, whose blood pressure was previously considered to be within the normal range.[2]

The 2017 ACC/AHA guidelines differ from the criteria of the Eighth Joint National Committee (JNC-8) report, which was published in 2014.[3] The new guidelines have developed a more aggressive approach that can be summarized as three main strands: (1) The threshold for defining hypertension has been decreased from 140/90 mmHg to 130/80 mmHg; (2) Independent of cardiovascular risk factors and blood pressure levels, the blood pressure target value has been set to < 130/80 mmHg; and (3) Selection of two antihypertensive drugs for patients with a blood

pressure of 140/90 mmHg and over has been adopted (which comprises stage 2 hypertension according to the 2017 ACC/AHA guidelines, or stage 1 hypertension according to other guidelines).[4] The new guidelines emphasize that cardiovascular disease, diabetes or a risk of more than 10% of developing cardiovascular disease within 10 years, are as important as the blood pressure values in treating hypertension. Other points of particular interest in the new guidelines are the importance placed on home blood pressure measurement and teamwork in hypertension management.[5]

Unlike the 2017 ACC/AHA guidelines, the 2013 guidelines of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) defined the threshold for stage 1 hypertension and for starting pharmacological treatment as 140-159 mmHg of systolic blood pressure (SBP) or 90-99 mmHg of diastolic blood pressure (DBP).[6] The 2018 ESH/ESC hypertension guidelines have now also been released and the blood pressure thresholds for classifying hypertension remain the same as in the previous European guidelines.[7]

Threshold values for identifying and classifying the diagnosis of hypertension, and for determining the time to start pharmacological treatment, the target values and the treatment strategies, are important for community health and for healthcare costs. In the present study, these two current guidelines, based on different threshold values for diagnosing hypertension and on different classification tables, were evaluated through our sample. In addition, the association between demographic and cardiovascular risk factors and hypertension was examined based on the diagnostic threshold values for hypertension that are accepted in each of the two guidelines.

OBJECTIVE

The objective of this study was to analyze the impact of each threshold, i.e. those accepted by 2017 ACC/AHA guidelines and the 2018 European hypertension guidelines, on patients' diagnoses. In addition, we sought to ascertain the associations between the cardiovascular risk factors and each of the thresholds.

METHODS

Design and setting

This observational cross-sectional study was conducted at Gülhane Educational and Research Hospital, Ankara, Turkey.

Participants, variables and data sources

A total of 437 consecutive patients who had been admitted to the hypertension outpatient clinic with a diagnosis of hypertension at the baseline assessment were recruited for this study. The baseline SBP/DBP values of this sample, from among all the enrolled patients for whom blood pressures were evaluated between 1990 and 2010, were extracted from the patients' medical files. Patients with mental disorders and malignancies, and those younger than 18 years, were excluded from the study. After the initial evaluation of inclusion criteria and after excluding patients with deficient laboratory results, a total of 372 participants (85.1%) remained enrolled in the study.

All the study variables including the blood pressure measurement were obtained at the baseline assessment on the patients. The personal characteristics surveyed included the patients' age group (≤ 45 years versus 46-65 years versus > 60 years), sex, obesity (body mass index, BMI ≥ 30 kg/m^2 versus BMI < 30 kg/m^2), smoking status (current smoker versus others) and family history of hypertension (yes versus no). Presence of any of the following diseases was also assessed: coronary artery disease (CAD), both types of diabetes mellitus (DM), dyslipidemia and chronic kidney disease (CKD). Presence of comorbidities was ascertained according to self-reports from the study participants at the baseline evaluation. The patients' laboratory values were obtained from the hospital's electronic biochemistry data service and from the patients' files.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Gülhane Education and Research Hospital of Ankara, Turkey (no. 1491-676-10/1539; date: February 19, 2010). This study was conducted in accordance with the principles of the Declaration of Helsinki. The researchers also guaranteed that the participants' identities and related health records would be kept confidential.

Statistical analysis

The patient groups were categorized according to the thresholds for the diagnosis of hypertension indicated by the two sets of guidelines. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software (version 22.0; SPSS Inc., Chicago, IL, USA).

Descriptive statistics were presented as percentages for categorical variables and as the mean ± standard deviation (SD) for continuous variables. All the continuous variables, including age, growth factor receptor (GFR) level, total cholesterol level, BMI and blood pressure values, were analyzed for normal distribution using the Kolmogorov-Smirnov test and were found to be normally distributed. Comparison of categorical variables was performed using the chi-square test.

Binary logistic regression modeling was used to examine the association between cardiovascular risk factors and the diagnosis of hypertension based on these two sets of guidelines, while controlling for and including all other variables.

The results were presented as odds ratios (OR) and 95% confidence intervals (95% CI). The data were considered to be statistically significant at P-values < 0.05.

RESULTS

A total of 372 patients with a mean age of 62.36 ± 11.45 years (range: 25-88) were enrolled in this study. Just over three-fourths (76.3%; n = 284) of the study participants were female. Among all the patients, 43.3% (n = 161) were in the age group > 65 years, while 48.7% (n = 181) were in the age group 46-65 years. Only a small proportion of the patients (14%) were smoking currently. Other cardiovascular risk factors and comorbid diseases are shown in **Table 1**.

In the whole study group, 74.5% (n = 277) of the patients were diagnosed as presenting hypertension according to the ESC guidelines for blood pressure classification (SBP/DBP > 140/90 mmHg), published in 2018. Conversely, 91.1% (n = 339) of the patient sample were hypertensive according to the 2017 ACC/AHA guidelines for blood pressure classification (SBP/DBP > 130/80 mmHg), published in 2017. Based on the 2018 ESH/ESC guidelines for blood pressure classification, 22.6% of the patients were in stage 1, 21.8% in stage 2 and 19.1% in stage 3 group. However, based on the 2017 ACC/AHA guidelines for blood pressure classification, 14.5% were in stage 1 and 76.6% were in stage 2 (**Figure 1**).

Using the definition of the 2018 ESH/ESC guidelines, and comparing the patients with and without hypertension, we found that the patients in the hypertension group had more family history of hypertension (50.5%, n = 140 versus 35.8%, n = 34; P = 0.013). Among the patients with hypertension, 26.0% (n = 72) were obese, while this was observed in 10.5% (n = 10) of the patients without hypertension (P = 0.002). Regarding osteoporosis, the

Table 1. Comparison of predictors for the diagnosis of hypertension according to the 2018 European Society of Hypertension and the European Society of Cardiology guidelines

	All % (n)	Hypertension (-) % (n)	Hypertension (+) % (n)	P*
Sex				
Female	76.3 (284)	76.8 (73)	76.2 (211)	0.895
Smoking status				
Current smoker	14.0 (52)	13.7 (13)	14.1 (39)	0.924
Diabetes mellitus				
Yes	26.1 (97)	20.0 (19)	28.2 (78)	0.118
Coronary artery disease				
Yes	13.2 (49)	13.7 (13)	13.0 (36)	0.864
Age groups				
< 45 years	8.1 (30)	9.5 (9)	7.6 (21)	0.787
46-65 years	48.7 (181)	49.5 (47)	48.4 (134)	
> 65 years	43.3 (161)	41.1 (39)	44.0 (122)	
Family history				
Yes	46.8 (174)	35.8 (34)	50.5 (140)	**0.013**
Obesity				
Yes	22.0 (82)	10.5 (10)	26.0 (72)	**0.002**
Osteoporosis				
Yes	13.4 (50)	20.0 (19)	11.2 (31)	**0.030**
Dyslipidemia				
Yes	44.9 (167)	38.9 (37)	46.9 (130)	0.177
Glomerular filtration rate (GFR) classes (ml/min/m²)				
GFR ≥ 90	28.9 (93)	25.6 (20)	29.9 (73)	0.761
GFR 60-89	58.1 (187)	60.3 (47)	57.4 (140)	
GFR 30-59	13.0 (42)	14.1 (11)	12.7 (31)	

*Chi-square test.

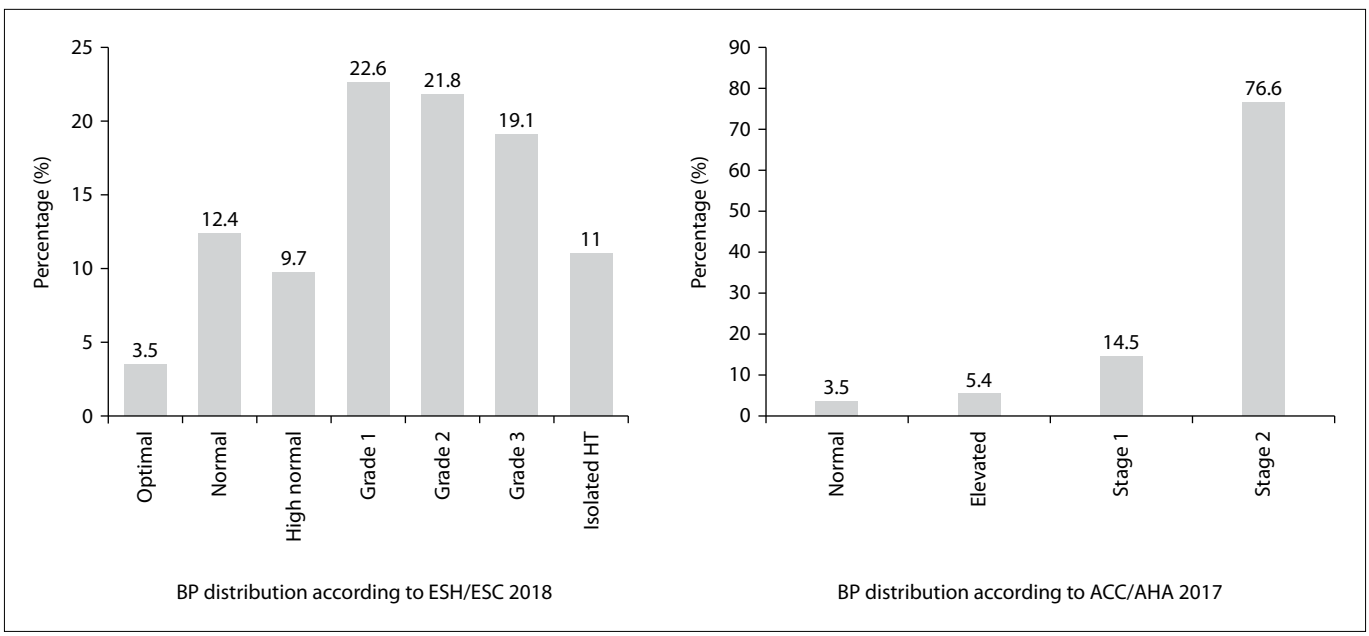

Figure 1. Classification of blood pressure (BP) values according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) and the 2018 European Society of Hypertension and the European Society of Cardiology (ESH/ESC) hypertension (HT) guidelines.

number of patients presenting this in the group with hypertension (11.2%, n = 31) was significantly lower than the number of patients with osteoporosis in the group without hypertension (20%, n = 19).

In accordance with the definition of the 2018 ESH/ESC guidelines, comparing the patients who had hypertension with those who did not, although the patients in the hypertension group were older and more frequently presented obesity, no statistically significant difference was detected based on cardiovascular risk factors and comorbidities (**Table 1**). According to the results from the univariate analysis, there were no significant variables associated with the diagnoses of hypertension that were defined in the 2017 ACC/AHA guidelines (**Table 2**).

The results from the multivariate logistic regression analysis revealed that the significant demographic and cardiovascular risk factors associated with the diagnosis of hypertension according to the 2018 ESH/ESC guidelines were the following: age (OR: 1.027; 95% CI: 1.001-1.054; P = 0.042), obesity (OR: 4.534; 95% CI: 1.830-11.237; P = 0.001) and family history of hypertension (OR: 2.199; 95% CI: 1.252-3.862; P = 0.006). According to the regression analysis, no significant difference was detected in terms of the association between cardiovascular risk factors and the diagnosis of hypertension according to the 2017 ACC/AHA guidelines (**Table 3**).

Table 2. Comparison of predictors for the diagnosis of hypertension according to the 2017 American College of Cardiology/American Heart Association guidelines

	All % (n)	Hypertension (-) % (n)	Hypertension (+) % (n)	P
Age groups				
< 45 years	8.1 (30)	18.2 (6)	7.1 (24)	
46-65 years	48.7 (181)	36.4 (12)	49.9 (169)	0.056
> 65 years	43.3 (161)	45.5 (15)	43.1 (146)	
Sex				
Female	76.3 (284)	81.8 (27)	75.8 (257)	0.438
Smoking				
Current smoker	14.0 (52)	12.1 (4)	14.2 (48)	0.747
Diabetes mellitus				
Yes	26.1 (97)	21.2 (7)	26.5 (90)	0.505
Coronary artery disease				
Yes	13.2 (49)	9.1 (3)	13.6 (46)	0.468
Family history				
Yes	46.8 (174)	36.4 (12)	47.8 (162)	0.209
Obesity				
Yes	22.0 (82)	9.1 (3)	23.3 (79)	0.060
Osteoporosis				
Yes	13.4 (50)	12.1 (4)	13.6 (46)	0.816
Dyslipidemia				
Yes	44.9 (167)	33.3 (11)	46.0 (156)	0.162
Glomerular filtration rate (GFR) classes (ml/min/m²)				
GFR ≥ 90	28.9(93)	22.2 (4)	29.3 (89)	
GFR 60-89	58.1 (187)	72.2 (13)	57.2 (174)	0.413
GFR 30-59	13.0 (42)	56 (1)	13.5 (41)	

*Chi-square test analysis.

DISCUSSION

It has been predicted that, through lowering the threshold for making the diagnosis of hypertension to 130/80 mmHg, the 2017 ACC/AHA guidelines will increase the number of patients who will be diagnosed with hypertension and need treatment. The proportion of our sample that was not hypertensive using the 2018 ESH/ESC guideline thresholds was approximately three times higher (25.5% versus 8.9%) than it was using the 2017 ACC/AHA guideline thresholds. Compared with the 2018 ESH/ESC guidelines, the number of hypertensive patients according to the 2017

Table 3. Multivariate regression analysis on associations of variables with the diagnosis of hypertension according to the 2018 European Society of Hypertension and the European Society of Cardiology guidelines and the 2017 American College of Cardiology/American Heart Association guidelines

Variables	2018 European Society of Hypertension and the European Society of Cardiology hypertension definition		
	Odds ratio	95% confidence interval	P
Sex (male)	1.167	0.621-2.194	0.631
Age	1.027	1.001-1.054	**0.042**
Coronary artery disease	0.829	0.399-1.722	0.615
Diabetes mellitus	1.182	0.613-2.278	0.618
Glomerular filtration rate	1.008	0.993-1.024	0.298
Smoking	1.518	0.680-3.389	0.308
Obesity	4.534	1.830-11.237	**0.001**
Dyslipidemia	0.892	0.513-1.552	0.686
Family history of hypertension	2.199	1.252-3.862	**0.006**
	2017 American College of Cardiology/American Heart Association hypertension definition		
Sex (male)	1.777	0.488-6.466	0.383
Age	1.042	0.995-1.091	0.082
Coronary artery disease	0.814	0.215-3.082	0.762
Diabetes mellitus	0.890	0.264-3.006	0.852
Glomerular filtration rate	1.004	0.975-1.034	0.795
Smoking	4.351	0.525-36.052	0.173
Obesity	1.336	0.001-2.005	0.997
Dyslipidemia	0.730	0.266-2.007	0.542
Family history of hypertension	2.793	0.927-8.420	0.068

ACC/AHA guidelines was 16.6% higher in our study sample. Age, obesity and family history of hypertension were significant variables according to the 2018 ESH/ESC guidelines, but use of the 2017 ACC/AHA guidelines did not give rise to any significant change among the factors associated with the diagnosis of hypertension, defined through these two different sets of guidelines.

The evidence supporting the lowering of the hypertension thresholds came from a meta-analysis on randomized controlled trial (RCTs) published in The Lancet in 2016, particularly from the data of the Systolic Blood Pressure Intervention Trial (SPRINT), in relation to antihypertensive drug treatment.[8,9] According to this meta-analysis in The Lancet, a reduction of about 25% in blood pressure was effective in preventing the development of cardiovascular events in patients with SBP of 130 mmHg and above. However, even though SPRINT is a well-organized study, some notable concerns remain when its results are adapted for use in guidelines or real-life daily practice. The beneficial results shown by studies that have early termination may sometimes be greater than should be expected.[8]

The difference between the 2017 ACC/AHA guidelines and the previous guidelines means that the number of hypertensive patients in the United States is expected to increase from 32% to 46%, simply through changing the definition of hypertension. Moreover, the target blood pressure has decreased along with the lowering of the diagnostic threshold. According to the authors of the 2017 ACC/AHA guidelines, the prevalence of hypertension was expected to increase significantly through these guidelines. However, they claimed that early diagnosing of cardiovascular events may become possible and awareness of hypertension among patients at risk will increase over the course of these individuals' future lives.[10]

In addition to hypertension, conditions of accompanying cardiovascular disease or diabetes, or 10-year risk of developing cardiovascular disease greater than 10%, should be taken into consideration in the management of antihypertensive treatment. The latest (2017) ACC/AHA guidelines have emphasized the importance of home blood pressure monitoring and teamwork in the management of disease.[10] The authors of these new guidelines claimed that, since drug treatment is recommended especially in cases of clinical cardiovascular diseases such as CAD, coronary heart disease (CHD) and stroke, or in cases with a risk of developing cardiovascular disease greater than 10%, in patients with stage 1 blood pressure values (130-139/80-89 mmHg), the new classification will not increase antihypertensive drug use.[2] However, other physicians have contested this assumption.[11]

The new blood pressure classification proposed in the 2017 ACC/AHA guidelines has been adapted to hypertension studies in different countries. Application of the threshold value of 130/80 mmHg to the latest national Chinese research data showed that the hypertension rate rose from 25% to 50%. The proportion of patients requiring medication in the Chinese population was 2.0% in the general population and 5.5% in the geriatric patient population according to the 2017 ACC/AHA guidelines.[12]

Based on the threshold of ≥ 140/90 mmHg, the current prevalence of hypertension in India is approximately 28.9% in both men and women. In the Indian population, in which there are interactions with various social, cultural and economic factors, hypertension management has become quite difficult with the lower blood pressure values that have redefined hypertension in the new 2017 ACC/AHA guidelines.[13] It seems to be taking time in India for implementation of another emphasis of the 2017 ACC/AHA guidelines, i.e. widespread adoption of out-of-office blood pressure measurement, across the country. The current situation in which the vast majority of the cost of medicines in India purchased through personal budgets is refunded also increases concern about the increased risk of antihypertensive drug usage. Moreover, the target values of the Indian hypertension guidelines published in 2013 have not yet been fully met in clinical practice.[14] In this regard, achieving the lower target values of the 2017 ACC/AHA guidelines does not seem applicable to daily practice in India.[15] In a study involving 6106 adults randomized from rural areas of India, a 14% increase in the number of stage 1 hypertension patients was observed, with re-evaluation of 2815 individuals according to the new thresholds.[14,16]

Another factor affecting the international generalizability of the new guidelines, which basically arose from the SPRINT study data, is blood pressure differences based on ethnicity disparities between countries. Since the proportion of East Asian ethnicity in the SPRINT trial was very low (< 2%), it is doubtful whether the results can be generalized to countries like Taiwan.[4]

In our study, the patients who enrolled at the hypertension outpatient clinic were evaluated regarding blood pressure thresholds, using both guidelines separately. From this perspective, the proportion of hypertensive patients increased from 74.5% (2018 ESH/ESC guidelines) to 91.1% (2017 ACC/AHA guidelines) in our patient sample. This increase in the proportion of hypertension diagnoses, of 16.6 percentage points, which was caused by lowering the threshold value to 130/80 mmHg, is quite spectacular. Projection of the new guidelines into various different communities has led to predictions that increases in the numbers of hypertensive patients of 14% in the United States,[10] 25% in China[12] and 14% in rural India[13] will be observed. It has been estimated that the differences in the rates of increase are caused by differences in sample selection, ethnicity and cultural lifestyles.

Another noteworthy point in the present study was that significant associations were detected between the presence of hypertension and the variables of family history of hypertension, obesity and age, according to the 2018 ESH/ESC guidelines. However, no

significant relationship between the presence of hypertension and these variables was observed regarding the 2017 ACC/AHA guidelines, although age and family history of hypertension were close to being significant. The results from this analysis indicate that the demographic and cardiovascular factors that are effective for making the diagnosis of hypertension might vary with the change in hypertension threshold values.

Our study conducted in Turkey can be considered to be a pilot reflecting the thresholds of the new 2017 ACC/AHA guidelines in our society. However, these increased rates of hypertension cannot be generalized to the entire Turkish population because our study had some limitations, including its small sample size and the structure of the outpatient clinic studied, which only serves hypertensive patients. Furthermore, the number of female patients evaluated was higher than the number of male patients.

CONCLUSIONS

The decreases in hypertension threshold values proposed through the 2017 ACC/AHA guidelines have increased the number of patients diagnosed with hypertension worldwide, including in Turkey. This increase was by 16.6 percentage points in our sample.

We consider that updates to the relationship between cardiovascular risk factors and the diagnosis of hypertension through the change in threshold values may come to be presented in the near future, consequent to ongoing studies in various countries worldwide. In the current study, age, obesity and family history of hypertension were significantly associated with the diagnosis of hypertension according to the 2018 ESC guidelines, while no relationship was detected between cardiovascular risk factors and the diagnosis of hypertension using the 2017 ACC guidelines. Studies involving higher numbers of patient samples will be effective in explaining the relationship between these risk factors and the diagnosis of hypertension.

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Use of oral isotretinoin to treat acne in the public system: a hospital-based retrospective cohort

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ABSTRACT

BACKGROUND: Acne needs to be treated early to prevent negative psychosocial impacts. In severe or moderate forms, which tend to leave scars, oral isotretinoin is the first-line therapy. However, concern about its adverse events, especially in developed countries, delays effective treatment. In contrast, isotretinoin is widely prescribed in Brazilian private clinics.

OBJECTIVES: To describe the use of isotretinoin for treating acne in a Brazilian public hospital, and to analyze whether its prescription is effective or belated.

DESIGN AND SETTING: Retrospective cohort study in a public hospital.

METHODS: Clinical and therapeutic data were obtained from the medical records of patients who were undergoing or had undergone acne treatment with isotretinoin in this hospital's general dermatology outpatient clinic over the last seven years, up to April 2018.

RESULTS: 1526 medical records from patients with acne were analyzed. Isotretinoin was prescribed for 279 patients (18.28%) with mild (1.19%), moderate (57.37%), severe (35.85%) or conglobata (5.57%) forms of acne vulgaris. Sequelae of acne were present at the start of most of these patients' treatment. An initial daily dose of 20 mg was usually prescribed. The average initial dose/weight ratio was 0.33 mg/kg/day. The average total dose/weight ratio was 127.61 mg/kg. There were only a few cases of laboratory abnormalities.

CONCLUSION: Sequelae of acne at the onset of treatment reveal delayed indication of isotretinoin, which can have negative psychosocial impacts on quality of life. Isotretinoin should be indicated early to prevent this. Its use is supported by its lack of laboratory alterations and controllable adverse events.

INTRODUCTION

Acne is a chronic and multifactorial disease that involves inflammation of pilosebaceous units.[1] It mostly affects the face, but may also affect the chest and back, and it presents different cutaneous lesions depending on the severity of the disease. It affects 80% to 90% of adolescents, but can occur at any age, and it has negative psychosocial impacts that may be permanent. For this reason, acne needs to be treated as early as possible, and its management should be directed towards prevention of scars.[2,3] Measures such as proper hygiene and sunlight protection form part of the topical and/or systemic therapy for acne, according to the severity of the disease.[4]

For moderate or severe forms of acne that do not respond to conventional therapy, and which tend to leave scars, oral isotretinoin is the first-line therapy. Some authors have stated that isotretinoin should be the first-line drug because of the chronic and unpredictable course of acne.[5] Isotretinoin is a synthetic analogue of vitamin A that acts epigenetically, through inhibiting sebocyte differentiation and sebaceous gland function and modulating toll-like receptors, regeneration and skin repair. It is used in monotherapy and is highly effective, leading to healing or longstanding remission, prevention and reduction of scars.[6]

Despite the high efficacy of isotretinoin, its use can cause some adverse events, which vary according to the daily dose. The most common and controllable are mucocutaneous conditions (cheilitis, xerophthalmia, nasal dryness and irritative dermatitis); elevated liver enzymes and triglycerides; and changes to cholesterol levels (increased low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol). These changes are generally mild and occur early on (after 6 to 8 weeks), and do not have any significant repercussions for the patient's subsequent follow-up. The effects are transient and reversible, and discontinuation of the treatment is only rarely required.[7,8]

Other previously reported adverse events that have been matters of controversy, such as depression, suicidal ideation and inflammatory bowel disease, have not been correlated with use of the drug, but with acne itself and not with any treatment.[9,10] Teratogenicity is the most serious risk, and extreme caution among women of fertile age is required, including repeated dosages of serum beta-HCG and use of two effective contraceptive methods at least.[11]

Concern regarding adverse events and teratogenicity caused by isotretinoin have mainly been raised in developed countries. These matters of controversy, with associated legal issues, have led to limitations on prescription of isotretinoin, thereby delaying effective treatment and contributing towards a situation in which many people continue to bear acne scars and experience negative repercussions on their quality of life. Such situations may be long-standing and even permanent.[12-14]

In contrast, isotretinoin is widely prescribed in Brazil for treating acne.[7,15] In this country, isotretinoin is freely distributed through the National Health System. According to recent research, isotretinoin was the first choice within the private sector in Brazil for treating moderate and severe acne, for which it was indicated by 76.7% and 94.6% of dermatologists, respectively.[15] Nonetheless, although isotretinoin is frequently prescribed within the Brazilian private healthcare sector and freely distributed through the public healthcare sector, there is little information on the timing of its prescription and on its effectiveness.

OBJECTIVE

The aim of this study was to describe the use of isotretinoin for treating acne in a Brazilian public hospital. The possibility of analyzing the efficacy and safety of this drug among a greater number of patients undergoing standardized treatment with adequate follow-up would make it possible to reach a higher level of evidence regarding its use.

METHODS

This was a hospital-based cohort study conducted in a large referral public center in São Paulo, Brazil. Data were obtained from the electronic system of medical records that was implemented in August 2011 in the general outpatient clinic of the Department of Dermatology of Hospital São Paulo. This is a public hospital within the Brazilian National Health System (Sistema Único de Saúde, SUS) and is the teaching hospital of Escola Paulista de Medicina, Universidade Federal de São Paulo.

The medical records of all patients with a diagnosis of acne up to April 2018 were searched. Individuals who were undergoing or had undergone treatment for acne with isotretinoin were selected for analysis. Information on the patients' clinical and sociodemographic characteristics was gathered, including gender, age, weight, severity and location of lesions and presence of scars and/or hyperpigmented sequelae; and on the aspects of their therapeutic plans, including the initial and total daily dose, length of treatment, age at the beginning of treatment, dose modification and symptomatic prescription. Data on adverse events like cheilitis, xerosis, xerophthalmia, nasal dryness, increased liver enzymes, alterations in total cholesterol and fractions and increased triglycerides were also analyzed.

The project was approved by the Research Ethics Committee of Universidade Federal de São Paulo/Hospital São Paulo on December 6, 2017 (CEP 1454/2017; CAAE 80370417.7.0000.5505). Even though this was a retrospective study based on medical records, we attempted to contact the participants to ask them to sign a consent statement. Thus, many participants signed this form, but not all of them could be contacted. Nevertheless, given that all the data were used together and were anonymized, we were able to use the data from all participants without any risk of personal identification.

Descriptive statistics were used to analyze the data, and variables were expressed as absolute numbers and percentage values. Laboratory values for the lipid profile and transaminases were compared with reference parameters adapted from Altman et al., 2002.[30]

RESULTS

In total, 1526 medical records from patients who had been diagnosed with acne were analyzed. Isotretinoin was prescribed for 279 patients (18.28%), of whom 175 (62.72%) were male. Most of them were between 10 and 19 years of age (153; 56.87%) or between 20 and 30 years of age (96; 35.68%). These individuals' acne began during adolescence in 170 cases (91.39%, out of a total of 186 patients for whom this information was available). Although family histories of acne were often poorly documented (only in 82 medical records), these histories were positive in 25 cases (30.4%).

Isotretinoin was indicated for all levels of severity of acne vulgaris: mild (1.19%), moderate (57.37%), severe (35.85%) and conglobata (5.57%). It was also prescribed for acne in adult women in 12 cases. Data about the lesion site was present in 241 medical records. The face was the site most affected, which showed typical lesions in 235 cases (97.51%), which were concomitant to scars in 148 cases (62.97%) and to post-inflammatory hyperpigmentation in 46 cases (19.57%). The chest and back were affected by acne in 90 patients (37.34%) and 146 patients (60.58%), respectively. In total, sequelae of acne (scars and/or hyperpigmentation) were presented at the start of treatment in 77.1% of the patients, regardless of the site.

An initial daily dose of 20 mg of isotretinoin was prescribed for 215 patients (83.98% of the 256 medical records in which this information was available). The average initial dose/weight ratio was 0.33 mg/kg/day. Among the 279 patients for whom isotretinoin was prescribed at the first medical appointment, 257 patients

were followed up subsequently, with further appointments at the outpatient clinic. According to the medical records, most treatments lasted for between 9 and 12 months (57.64%). The average total dose/weight ratio was 127.61 mg/kg.

Mucocutaneous adverse events were the most common type. Most of these patients were given prescriptions for symptomatic treatment, mostly consisting of lip balm and eye drops, together with their prescriptions of isotretinoin. Occurrences of cheilitis were reported in 142 medical records (55.25%), beginning on average after 3.23 months of treatment, with previous prescription of lip balm in 71.12% of these cases. Xerophthalmia was presented by 65 patients (25.29%), starting on average after 4.17 months of therapy, with previous prescription of eye drops in 78.46% of these cases. Presence of xerosis was reported in 40 medical records (15.56%), starting on average after 6.43 months of treatment, with previous prescription of body moisturizer in 10% of these cases. Nasal dryness was the least frequent mucocutaneous event according to the medical records, present in 31 of them (12.06%), beginning on average after 3.93 months of therapy, with previous prescription of nasal saline in 22.58% of these cases.

There were only a few cases of laboratory abnormalities. Regarding the lipid profile, 46 patients (17.89%) reached total cholesterol and/or triglyceride levels above the upper reference limit. Among these, there were some cases with very high values requiring monitoring (9 cases; 3.5%) and one case that would have needed suspension of treatment (0.38%), as specified by Altman et al. (2002).[30] Regarding hepatic transaminase levels, 29 patients (11.28%) reached aspartate transaminase and/or alanine transaminase levels above the upper reference limit. Among these, there were also a few cases with very high values requiring monitoring (22 cases; 8.56%) and 13 cases that would have needed suspension of treatment (5.05%). Regarding the hemogram, there were no cases of leukopenia or thrombocytopenia, and only one case of mild normocytic normochromic anemia (hemoglobin of 11.8 g/dl), which started after six months of treatment and normalized spontaneously within four months, while this patient was still undergoing treatment.

There were also some reports of other adverse events, which happened rarely or without any relationship established with the drug. After two to three months of treatment, a few medical records reported cases of headache (three cases), myalgia (two), arthralgia (two), "visual blackout" (one), pain and edema in lower limbs (one) and dyspnea (one). After four to five months of treatment, there were a few cases of irritability (three cases) and "sadness" (one case). One case of hypochromia of the lips after six months of treatment was reported, and one case of vaginal dryness after 12 months of treatment. Lastly, there were complaints relating to the gastrointestinal tract in a few medical records: constipation (one case), diarrhea (two cases) and dysphagia (two cases).

Dose reduction due to adverse events was only done in the cases of 24 patients (10.76%). The majority of the medical records showed increases in the doses (102 cases; 45.73%) or maintenance of the doses (68 cases; 30.49%). Some patients had their doses reduced for other reasons (29 cases; 13%), mostly in order to prolong the treatment. Suspension of treatment occurred only in 10 cases, due to clinical symptoms (five cases) or laboratory alterations (five cases).

However, most of the clinical symptoms did not have any clear association with isotretinoin: diarrhea (two cases), headache (one case), "visual blackout" (one case, in which there was also a tendency towards elevated lipid profile and a family history of dyslipidemia) and myalgia, low back pain and lower-limb pain (one case). Regarding laboratory alterations, these were four cases with transaminase levels that would imply drug withdrawal, as specified by Altman et al. (2002),[30] i.e. aspartate transaminase > 80 U/l and/or alanine transaminase > 62 U/l. One of these cases just needed close monitoring, and isotretinoin was reintroduced after two weeks of suspension.

DISCUSSION

In comparison with a recent analysis on isotretinoin prescription in Brazilian private clinics, which showed that 76.7% and 94.6% of dermatologists would prescribe the drug in cases of moderate and severe acne respectively,[15] indication of isotretinoin in the public hospital studied here over the period analyzed was only implemented for a small percentage (18.28%) of the patients diagnosed with acne.

This was an unexpected result, since the drug is provided free-of-charge through the Brazilian National Health System and because people who seek care in public hospitals generally present the disease with longer evolution and greater severity, such that isotretinoin would be the first-choice treatment. However, public hospitals are also the first places for treatment sought by people experiencing financial difficulties and social problems, and in those cases, acne may present a mild level of severity according to the perceptions of both the patient and the family. These patients receive topical treatments with or without association with oral antibiotics, which may be enough to properly control the disease.

It should be noted that prescription of topical and oral antibiotics for treating acne has been reviewed. It was concluded that such prescriptions should follow recommendations for limited and rational use, given the increasing degrees of bacterial resistance, which are leading to repercussions regarding upper respiratory infections.[16,17] Furthermore, the existence of wrong and even frightening information about isotretinoin, especially among people with lower education, may interfere with patients' and their families' acceptance of this medication. This would corroborate the low percentage of prescription that was seen in the present study.[18]

Among the patients of the present study, isotretinoin was more prescribed for males, and for adolescents and young adults, and this finding agreed with data in the literature.[15,19] In the vast majority of cases, acne started in adolescence and consisted of acne vulgaris. Unfortunately, only a few of the medical records gave any information about presence or absence of a family history of acne. Investigation of this matter needs to be emphasized in obtaining the anamnesis, because this information is important and can provide evidence of the severity and evolution of acne.[19]

The results regarding types of acne corroborated the data in the literature, since more than 90% of the patients treated with ISO had moderate or severe acne. It was observed that almost all the patients presented acne on the face, and some also on the chest and the back.

Scars were commonly present, and were already visible at the beginning of the treatment, particularly on the face. This revealed that there had been delays in drug indication.[14] Such delays lead to psychosocial repercussions that can be long-lasting and may have a negative impact on these individuals' quality of life. For this reason, emphasis is placed on the importance of early prescription.[4]

Most of the patients undergoing treatment at the outpatient clinic were properly followed up, in accordance with guidelines that have been published since the 1990s.[19,20] This is important, because isotretinoin is a teratogenic drug with possible side effects.[11]

On average, the therapeutic regimens used an initial daily dose of 0.33 mg/kg. The dose most commonly used was 20 mg, which was lower than what is recommended in the package insert, which is 0.5-1.0 mg/kg/day. This dosage level was probably adopted because of the impossibility of monthly follow-up in this public hospital, given the high level of demand for appointments from patients. It is known that a low starting dose prevents the initial exacerbation that occurs in some cases, which scares patients and may cause poor adherence to the treatment.[21] In addition to greater patient adherence, it has been shown in several studies that a low daily dose regimen has the same efficacy, but with fewer adverse events that are dose proportional, and higher satisfaction among the patients.[22-24]

Isotretinoin was well tolerated by many patients, as shown by the gradual increase in the daily dose that they tolerated. For other patients, the dose of 20 mg/day was maintained until the end of treatment, thus extending the duration of the treatment to an average of 9 to 12 months, instead of the 4-6 months, as has been recommended since isotretinoin was introduced in the market, more than 30 years ago.[25] Nevertheless, the total dose was 127.61 mg/kg, which was within the range recommended in the package insert, i.e. 120-150 mg/kg, and also in line with the opinions of some authors like Rademaker[26] and Tan et al.[20]

All the patients who completed the treatment were referred for maintenance treatment, as recommended in the literature. Maintenance treatment using several topical products, except antibiotics, has been recommended for periods of 6 to 12 months after the disease has been resolved.[27,28]

Mucocutaneous adverse events of mild intensity occurred, as expected, and were controllable through symptomatic treatment. This was prescribed at the same time as isotretinoin, for prevention of the most common mucocutaneous adverse events: cheilitis, xerophthalmia, nasal dryness and xerosis. This management approach was fully in accordance with the well-known recommendations.[29] It needs to be borne in mind that appointments were made every three months and, for this reason, the medical records did not precisely define the time at which the symptoms began, which tended to be earlier than what was seen.

There were very few cases of laboratory abnormalities caused by use of isotretinoin, and even fewer cases that required dose reduction or suspension of treatment due to adverse events. The criteria for such decisions were the reference values defined by Altman et al. (2002).[30] These findings are consistent with the data in the recent literature, in which reduced levels of monitoring are recommended, i.e. only for tests that show significant changes, thereby diminishing the associated costs.[8,31-33]

There were no reported cases of depression, suicide or inflammatory bowel disease. This confirmed the findings from population-based studies, which have not shown any association of these diseases with use of isotretinoin.[9,10] It is known that depressive states are related to acne itself,[34] while inflammatory bowel disease is associated with many chronic inflammatory diseases and with use of antibiotics, including those used in treating acne.[35]

The present study had potential limitations. Firstly, it was based on medical records, which are not always filled out in detail. Secondly, it analyzed patients from a single public hospital, which may not have reflected the reality of the public system as a whole. Lastly, since it was a cross-sectional study, no "cause and effect" relationship could be established.

CONCLUSION

The large presence of acne sequelae at the onset of treatment revealed the existence of delayed indication of drug treatment, which may lead to scars and may have a strong negative psychosocial impact on quality of life. The wide indication of isotretinoin for treating moderate forms of acne was an important measure for avoiding this scenario. The results from this study are in agreement with the data from the most recent studies in the literature: low daily dose, total dose according to package insert recommendations, common side effects and laboratory alterations that were few in number, mild and controllable. Further studies like this one are necessary in order to analyze whether recent data on oral isotretinoin therapy for acne has indeed been applied to clinical practice.

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Potential drug interactions in drug therapy prescribed for older adults at hospital discharge: cross-sectional study

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KEY WORDS:
Drug interactions.
Frail elderly.
Patient discharge.
Drug therapy.

ABSTRACT

BACKGROUND: Older adults with a range of comorbidities are often prescribed multiple medications, which favors drug interactions.

OBJECTIVES: To establish the frequency of potential drug interactions in prescriptions at hospital discharge among older adults and to identify the associated factors.

DESIGN AND SETTING: Cross-sectional study conducted in a public hospital.

METHODS: An initial face-to-face interview, data collection from the electronic medical records (covering sociodemographic, clinical, functional and drug therapy-related variables) and telephone follow-up after discharge were conducted to confirm the medication prescribed at discharge. Drug interactions were identified through the Micromedex DrugReax software, along with interactions that should be avoided among the elderly, as per the 2015 American Geriatric Society/Beers criteria. Multivariable logistic regression was performed.

RESULTS: Potential for drug interactions was identified in the discharge drug therapy of 67.8% of the 255 older adults evaluated (n = 172), and 54.5% (n = 145) of the drug interactions were major. Among the drug interactions that should be avoided among older adults, those that increase the risk of falls were the most frequent. The drug interactions thus identified were independently associated with polypharmacy (odds ratio, OR = 12.62; 95% confidence interval, CI 6.25-25.50; P = 0.00), diabetes mellitus (OR = 2.16; 95% CI 1.05-4.44; P = 0.04), hypothyroidism (OR = 7.29; 95% CI 2.03-26.10; P = 0.00), chronic kidney disease (OR = 3.41; 95% CI 1.09-10.64; P = 0.03) and hospitalization in geriatric units (OR = 0.45; 95% CI 0.22-0.89; P = 0.02).

CONCLUSION: The frequency of potential drug interactions in drug therapy prescribed at discharge for these older adults was high. Polypharmacy, diabetes mellitus, hypothyroidism and chronic kidney disease were positively associated with occurrences of drug interactions, while hospitalization in geriatric units showed an inverse association.

INTRODUCTION

The number of older adults in the world is expanding rapidly as a consequence of increased quality of life and technological advances.[1,2] This demographic transition is increasing the prevalence of chronic-degenerative diseases. One of the consequences is higher consumption of medicines, which implies a great challenge for the healthcare system.[3]

Given that use of several drugs is needed to treat the multimorbidity commonly seen in older adults, it can be expected that the prevalence of polypharmacy among older adults and the risk of drug interactions will increase substantially.[4] Drug interactions are a common cause of adverse drug reactions among older adults, and these include arrhythmias, acute kidney injury and increased risk of falls.[5-7] A direct correlation between the number of medications and their interactions and the risk of adverse drug reactions has been shown.[4-7] The reasons for this are multifactorial and particularly include age-related changes in the pharmacodynamics and pharmacokinetics of drugs, reduced renal function and lower hepatic clearance.[6-8]

At hospital discharge, older adults generally present changes to their drug therapy, with higher numbers of prescribed medications, which leads to higher frequency of drug interactions.[8] Thus, it is essential to know the frequency of these interactions at hospital discharge among older people and their determinants, in order to promote safer use of drugs among older adults.

OBJECTIVE

The aims of this study were to determine the frequency of potential drug interactions in the drug therapy prescribed at discharge among older adults and to evaluate the factors associated with this outcome.

METHODS

Study design and setting

This was a cross-sectional study carried out in a public hospital located in southeastern Brazil that is responsible for attending public servants. The hospital provides medium and high-complexity levels of care.

Sample

The sample was non-probabilistic, covering older inpatients admitted from April to November 2017. Age ≥ 60 years was adopted to define older adults, as established by the World Health Organization for developing countries.

Selection criteria

This study included older patients hospitalized in the internal medicine and geriatric units over the period from April 4 to November 1, 2017. All patients who were hospitalized for more than 24 hours during the period of the investigation at the hospital were invited to participate in the research. The exclusion criteria were defined as occurrences of death during hospitalization, hospitalization for more than 60 days, self-discharge from the hospital or loss of contact after discharge.

Data collection and ethics

The patients were identified through the computerized system for hospitalization management of the hospital and were approached in person, in the hospital. All patients or their legal guardians gave their agreement to participate by signing an informed consent statement. This study was approved by the research ethics committee of Universidade Federal de Minas Gerais under the approval number 1.952.130.

An interview was conducted with patients to collect sociodemographic information. Clinical information was collected by consulting the patients' electronic medical record. The interviews and data collection were performed by a pharmacist researcher and recorded in the structured form. The pharmacist researcher also made a telephone follow-up within 48 hours after discharge in order to confirm which medications had been prescribed. The medications prescribed were registered on the structured form.

The dependent variable was the presence of potential drug interactions between the drugs prescribed at hospital discharge, using the data collected from the medical records and the confirmations from the telephone interviews. These potential drug interactions were identified using the IBM Micromedex DrugReax software,[9] considering the medications prescribed at discharge and confirmed during the telephone contact. DrugReax presents adequate sensitivity and specificity for identifying drug interactions within older adults' drug therapy.[10]

Drug interactions were classified regarding their severity, adopting the DrugReax specifications: contraindicated (when the medications are contraindicated for concomitant use); major (when the interaction may be life-threatening for the patient and requires immediate medical intervention); or moderate (when the interaction may result in exacerbation of the patient's clinical condition or require a change of therapy).[9] This investigation did not include the interactions defined by DrugReax as minor (when the interaction may have limited clinical effects without requiring drug therapy changes) or unknown effects (when the level of severity of the interaction is undefined).[9]

The dose of acetylsalicylic acid (ASA) was observed for the purpose of identifying the interactions involving this drug. For specific interactions involving ASA, the clinical management section of the DrugReax software informs whether this occurs with doses used for analgesia and antipyresis (> 300 mg) or doses used for antiplatelet effect (70-300 mg).[9] Furthermore, the frequency of potential clinically-relevant drug interactions with non-anti-infective agents that should be avoided among the older adults, as per the 2015 American Geriatric Society (AGS)/Beers criteria,[11] was established.

The demographic, clinical, functional and drug therapy-related independent variables of these older individuals were collected through interviews conducted during their hospitalization. These data were complemented through a search in each patient's medical records.

Presence of polypharmacy was defined as use of five or more medications. Admission diagnoses were classified in accordance with the International Classification of Diseases, 10th edition (ICD-10).[12] The patients were assessed using the Charlson Comorbidity Index (CCI).[13] The complexity of the drug treatment regimen prescribed at discharge was determined by calculating the Medication Regimen Complexity Index (MRCI), using the Brazilian version.[14] The drug therapy complexity was stratified as high (MRCI value > 16.5) or not high (MRCI ≤ 16.5), as per the MRCI standardization proposed for Brazilian older adults.[1] The patients' vulnerability was evaluated by means of the Vulnerable Elders Survey-13 tool (VES-13).[16]

Statistical analysis

The data collected were double-entered into a dataset elaborated in EpiData 3.1. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 25.0 software.

Absolute and relative frequencies were determined for dichotomous variables, and numerical variables were described in terms of their mean (with standard deviation, SD) or median (with interquartile range, IQR). The Shapiro-Wilk test was used to assess whether the data presented normal distribution. Numerical variables were dichotomized using the median. Associations between independent variables and occurrences of drug interactions were

evaluated using the chi-square test and Fisher's exact test, with due regard to the premises of each test.

The level of statistical significance of the study was considered to be $P < 0.05$. Variables with $P < 0.20$ in univariate analysis were included in the multivariate analysis through the logistic regression model. The forward stepwise method was used to obtain the final model, and variables presenting $P < 0.05$ were kept in the model. The goodness of fit of the final model was evaluated using the Hosmer-Lemeshow test, such that $P > 0.05$ was considered to indicate good logistic regression model fit.

RESULTS

In total, 300 older adults were interviewed. Among these, 27 (9%) died during hospitalization, one (0.3%) self-discharged from the hospital, one (0.3%) was transferred to another hospital and three (1%) were excluded due to prolonged hospitalization, since the duration of data collection was limited. Out of the 268 elderly subjects who were discharged, 13 (4.3%) were subsequently lost to contact. Thus, 255 older people were included in this study **(Figure 1)**.

The sample had a median age of 75 years (IQR 13.0) and consisted mostly of women (57.3%). The median score in the Charlson Comorbidity Index was 5.0 (IQR 2.0), and the median score in the Vulnerable Elders Survey-13 (VES-13) was 5.0 (IQR 6.0).

Among the participating older adults, 158 (62.0%) were hospitalized in the internal medicine unit and 97 (38.0%) in the geriatric unit. The median length of hospital stay was 12 days (IQR 10). The most frequent admission diagnoses were respiratory system diseases (64; 25.1%), genitourinary system diseases (43; 16.9%) and circulatory system diseases (30; 11.8%). The most frequent comorbidities among the elderly subjects were arterial hypertension (n = 181; 71.0%), diabetes mellitus (DM) (n = 110; 43.1%) and pneumonia (n = 53; 8%).

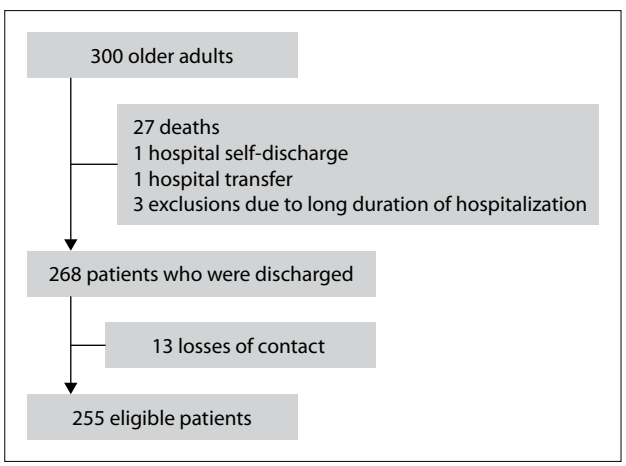

Figure 1. Study flowchart.

The frequency of polypharmacy was 68.2%, and the number of medications used by these older adults was higher after discharge (median = 6.0; IQR 4.0) than the total number of medications used before admission (median = 5.0; IQR 5.0). Potential drug interactions were identified in 173 patients (67.8%), with a median of six interactions per older adult (IQR = 4; minimum = 1, maximum = 15) (**Table 1**).

Overall, 266 types of potential drug interactions were observed, of which 145 (54.5%) were classified as major, 116 (43.6%) as moderate and five (1.9%) as contraindicated. The most frequent major

Table 1. Sociodemographic, clinical and drug therapy-related characteristics of the sample of 255 older adults

Characteristics	Value (%)
Sociodemographic characteristics	
Age in years, median (IQR)	75 (13)
Female gender, n (%)	146 (57.3)
Clinical characteristics	
VES-13 score, median (IQR)	5 (6.0)
Charlson Comorbidity Index, median (IQR)	5 (2.0)
Internal medicine unit, n (%)	158 (62.0)
Geriatrics unit, n (%)	97 (38.0)
Length of hospital stay, median (IQR)	12 (10)
Functional characteristics	
VES-13 score, median (IQR)	5 (6.0)
Admission diagnoses, n (%)	
Respiratory system diseases	64 (25.1)
Genitourinary system diseases	43 (16.9)
Circulatory system diseases	30 (11.8)
Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified in ICD-10 codes R00-R99	25 (9.8)
Some infectious and parasitic diseases	21 (8.2)
Digestive system diseases	18 (7.1)
Mental and behavioral disorders	14 (5.5)
Endocrine, nutritional and metabolic diseases	11 (4.3)
Other*	40 (15.6)
Comorbidities, n (%)	
Arterial hypertension	181 (70.9)
Diabetes	110 (43.1)
Pneumonia	53 (20.8)
Chronic renal failure	45 (17.6)
Hypothyroidism	43 (16.9)
Heart failure	38 (14.9)
Drug therapy-related characteristics	
Polypharmacy, n (%)	174 (68.2)
Number of medicines used after discharge, median (IQR)	6 (4.0)
Number of medicines used before admission, median (IQR)	5 (5.0)
Patients with interactions, n (%)	173 (67.8)
Number of interactions per patient, median (IQR)	6 (4.0)
Number of interactions per patient, minimum-maximum	1 (15)

ICD-10 = International Classification of Diseases, tenth edition; * = Sum of low-frequency admission diagnoses found in the study but not included in the other categories shown in this table; IQR = interquartile range; VES-13 = Vulnerable Elders Survey 13: individuals with scores ≥ 3 were 4.2 times more likely to be at risk of functional decline within two years, compared with individuals with lower scores.[16]

interaction in this study was between amlodipine and simvastatin, which was identified in 16 (6.3%) of all the prescriptions. The ten most frequent major drug interactions and their clinical effects, as per DrugReax, are shown in **Table 2**.

The most common moderate interaction was between insulin and losartan, which was observed in the drug therapy prescribed for 17 patients (6.7%). The most common moderate interactions identified in this study and their clinical consequences, as per DrugReax, are shown in **Table 2**.

Five types of contraindicated drug interactions were identified, from which the most frequent clinical effects were increased risk of QT prolonged interval (fluconazole plus salmeterol; and domperidone plus fluconazole), followed by increased risk of extrapyramidal reactions (bromopride plus venlafaxine) and increased risk of myopathy and rhabdomyolysis (ketoconazole plus simvastatin; and clarithromycin plus simvastatin).

Drug interactions that increase the risk of falls and fractures were the most frequent (n = 4) among those that should be avoided among older adults, as per the 2015 AGS/Beers criteria. Among the older people investigated here, three presented potential drug interactions between opioid receptor agonist analgesics and two or more drugs acting on the central nervous system (CNS). The potential drug interactions identified in this study, which should be avoided among older adults, as per the 2015 AGS/Beers criteria, are described in **Table 3**.

Table 4 shows the results from the univariate and multivariate analyses on the factors associated with occurrences of drug interactions. In the univariate analyses, statistically significant associations were found between drug interactions and polypharmacy (P = 0.00)

Table 2. Description of major and moderate drug interactions with frequencies higher than four in the drug therapy prescribed at hospital discharge among the 255 elderly subjects, and their clinical effects

Drug interactions	Clinical effects	Absolute frequencies	Relative frequencies (%)
Major			
Amlodipine + simvastatin	Increased risk of myopathy, including rhabdomyolysis	16	6.3
Codeine + ondansetron	Increased risk of serotonergic syndrome	5	2.0
Clopidogrel + omeprazole	Reduced platelet antiaggregant activity	5	2.0
Allopurinol + enalapril	Hypersensitivity reactions	5	2.0
Simvastatin + warfarin	Increased risk of bleeding, including rhabdomyolysis	4	1.6
Simvastatin + diltiazem	Increased risk of myopathy, including rhabdomyolysis	4	1.6
Risperidone + simvastatin	Increased risk of myopathy, including rhabdomyolysis	4	1.6
Donepezil + quetiapine	Increased risk of prolonged QT interval	4	1.6
Clonazepam + tramadol	Increased risk of depression of the CNS	4	1.6
Ciprofloxacin + insulin	Glycemic alterations	4	1.6
Moderate			
Insulin + losartan	Increased risk of hypoglycemia	17	6.7
Insulin + metformin	Increased risk of hypoglycemia	16	6.3
Enalapril + metformin	Increased risk of hypoglycemia	15	5.9
Levothyroxine + omeprazole	Reduced effectiveness of levothyroxine	14	5.5
Enalapril + insulin	Increased risk of hypoglycemia	14	5.5
Levothyroxine + simvastatin	Reduced effectiveness of levothyroxine	12	4.7
Carvedilol + insulin	Glycemic alterations; reduced hypoglycemic symptoms	11	4.3
Atenolol + metformin	Glycemic alterations; reduced hypoglycemic symptoms	11	4.3
Carvedilol + metformin	Glycemic alterations; reduced hypoglycemic symptoms	7	2.7
Captopril + hydrochlorothiazide	Hypotension risk	6	2.3
Atorvastatin + clopidogrel	Reduced effectiveness of clopidogrel	6	2.3
Enalapril + hydrochlorothiazide	Hypotension risk	5	2.0
Enalapril + furosemide	Orthostatic hypotension	5	2.0
Captopril + insulin	Increased risk of hypoglycemia	5	2.0
Atenolol + insulin	Glycemic alterations; reduced hypoglycemic symptoms	5	2.0
Ferrous sulfate + omeprazole	Reduced iron bioavailability	4	1.6
Ferrous sulfate + levothyroxine	Reduced levothyroxine serum levels	4	1.6
Levothyroxine + pantoprazole	Reduced effectiveness of levothyroxine	4	1.6
Atenolol + warfarin	Increased prothrombin time or INR	4	1.6

CNS = central nervous system; INR = international normalized ratio.

Table 3. Description of drug interactions that should be avoided among older adults, as per the 2015 American Geriatric Society (AGS)/ Beers criteria, in the drug therapy prescribed for older adults at hospital discharge

Object drug and class	Interacting drug and class	Absolute frequency	Risk rationale
Benzodiazepines	**≥ 2 medications that act on the CNS**		
Clonazepam	Tramadol + quetiapine	1	Increased risk of falls and fractures
Opioid receptor agonist analgesic	**≥ 2 medications that act on the CNS**		
Tramadol	Clonazepam + sertraline		
Codeine	Quetiapine + sertraline	3	Increased risk of falls
Methadone	Haloperidol + lorazepam		
Peripheral alpha-1 blocker	**Loop diuretics**		
Doxazosin	Furosemide	1	Increased risk of urinary incontinence in women
	NSAIDs		
Warfarin	Nimesulide	1	Increased risk of bleeding

CNS = central nervous system; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 4. Univariate and multivariate analyses on factors associated with occurrences of drug interactions in the drug therapy prescribed for 255 older adults at hospital discharge

Description	Interactions		Univariate analysis		Multivariate analysis	
	Frequency					
Variable	Yes n (%)	No n (%)	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Sociodemographic characteristics						
Gender						
Female	103 (59.5%)	43 (52.4%)	1.33 (0.79-2.26)	0.28		
Male	70 (40.5%)	39 (45.6%)	1			
Age						
≥75	91 (52.6%)	49 (59.8%)	0.75 (0.44-1.27)	0.28		
<75	82 (47.4%)	33 (40.2 %)	1			
Clinical characteristics						
Geriatric unit						
Yes	58 (33.5%)	39 (47.6%)	0.56 (0.32-0.95)	0.03*	0.45 (0.22-0.89)	0.02
No	115 (66.5%)	43 (52.4%)	1		1	
Stroke						
Yes	26 (15.0%)	11 (13.4%)	1.14 (0.53-2.44)	0.73		
No	147 (85.0%)	71 (86.6%)	1			
Heart failure						
Yes	35 (20.2%)	3 (3.7%)	6.68 (1.99-22.42)	0.00*		
No	138 (79.8%)	79 (96.3%)	1			
COPD						
Yes	25 (14.5%)	9 (11.0%)	1.37 (0.61-3.09)	0.45		
No	148 (85.5%)	73 (89.0%)	1			
Cancer						
Yes	18 (10.4%)	11 (13.4%)	0.75 (0.34-1.67)	0.48		
No	155 (89.6%)	71 (86.6%)	1			
Diabetes mellitus						
Yes	90 (52.0%)	20 (24.4%)	3.36 (1.87-6.04)	0.00*	2.16 (1.05-4.44)	0.04
No	83 (48.0%)	62 (75.6%)	1		1	
Pneumonia						
Yes	32 (18.5%)	21 (25.6%)	0.66 (0.35-1.23)	0.19*		
No	141 (81.5%)	61 (74.4%)	1			
Dementia						
Yes	50 (28.9%)	29 (35.4%)	0.74 (0.42-1.30)	0.30		
No	123 (71.1%)	53 (64.6%)	1			

Continue...

Table 4. Continuation

Description	Interactions		Univariate analysis		Multivariate analysis	
	Frequency					
Variable	Yes n (%)	No n (%)	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Hypothyroidism						
Yes	39 (22.5%)	4 (4.9%)	5.67 (1.95-16.48)	0.00*	7.29 (2.03-26.10)	0.00
No	134 (77.5%)	78 (95.1%)	1		1	
Chronic kidney disease						
Yes	40 (23.1%)	5 (6.1%)	4.63 (1.75-12.23)	0.00*	3.41 (1.09-10.64)	0.03
No	133 (76.9%)	77 (93.9%)	1		1	
Peripheral vascular disease						
Yes	9 (5.2%)	7 (8.5%)	0.59 (0.21-1.64)	0.30		
No	164 (94.8%)	75 (91.5%)	1			
Asthma						
Yes	3 (1.7%)	0 (0.0%)	1.48 (1.36-1.61)	0.55**		
No	170 (98.3%)	82 (100.0%)	1			
Arterial hypertension						
Yes	131 (75.7%)	50 (61.0%)	1.99 (1.14-3.51)	0.01*		
No	42 (24.3%)	32 (39.0%)	1			
Acute myocardial infarction						
Yes	16 (9.2%)	3 (3.7%)	2.68 (0.76-9.48)	0.11*		
No	157 (90.8%)	79 (96.3%)	1			
Depression						
Yes	36 (20.8%)	10 (12.2%)	1.89 (0.89-4.03)	0.09		
No	137 (79.2%)	72 (87.8%)	1			
Functional characteristics						
VES-13 median						
≥ 5	90 (52.0%)	46 (56.1%)	0.85 (0.50-1.44)	0.54		
< 5	83 (48.0%)	36 (43.9%)	1			
Drug therapy-related characteristics						
Polypharmacy with 5 drugs						
Yes	149 (86.1%)	25 (30.5%)	14.15 (7.48-26.79)	0.00*	12.62 (6.25-25.50)	0.00
No	24 (13.9%)	57(69.5%)	1		1	
MRCI index						
Yes	117 (67.6%)	16 (19.5%)	8.62 (4.58-16.22)	0.00*		
No	56 (32.4%)	66 (80.5%)	1			

*P-value < 0.2: variable selected for the multivariate logistic regression; **P-value was calculated using Fisher's exact test; Hosmer-Lemeshow test: chi-square = 4.958; degrees of freedom = 7; P = 0.665.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; VES-13 = Vulnerable Elders Survey-13; MRCI = Medication Regimen Complexity Index.

and between drug interactions and high drug therapy complexity index (P = 0.00). In the multivariate analysis, the factors that remained associated with drug interactions were polypharmacy (odds ratio, OR = 12.62; 95% confidence interval, CI 6.25-25.50; P = 0.00), diabetes mellitus (OR = 2.16; 95% CI 1.05-4.44; P = 0.04), hypothyroidism (OR = 7.29; 95% CI 2.03-26.10; P = 0.00), chronic kidney disease (OR = 3.41; 95% CI 1.09-10.64; P = 0.03) and hospitalization in geriatric units (OR = 0.45; 95% CI 0.22-0.89; P = 0.02).

DISCUSSION

This study showed that potential drug interactions occurred very frequently in the drug therapy that was prescribed for older adults at discharge from hospital. This result is compatible with the findings from previous studies involving older patients at hospital discharge, which also showed high prevalence of drug interactions in this setting.[17,18] The number of drugs prescribed was significantly associated with the number of drug interactions. Patients with diabetes mellitus, hypothyroidism or chronic kidney disease (CKD) also had more drug interactions than did those with other comorbidities. The frequency of drug interactions was lower among the older adults who had been hospitalized in the geriatric unit.

High prevalence (54.5%) of major drug interactions was observed in this study. These can potentially increase the risks

of cardiotoxicity, bleeding, rhabdomyolysis and hypoglycemia, which may compromise the functionality and quality of life of older people.[9] As shown in previous studies, high frequency of potentially harmful drug interactions at hospital discharge was noted. Angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, beta-blockers, antiplatelet agents, antidiabetics and oral anticoagulants were the drugs most involved in these interactions.[18,19]

Among the most common major drug interactions, the interaction between amlodipine and simvastatin was most prevalent. This drug interaction may increase the risks of rhabdomyolysis and myopathy.[20,21] Combined therapies between statins and other cardiovascular medications are common, and the potential for significant drug interactions needs to be borne in mind, since such interactions increase the exposure to statins and, consequently, elevate the risk of myopathy.[20-22]

High prevalence of drug interactions with medications of the ACE inhibitor class was frequently observed in this study. Changes to renal function relating to aging increase the susceptibility of older adults to the nephrotoxic effects of ACE inhibitors, especially if administered with other medications. A prospective study in which the aim was to identify current drug-drug interaction (DDI) that resulted in adverse drug reactions among older patients within 30 days of discharge from an internal medicine clinic found that older adult patients who had been prescribed furosemide and ACE inhibitors presented asymptomatic elevated serum creatinine during the treatment and underwent dose adjustment of ACE inhibitors and diuretics.[18]

Studies on older patients receiving outpatient treatment have also identified high prevalence of concomitant use of ACE inhibitors and diuretics for blood pressure control.[23,24] Despite the greater effectiveness of this combination of antihypertensives, the combination of these medications increases the risk of orthostatic hypotension, especially among older people, with a risk of injury due to falls.[25]

In a study conducted in the south of Brazil, the frequency with which patients used antidiabetics and antihypertensives was high,[26] due to high prevalence of diabetes mellitus and arterial hypertension. While some interactions with antidiabetics are desirable and promote glycemic control in patients with diabetes, continuous blood glucose measurement should be performed to ensure that hypoglycemia does not occur in older adults.[26] Hypoglycemic events among the elderly are associated with worsened cognitive decline and increased frequency of cardiovascular events. Furthermore, sarcopenia, peripheral neuropathy, dysautonomia and reduced visual acuity among older people elevate the risk and severity of falls, favored by episodic hypoglycemic events.[27]

Among the drugs for which concomitant prescriptions are contraindicated, those that had the clinical effect of increasing the risk of prolonged QT interval were observed more frequently. Among the risk factors for this event were female sex, aging and a combination of drugs that alone prolong the QT interval or increase the likelihood of this event through inhibiting drug metabolism. This prolongation may trigger the onset of ventricular arrhythmias and result in sudden death, which highlights the importance of avoiding drug interactions that expose older adults to higher risk of prolonging the QT interval and the importance of monitoring patients in cases in which such combinations are necessary.[25]

One innovative approach in the present study comprised identification of drug interactions that should be avoided among older people, as per the 2015 AGS/Beers criteria. The recommendations of these criteria stem from observation that these interactions are highly associated with clinically relevant adverse events among older adults.[11]

Associations that elevated the risk of falls were most frequent. Besides the clinical consequences, such as increased morbidity and mortality, falls among older people lead to social, economic and psychological harm, thereby increasing dependence and institutionalization.[28] An ecological study on fall-related admission and mortality rates among older adults showed that the mortality and hospitalization rates due to falls were higher among older people in Brazil. This emphasizes that use of three or more drugs acting on the central nervous system should be avoided in the geriatric population.[29]

Occurrences of drug interactions were positively associated with the number of drugs used, which was in line with other published studies.[30,31] A retrospective study in which the trends and determinants of polypharmacy among patients discharged from an internal medicine unit in a teaching hospital were measured showed that the risk factors for polypharmacy were age older than 75 years, high CCI and multiple morbidities.[17] The presence of multiple morbidities in older adults favors prescription of several medications. Moreover, the widespread reality is that doctors do not have access to all the medicines that their patients are already using. This favors prescription of a more significant number of medications and highlights the importance of drug therapy reconciliation during the transition of care from the hospital setting to the patient's home.[25]

In addition to polypharmacy, the multivariate analysis identified that the factors relating to higher frequencies of drug interactions were diabetes mellitus, hypothyroidism and CKD. Regarding glycemic control among patients with diabetes, prescription of oral antidiabetics such as metformin, with or without associated prescription of insulin, may be necessary to improve the effectiveness of treatment. This may favor drug interactions among older adults, since the present study showed that metformin and insulin are medications often associated with potential drug interactions. Also, diabetes in older people is usually accompanied by cardiovascular

complications and other comorbidities.[27,32] Therefore, in this population, use of five or more medications is frequent and enables drug interactions.[32]

Regarding hypothyroidism, it is known that thyroid-related diseases are highly prevalent and occur more frequently among older women.[33] The treatment indicated for this condition is based on replacement doses of levothyroxine sodium, a medication for which bioavailability is modified by drug interactions with ferrous sulfate and proton pump inhibitors.[34] This may explain the positive association between hypothyroidism and drug interactions among the older adults investigated here.

Furthermore, it was observed that the elderly individuals with CKD had higher numbers of drug interactions. Patients with this disease are at high risk of metabolic and cardiovascular complications and, consequently, require use of polypharmacy, which is one of the factors involved in occurrences of drug interactions.[35]

Lastly, it was observed that hospitalization in the geriatric unit gave rise to lower likelihood of drug interactions at hospital discharge. Older individuals have particular health characteristics and specific medical needs that are more likely to be taken into consideration by geriatricians, who have specialized knowledge and skills. Geriatricians have greater awareness of the risks of adverse drug events among older adults and, therefore, during hospitalization. They can streamline the drug therapy strategy, including deprescription of medications, which may contribute towards lower levels of interactions.[36]

Given the high frequency of drug interactions and polypharmacy, there is an evident need for an approach that ensures safe drug therapy for older adults at discharge from hospital. The strategies that might be involved include analysis of the dose used, consideration of possible therapeutic alternatives and patient monitoring, along with the structuring of a multidisciplinary team composed of a geriatrician, a clinical pharmacist and a nurse.[4,26] Interventions conducted by pharmacists within this practical setting, such as drug therapy reviews and actions planned with the prescriber, may reduce the number of older patients with clinically-relevant drug interactions.[5]

The strength of the present study lay in its use of software with sensitivity and specificity that were suitable for identifying drug interactions among older adults. However, this study had significant limitations. First, the sample was non-probabilistic, which may have compromised the external validity of the results found. Second, the study was conducted in a hospital that is not part of the Brazilian National Health System (Sistema Único de Saúde, SUS) and thus may not reflect the reality of most older people in Brazil. Also, this study focused on potential drug interactions and did not identify interactions with clinical manifestations. Furthermore, the durations of treatments were not considered in identifying drug interactions. Therefore, the frequency of drug interactions may have been overestimated, since some of these interactions need mechanisms for enzyme induction and inhibition that are time-dependent.

CONCLUSIONS

The frequency of potential drug interactions in the drug therapy prescribed to these older adults at discharge from hospital was high. Polypharmacy, diabetes mellitus, hypothyroidism and chronic kidney disease were positively associated with occurrences of potential drug interactions, and admission to a geriatric unit was inversely associated with such occurrences.

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Relationship between seasons and pregnancy rates during intrauterine insemination. A historical cohort

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Circadian rhythm.
Ovulation induction.
Pregnancy.
Melatonin.

ABSTRACT

BACKGROUND: The underlying cause of seasonal infertility in humans is unclear, but is likely to be multifactorial.

OBJECTIVE: The aim of our study was to compare the pregnancy rates among infertile women who underwent induced ovulation and intrauterine insemination (IUI) with the season in which the fertility treatment was performed.

DESIGN AND SETTING: This retrospective cohort study was conducted on 466 patients who were treated in the reproductive endocrinology and infertility outpatient clinic of a tertiary-level women's healthcare and maternity hospital.

METHODS: Retrospective demographic, hormonal and ultrasonographic data were obtained from the patients' medical records. Clomiphene citrate or gonadotropin medications were used for induced ovulation. The patients were divided into four groups according to the season (spring, winter, autumn and summer) in which fertility treatment was received. Clinical pregnancy rates were calculated and compared between these four groups.

RESULTS: There were no significant differences between the seasonal groups in terms of age, infertility type, ovarian reserve tests, duration of infertility, medications used or length of stimulation. A total of 337 patients (72.3%) were treated with clomiphene citrate and 129 (27.7%) with gonadotropin; no significant difference between these two groups was observed. The clinical pregnancy rates for the spring, winter, autumn and summer groups were 15.6% (n = 24), 8.6% (n = 9), 11.5% (n = 13) and 7.4% (n = 7), respectively (P = 0.174).

CONCLUSIONS: Although the spring group had the highest pregnancy rate, the rates of successful IUI did not differ significantly between the seasonal groups.

INTRODUCTION

Many environmental factors influence human fertility outcomes. Although extensive research has shown that mammalian fertility is influenced by seasonal changes, few studies have specifically evaluated seasonal effects on the human reproductive system.[1] Seasonal infertility may be due to physiological changes that are season-dependent. It was previously shown that season-dependent high environmental temperatures negatively affect sexual function and nutrient intake.[2-4] Conversely, a five-year study conducted in France, in which the effect of the photoperiod on seasonal infertility was examined, demonstrated that seasonal infertility was independent of environmental temperatures.[5]

Melatonin affects several daily and seasonal rhythms, such as endocrine signaling during both circadian time and daytime. Melatonin concentrations follow different circadian rhythm in different living things. Nighttime exposure to light inhibits melatonin synthesis and secretion in both animal models[6] and humans.[7] Serum levels of melatonin are affected by the complex interaction of daily rhythm, exogenous factors and endogenous factors. Melatonin receptors have been identified in human reproductive tissues.[8]

Melatonin plays a major role in reproductive activity and blastocyst implantation. It is transferred maternally to the fetus via the placenta or milk, during pregnancy and lactation, respectively, thus indicating that the maternal photoperiod is transferred to the fetus.[9] In addition, it has been shown that melatonin causes seasonal changes relating to fertilization, embryo quality, sperm concentration and chromatin condensation rates.[10] The impact of melatonin on reproductive function in women has been demonstrated in studies that showed that high levels of

melatonin cause amenorrhea, which leads to decreased secretion of gonadotropin and prolactin in response to the photoperiod.[11]

Several retrospective studies have evaluated the impact of seasonal variation on in vitro fertilization outcomes. Some of these studies considered climatic conditions, especially temperature and the number of hours of daylight.[12] However, few studies have evaluated seasonal effects on pregnancy rates among human patients undergoing intrauterine insemination (IUI).[13,14] Seasonality of infertility treatment may alter reproductive performance; and therefore, the timing of infertility treatment may result in improved pregnancy rates.

OBJECTIVE

This study compared pregnancy rates during different seasons in which fertility treatments were performed, in order to investigate whether seasonal variations were associated with pregnancy outcomes among infertile women who underwent induced ovulation and IUI.

METHODS

Study design, settings and ethics

A retrospective cohort study based on medical records was conducted among infertile women who underwent induced ovulation with IUI treatment at Dr. Zekai Tahir Burak Women's Health Education and Research Hospital between May 2013 and June 2015. Informed consent was not obtained from the participants because of the retrospective study design. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by this hospital's Institutional Review Board (date: May 27, 2015; decision no. 19).

All consecutive infertile couples who met the inclusion criteria during the study period of two years were recruited for this study. All the study participants met the following criteria: < 41 years of age; normal hysterosalpingography (HSG) and/or laparoscopy findings; regular menstrual cycles with normal baseline levels of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin and thyroid-stimulating hormone (TSH); normal spermiogram parameters in the husband (according to the World Health Organization's 2010 criteria);[15] and serum progesterone levels > 5 ng/ml during the midluteal phase. Couples with poor ovarian reserve, endometriosis, tubal or uterine factors, male infertility or systemic disorders such as thyroid disease or diabetes mellitus were excluded from the study.

Patients undergoing treatments (both induced ovulation and IUI) that were performed in one season were included in the study. When a treatment (induced ovulation or IUI) overlapped with the previous or next season, the patient was excluded from the study.

This study was conducted in Ankara (latitude: 32.87° N, longitude: 39.87° E; altitude: 891 m). Ankara has a continental climate, which means that it has cold, snowy winters and hot, dry summers. Rainfall is mostly seen during the spring and autumn months. During the 24-month study period, the average seasonal air temperatures were 22.3 °C in the summer, 12.9 °C in the autumn, 1.4 °C in the winter, and 11.0 °C in the spring.[16]

Demographic, hormonal and ultrasonographic data relating to the patients were copied from the patients' files and the hospital's electronic database. The patients were divided into spring, winter, autumn and summer groups.

Fertility treatments

Patients with unexplained or anovulatory infertility were first treated with clomiphene citrate. Women who received clomiphene citrate treatment but were unable to conceive were next treated with gonadotropin. Patients who declined clomiphene citrate treatment, were over the age of 35 years or had experienced infertility over a relatively long period of time (greater than or equal to three years) directly received gonadotropin treatment as the initial treatment. Induced ovulation was planned together with administration of clomiphene citrate (50-150 mg/day, orally) or gonadotropin (37.5-150 IU of pure FSH or human menopausal gonadotropin, HMG), starting on day 2 or day 3 of the menstrual cycle.

Follicular development was monitored by means of transvaginal ultrasound on days 2-3 (baseline) and then on either day 8 of the gonadotropin cycle or day 12 of the clomiphene citrate cycle. Subsequent monitoring was performed until the follicular diameter reached 18 to 20 mm, and then a 250-mcg dose of recombinant human chorionic gonadotropin (rHCG) was administered subcutaneously.

The patients underwent a serum pregnancy test on day 14 following IUI. Clinical pregnancy was defined as the presence of a gestational sac with an accompanying fetal heartbeat detected by means of ultrasound, at least five weeks after IUI.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences 15.0 (SPSS, Chicago, IL, USA) for Windows. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation (SD). Intragroup differences were investigated using one-way analysis of variance (ANOVA). Categorical variables were expressed as the number (with percentage). Differences between data categories were evaluated using the chi-square or Fisher's exact test. Statistical significance was assumed based on a probability of 0.05.

The sample size calculation was performed using the DSS statistical software package for research sample size calculations.[17] The primary aim of this study was to compare the differences in

clinical pregnancy rate between the seasons. It was calculated that a minimum of 80 participants in each group would be required to demonstrate a difference of at least 10% between the groups, with a power of 80% at the 5% significance level. This difference of 10% was taken both from a pilot study[14] and from our clinical experiments.

RESULTS

A total of 466 women were enrolled in the study. The study participants were divided into four groups according to the season in which induced ovulation and IUI treatment were received. The spring, winter, autumn and summer groups contained 154, 105, 113 and 94 patients, respectively. No significant differences were observed between the groups in terms of age, primary infertility rate, baseline hormone levels, antral follicle count or duration of infertility (P > 0.05). The cycle characteristics, including the induced ovulation treatment protocol and duration of stimulation, were also similar among the groups (**Table 1**).

A total of 337 patients were treated with clomiphene citrate and 129 patients were treated with gonadotropin. There was no significant difference among the initial indications for gonadotropin. The number of patients who received clomiphene citrate treatment was 105 in the spring (68.2%), 77 in the winter (73.3%), 84 in the autumn (74.3%) and 71 in the summer (75.5%). The number of patients who received gonadotropin treatment was 49 in the spring (31.8%), 28 in the winter (26.7%), 29 in the autumn (25.7%) and 23 in the summer (24.5%).

The peak E2 level was highest in the autumn (924.29 ± 712.02 pg/ml) and was lowest in the summer (629.09 ± 432.74 pg/ml). The endometrial thickness on the HCG day and the duration of stimulation (days) were similar in the four seasons (P = 0.084).

The overall clinical pregnancy rate was 11.4% in this cohort. The pregnancy rates in the spring, winter, autumn and summer groups were 15.6%, 8.6%, 11.5% and 7.4%, respectively (P > 0.05). Although the clinical pregnancy rate was highest in the spring season, there was no significant difference between the seasons.

DISCUSSION

In this study, we aimed to investigate the seasonal variations of IUI success. To the best of our knowledge, this was the first study to analyze the seasonal variations of pregnancy rates following IUI in Turkey. Women were evaluated over a period of more than 24 months in this study. Regardless of whether the analysis compared all couples, age, day-3 FSH, duration of infertility (years) or duration of stimulation (days), the endometrial thickness on the HCG day (in mm) was not altered by seasonal effects. Although the clinical pregnancy rate among infertile couples varied according to the season, especially in the spring (15.6%), no statistically significant differences between the seasons were observed.

The seasonal effect on mammalian reproduction has long been known. Several studies have shown that hot weather reduces sperm quality and fertility rates.[18-20] These effects have been also associated with melatonin production and secretion.[7] Melatonin concentration shows a distinctive circadian rhythm in all species. Daily changes in the synthesis of melatonin are regulated by the ambient light-dark cycle. Light provides strong synchronization of the rhythms of the suprachiasmatic nuclei.[21]

The field of metabolomics or metabolic profiling investigates the connections between melatonin, circadian rhythm, sleep and metabolism.[22,23] Declines in reproductive capacity due to seasonal infertility have been observed in the United States[24] and in Germany.[25] Further studies with large numbers of participants are needed in order to evaluate the role of melatonin rhythm and amplitude in human metabolism, and such evaluations may reveal new perspectives regarding the physiological role of melatonin.

Table 1. Baseline, laboratory and clinical parameters of all seasonal groups

Season		Spring group (n = 154)	Winter group (n = 105)	Autumn group (n = 113)	Summer group (n = 94)	P
Age (years)		27.18 ± 4.54	26.41 ± 4.88	26.97 ± 4.89	27.23 ± 5.17	0.575*
Basal FSH (IU/ml)		6.64 ± 1.86	6.69 ± 2.23	6.65 ± 2.01	6.33 ± 1.79	0.541*
Basal E_2 (pg/ml)		41.78 ± 12.99	39.79 ± 15.47	39.91 ± 20.58	43.31 ± 18.55	0.747*
Duration of infertility (years)		4.02 ± 2.74	3.51 ± 2.19	3.49 ±1.80	3.32 ± 1.94	0.078*
Antral follicle count		9.41 ± 2.51	10.32 ± 5.18	9.53 ± 2.36	9.85 ± 2.20	0.301*
Duration of stimulation (days)		12.23 ± 1.55	12.10 ± 1.34	12.18 ± 1.33	12.03 ± 1.37	0.707*
Stimulation protocol	CC (%)	105 (68.2)	77 (73.3)	84 (74.3)	71 (75.5)	0.559**
	Gonadotropin (%)	49 (31.8)	28 (26.7)	29 (25.7)	23 (24.5)	
Peak E_2 (pg/ml)		699.37 ± 556.73	740.88 ± 564.30	924.29 ± 712.02	629.09 ± 432.74	0.274*
Endometrial thickness on HCG day (mm)		8.46 ± 1.06	8.88 ± 1.74	8.44 ± 2.09	8.78 ± 1.99	0.084*
Clinical pregnancy rate (%)		24 (15.6)	9 (8.6)	13 (11.5)	7 (7.4)	0.174***

FSH = follicle stimulating hormone; E_2 = estradiol; CC = clomiphene citrate; HCG = human chorionic gonadotropin.
P-values of less than 0.05 were considered statistically significant.
*Analysis of variance (ANOVA); **Chi-square test; ***Fisher's exact test.

Seasonal infertility has been correlated with a number of environmental factors, including the photoperiod. Although the photoperiod plays a role in seasonal infertility, high temperatures may also cause direct or cumulative adverse effects on fertility.[5] High temperatures above the thermo-neutral zone have been shown to reduce birth rates and delay the onset of puberty.[26] It has been suggested that heat stress is a probable factor in the development of seasonal infertility[27] and that this negatively affects embryo development.[28] Heat shock proteins, which appear in response to heat stress,[29] are found in the ovaries.[30] It has been shown that hyperthermia affects developing oocytes.

In a study by Palacios, the pregnancy rate after artificial insemination of dairy sheep was significantly affected by seasonal meteorological variables.[31] In that study, winter was the season with the lowest percentage for overall fertility (42.4%), and this was significantly different ($P < 0.001$) from spring (45.4%), summer (45.6%) and autumn (46.0%). Successful inseminations were performed at significantly lower maximum temperatures in the summer.

Santolaria et al. investigated the pregnancy rates among sheep at the same latitude (41° N) between July and October. They examined the period from 12 days before insemination to 14 days after insemination and found that the pregnancy rate was lower when the temperature was above 30 °C, over a two-day period before insemination.[32]

In another study, Hashem et al. detected the presence of relativity of the estrous phase. They found that efficient fertile mating was positively correlated with high temperature and a long photoperiod (summer season conditions), while it was negatively correlated with rainfall (winter season condition) in Egypt.[33]

However, we did not find any significant difference in relation to seasonal changes. On the other hand, we did not measure temperature, weather or daily exposure to light.

The relationship between birth, fertility and seasonal change is unclear. Roenneberg and Aschoff[34] defined a circadian rhythm that changed over time for birth rates around the world. Pregnancy rates in relation to seasonal fecundability were also analyzed in their study. They hypothesized that the biological rhythm of conception is influenced by social or by environmental factors. Their conclusion was that although conception and birth rhythms vary from country to country, these rhythms have changed their characteristics recently, after having remained stable for more than a century.

The limiting feature of our study was that we did not know the exact meteorological data and temperatures. The sleep patterns and stress levels, which may have been affected by melatonin, were unknown. In addition, changes to people's lifestyles are increasing, as an inevitable consequence of modern life. Today, people live in houses with a constant temperature, are exposed to artificial light instead of sunlight and come into less and less contact with the external environment. All of these factors may lead to lower but more stable reproductive performance, through elimination of the confounding effects of environmental conditions.

CONCLUSION

Although we found a higher pregnancy rate among women undergoing infertility treatment during the spring season, we did not detect that seasonal variation had any statistically significant influence on the success of IUI. New studies with higher power may find a significant difference between the outcomes from infertility treatment and seasonal changes. In this regard, further large-scale studies are required, in order to better evaluate the effects of seasonal variability on pregnancy.

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Antimicrobial resistance and a diminishing pool of reserved antibiotics

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Dear Editor,

During the second half of the nineteenth century, infectious diseases were a prominent cause of morbidity and mortality. Almost one-third of the infants in the United States and Western Europe were unable to reach their first birthday due to causes attributable to infectious diseases.[1]

Antibiotics have played a significant role in saving patients' lives through prevention and treatment of complicated infections, such as their use after the surgical procedures of joint replacement, organ transplantation or cardiac surgery. In fact, in areas of poor sanitation, antibiotics have also helped in lowering the morbidity and mortality associated with food-borne diseases.

However, through overuse of antibiotics, inappropriate use, self-medication, lack of adherence and inappropriate prescribing, the phenomenon of antibiotic resistance has rapidly spread from healthcare settings to the community worldwide.[2] With the passage of time, the concept of multidrug-resistant (MDR) bacterial strains has emerged and, as a result, antibiotics have lost their efficacy. This has further progressed towards extended hospitalization, complications, massive costs and an upswing in morbidity and mortality.[3]

Currently, antimicrobial resistance (AMR) is one of the major public health challenges across the globe. If the process of drug resistance does not become controlled smartly, it is estimated that mortality attributable to antimicrobial resistance will exceed 10 million deaths annually by 2050, compared with current estimates of 0.7 million deaths. In other words, one person will die every three seconds due to a resistant organism. Excessive and irrational use of antibiotics in the community and in healthcare settings is one of the key factors that promote drug resistance.[4]

Entry to the post-antibiotic era, i.e. the time when most antibiotics will have become ineffective due to development of resistance against them, requires serious measures with the capacity to tackle this global issue in the form of collaborative effort. The Lancet Infectious Diseases Commission and the World Health Organization (WHO) have emphasized the need for a common approach to help developing countries improve their use of antibiotics through stewardship and education, and also through the requirement to develop national action plans for antimicrobial resistance. The Antimicrobial Stewardship Program (ASP) has been described by the Society of Healthcare Epidemiology of America and the Infectious Diseases Society of America as "a multidisciplinary approach by a team consisting of infectious disease clinicians, pharmacists, microbiologists, hospital epidemiologists and infection preventionists".[5] This stewardship can be divided into core and additional elements. Its core elements comprise various activities such as pre-authorization and formulary restriction, feedback and prospective audit, whereas its additional elements include development of evidence-based guidelines, education, antimicrobial ordering forms, optimization of doses by means of de-escalation and parenteral-to-oral conversions of antimicrobials (where required).

For limited-resource settings, the easiest way to start containment of antimicrobial resistance through the Antimicrobial Stewardship Program is to conduct surveillance of antibiotic use that initially targets the WATCH group (antibiotics that are recommended for specific indications and are at greater risk of becoming ineffective due to development of resistance against them) and the RESERVE group (antibiotics that are lifesaving last lines of defense, which include medicines

like intravenous fosfomycin and colistin). This can be followed by interventions to contain any inappropriate use through education, restrictions and raised public health awareness.

Thus, through following these steps, the diminishing pool of reserve antibiotics can be safeguarded for the coming generations around the world.

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What would be a trigger tool with better performance for detecting drug-induced hyperkalemia?

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Dear Editor,

A trigger tool is defined as an occurrence (flag or prompt) that is easily recognized in the medical record and can alert the healthcare professional to the potential for an adverse drug event (ADE) that may not have been identified.[1] This technique has proved to be more practical and less laborious for detecting ADEs[2,3] than has retrospective analysis of medical records, which is more expensive and requires more time.[4]

In 2003, the Institute for Healthcare Improvement (IHI) suggested 24 trigger tools for detecting ADEs.[2] Among these, we highlight sodium polystyrene (SPS), which is an ion-exchange resin that is used to treat hyperkalemia. It is sometimes used with sorbitol, an osmotic laxative that prevents constipation.[5]

Prescription of SPS may indicate (or "flag") drug-induced hyperkalemia or renal impairment.[2] Therefore, SPS can be applied as a trigger tool to detect drug-induced harm. Presence of two out of three triggers screened through use of SPS is considered to represent the existence of definite or probable ADEs, thus making SPS a trigger tool with good performance.[6]

A systematic review identified 23 therapies used in management of hyperkalemia, other than SPS.[7] However, it was not possible to establish which therapy was the most effective and safest because of the poor quality of the studies included. In addition, there is no consensus about what serum potassium concentration is considered to represent hyperkalemia.[7]

Thus, the guidelines available for management of hyperkalemia are based on clinical experiences and practices, and on off-label use of drugs. Screening for cases of drug-induced hyperkalemia by means of serum potassium concentration can thus increase the rate of ADE reporting.

Furthermore, although SPS is standardized and available in most hospitals (given its low cost), use of SPS is questionable because of the risk of intestinal necrosis, among other serious gastrointestinal events.[7] For this reason, use of SPS is increasingly being replaced by use of new potassium binders (patiromer and zirconium), which potentially have safer profiles than that of SPS.[8]

Hence, the physician's choice of drug will depend on the patient's clinical evaluation and on the safety profile of the therapies available in the healthcare services. For example, furosemide might also be a trigger for screening for drug-induced hyperkalemia since the guidelines consider it to be an option for decreasing serum potassium concentrations. Despite the off-label use, furosemide enables identification of errors or near misses. However, it cannot improve underreporting.

In this context, we consider that the serum potassium level is a more sensitive trigger tool than SPS, because using serum potassium levels as a trigger can decrease the underreporting of drug-induced hyperkalemia and increase the prevention and resolution of possible medication problems. In neonatal clinics, for instance, monitoring of serum potassium levels was found to yield performance of 100% in screening for ADEs.[9]

However, we would expect lower specificity for ADE screening in comparison with potassium binders, in the presence of clinical conditions such as renal impairment or heart failure that are considered to be confounding variables and which could lead to hyperkalemia. Similar reasoning should be applied to the serum creatinine trigger (> 1.2 mg/dl), for which specificity is only 10%, because of confounding variables such as renal failure, which decrease its performance.[6]

Therefore, further studies are needed in order to compare the performance of serum potassium levels as a trigger. Additionally, knowledge of confounding variables would enable optimization of the screening and analysis of causality.

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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

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São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

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The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

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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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.

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;
4. a brief description of the contributorship of each author;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

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

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

Trial and systematic review registration policy

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

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

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]

Short communications

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

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

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

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

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the

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

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
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9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

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

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
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References

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

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

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

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

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

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

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

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

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

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

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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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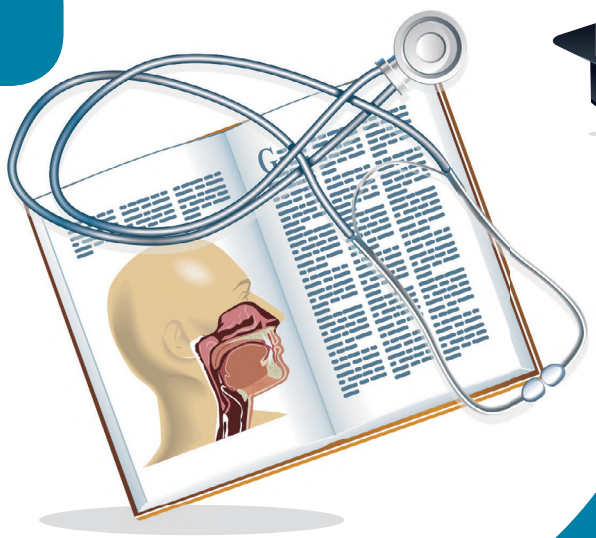

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