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COVID-19: the virus in the control of culture?

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Much has been written and published about COVID-19. There are more than 5,000 works within the past 3 months, varying in themes like etiology, diagnosis, treatment and prognosis, with many more still to be published[1-15].

There are countless estimates and predictions on viral progression, whether related to the doubling rate (e.g. 2.5 times per patient), multiplication factors (e.g. 23), indirect calculations based on mortality (e.g. 1%), or even the association of all these factors, leading to corrections in the number of reported cases in the order of 6, up to 80 times, called by some as optimistic or pessimistic.

The equal adjustment of lethality and mortality rates has occupied the time of many mathematicians, statisticians, epidemiologists and health professionals, in an attempt to contribute to decision making of the system.

There're several discussions about horizontal or vertical lockdowns, social distancing (varying from 1 to 7.5 meters), types of masks for asymptomatic patients (cloth, medical or surgical), masks for sick patients (medical or surgical), and morbidities that increase the risk of severity.

It has been discussed which individual protection materials health professionals should use (e.g., N95 masks), and regarding the hospital care process, which structural changes are necessary, due to the increased demand in the Intensive Care Unit (ICU) and hospitalization of patients with COVID-19.

We have heard national and global reports on the difficulty of processing diagnostic tests (e.g. RT-PCR) to effectively identify cases, leading to a point where, most emergency services do not investigate patients with mild symptoms of upper respiratory infection, advising them to return if symptoms worsen. Thus, the identification of COVID-19 cases has been done superficially and is limited to symptomatic cases with signs of severity.

Most global health systems have been overloaded with an unmanageable overflow, creating direct impact on mortality, while feeding into a cycle that impedes the possibility of any organized action in order to administer the local epidemic.

In the search for treatment many opted in, dropped out, opted in again, and dropped out once more, within just a few weeks, as part of an endless and exhausting media dance, whose main objective is clearly the search for solutions; but perhaps desperate and oftenly irresponsible, producing more damage than benefit.

To make matters worse, patients with other "non-COVID" diseases have been naturally neglected, allowing their conditions to unjustly aggravate, consequently increasing the systems inefficiency and amount of damage.

These negative experiences are striking, and invariably make us forget about successful initiatives (as such seen in South Korea), holding our attention to an indifferent view: "The same will inevitably happen here"; or perhaps romantic: "Let's go resist this small microorganism, we are bigger than THAT".

Up to this point in our reflection, you must be thinking: "I know all of this, and not just me, but everyone knows all of it. What's the point? What's the matter in here? Am I reading yet another article that says a lot but makes no recommendations? Is this article an end in itself?

You are almost right. In fact, our approach here focuses on three (3) slightly more critical aspects and, therefore, may (or may not) be considered in our decision-making strategies:

1. Epidemics are not controlled acutely and exclusively by cultural changes. Those "without knowledge" or perhaps "without appropriate education" should not hold themselves responsible for the consequences, without the opportunity and time to learn in advance. This is like an aggressive agent (in this case, the virus) who blames the victim (patient) for its consequences (death) in themselves (population). To the least, this is an unjust concept – characteristic of an impotent and incompetent system – which should be educating, protecting and caring for those under one's responsibility;

2. Sick cases (asymptomatic or not) should not be broken down into home "clusters", and here is a natural and non-medical example: this is like dividing the sections in a wildfire into small new sections, which will expand into new fires, and so on. Wildfire is fought with a holistic approach, by locating the focal points, working your way in until the fire sections are extinguished – because you can hide the cases, but you cannot hide the deaths. The inter-cluster transmission is reduced, but the intra-cluster transmission will continue to feed in new cases. The attitude to wait and see what happens without any scientific strategy, is easy, and again transfers the responsibility to the patient in solving the problem;

3. The third aspect relates to the absurd and again unjust attribution of responsibility to "those who must work" and "not just to support" controlling the spread, without minimum working conditions, whether structural or human. Doctors and healthcare professionals, generically called the workforce and front-lines, have been neglected, exploited, humiliated, scrapped and devalued in the last 30 years! There's no need for "panels", "clapping" or "homage" to deliver the function they have always fulfilled, regardless of disrespect or lack of adequate resources for their livelihood. Not to mention, these workers when contaminated or sick, make it difficult to manage their condition, participating involuntarily in the transmission by going to work without testing, diagnosis and care.

Our epidemic companion, the virus, has no conscience, and doesn't even know what it's doing. Its survival is blind and programmed. It ignores all the technology, modern/expensive drugs produced by a selfish and profit-centered industry, who pressures and breaks the health system with ridiculous benefits and assumed damage. Those who are needed most at the moment show their inefficiency to act against a known – over 20 years – "little" agent, which is the cause of so many deaths and suffering.

The "mea culpa" has no use in proposing solutions, but it is fundamental because it establishes memory and responsibilities, alleviating the weight on a population that despite resilient is still vulnerable.

WHAT ARE THE SOLUTIONS?

1. Locate the "little guy" in individuals (at least symptomatic) and their contacts, individually isolating them;

2. Mapping and monitoring cases at the local level, and not at the national level, which is politically and mathematically pointless;

3. Appropriately assisting serious cases so that they feel cared for. Only then, can we attribute outcomes to the "little guy";

4. Investing in the ethical generation of centralized and multicentric scientific evidence, by restraining repeated and self-centered disaggregated efforts;

5. Taking advantage of the opportunity to educate the population, in an understanding and kind manner – at the same time rigorous and adamant – through the reinforcement of democratic thinking, where not everything is allowed when considering others;

6. Seeking equity in a fragmented and inequitable health system, using as a model the private assistance system;

7. Finally, although we know that we're not in control of life, remember that everyone has a role in this process, including the virus. The latter, however, cannot be in control, and its high time that those with responsibility showed that they are the ones in control.

Times passing by, and together the consequences may be – or already are – greater or lesser depending on future decisions.

It is critical to stop investing in a denial strategy, (which only aspires pity from those who know science), and prompt despair in those who don't.

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Happiness and satisfaction with life: potential social indicators for periodic measurement in Brasil?

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Dear Editor,

In essence, all human beings are in pursuit of happiness, a multidimensional and complex construct that is the result of individual subjective experiences[1]. Thus, it is challenging to compare data on happiness and its multidimensional measures between different cultures and specific populations[1]. Studies on happiness have gained increasing attention, not only from researchers but also in journalistic and political debates since happiness indices are also used as indicators of economic growth and social development and are already included in public policies in several countries[2].

The Sustainable Development Solutions Network, linked to the United Nations (UN), has been publishing since 2013, the global happiness ranking called the *World Happiness Report*. It is based on how happy people feel, but it also estimates how much of this happiness is influenced by the Gross Domestic Product (GDP) *per capita*, public policies, life expectancy, generosity, levels of corruption, and individual freedom[2]. Among a total of 156 countries, Brasil ranked in the 22nd, 28th, and 32nd positions in 2017, 2018, and 2019, respectively. The best ranking was recorded in 2014, in the 17th position[2]. Thus, Brasil still does not feature among the countries with the highest levels of happiness, indicating a potential for improving the planning and development of public policies geared to this purpose[2].

Our research group on Quality of Life has assessed happiness and satisfaction with life indices among health professionals, students, chronic patients, and their caregivers. Recently, we evaluated

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TABLE 1. AVERAGES OF HAPPINESS AND SATISFACTION WITH LIFE BASED ON THE HUMAN DEVELOPMENT INDEX (HDI) AND SOCIAL VULNERABILITY INDEX (SVI) IN THE CITIES IN WHICH THE PARTICIPANTS LIVED

Variable	HDI and SVI	Mean (SD)	Median (Minimum/Maximum)	p-value
Happine[ssa]	HDI			0.076
	Very low/Low	7.50 (2.12)	8.18 (2.18- 10.00)	
	Medium	7.18 (1.79)	7.55 (2.00- 10.00)	
	High	6.91 (2.01)	7.45 (0.09- 10.00)	
	Very high	7.12 (1.82)	7.64 (0.18- 10.00)	
	SVI			0.392
	Very low	7.08 (1.89)	7.55 (0.27- 10.00)	
	Low	6.99 (1.94)	7.55 (0.09- 10.00)	
	Medium	6.85 (2.05)	7.27 (0.64- 10.00)	
	High/Very high	7.22 (2.11)	8.00 (2.18- 10.00)	
Satisfaction with life[b]	HDI			0.759
	Very low/Low	25.26 (6.64)	25.00 (13.00- 35.00)	
	Medium	24.32 (6.65)	26.00 (7.00- 35.00)	
	High	24.65 (6.75)	26.00 (5.00- 35.00)	
	Very high	24.91 (6.64)	26.00 (5.00- 35.00)	
	SVI			0.004
	Very low	25.55 (6.51)	27.00 (5.00- 35.00)	
	Low	24.63 (6.71)	26.00 (5.00- 35.00)	
	Medium	23.76 (6.93)	25.00 (5.00- 35.00)	
	High/Very high	24.17 (6.39)	25.00 (7.00- 34.00)	

a Assessed based on the Pemberton Happiness Index (PHI). **b** Assessed based on the Satisfaction With Life Scale (SWLS). Human Development Index (HDI): Very low: 0.000 – 0.499/Low: 0.500 – 0.599/Medium: 0.600 – 0.699/High: 0.700 – 0.799/Very high: 0.800 – 1.000. Social Vulnerability Index (SVI): Very low: 0.000 – 0.199/Low: 0.200 – 0.299/ Medium: 0.300– 0.399/High: 0.400 – 0.499/Very high: 0.500 – 1.000.

the happiness and satisfaction with life indices in a sample of the general Brazilian population that uses social media. To do that, participants responded to the Pemberton Happiness Index (PHI) and the Satisfaction With Life Scale (SWLS), duly validated for use in Portuguese/Brasil[3]. We identified that out of the 2,151 participants, 1,311 (60.9%) considered themselves happy. There was no difference between the North (63.2% [95% CI:56-70]), Northeast (62.1% [95% CI:56-68]) and Central-West (60.4% [95% CI:53-68]) regions or in relation to the others regions. However, although the analyses included only users of social media, the results showed that residents of the South region (66.9% [95% CI:63-71]) reported being happier than those in the Southeast (56.9% [95% CI:54-60]). The South of Brasil, which historically was influenced by European colonization, had already previously presented, in other studies, above-average indices of happiness[4,5].

Most participants lived in municipalities with high human development index scores (HDI; n=1361; 63.3%) and low social vulnerability indexes (SVI; n=1,373; 63.8%). The municipalities' HDI scores had no influence on the averages of happiness and satisfaction with life; however, participants were less satisfied in cities with higher SVI (Table 1).

The SVI evaluates the absence or deficiency of resources essential for the well-being and quality of life of the population, characterizing, thus, situations of social vulnerability; the higher the index, the greater the vulnerability. In 2010, the Brazilian SVI was 0.326, and it decreased to 0.243 (in 2014) and 0.248 (in 2015)[6].

The publications of the results from this study could stimulate managers to optimize public policies appropriate to the reality of each area, large or small, in order to benefit the quality of life and, consequently, the more vulnerable populations' satisfaction with life. Furthermore, we believe that measurements of happiness and the constructs involved in it should be considered potential social indicators for periodic assessment in our country.

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Severe amitriptyline poisoning treated successfully with combined hemoperfusion and hemodialysis

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Dear Editor,

We read with great interest the review by Camargo et al.[1] and the study by Günalay et al.[2] in which they summarize that the clinical presentations of uremic neuropathy are broad and non-specific and that malnutrition is associated with quality of life in hemodialysis and peritoneal dialysis patients. Their opinion was helpful for clinical work.

In our clinical study, a 15-year-old male patient that progressed to coma and limb convulsion due to a one-time oral administration of 100 amitriptyline tablets (25mg/ tablet) was enrolled in our hospital. The patient's family found and sent him to the local county hospital for treatment 6 hours after the onset. Since 6 hours had already gone by, the county hospital did not perform gastric lavage, but direct hemoperfusion treatment, rehydration, anti-epilepsy, awakening, and other treatments. After treatment for 2 days, the conscious state and convulsive state of the patient had not improved, so he was transferred to the emergency ICU of our hospital. The patient was GCS6, with bilateral pupil diameter of about 4.0 mm, slow light reflexes, paroxysmal, limb tics last about 3 minutes each time, fever of 38.5°C, electrocardiogram, sinus tachycardia, BP 120/80 mmHg, blood gas analysis: PH 7.40, PCO2 34.20 mmHg and PO2 103.00 mmHg, cLac1.30 / L, ABE - 2.90, HCO3 - 20.70 / L, liver and kidney function of electrolyte in the normal range. After admission, continuous gastrointestinal decompression and about 300ml of pale dark green gastric material were immediately obtained, and filtrate from the German multifil rate and HP330 perfusion apparatus were used to maintain CRRT after two hours of perfusion and CVVH mode. After 6 hours, hemoperfusion performed again, and phenobarbital antiepileptic therapy administered at the same time. After 12 hours of treatment, the pupil diameter of the patient was restored to 3.0mm,

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and the patient became sensitive to light relaxation. After 24 hours, the consciousness of the patient was restored, and he was able to ask and answer questions and follow instructions to shake hands; limb convulsions did not occur again. The patient was conscious 48 hours later and with a GCS14 score.The patient was transferred out of the EICU after 4 days of treatment and discharged 7 days later. When discharged from the hospital, he had clear consciousness, could answer questions accurately, had a GCS515 score, and stable vital signs.

In conclusion, various blood purification models have been reported to be effective treatments[3]. Although there is a lack of large sample data analysis to support it, blood purification therapy, especially hemoperfusion therapy, should be used as early as possible.

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Do erection-inducing drugs increase the incidence of sexually transmitted diseases among the elderly?

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It is estimated that 22% of the world population will be 60 years old or older by the year 2050[1]. This increase in the population of seniors is attributed to improvements to sanitary conditions, changes in lifestyle (regular physical activity and adequate eating habits), and advances in medicine, including vaccines and antibiotics[2].

Both the libido and desire to maintain sexual relations diminish with age due to the reduction in testosterone levels. Nonetheless, evidence suggests that despite a reduction in the frequency of sexual activity, older adults continue to have a sexual interest and/or be sexually active at an advanced age[3]. Although the rate of sexually transmitted diseases (STDs) is lower among seniors than younger individuals, the prevalence of some diseases, including HIV, has increased in this group[3]. Thus, this population is not free from the risk of STDs but should also not be deprived of sources of pleasures, health, and wellbeing[4].

Epidemiological data show an increase in the incidence of STDs among seniors, especially those with low levels of schooling[5]. For example, the prevalence of acquired immunodeficiency syndrome (AIDS) increased from 7.5% per 100,000 seniors in 1998 para 9.4% in 2010[4]. These data reflect an increase in the practice of unprotected sex in this population, which is the main transmission cause for STDs in all age groups[5]. This may be due to the fact that STD prevention campaigns are mainly directed at young people[5], and there is a reduction in the use of condoms with age[6].

Reluctance to use condoms may be associated with a lack of awareness regarding the importance of the protection measure, embarrassment when purchasing the product, a lack of knowledge on how to use it, fear of not being able to maintain an erection, an erroneous notion that it only serves to avoid pregnancy, and a difficulty in negotiating non-use with one's partner[4].

The advent of oral medications for the treatment of erectile dysfunction (ED), such as sildenafil (Viagra), which was approved in the 1990s, assisted middle-aged men and seniors in overcoming ED, which is highly prevalent in this population, affecting 40% of men between 57 and 85 years of age. Such medications

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have been prescribed to more than 16 million individuals worldwide since they first came onto the market[6,7].

One study found an association between the use of sildenafil and an increase in risky sexual behavior[6], reporting that users of this medication are twofold more likely to be diagnosed with HIV, and those who are HIV positive are more likely to be diagnosed with gonorrhea, chlamydia, or syphilis[7].

As public health campaigns addressing SDTs are generally directed at the younger population, despite the growing evidence demonstrating that these diseases are a concern for patients of all ages[3], educational programs should be implemented for health professionals, offering specific medical training for the needs of seniors[3] and raising awareness regarding the use of condoms and its association with STDs, especially when taking medication for erectile dysfunction.

Conflicts of interest

The authors declare there are no conflicts of interest associated with this publication.

Author's contribution

AFAQ, BE, LCFS, FNFJ - Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval.

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Hysterosalpingography: Balloon Catheter or Metal Cannula?

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

INTRODUCTION

Hysterosalpingography (HSG) is a traditional method widely used in basic infertility diagnostic assessment. Tubular factors alone account for 14% of subfertility causes. HSG is recommended to assess fallopian tube permeability in the absence of comorbidities. Compared with laparoscopy, it is less invasive and has a lower cost. Hysteroscopy is recognized as the gold standard exam to identify uterine abnormalities because it allows direct visualization of the uterine cavity.

HSG defines the contour and the size of the uterine cavity, cervical canal, and allows the visualization of the bilateral tube filling. Unfortunately, HSG is widely known as a painful procedure, with pain affecting all women who undergo the procedure. Recent studies have reported several techniques developed to improve not only the quality of the uterine cavity and tubal passage imaging but also patient comfort.

Several balloon catheters, vacuum cannulas, and traditional metal cannulas have bee compared to determine the best procedure for patients.

OBJECTIVE

The goal of this assessment is to compare the metal cannula routinely used in clinical practice with the hysterosalpingography intrauterine balloon catheter as a possible alternate device.

METHODS

The clinical question is: "Is the use of a hysterosalpingography (HSG) intrauterine balloon catheter safe and effective in comparison with a metal cannula?"

The eligibility criteria for the studies are:

1. Adult patients with an indication for hysterosalpingography.

2. Use of a balloon catheter compared to a metal cannula.

3. Outcomes: pain during the procedure, complication rates, and reinsertion.

4. Intermediate outcomes such as satisfaction with the treatment, fluoroscopy time, and volume of contrast were excluded.

5. Randomized clinical trial.

6. No time or language restrictions.

7. Full text available for access.

The search for evidence was conducted in two virtual databases of scientific information: Medline, using the following as search strategy: Hysterosalpingography AND (Balloon Catheter) AND (metal cannula OR Metals); and Central (Cochrane), with a search for Hysterosalpingography AND (Balloon Catheter) AND (metal cannula).

We extracted the following data from the studies: name of the author and year of publication, study population, intervention and comparison methods, the absolute number of adverse events, average pain score (SD), and follow-up time.

Randomized clinical trials had their risk of biases analyzed according to the following criteria: randomization, blinded allocation, double-blinding, losses, prognostic characteristics, presence of relevant outcome, time for the outcome, the method for outcome measurement, sample size calculation, early interruption, presence of other biases.

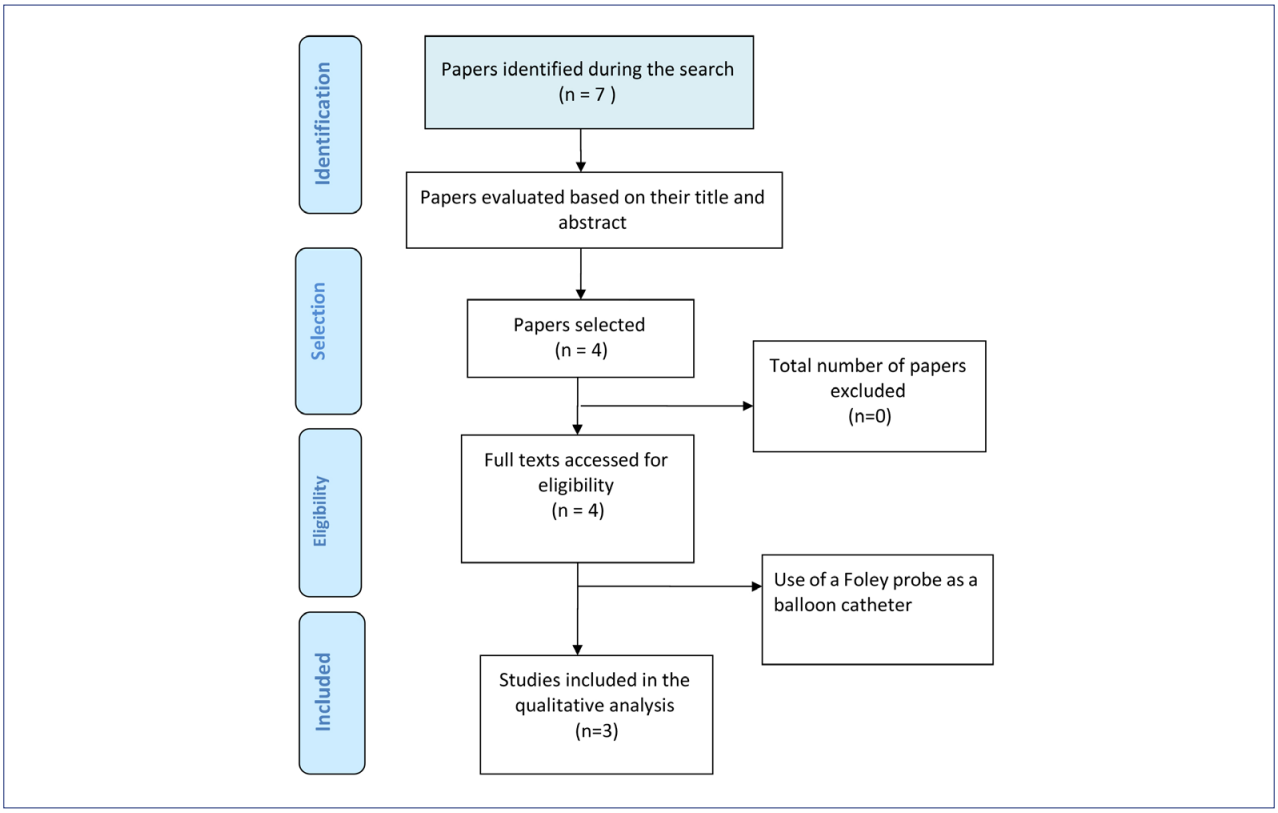
The results were expressed by the difference in the risk of adverse events and the difference in the mean pain score between the balloon catheter and the metal cannula for HSG. The confidence level adopted was 95%.

Furthermore, the quality of evidence was graded as strong, moderate, low, or very low using the Grade instrument[1] and taking into account the risk of bias, the presence of inconsistency, imprecision, or indirect evidence in the outcomes of pain reduction and adverse events, and the presence of publication bias.

RESULTS

The search for evidence retrieved seven studies, of which four were selected based on their titles and abstracts comparing balloon-catheter *versus* metal cannula in HSG. Since all four met the eligibility criteria, their full texts were accessed for analysis. Of the four studies selected to support this assessment, only three were included since one of them used a Foley catheter as the balloon catheter(Figure 1).

FIGURE 1. THE SELECTION OF RETRIEVED FROM THE VIRTUAL DATABASES OF SCIENTIFIC INFORMATION IS DETAILED IN THE FLOWCHART BELOW:



The population included comprises 258 patients who underwent HSG for evaluation of tubal permeability, without anesthetic block, using a balloon catheter (N=143) or metal cannula (N=115) and followed-up to measure the outcome of pain during the procedure or up to one hour after it and adverse events (Table 1).

Regarding the risk of biases of the three studies included, only one describes the randomization and allocation process; none of them is double-blind, and only one calculated the sample size; thus, the overall risk of the studies can be considered moderate (Table 2).

Two studies[3.4] assessed the pain during the procedure, but one of them[3] does not report the standard deviation, which prevents the pooling of results. These two studies also assessed pain during the injection of contrast medium, using different measures (VAS scores and percentage of patients in pain, uncomfortable, or without pain), making grouping impossible. (Table 3 and 4)

All three studies[2-4] included in this evaluation show a reduction of pain during the procedure with the use of a balloon catheter in comparison with the metal cannula. One of them shows that this reduction was maintained until one hour after the HSG[2]. The most frequent adverse events were nausea and need for reapplication and both were reduced with the use of a balloon catheter. However, there was no statistical difference regarding reapplication in comparison[2].

TABLE 1. HYSTEROSALPINGOGRAPHY - BALLOON CATHETER VS. METAL CANNULA – DESCRIPTION OF THE STUDIES INCLUDED.

STUDY	POPULATION	INTERVENTION (N)	COMPARISON (N)	TIME
Kiykac Altinbas S, 2015	HSG	Balloon catheter (83)	Metal cannula (85)	During and 1 hour after the procedure
de Mello JF Sr, 2006	HSG	Balloon catheter (30)	1. Metal cannula without anesthesia (30) 2. Metal cannula with paracervical block anesthesia (29) -Not compared in this assessment	During and immediately after the procedure
Tur-Kaspa I, 1998	HSG	Balloon catheter (30)	Metal cannula (31)	During and immediately after the procedure

TABLE 2. HSG - BALLOON CATHETER VS. METAL CANNULA – RISK OF BIASES OF THE STUDIES INCLUDED

STUDY	RANDOM	ALLOCATION	BLINDED	LOSSES	PROGNOSIS.	OUTCOME	SAMPLE	ITT	EARLY I.
Kiykac Altinbas S, 2015									
de Mello JF Sr, 2006									
Tur-Kaspa I, 1998									

(orange = presence; blue = absence; yellow = unclear - risk of bias). ITT = intention-to-treat analysis.

TABLE 3. HSG - BALLOON CATHETER VS. METAL CANNULA – RESULTS OF THE STUDIES INCLUDED MEASUREMENT OF PAIN DURING THE PROCEDURE.

STUDY	MOMENT OF PAIN	BALLOON CATHETER	METAL CANNULA	MD (95%CI)	p
Kiykac Altinbas S[2], 2015	During device placement	*2.11 ± 0.87 (VAS)	*2.51 ± 1.07 (VAS)	−0.4 (−0.69 to -0.10	0.008
	During contrast injection	*2.63 ± 0.93	*3.74 ± 0.91	-1.11 (-1.39 a -0.82)	<0.00001
	1 hour after	*2.13 ± 1.18	*3.07 ± 1.02	−0.94 (−1.27 to −0.60	<0.00001
de Mello JF Sr[3], 2006	Pain during the procedure	4.3 ± ? (VAS)	6.8 ± ? (VAS)	-2.25	<0.05
Tur-Kaspa I[4], 1998	Pain during the procedure	3.8 ± 2 (VAS)	5.6 ± 2 (VAS)	−1.8 (−2.8 to -0.77)	0.0008

*The Wong-Baker Faces Pain Rating Scale (WBS) goes from 0 to 5 - there is an agreement between the facial pain assessment scale and the visual analog score (VAS); ? = not reported; MD = mean difference; CI = confidence interval.

TABLE 4. HSG - BALLOON CATHETER VS. METAL CANNULA RESULTS OF THE STUDIES INCLUDED MEASUREMENT OF ADVERSE EVENTS

STUDY	ADVERSE EVENT	BALLOON CATHETER	METAL CANNULA	ARR (95%CI)	NNT (95% CI)
Kiykac Altinbas S[2], 2015	Nausea	1 pac (1.2%)	12 pac (14.1%)	12.9% (0.051 to 0.125)	8 (5 a 9)
	Reapplication	2 pac (2.4%)	7 pac (8.2%)	5.8% (−0.009 to 0.125)	NS
de Mello JF Sr[3], 2006	Not reported	–	–	–	–
Tur-Kaspa I[4], 1998	No adverse events	0	0	–	–

ARR = absolute risk reduction; NNT = number needed to treat.

TABLE 5. ANALYSIS OF THE QUALITY OF EVIDENCE (GRADE PRO SOFTWARE)[1]

EVALUATION OF CERTAINTY							# of patients		Effect		CERTAINTY	Importance
No of studies	Design of the study	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	HSG with balloon catheter	HSG with metal cannula	Relative (95% CI)	Absolute (95% CI)		
Pain during device placement												
1	randomized clinical trial	not severe	not severe	not severe	not severe	None	83	85	-	MD 0.4 lower (0.69 lower for 0.1 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: confidence interval; MD: mean difference.

QUALITY OF EVIDENCE FOR THE OUTCOME OF PAIN DURING DEVICE PLACEMENT

One study evaluated this outcome[2].

Question: Does the use of a balloon-catheter in HSG, in comparison with the use of a metal cannula, for basic infertility diagnostic evaluation reduce pain during device placement? (Table 5)

SYNTHESIS OF EVIDENCE

In patients submitted to HSG, the use of a balloon catheter, in comparison with a metal cannula, reduces pain during the procedure and up to one hour after it and can also reduce nausea. The quality of the evidence that supports this result is high.

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Studies excluded and reason

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Advanced non-small cell lung cancer – treatment with Pembrolizumab

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Question: What is the impact of pembrolizumab, associated or not to chemotherapy, on the outcomes of overall mortality (death from any cause) and adverse events in the treatment of patients with advanced NSCLC when compared to chemotherapy alone?[1]

Answer: The treatment with Pembrolizumab, associated or not with chemotherapy, in adult patients with squamous or non-squamous NSCLC, locally advanced or metastatic, without previous systemic therapy, without mutations in the EGFR gene and gene rearrangement of the ALK, with a score of 0 or 1 in the ECOG performance scale, with at least one measurable lesion evaluated by Recist version 1.1, and PD-L1 expression [Tumor Proportion Score (TPS)] ≥1% (positive PDL-1). High quality of evidence.

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Do different pedagogical conceptions result in different quality of life levels?

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SUMMARY

OBJECTIVE: *The present study aims to compare medical students' quality of life (QoL) at two Brazilian institutions with different pedagogical conceptions.*

METHODS: *We studied students during the first four years of medical school at two institutions (one using active methodologies and small groups and the other using traditional lectures and large groups). We used a demographic questionnaire and the WHOQOL-BREF.*

RESULTS: *820 medical students were included. No significant differences in quality of life were found in general, nor while evaluating the course phase, except for the physical WHOQOL, which was lower for 2nd-year students at the institution with traditional lectures, even when adjusted for gender.*

CONCLUSION: *Our findings revealed that, despite having very distinct pedagogical conceptions and characteristics, there were no significant differences in medical students' QoL scores between both institutions. These results are surprising and differ from our initial hypothesis, which expected better QoL for those using more active and student-centered methods.*

KEYWORDS: *Education, medical. Students, medical. Quality of life. Problem-based learning.*

INTRODUCTION

Individual and medical education factors can have remarkable influences on students' wellbeing. Studies in different parts of the world have shown that medical students constitute a population at high risk for lower levels of quality of life and that medical schools are responsible for some of these outcomes[1,2]. The quality of life deterioration is associated with weak academic performance, lower motivation, and a decline in empathy, which, in turn, affects the doctor-patient relationship[3].

Traditional curricula that present pedagogical strategies giving priority to expositive classes, with activities centered on the professor in a traditional model, have been used in Brazilian medical schools

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for many years and have been the object of criticisms and reflections[2]. On the other hand, student-centered curricula using strategies like Problem-Based Learning (PBL) and Team-Based Learning (TBL) have increasingly found their space in the changing paradigms now being implemented[2].

Nevertheless, there are still doubts if active educational strategies may be responsible for better well-being outcomes[1,4]. Even though studies published in several countries have examined questions involving medical students' quality of life (QoL), few have compared students from different institutions by using the same instrument, in similar course phases and considering institutional peculiarities[3,5].

Therefore, this study aims to compare medical students' QoL at two Brazilian schools with different pedagogical conceptions. Our hypothesis was that there would possibly be differences in the QoL of students subjected to different learning environments.

METHODS

This comparative study was undertaken during the first semester of 2016 involving students in the first through fourth years of medical schools at two Brazilian institutions. The study's objectives were explained to students during class time, and the questionnaires were applied in-person and online during the same period at both institutions.

Institution 1 (Dr. Paulo Prata School of Health Sciences at Barretos, FACISB) is a private institution. The school makes intense use of student-centered strategies like PBL and TBL, formative and summative assessments, is structured in cycles, and provide students with mentoring and psychological support. Institution 2 (the Federal University of Juiz de Fora, UFJF) is a public institution. It uses a model that presents traditional lectures and summative assessments, is structured around disciplines, and had neither a mentoring program nor a psychological support structure at the time the study was conducted. Both, at present, have 180 students per year. Further details concerning institutions' characteristics can be visualized in Table 1.

The questionnaire was self-reported and contained data related to gender, course year, age, and the WHOQOL-BREF instrument[6]. That scale, validated for Brazilian Portuguese, comprises 26 items, on a 5-point Likert scale, with four domains: physical, psychological, social relationships, and environment, and it is widely used in medical education[6].

Statistical analysis was done using SPSS version 21. Chi-squared was used to analyze differences in gender, and the t-test for independent samples was used to compare age and quality of life scores (WHOQOL-BREF) for students at both schools. Since differences were found between genders at the two institutions, results were also controlled by gender.

The project was approved by the ethics committees at both UFJF and FACISB, and students signed a consent term.

RESULTS

A total of 820 medical students were included – 277 out of 330 (83.9%) from Institution 1 and 543 out of 720 (75.4%) from Institution 2. Tables 2 and 3 present the demographic differences and WHOQOL-BREF scores for students at both institutions, respectively. Differences in gender (p=0.003), but not age (p=0.262), were found (Table 2). After comparing students' quality of life from the two schools, no significant differences were found in general nor while evaluating the course phase, except for the physical WHOQOL, which was lower for 2nd-year students at Institution 2, even when adjusted for gender (Table 3).

DISCUSSION

Our findings revealed that, despite having very distinct pedagogical conceptions and characteristics, there were no marked differences in medical students' QoL scores between both institutions. These results are surprising and differ from our main hypothesis that expected better QoL for those using more active and student-centered methods.

In a recent study, the QoL scores for students at an American medical school (Southern Illinois University) and another in Brasil (the very same UFJF that participated in this study) were compared. Greater scores were found for the environment and social WHOQOL domains of American students when compared with Brazilian students. The latter showed a greater quality of physical health, probably because of the younger age at which Brazilian students enter medical school. In researching possible reasons for the differences found, US students were older (more mature) and experienced smaller class sizes, earlier patient encounters, problem-based learning, and psychological support[7].

Curiously, despite the Brazilian institution

TABLE 1. INSTITUTIONAL CHARACTERISTICS OF TWO BRAZILIAN MEDICAL SCHOOLS

Characteristics	Dr. Paulo Prata School of Health Sciences at Barretos	Federal University of Juiz de Fora School of Medicine
Total course length (in hours)	8440 hours (for all 6 years)	7,745 hours (for all 6 years)
Average hours of student activities at medical school per week, years 1 through 4	32/week	34/week
Number of students/year	Beginning in 2012, admission of two initial groups of 30 students, followed by another two groups of 60, and, currently, 90 students/year	90/year
Curriculum	Made up of curricular components: Modules, Curricular Units, Medical Internships - Curricular Stages and Optional Components, organized in 12 semesters with 2 learning cycles: Cycle I - Basic Clinical Integration (semesters 1 through 8) and Cycle II - clerkship (semesters 9 through 12)	Organized by subject (Anatomy, Physiology, Semiology, etc.), divided into pre-clinical, clinical and clerkship phases (2 years each)
Teacher/student ratio	Theoretical class – 30-90 student per teacher Practical – varies, most practical classes have 15-30 students per teacher	Theoretical class – 90 students per teacher Practical – varies, most practical classes have 20-25 students per teacher
Content Delivery (lecture, laboratory, clinical, etc.)	Based on modules for learning objectives with active search for knowledge, practical activities in laboratory environment, and realistic simulations; few lectures. Clerkship, strongly practical, years 5 to 6	Strongly theoretical, lecture-based, from years 1 to 4, with some practical activities. Strongly practical from years 5 to 6
Methodology or Pedagogical Model	Mostly active (TBL and PBL). Lectures at a few points	Mostly Traditional. 30 hours of PBL per year Includes TBL and flipped classroom at a few points
Assessment	Cognitive assessment based on clinical cases from year 1 on, clinical skills and gestures. Formative in specific subjects, humanistic-behavioral involvement	Mostly summative with cognitive assessment. Formative is limited to some subjects: one discipline has OSCE (year 3) and another has long case (year 1)
Mentoring	Yes	No
Student representation	Has the following organized student groups: - physical activities (Atlética) - academic activities (DA) - religious activities (GOL and ONDA)	Has the following organized student groups: - physical activities (Atlética) - academic activities (DA) - religious activities - sports activities - musical activities
Primary Health Care	Students have some contact, beginning in year 1	Students have some contact beginning in year 1. However, they have more contact during clerkship, when on a team
Medical support for students (provided by medical school)	No	No
Psychological support for students (provided by medical school)	Yes. Psychological support for students (provided by medical school) from year 1 on, via referral by psycho-pedagogical department	No
Medical student well-being/wellness program	No	No
Well-being day	No	No
Workshops and presentations promoting wellness	No	Yes, beginning in 2017. Cohort used in study did not have this.
Library	Yes	Yes
Fitness Center for students	No	No
Student lounge	Yes, inside building with armchairs for rest and TV.	Yes, inside building (TV, snooker table, tennis)
Free wi-fi	Yes	Yes
Mental health screening	Yes	No
Student Life Advising	No	No
Mindfulness Based Stress Reduction Program	No	Yes
Student Parties	Yes, off campus	Yes, off campus
Cafeteria	Yes	Yes
Parking lots	Yes, for teachers and students	Only for professors at medical school Student parking available at a distance of 500 meters (1640 feet). Seen as a great problem
Other well-being initiatives	No	- Live Music for students (once a week)

TABLE 2. COMPARISON BETWEEN STUDENTS AT INSTITUTIONS 1 (DR. PAULO PRATA SCHOOL OF HEALTH SCIENCES AT BARRETOS) AND 2 (FEDERAL UNIVERSITY OF JUIZ DE FORA SCHOOL OF MEDICINE)

	Institution 1 (n=277)	Institution 2 (n=543)	
Age*	21.41 (2.77)	21.18 (2.73)	0.262
Gender			
Male	94 (33.9%)	244 (44.9%)	
Female	183 (66.1%)	299 (55.1%)	0.003
Year			
1st	118 (42.8%)	152 (28.0%)	
2nd	59 (21.4%)	116 (21.4%)	
3rd	51 (18.5%)	142 (26.2%)	
4th	48 (17.4%)	133 (24.5%)	<0.001

TABLE 3. COMPARISON BETWEEN WHOQOL-BREF SCORES FOR STUDENTS AT INSTITUTIONS 1 (DR. PAULO PRATA SCHOOL OF HEALTH SCIENCES AT BARRETOS) AND 2 (FEDERAL UNIVERSITY OF JUIZ DE FORA SCHOOL OF MEDICINE)

	Institution 1 (n=277)	Institution 2 (n=543)	
Domains	Mean (SE)**	Mean (SE)**	p
All years			
WHOQOL - Physical	13.85(0.14)	13.75(0.10)	0.593
WHOQOL -Psychological	13.36(0.15)	13.62(0.10)	0.162
WHOQOL - Social	14.09(0.19)	14.53(0.13)	0.069
WHOQOL - Environment	14.09(0.13)	14.17(0.09)	0.622
1st year			
WHOQOL - Physical	13.06(0.22)	13.40(0.20)	0.260
WHOQOL - Psychological	12.85(0.22)	13.34(0.19)	0.099
WHOQOL - Social	13.58(0.30)	14.28(0.26)	0.084
WHOQOL - Environment	13.62(0.20)	14.14(0.18)	0.061
2nd year			
WHOQOL - Physical	14.54(0.30)	13.14(0.21)	<0.001
WHOQOL - Psychological	13.45(0.33)	12.95(0.23)	0.230
WHOQOL - Social	14.06(0.43)	13.99(0.30)	0.894
WHOQOL - Environment	14.21(0.30)	13.54(0.21)	0.075
3rd year			
WHOQOL - Physical	14.81(0.35)	14.04(0.20)	0.061
WHOQOL - Psychological	14.57(0.34)	13.93(0.20)	0.113
WHOQOL - Social	15.38(0.42)	15.10(0.25)	0.570
WHOQOL - Environmental	14.79(0.32)	14.45(0.19)	0.374
4th year			
WHOQOL - Physical	14.04(0.32)	14.36(0.19)	0.405
WHOQOL - Psychological	13.38(0.33)	14.15(0.20)	0.052
WHOQOL - Social	14.18(0.43)	14.65(0.26)	0.358
WHOQOL - Environmental	14.48(0.29)	14.44(0.18)	0.907

** Mean adjusted for gender

analyzed in that study having some characteristics like the American one, including the use of the PBL model, the results were different from those found in the Brasil-USA comparison. If, on one hand, some studies have shown that PBL curriculums can lead to a reduction in psychological disorder and an increase in students' general satisfaction[4], other have also demonstrated that this specific method can cause high levels of stress and anxiety, motivated by students' doubts about the consistency of their education[1]. Thus, the way the teaching strategy is linked is fundamental for students' good or poor outcomes. Personal and cultural factors seem to also exercise a determinant influence on QoL scores and should be

taken into consideration by educators.

This study has some limitations that should be considered. It involved only two schools (a public and a private), meaning that one should be cautious when generalizing its findings. Although we recognize that students from private medical schools have a better socioeconomic status and tend to have a better quality of life, it is surprising that we found no differences between the institutions. Therefore, both socioeconomic aspects and pedagogical conceptions seem to have little influence on the quality of life of these students. The identification of predictive factors was also not part of the study's design. Future studies can use learning environment scales to identify these factors.

It is concluded that, despite the differences between the two institutions in both the pedagogical conceptions used and in offering mentoring and psychological support, in practical terms, the two populations are similar regarding the quality of life. These findings can be explained by the array of factors involving the promotion of quality of life that go beyond pedagogical conceptions choices for medical education, choices which are, in and of themselves, highly stressful.

Author contributions

Oscarina da Silva Ezequiel: Substantial contributions to the study concept and design. Data analysis and interpretation. Drafting of the article. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

Bianca Sakamoto Ribeiro Paiva: Substantial contributions to the study concept and design. Data interpretation. Critical review of the study with relevant intellectual input. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

Carlos Eduardo Paiva: Substantial contributions to the study concept and design. Data interpretation. Critical review of the study with relevant intellectual input. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

Ivana Lúcia Damásio Moutinho: Substantial contributions to the study concept and design. Data collection and interpretation. Critical review of the study with relevant intellectual input. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

Robson Aparecido dos Santos Boni: Substantial contributions to the study concept and design. Data collection and interpretation. Critical review of the study with relevant intellectual input. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

Giancarlo Lucchetti: Substantial contributions to the study concept and design. Data collection and interpretation. Drafting of the text. Approval of the final version for publication. Accountability for all aspects of this study, assuring that all aspects related to the exactness and integrity of all its parts are dully investigated and resolved.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

RESUMO

OBJETIVO: *O presente estudo tem como objetivo comparar a qualidade de vida (QV) de estudantes de medicina de duas instituições brasileiras com diferentes concepções pedagógicas.*

MÉTODOS: *Estudo comparativo incluindo estudantes do 1º ao 4º ano do curso de medicina de duas instituições no Brasil (uma usando metodologias ativas e pequenos grupos e a outra aulas expositivas tradicionais e grandes grupos). Utilizou-se um questionário demográfico e o instrumento WHOQOL-Bref.*

RESULTADOS: *Foram incluídos 820 estudantes de medicina. Nenhuma diferença significativa na qualidade de vida foi encontrada no geral e na avaliação por fase do curso, com exceção do WHOQOL físico, que mostrou ser mais baixo para os estudantes da da instituição com aulas tradicionais, mesmo quando ajustado para o gênero.*

CONCLUSÃO: *Nossos achados revelaram que apesar de terem concepções e características pedagógicas bem distintas, não se observaram diferenças significativas nos escores de QV dos estudantes de medicina das duas instituições. Esses resultados são surpreendentes e diferem da nossa principal hipótese, uma vez que esperávamos uma melhora de QV para aqueles que usam métodos mais ativos e centrados no estudante.*

PALAVRAS-CHAVE: *Educação médica. Estudantes de medicina. Qualidade de vida. Aprendizagem baseada em problemas.*

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Thrombolysis in acute pulmonary embolism

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SUMMARY

OBJECTIVES: *Acute pulmonary embolism (APE) is an important cause of cardiovascular mortality, due mainly to hemodynamic instability. In these cases, the recommendation is to perform some reperfusion procedure, with systemic thrombolysis being the main therapy used. However, national data evaluating the efficacy and safety of thrombolysis are scarce.*

METHODS: *Retrospective analysis of a case series. We included 13 patients diagnosed with high-risk APE and 4 patients with intermediate-high risk from a single-center, who were treated with alteplase 100mg.*

RESULTS: *The mean age of the patients was 55 years, most of them female (76.4%). Among the risk factors for VTE were immobilization (41.17%), contraceptive use (35.29%), cancer (17.63%), and previous history of DVT (11.76%). The most frequent clinical manifestations of APE were dyspnea (88.23%), hypoxia (82.35%), hypotension (82.35%), and tachycardia (64.70%). 82.35% of the patients had echocardiographic signs of right ventricular dysfunction, and 52.94% had increased troponin and BNP. Severe bleeding associated with thrombolysis occurred in 17.54% of cases. No patient died due to bleeding. There were 8 deaths from right ventricular failure (47%), 6 in the cases of patients presenting as high-risk APE (35.3%), and 2 in the cases of intermediate-high risk (11.8%).*

CONCLUSION: *Thrombolysis in patients with high-risk APE or intermediate-high risk had a severe bleeding rate of 17.6%. However, the high mortality of this population (47%) due to right ventricular failure justifies the use of this therapeutic modality.*

KEYWORDS: *Pulmonary embolism. Thrombolytic therapy. Tissue plasminogen activator. Ventricular dysfunction, right.*

INTRODUCTION

Acute pulmonary embolism (APE) is the third leading cause of death from a cardiovascular cause, behind only acute myocardial infarction and cerebrovascular accidents[1]{Fernandes, 2016, New anticoagulants for the treatment of venous thromboembolism}. Although it is an easily preventable and treatable disease, it is estimated that every year, more than 3 million people die as a result of venous thromboembolism (VTE) and its most severe clinical manifestation, APE[2-4].

The main determinant of APE's clinical outcome is the right ventricle (RV) response to the acute increase of its afterload due to the increased pulmonary vascular resistance induced by the presence of a clot and its induced vasoconstriction[5,6]. When there is clear

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right-ventricular failure induced by APE with hemodynamic instability and hypotension, the recommendation, as a consensus, is some reperfusion procedure to reduce the afterload sharply and revert RV failure[7-9]. As a rule, the therapy of choice in these cases is systemic thrombolysis. However, due to the risk of its main adverse event, i.e., bleeding, the use of thrombolytic drugs is still well below the actual clinical need of APE patients with hemodynamic instability[10]. Another aggravating factor is that, in the medical literature, there is still scarce safety and efficacy data stating the role of this therapeutic strategy in the clinical management of APE patients at high risk of death, mainly in the national environment.

In certain situations, thrombolytic treatment is also an option for patients with medium-high risk APE. These patients are those who are able to maintain systemic perfusion with adequate systemic arterial pressure at the expense of RV stress. That stress is identified by the presence of abnormal biomarkers (BNP or troponin) RV imaging (via echo with pulmonary hypertension or RV dilation, or even an abnormal RV/LV ratio on a tomography)[11]. The benefits of using a thrombolytic drug in this situation are more questionable, and there is also no data available in the literature on the clinical outcomes of thrombolysis in this population for our location[12].

In this study, we present a series of 17 cases from a secondary general hospital who were submitted to thrombolytic therapy with alteplase for the treatment of PTE. We evaluated its effectiveness and safety.

METHODS

This is a case-series study, analyzed retrospectively through the review of medical records. The study included 13 patients with a diagnosis of high-risk PTE and four patients of medium-high risk, according to the classification suggested by the consensus of the European Society of Cardiology/European Respiratory Society[11], from January 2014 to May 2016, in the General Hospital of Florianópolis - SC, and who were submitted to thrombolytic therapy with alteplase at a dose of 100 mg.

RESULTS

The mean age of patients was 55 years (23 to 84 years). Most patients were female (76.4%). Among the most prevalent risks for VTE, immobilization was present in 41.17%, followed by the use of oral contraception (35.29%). Three patients had a history of cancer (17.63%), demonstrating the relevance of this clinical condition, particularly in our area[13,14]. Two cases had a history of deep vein thrombosis (11.76%). The epidemiological data of patients with APE are expressed in Figure 1.

The most frequent clinical manifestation of APE was sudden-onset dyspnea (88.23%), followed by O2 saturation lower than 90%, and systemic hypotension (defined as systolic blood pressure below 100 mmHg (82.35%). Tachycardia and lower levels of consciousness were observed in 11 patients (64.70%), while

FIGURE 1. RISK FACTORS IDENTIFIED IN PATIENTS WITH APE

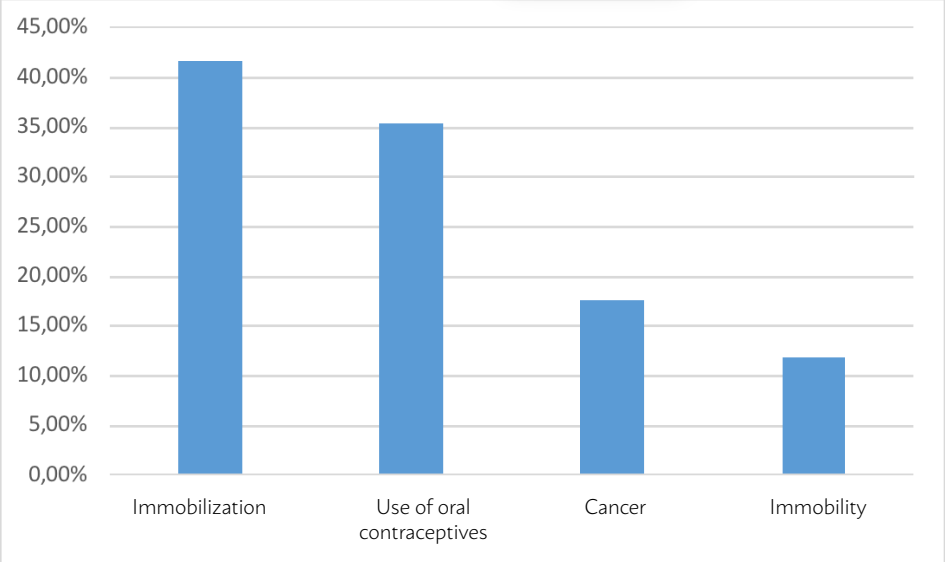


FIGURE 2. MAIN SIGNS AND SYMPTOMS PRESENTED BY APE PATIENTS.

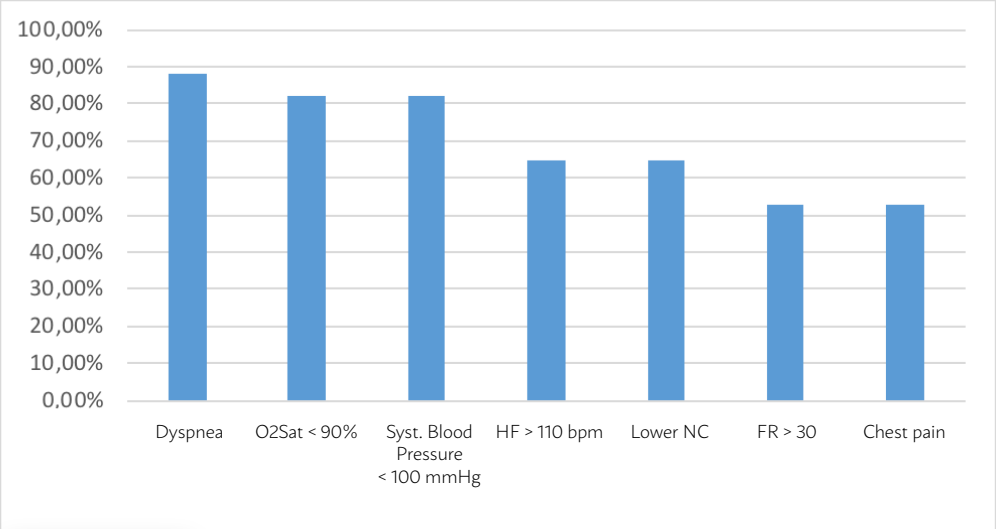
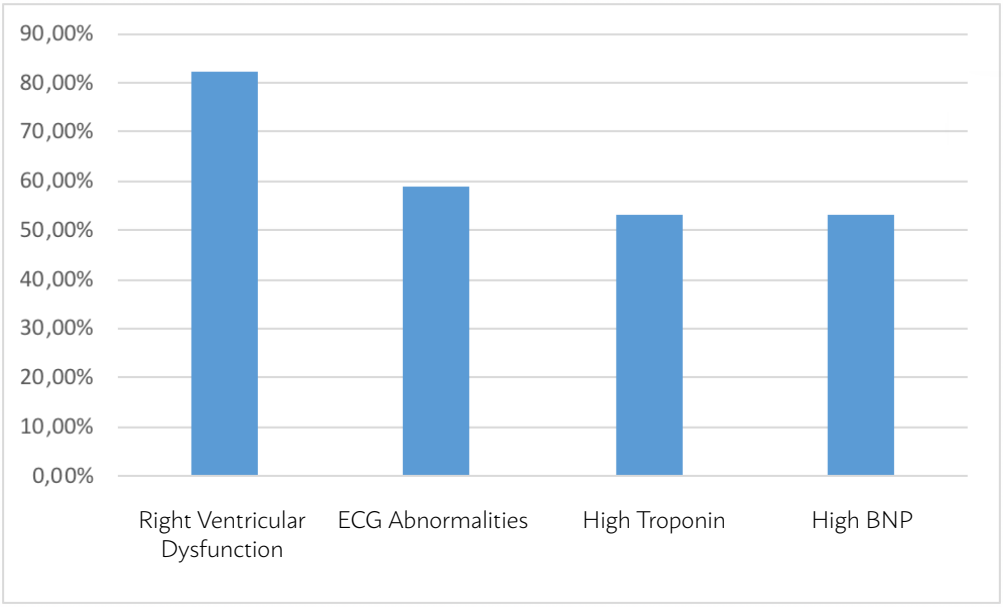


FIGURE 3. MAIN PROPAEDEUTICS CHANGES PRESENTED BY APE PATIENTS.



tachypnea and chest pain was observed in 52.94% (Figure 2).

Fourteen patients (82.35%) presented echocardiographic signs of right ventricular dysfunction, such as the RV hypokinesis, increased pulmonary artery systolic pressure (PASP), paradoxical septal movement, and dilatation of the right chambers. Electrocardiographic abnormalities were observed in 10 patients (58.82%), with a S1Q3T3 pattern in two cases, sinus tachycardia in one case, and atrial fibrillation in another. Nine cases had increased troponin and brain natriuretic peptide (BNP) values, corresponding to 52.94% (Figure 3)

Severe bleeding associated with thrombolytic therapy occurred in three cases (17.54%). The sites of the bleeding were retroperitoneal hematoma and hematoma associated with the puncture site of the central venous catheter. No patient died due to bleeding. There were, in total, eight deaths due to right ventricular failure (47%): six among the cases of patients who presented initially as high-risk APE (35.3%) and two among the cases of medium-high risk (11.8%). The data regarding the efficacy and safety of thrombolytic therapy are shown in Table 1

DISCUSSION

The most severe clinical presentation of venous thromboembolic disease is APE with hemodynamic

TABLE 1. EFFICACY AND SAFETY OF THROMBOLYTIC TREATMENT FOR APE

	Efficacy (death due to right ventricular failure)	Safety (greater bleeding)
high-risk APE - systolic BP <90 mmHg (n=13)	6 (35.3%)	3 (17.6%)
Medium-risk high APE - systolic BP >90 mmHg, with RV dysfunction -image plus laboratory testing (n=4)	2 (11.8%)	0

instability. Our study highlights the seriousness of this situation in the national context (47% mortality) and demonstrates that the use of thrombolytic therapy is a viable alternative, with a quite acceptable rate of adverse events (greater bleeding in 17.6% of cases), considering the high lethality of the clinical situation. Data evaluating the efficacy and safety of thrombolytic treatment in Brasil are extremely rare. To our knowledge, this is the first time a series of cases reporting this treatment in the Brazilian context of APE is published.

Thrombolysis is the treatment of choice for high-risk APE, recommended by the most recent international consensuses[11]. However, its main adverse event, i.e., severe bleeding, is an inhibiting factor to its use in patients with a clear indication[8]. Our data demonstrate that, in the national context, although bleeding is, indeed, a condition associated with the use of thrombolytic therapy, its frequency is equivalent to half of the deaths induced by RV dysfunction associated with APE. Thus, the use of thrombolytic drugs in these more difficult situations, with hemodynamic instability and high risk of death, is justified.

For severe patients, considered as of medium-high risk, the role of thrombolysis is less clear. The Peitho study evaluated 1,006 patients in this situation and, despite having identified a benefit from thrombolysis performed with tenecteplase, which reduced the use of intubation or vasoactive drugs, could not identify benefits in terms of mortality. In addition, the use of thrombolytic drugs presented a rate of central nervous system bleeding ten times greater than the conventional treatment with conventional anticoagulation (2 *vs.* 0.2%, p=0.003)[15]. Systemic thrombolysis also had no impact on the residual dyspnea or the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after two years[16]. Full anticoagulation would be the main treatment for CTEPH prevention[17]. However, our data demonstrated that this population, in the national context, presents a high mortality rate and is not considered a candidate for thrombolytic treatment; thus, it must be monitored intensively for early identification of organic dysfunction and tissue hypoperfusion.

Recent national data evaluated different aspects of APE diagnosis and risk stratification in our context. The validation of the Pesi risk score[18], the lack of relevance of the Wells and Geneva scores for the APE diagnosis in patients with clinical comorbidities[19], and the use of magnetic resonance imaging to identify the severity of APE {Pasin, 2017 #7398} demonstrate the relevance of APE in the Brazilian medical literature. However, objective data on the treatment of more severe presentations of APE in the Brazilian context are still not available. Thus, our study aims to bridge part of this gap in science, contributing to the construction of epidemiological data on APE in Brasil.

Our study has a number of limitations. It is an uncontrolled case series from a single center. The indication for thrombolytic therapy was systematical, but at the discretion of the assistant physician. Moreover, we do not have data on APE patients with an indication to receive thrombolytic treatment, but who, for some reason, did not receive it. However, the considerable number of patients included and the scarcity of Brazilian data in the literature justify the analysis and interpretation of our data with due caution.

CONCLUSION

Thrombolytic therapy in this series of 17 cases from a single Brazilian center with high-risk or medium-high risk APE patients presented a rate of severe bleeding of 17.6%. However, the high mortality in this population (47%) due to right ventricular failure justifies the use of this therapy, despite the potential morbidity. No patient died due to bleeding in this series.

Ethical aspects

No conflict of interest have been reported by any author

Contributions of the authors

TSB, MGV, and HB were responsible for data acquisition. EPO and CLMD completed the first draft. CJF supervised the study and reviewed the draft and final version.

RESUMO

OBJETIVOS: *A embolia pulmonar aguda (EAP) é uma causa importante de mortalidade cardiovascular ao causar instabilidade hemodinâmica. Nesses casos, a recomendação é a realização de algum procedimento de reperfusão, sendo a trombólise sistêmica a principal terapia utilizada. No entanto, dados nacionais avaliando a eficácia e a segurança da trombólise são escassos.*

MÉTODO: *Análise retrospectiva de uma série de casos. Foram incluídos 13 pacientes com o diagnóstico de EAP de alto risco e quatro pacientes de risco intermediário-alto, de um único centro, e que foram tratados com alteplase 100 mg.*

RESULTADOS: *A média de idade dos pacientes foi 55 anos, sendo a maioria do gênero feminino (76,4%). Dos fatores de risco para TEV, estavam presentes a imobilização (41,17%), o uso de anticonceptivos (35,29%), câncer (17,63%) e história prévia de TVP (11,76%). As manifestações clínicas mais frequentes da EAP foram dispneia (88,23%), hipóxia (82,35%), hipotensão (82,35%) e taquicardia (64,70%); 82,35% dos pacientes apresentaram sinais ecocardiográficos de disfunção ventricular direita e 52,94% apresentaram aumento da troponina e BNP. Sangramento grave associado à trombólise ocorreu em 17,54% dos casos. Nenhum paciente faleceu em decorrência de sangramento. Houve oito mortes por insuficiência ventricular direita (47%): seis nos casos de paciente que se apresentaram como EAP de alto risco (35,3%) e duas nos casos de risco intermediário-alto (11,8%).*

CONCLUSÃO: *A trombólise nos pacientes com EAP de alto risco ou risco intermediário-alto apresentou uma taxa de sangramento grave de 17,6%. No entanto, a alta mortalidade dessa população (47%) por insuficiência ventricular direita justifica o uso desta modalidade terapêutica.*

PALAVRAS-CHAVE: *Embolia pulmonar. Terapia trombolítica. Ativador de plasminogênio tecidual. Disfunção ventricular direita.*

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ORIGINAL ARTICLE

Vitamin D serum levels and peripheral arterial disease among southern Brazilian adults

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SUMMARY

OBJECTIVE: *To investigate the association between low serum vitamin D levels and peripheral arterial disease (PAD).*

METHODS: *A cross-sectional study with a consecutive sample of 133 individuals from Caxias do Sul, Brasil. We considered PAD patients those with an ankle-brachial index (ABI) ≤ 0.90 or with arterial revascularization. Vitamin D serum level was categorized as sufficient (≥30 ng/mL), insufficient (>20 to 29 ng/mL), and deficient (<20 ng/mL). Prevalence ratios (RP) were calculated through Poisson regression.*

RESULTS: *The prevalence of PAD was 50.7% (95% CI 42-59). After adjustment for potential PAD risk factors, RP were 1.08 (95% CI 0.66-1.76) for insufficient serum level and 1.57 (95% CI 0.96-2.57) for deficient vitamin D serum level; (p for trend = 0.020).*

CONCLUSION: *Vitamin D serum levels showed an inverse and significant dose-response relationship with PAD.*

KEYWORDS: *Peripheral arterial disease. Atherosclerosis. Vitamin D. Ambulatory care. Observational study.*

INTRODUCTION

Peripheral arterial disease (PAD) is among the most common causes of death by cardiovascular diseases in Brasil, with an increase of 82.1% between 1990 and 2015[1]. The worldwide prevalence of PAD is estimated in 10%, reaching 30% among populations aged 50 years or more[2]. In Brasil, the prevalence of this disease is around 5%[3].

PAD is the arterial narrowing caused by atherosclerotic lesions in the abdominal and iliac aorta, as well as in lower-body extremities[4]. Atherosclerotic plaques decrease blood flow and consequently lessen the oxygenation in lower-body extremities, causing claudication (pain at walking), ischemic pains at resting, ischemic ulcerations, gangrene, and may lead to amputations in advanced stages of the disease[4-6].

The main risk factors for PAD are increasing age, smoking, dyslipidemia, diabetes mellitus (DM), and systemic arterial hypertension (SAH)[5,7]. Some studies have shown that low serum levels of vitamin D may also be a risk factor for PAD onset and progression[8-11].

Vitamin D deficiency is highly prevalent all over the world[12]. Data from studies conducted in Brazilian

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health services with adults showed that vitamin D deficiency is also high, ranging from 26.5% to 33%[13,14].

Considering the impact of PAD on CVD mortality in Brasil, the high prevalence of lower vitamin D levels, and its possible effect on PAD occurrence, the present study aims to investigate the association between vitamin D serum levels and PAD among users of a reference outpatient clinic specialized in vascular diseases located in Caxias do Sul, Brasil. In addition, to date, we are not aware of studies that have explored this association in Brasil.

METHODS

A cross-sectional study with individuals of both sexes, aged 40 years or more, who had visited a reference public outpatient clinic specialized in vascular diseases, which provides healthcare to populations of 49 municipalities and is located in a medium-sized city in the south of Brasil.

The sample was obtained consecutively among those who attended the clinic between March 2016 and January 2017. Patients with conditions that impaired vitamin D absorption or increased needs of this vitamin (pregnant and nursing women), vegans, those in use of vitamin D supplements, and patients with poor cognition, unable to answer the questionnaire, were excluded from this study.

At the end of the data collection period, 133 subjects were recruited for the study. Considering the sample size obtained, the margin of error for prevalence estimation of 50% of PAD was about 8.0 percentage points. For the associations, the study had a power of 80% to detect prevalence ratios equal to or greater than 1.7 for exposures between 60% and 80% of the population, with a prevalence of PAD 20%-40% in the non-exposed, 95% confidence level.

Patients had their records checked, and those who meet the eligibility criteria were invited to participate voluntarily in the study. Then, the patients were referred to the vascular surgeon, who measured the ankle-brachial index (ABI) using a Doppler ultrasound device (brand DV610 Medmega®) and prescribed laboratory tests. ABI is composed of the ankle's highest systolic arterial pressure (measured at the posterior tibial artery or at the foot's dorsal artery) and the highest brachial artery systolic pressure. After the medical consultation, trained interviewers applied a standardized, pre-coded, and pre-tested questionnaire and performed the anthropometric assessment. The interviews were carried out inside the outpatient clinic, and each patient was interviewed a single time, even if they had new medical appointments during the period of this study.

Patients were considered to have PAD if they had an ABI ≤ 0.90 or had undergone some arterial revascularization procedure. ABI is defined as the ratio of the ankle's highest systolic arterial pressure (measured at the posterior tibial artery or at the foot's dorsal artery) and the highest brachial artery systolic pressure.

The main exposure variable, vitamin D serum levels, was obtained from the biochemical analysis of blood samples. The serum levels were determined by the electrochemiluminescence method, using Cobas® and Roche®'s 411 devices, and rated as sufficient (≥30 ng/mL), insufficient (>20 a 29 ng/mL), and deficient (<20 ng/mL)[12].

Demographic, socioeconomic, and behavioral characteristics and comorbidities were the independent variables. Demographic variables included sex, age, skin color, and marital status. Socioeconomic variables were education and family income. Behavioral variables were frequency of physical activity and time of physical practice, smoking, and alcoholic beverages consumption. Comorbidities included general obesity, abdominal obesity, DM, dyslipidemia, and SAH. General obesity was assessed by body mass index (BMI – weight in kilograms/height in meters squared) and defined as BMI ≥ 30 kg/m^2 [15]. Abdominal obesity was defined as waist circumference ≥ 88cm for women and ≥ 102cm for men[16]. For other comorbidities, we considered the patient as having it if they continuously took drugs to treat it.

Data were entered into Epidata software (Epidata *Association, Odense*, Denmark), version 3.1, with double entry. Statistical analyses were performed using the Stata software (StataCorp, *CollegeStation*, Texas, United States), version 14. The sample was described by univariate analysis (categorical variables were presented as proportion and numeric variables as average and standard deviation), and the associations of vitamin D serum levels and other explanatory variables with PAD were tested by bivariate analysis. The prevalence ratio (PR) and its respective 95% confidence interval (95% CI) were calculated through Poisson regression with robust variance. The association between serum levels of vitamin D and PAD was tested in eight models. Model 1 was unadjusted. Model 2 was adjusted for sex and age. Model 3 was adjusted for model 2 and smoking. Model 4 was adjusted for

models 2 and 3 and physical activity. Model 5 was adjusted for models 2, 3, and 4, and abdominal obesity. Model 6 was adjusted for models 2, 3, 4, and 5, and DM. Model 7 was adjusted for models 2, 3, 4, 5, and 6, and dyslipidemias. Model 8 was adjusted for models 2, 3, 4, 5, 6, and 7, and SAH. Variables were retained in models if they had a *P*-value ≤ 0.20.

The project was approved by the Research Ethics Committee of Caxias do Sul University, through protocol number 1.251.714. All participants validated their participation in this research by reading and signing the Informed Consent Form.

RESULTS

In all, 144 patients fulfilled the selection criteria and underwent ankle-brachial index measurement. Of these, 11 (7.4%) did not undergo the examination for vitamin D serum levels and were excluded from the multivariate analysis. Among those participants, we observed a higher proportion of women, aged 60 years or more, with education between 5 and 8 years, former smokers, with abdominal obesity, and no previous records of high blood pressure, DM, or dyslipidemia. However, these particularities were not statistically significant.

According to Table 1, the majority of the study participants was female (53.5%), aged 60 years or more (54.2%), with a mean age of 60.7±11.1 years, white (65.3%), with a partner (52.3%), up to four years of education (41.6%), and earned more than BRL 2,000.00 per month. With regard to behavioral variables, 48.6% were former smokers, 66.7% did not practice physical activities, and 52.1% did not drink alcoholic beverages. In relation to comorbidities, general and abdominal obesity affected 42% and 62.7% of the participants, respectively; 22.2% had DM, 50.7% had dyslipidemia, and 61.1% had SAH. Vitamin D insufficiency and deficiency prevalences were 36.1% (95% CI 28-44) and 45.1% (95% CI 36-53), respectively.

PAD prevalence was 50.7% (95% CI 42-59). This condition increased linearly with age and was higher among men, smokers, and former smokers, among patients with DM, SAH, dyslipidemia, and among participants with insufficient and deficient vitamin D levels. In the crude analysis, PAD showed an inverse dose-response relationship with vitamin D serum levels (p=0.028). The PR for PAD among individuals with insufficient and deficient vitamin D levels were 1.27 (95% CI 0.69-2.34) and 1.71 (95% CI 0.98-3.00), respectively (Table 1).

Figure 1 describes the prevalence of PAD according to serum 25OHD concentrations. The highest prevalence was observed in the deficient vitamin D serum

TABLE 1. SAMPLE CHARACTERISTICS, PREVALENCE AND PREVALENCE RATIO OF PERIPHERAL ARTERIAL DISEASE AMONG USERS OF A REFERENCE OUTPATIENT CLINIC SPECIALIZED IN VASCULAR DISEASES IN CAXIAS DO SUL, BRASIL (N=144).

Variable	n (%)	% PAD	PR	95% CI	P value
Total:	144 (100)	50.7	-	(42.4-59.0)	-
Sex					< 0.001a
Female	77 (53.5)	23.4	1.00		
Male	67 (46.5)	82.1	3.51	(2.30-5.35)	
Age (years)					<0.001b
40-49	27 (18.7)	25.9	1.00		
50-59	39 (27.1)	38.5	1.48	(0.70-3.15)	
≥ 60	78 (54.2)	65.4	2.52	(1.14-5.55)	
Color of skin					0.903a
White	94 (65.3)	51. 1	1.00		
Non-white	50 (34.7)	50.0	0.98	(0.70-1.38)	
Marital Status					0.745a
With partner	75 (52.3)	52.0	1.00		
Without partner	69 (47.7)	49.3	0.95	(0.68-1.31)	
Education (years)					<0.093b
≥ 9	26 (18.1)	46.2	1.00		
5-8	58 (40.3)	41.4	0.90	(0.53-1.50)	
0-4	60 (41.6)	61.7	1.34	(0.84-2.12)	

Variable	n (%)	% PAD	PR	95% CI	P value
Per capita income (tertiles)					<0.969b
I < BRL 1,400.00	34 (23.6)	52.9	1.00		
II BRL 1,400.00 – 2,000.00	50 (34.7)	48.0	0.91	(0.59-1.39)	
III >BRL 2,000.00	60 (41.7)	51.7	0.98	(0.65-1.46)	
Smoking					< 0.001b
Never smoked	51 (35.4)	27.5	1.00		
Ex-smoker	70 (48.6)	64.3	2.34	(1.45-3.79)	
Smoker	23 (16.0)	60.9	2.22	(1.27-3.86)	
Physical Activity (quantity)					0.129b
Practice ≥ 150 min/week	22 (15.2)	56.2	1.00		
Practice < 150 min/week	26 (18.1)	38.5	0.94	(0.47-1.89)	
Do not practice	96 (66.7)	40.9	1.37	(0.81-2.35)	
Physical Activity (time)					0.064b
Practices for > 12 months	41 (27.0)	35.5	1.00		
Practices for ≤ 12 months	7 (5.6)	47.1	1.32	(0.66-2.66)	
Do not practice	96 (67.4)	56.2	1.58	(0.95-2.63)	
Alcoholic beverages consumption					0.710b
Do not drink	75 (52.1)	52.0	1.00		
<30g /day ♂ and <15g /day ♀	56 (38.9)	44.6	0.86	(0.87-2.03)	
≥30g /day ♂ and ≥15g /day ♀	13 (9.0)	69.2	1.33	(0.87-2.03)	
General obesity					0.090a
No	83 (58.0)	56.3	1.00	(0.52-1.05)	
Yes	60 (42.0)	41.7	0.73		
Abdominal obesity					0.068a
No	53 (37.3)	60.4	1.00	(0.54-1.02)	
Yes	89 (62.7)	44.9	0.74		
Diabetes Mellitus					<0.001a
No	112 (77.8)	42.9	1.00	(1.37-2.42)	
Yes	32 (22.2)	78.1	1.82		
Dyslipidemias					<0.001a
No	71 (49.3)	25.3	1.00	(1.95-4.53)	
Yes	73 (50.7)	75.3	2.97		
Hypertension					0.008a
No	56 (38.9)	35.7	1.00	(1.14-2.49)	
Yes	88 (61.1)	60.3	1.68		
Vitamin D serum levels (ng/ml)					0.028b
Sufficient	25 (18.8)	36.0	1.00	(0.69-2.34)	
Insufficient	48 (36.1)	45.8	1.27	(0.98-3.00)	
Deficient	60 (45.1)	61.7	1.71	(0.98-3.00)	

PAD - Peripheral arterial disease, PR - Prevalence ratio, CI - 95% Confidence Interval. Wald test for heterogeneity, b Wald test for linear tendency

level (61.7%) and the lowest was in the sufficient serum level (36.0%) (p=0.021).

Table 2 shows the PRs for PAD. The inverse dose-response relationship between vitamin D serum levels and PAD remained significant among the different adjustment models, but with a reduction in the magnitude of the effect measure. In the last model, after adjustment for potential PAD risk factors investigated in the present study, PRs were 1.08 (95% CI 0.66-1.76) for insufficient serum level and 1.57 (95% CI 0.96-2.57) for deficient vitamin D serum level; (p for linear trend = 0.020).

DISCUSSION

In the present study, the prevalences of vitamin D deficiency and of PAD were high. Vitamin D serum levels showed an inverse and significant dose-response relationship with PAD. In the model adjusted for all risk factors, PAD probability was 57% higher among participants with deficiency when compared to those with a sufficient serum level.

The high prevalence of PAD found in this study (50.7%) is consistent with the data obtained in specialized health services, where values ranged from 51%

TABLE 2. PREVALENCE RATIO OF PERIPHERAL ARTERIAL DISEASE AND 95% CONFIDENCE INTERVAL, ACCORDING TO DIFFERENT ANALYSIS MODELS, AMONG USERS OF A REFERENCE OUTPATIENT CLINIC SPECIALIZED IN VASCULAR DISEASES IN CAXIAS DO SUL, BRASIL. (N=133)

Variable	Model 1 P-value PR (95% CI)	Model 2 P-value PR (95% CI)	Model 3 P-value PR (95% CI)	Model 4 P-value PR (95% CI)	Model 5 P-value PR (95% CI)	Model 6 P-value PR (95% CI)	Model 7 P-value PR (95% CI)	Model 8 P-value PR (95% CI)
Vitamin D serum levels (ng/ml) Sufficient Insufficient Deficient	0.028a 1.00 1.27 (0.69-2.34) 1.71 (0.98-3.00)	0.035a 1.00 1.08 (0.65-1.81) 1.50 (0.92-2.46)	0.037a 1.00 1.11 (0.66-1.88) 1.51 (0.92-2.50)	0.038a 1.00 1.08 (0.65-1.81) 1.50 (0.92-2.44)	0.036a 1.00 1.07 (0.64-1.77) 1.53 (0.93-2.52)	0.042a 1.00 1.06 (0.63-1.78) 1.52 (0.91-2.55)	0.014a 1.00 1.08 (0.67-1.75) 1.60 (0.99-2.58)	0.020a 1.00 1.08 (0.66-1.76) 1.57 (0.96-2.57)

PR – Prevalence Ratio, 95% CI – 95% Confidence Interval, a Wald test for the linear tendency. Model 1 = no adjustment. Model 2 = adjusted for sex and age. Model 3 = adjusted for sex, age and smoking. Model 4 = adjusted for sex, age, smoking, and practice time of PA. Model 5 = adjusted for sex, age, smoking, practice time of PA, and abdominal obesity. Model 6 = adjusted for sex, age, smoking, practice time of PA, abdominal obesity and DM. Model 7 = adjusted for sex, age, smoking, practice time of PA, abdominal obesity, DM and dyslipidemias. Model 8 = adjusted for sex, age, smoking, practice time of PA, abdominal obesity, DM, dyslipidemias, and hypertension.
PA – Physical Activity; DM – Diabetes Mellitus.

to 75%[17,18]. It should be noted that both the method for PAD diagnosis as well as the participants' mean age were similar to those in the present study.

The inverse dose-response relationship between the vitamin D serum levels and PAD found in the present study is supported by literature data, although with different outlines, populations, and cut-off points for rating vitamin D serum levels[8-11]. In the United States, data on 5,000 individuals aged 40 years or more, researched by the *National Health and Nutrition Examination Survey* (NHANES)[9], showed that the lower the vitamin D serum level, the higher the chances of PAD (p<0.001). The adjusted OR was 1.80 (95% CI 1.19-2.74) for individuals rated in the lowest quartile (<17.8 ng/mL) when compared to the highest quartile of this vitamin (≥29.2 ng/mL)[9]. PAD incidence according to vitamin D serum levels was researched at the *Atherosclerosis Risk in Communities Study* (ARIC)[19], a cohort study; 11,789 patients were assessed. The results, adjusted for sociodemographic and behavioral variables, showed that PAD risk increased linearly and inversely with vitamin D serum levels (p=0.02). However, when biochemical parameters (HDL-col, LDL-col and C-reactive protein), comorbidities (DM and SAH), and the use of drugs for cholesterol and SAH were included in the analysis, the association lost statistical significance. The authors believe this result is due to the mediation role these factors may play in the vitamin D and PAD relationship, which could attenuate its effect[19]. A meta-analysis of observational studies with data of 6,418 participants showed that the vitamin D serum levels were significantly lower among individuals suffering from PAD when compared to others without this condition (standardized mean difference = -0.32; 95% CI: -0.58; -0.05; p = 0.02)[20].

Other studies also assessed the association between vitamin D and PAD, however, without considering exposure as a categorical ordinal or continuous variable. In Israel, a cross-sectional study with 8,175 men (mean age 55 ± 17 years) and 26,699 women (mean age 55 ± 15 years), all of them users of a health system, showed that the ROs of PAD were 1.35 (95% CI 0.88-2.07; p=0.175) and 1.31 (95% CI 0.87-1.98; p=0.198), respectively, for men and women classified in the average level of vitamin D (≥15 ng/mL to < 30 ng/mL), compared to those at the highest level (≥ 30 ng/mL). When the lowest level of vitamin D (< 15 ng/mL) was compared to the highest level of vitamin D, the ROs were 1.73 (95% CI 1.05-2.84; p=0.031) for men and 1.85 (95% CI 1.17-2.91; p=0.008) for women[8]. Also conducted among users of a health service, a cohort study researched the incidence of PAD and vitamin D serum levels in the state of Utah, in the United States. About 42,000 electronic patient records were assessed (users mean age of 55 ± 21 years). The adjusted risk of PAD was 1.01 (95% CI 0.78-1.31; p=0.93) among those with a lower serum level (16 to 30 ng/mL) and 1.42 (95% CI 1.04-1.94; p=0.03) among those with

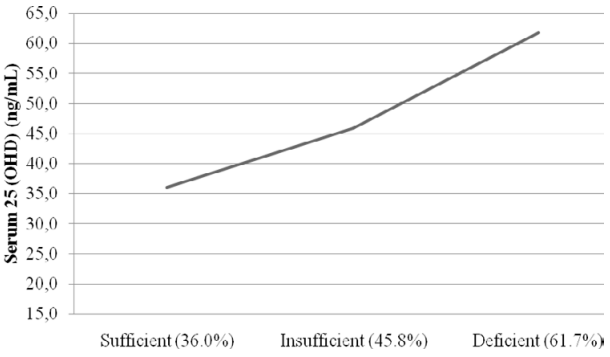

FIGURE 1. PREVALENCE OF PERIPHERAL ARTERIAL DISEASE (PAD) ACCORDING TO SERUM VITAMIN D LEVELS AMONG USERS OF A REFERENCE OUTPATIENT CLINIC SPECIALIZED IN VASCULAR DISEASES IN CAXIAS DO SUL, BRASIL (N=133). *TEST FOR LINEAR TREND. P<0.05.

a very low serum level (< 16 ng/mL) when compared to individuals with regular vitamin D serum levels (> 30 ng/mL)[10]. Based on these results, which showed no association between the intermediary vitamin D level and PAD, we conducted an analysis where the vitamin D serum level was dichotomized in order to isolate the deficient category (sufficient/insufficient and deficient). We observed that the association between vitamin D and PAD remained significant across all adjustment models. In the last model, the probability of PAD was 46% higher (1.46; 95% CI 1.13-1.90; p=0.04) among individuals with deficient serum levels when compared to those with sufficient/insufficient serum levels (data not displayed on the table). This result and those in the mentioned studies lead one to think that vitamin D deficiency – more than its insufficiency – would be the risk factor for PAD. However, this must be cautiously stated, since these studies considered different cut-off points for rating vitamin D serum levels. Another aspect to be considered is that, although dichotomization increased the precision of effect measurement, this was smaller than the one obtained in the analysis considering vitamin D as an ordinal categorical variable (PR 1.46 vs. PP 1.57). Besides, from a public health point of view, it would be more useful to consider the dose-response relationship between vitamin D and PAD, since intervention measures for increasing vitamin D serum levels could be implemented earlier among individuals presenting insufficiency for this vitamin.

Conversely, other studies have not been able to show an association between vitamin D and PAD. In the multiple linear regression analysis of data from 275 Australian users of a hospital cardiology sector (75 of them PAD patients), with a median age of 66 ± 11.2 years, the vitamin D serum level was not a PAD predictor. The researchers ascribed this result to the small number of individuals suffering from PAD; however, they represented 27.3% of the sample[17]. A cross-sectional study, conducted in the USA, selected 402 PAD patients (median age of 73.1 ±7.7 years) and 305 participants who were free from this condition (median age of 70.2 ±7.2 years) in medical services. The average vitamin D serum level was lower among PAD patients (53.7 ± 24.9 nmol/L) when compared to PAD free individuals (54.6 ±23.7 nmol/L); however, the difference was not statistically significant (p=0.63). According to the authors, patients without PAD also had lower vitamin D serum levels, and this could be explained by the high prevalence of chronic conditions among them[21].

The studies described here so far indicate controversial results regarding the relationship between vitamin D serum levels and PAD, but the differences among the studied populations, as well as the ratings and analysis performed could account for these results. In Brasil, as far as we are aware, this association has not been researched. Since PAD has been an important CVD cause of death, with almost double the prevalence in the last decades, and may occur through different mechanisms, it is fundamental to verify vitamin D as a predictor of its onset and progression as a way of helping strategies to prevent these mechanisms.

The role of vitamin D in the onset of PAD may take place through different biological mechanisms. Directly, vitamin D affects atherosclerosis through its effect on endothelial function, modulating the inflammatory process, and producing smooth muscle cells[22]. Indirectly, vitamin D effect takes place through its operation on PAD risk factors, such as SAH, DM, and dyslipidemia[23-25]. In relation to SAH, it is observed that lower levels of this vitamin lead to an increase in vascular rigidity through the renin-angiotensin-aldosterone system activation[23]. Regarding DM, individuals with vitamin D deficiency have a dysfunction in the pancreas beta cells, which produces modifications in insulin secretion, creating resistance to this hormone[24]. In dyslipidemias, vitamin D deficiency favors the capture of LDL-cholesterol molecules oxidized by macrophages[7,25].

This study shows that low serum vitamin D levels may be an independent risk factor for the development of PAD. However, it is plausible to think of the indirect effect it may have on the onset of PAD since the attenuation of effect measures observed after adjustment for DM and SAH could indicate that part of this effect may have been mediated by these factors[19,22].

Our results should be interpreted in light of certain limitations. Firstly, the small number of individuals resulted in low accuracy of effect measures, which can be observed by the 95% CI amplitude on main exposure categories. Nevertheless, since explanatory analysis between the main exposure and the outcome showed a dose-response effect, vitamin D remained categorized as sufficient, insufficient, and deficient, in order to emphasize the biological gradient verified in the bivariate analysis. Secondly, the inherent reverse causality of cross-sectional studies cannot be discarded. If so, individuals suffering from PAD may have less sun exposure because of the disease's complications, resulting in lower vitamin D serum levels. Another limitation is the fact that vitamin D daily intake wasn't evaluated. Longitudinal studies could clarify this relation.

CONCLUSION

Our findings support the association between insufficient and deficient vitamin D serum levels and PAD, and, as far as we know, this is the first Brazilian study to research such association. Considering the high prevalence of lower vitamin D serum levels, their direct effect on PAD, as well as in the occurrence of mediator risk factors for this and other cardiovascular diseases, it is important to encourage the population to seek sufficient and adequate sun exposure and as well to intake vitamin-D-rich food.

RESUMO

OBJETIVO: *Investigar a associação entre níveis séricos de vitamina D e doença arterial obstrutiva periférica (DAOP).*

MÉTODOS: *Estudo transversal, com amostra consecutiva de 133 indivíduos. Foram considerados com DAOP pacientes com índice tornozelo braquial ≤ 0,90 ou com revascularização arterial. O nível sérico de vitamina D foi classificado em: suficiente (≥30 ng/mL), insuficiente (>20 a 29 ng/mL) e deficiente (<20 ng/mL). Razões de Prevalência (RP) foram calculadas por meio de regressão de Poisson.*

RESULTADOS: *A prevalência de DAOP foi de 50,7% (IC95% 42-59). Após ajuste para potenciais fatores de risco para DAOP, as RP foram de 1,08 (IC95% 0,66-1,76) para nível sérico insuficiente e de 1,57 (IC95% 0,96-2,57) para o nível sérico deficiente de vitamina D; (p para tendência = 0,020).*

CONCLUSÃO: *O nível sérico de vitamina D mostrou uma relação dose/resposta inversa e significativa com DAOP.*

PALAVRAS-CHAVE: *Doença arterial periférica. Aterosclerose. Vitamina D. Assistência ambulatorial. Estudo observacional.*

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ORIGINAL ARTICLE

Overall survival predictors in hepatocellular carcinoma patients treated with sorafenib

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SUMMARY

Malignant liver tumors are the fourth leading cause of cancer death worldwide. Hepatocellular carcinoma (HCC) accounts for 75-85% of these. Most patients are diagnosed at incurable stages. Palliative care is the appropriate treatment course in these circumstances (chemoembolization and sorafenib). There are few national studies on sorafenib. The objective is to evaluate survival predictors of HCC patients treated with sorafenib and evaluate the compliance of its indication in relation to BCLC recommendations.

METHODS: *A total of 88 patients with an indication of sorafenib from 2010 to 2017 at the ISCMSP were retrospectively analyzed. Univariate and multivariate analyzes were performed in the search for predictors of survival.*

RESULTS: *The mean age was 61.2 years, 70.5% were men, most were classified as Child-Pugh A (69.3%), and BCLC C (94.3%). Cirrhosis was present in 84.6% and portal hypertension in 55.7%. Hepatitis C virus was the most common etiology (40.9%). Sixty-nine (78.4%) patients received the medication, with the average duration of treatment being 9.7 months. The mean overall survival was 16.8 months. Significant differences were observed in the multivariate analysis: ECOG PS (p = 0.024): Child-Pugh (p = 0.013), time of medication use (p <0.001), clinical worsening (p = 0.031) and portal thrombosis (p = 0.010).*

CONCLUSION: *Absence of portal thrombosis, Child-Pugh A, longer time of medication use, ECOG PS 0, and absence of suspension due to clinical worsening were predictors of better overall survival in the study. The drug's indication complies with BCLC guidelines in 94% of patients.*

KEYWORDS: *Liver neoplasms, hepatocellular carcinoma, sorafenib, protein kinase inhibitors.*

INTRODUCTION

Malignant primary liver tumors are the fourth leading cause of cancer deaths worldwide. Hepatocellular carcinoma (HCC) is its main subtype, accounting for 75-85% of all primary liver tumors[1].

Most patients with HCC receive a late diagnosis[2,3]. Patients in different situations such as multifocal lesions, locally advanced tumor, or comorbidities that limit curative treatment - surgical resection, transplant, radiofrequency ablation, or alcoholization - may only undergo palliative care.

Sorafenib (Nexavar®, Bayer, German) is an oral multiple tyrosine kinase inhibitor, which acts both on tumor cells, inhibiting their proliferation, and on tumor vascular cells, inhibiting angiogenesis. It impedes the autophosphorylation of multiple receptors, such as vascular endothelial growth factor

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receptor 1,2,3, platelet-derived growth factor receptor β, stem cell factor receptor, RET proto-oncogene, fibroblast growth factor receptor 1, FMS-like tyrosine kinase 3 receptor and Ras/Raf MAPK intracellular pathways[4,5].

The U.S. Food and Drug Administration approved this medication in 2007 for the treatment of advanced HCC based on two randomized clinical trials that demonstrated its safety and effectiveness[6,7].

In Brasil, HCC's diagnosis is usually made in the intermediate and late phases[8]. Sorafenib is the only systemic therapy approved and in use by The Brazilian Unified Health System (*Sistema Único de Saúde* – SUS). Therefore, the analysis of non-interventional trial results is relevant, since the patient population is considerably different from the one used in randomized clinical trials - with their strict eligibility criteria. In addition, the assessment of these data is especially important to demonstrate the safety and effectiveness of Sorafenib in a real-life setting.

Thus, we proposed to study patients who had indication of Sorafenib, regardless they received the medication or not. This study sought to define predictors of overall survival (OS) with a more reliable view, in the clinical practice, in real conditions, out of the randomized clinical trial setting, and to assess the indication to treatment, according to the Barcelona Clinic Liver Cancer (BCLC) guidelines.

METHODS

This cross-sectional retrospective study included all patients with advanced hepatocellular carcinoma who received sorafenib treatment indication at Irmandade Santa Casa de São Paulo (ISCMSP) from January 2010 to November 2017. Patients were diagnosed histologically or imagiologically according to AASLD guidelines with advanced HCC. They kept sorafenib until radiological progression – according to guideline Response Evaluation Criteria In Solid Tumors modified- clinical worsening or unacceptable adverse effects. The decision to treat patients with sorafenib was been made under real-life practice conditions. Data were collected using case report forms.

Data on demographics, liver disease, Child-Pugh (CP)[9,10], tumor-related, previous treatment, indication, receipt and suspension of the medication, alpha-fetoprotein levels (AFP), ECOG-PS[11] (Eastern Cooperative Oncology Group-Performance Status), and BCLC[12] classification were collected.

Survival analysis

Overall survival (OS) was measured from the date of indication of sorafenib until the date of death or end of follow-up (the last outpatient appointment). In patients who remained alive, the event was the final date of data collection (November 30, 2017).

Statistical analysis

The existence of associations between two categorical variables was evaluated using the Chi-Square test or Fisher's exact test. Patient survival was assessed by Kaplan-Meier curves, and groups were compared using the Log-Rank test (univariate analysis-UA). Multivariate analysis was performed using the Cox model. Due to the large number of variables, predictor variables were selected when their association with the dependent variable reached 10% significance in the univariate analysis (UA). Initially, all selected variables were included; then, variables not reaching 5% significance were excluded one by one in order of significance (backward method). All calculations were conducted using the statistical software IBM SPSS Statistics® 20.0 and STATA® 12. This study was approved by the Research Ethics Committee of the Faculty of Medical Sciences of ISCMSP, CAAE: 62130416.2.0000.5479

RESULTS

Eighty-eight patients were enrolled in this study. The mean age was 61.2 years [Standard Deviation (SD) = 13.0 years], and the clinical and demographic characteristics are summarized in Table 1.

The presence of cirrhosis was common (86.4%). The most common etiology was hepatitis C (40.9%), followed by alcohol (33%) and hepatitis B (15.9%). Other causes were: NAFLD, Budd-Chiari, and autoimmune hepatitis. Alcohol consumption was the second risk factor in 28% of HCV patients, and 11.4% of HBV patients.

Regarding portal hypertension, 55.7% of the patients had it, and 30.6% did not have it. Thirty patients (34.1%) were completely healthy and asymptomatic (ECOG PS 0), but most of them already had some alteration in their performance status.

Vascular invasion and extrahepatic metastasis were found in 40.9% and 39.8% of the sample, respectively. The most common site of distant metastasis was the lung (17%), followed by the bones (14.8%). Other affected sites were: adrenal, peritoneum and

retroperitoneum, subcutaneous cell tissue, and skin.

According to the Child-Pugh classification, 69.3% and 30.7% of patients were A and B, respectively. Most of the sample, 94.3%, were classified as BCLC C at the time of sorafenib treatment indication, and 44.3% had an indication of sorafenib after the failure of some locoregional treatment. Surgical resection and TACE were performed before sorafenib in 17 and 13 patients, respectively. Five patients had TACE after surgery, and one patient had alcoholization associated with the surgical procedure. Two transplant patients who had undergone TACE as a bridge therapy had a recurrence (distant metastasis) after transplantation and, then, the indication of sorafenib. One patient underwent surgical resection, TACE, and alcoholization prior to sorafenib indication. Most patients (55.7%) had an indication of sorafenib as the initial therapeutic modality.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH INDICATION OF SORAFENIB AT ISCMSP, N (%)

Characteristic	Percentage
Male/ Female	70.5 / 29,5
Etiology, HCV/ Alcohol/ HBV/ Other/ Unknown	40.9/ 33/15,9/6,8/9,1
ECOG-PS, 0/1/2	34,1/47,7/18,2
Child-Pugh, A/B	69.3/30,7
BCLC, B/C	5,7/ 94,3
Vascular invasion	40.9
Extrahepatic metastasis	39,8
Previous therapy, Surgery/ Transplant/ Alcoholization/ TACE	26,1/2,3/3,4/25
Portal hypertension, Yes/ No/ Absent data	55,7/ 30,7/13,6
Cirrhosis, Yes/No/ Absent data	86,4/9,1/4,5
Comorbidities, SH/CAD/ Prior Stroke/ DLP/Diabetes	36,4/9,1/3,4/8,0/30,7

HCV: Hepatitis C virus. HBV: Hepatitis B virus. ECOG PS: *Eastern Cooperative Oncology Group performance status*; BCLC: *Barcelona Clinic Liver Cancer Group*; SH: Systemic hypertension; HF: Heart failure; CAD: Coronary artery disease; DLP: dyslipidemia; TACE- *transarterial chemoembolization*

Administration of sorafenib

Among 88 patients who had the medication prescribed, 69 received it, and 19 patients did not receive the treatment.

Patients who received medication

The mean OS time of sorafenib recipient patients was 16.8 months (95% CI: 355.13 – 654.35 days). The mean time of sorafenib treatment duration was 9.7 months. Approximately 84% received the standard dose of 800 mg, and 13% received half the dose. There was no uniformity in the reasons for prescribing half the dose.

Among the 69 drug-recipient patients, almost 70% had adverse effects (AE) described in the medical report. The main AEs were diarrhea (33%), hand-foot syndrome (20.5%), mucositis (11.4%), fatigue (11.4%), and nausea (11.4%). Other AEs described were skin rash, anorexia, alopecia, thrombocytopenia, weight loss, itching, increased transaminases, cramp, increased blood pressure, insomnia, weight loss, sialorrhea, dyspepsia, and facial keratoacanthoma.

There was a 45% rate of medication suspension, with 48.4% of them for disease progression, 29% for clinical worsening, and 16.1% for AE. In 50.7% of the patients, the medication was maintained until the date of death.

TABLE 2. RESULTS OF THE INITIAL AND FINAL COX MULTIVARIATE REGRESSION MODELS

	Initial Model		Final Model	
	Adjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
ECOG - PS				
1	2.57 (1.22 – 5.43)	0.013	2.18 (1.11 – 4.32)	0.024
2	1.07 (0.37 – 3.09)	0.903	1.07 (0.39 – 2.93)	0.896
CP				
B	3.17 (1.33 – 7.57)	0.009	2.90 (1.25 – 6.71)	0.013
BCLC				
B	2.52 (0.6 – 10.58)	0.208	-	-
Treatment prior to sorafenib	0.76 (0.37 – 1.57)	0.457	-	-
Time of medication use (days)	0.996 (0.994 – 0.998)	<0.001	0.996 (0.994 – 0.998)	<0.001
Suspension due to clinical worsening	2.67 (1.13 – 6.31)	0.025	2.55 (1.09 – 5.96)	0.031
Suspension due to side effect	1.18 (0.43 – 3.29)	0.747	-	-
Portal Vein Thrombosis	2.67 (1.21 – 5.89)	0.015	2.60 (1.26 – 5.37)	0.010

Proportional risk test based on Schoenfeld residuals – Chi (6) = 3.44 – p=0.752. ECOG PS: Eastern Cooperative Oncology Group performance status; BCLC: Barcelona Clinic Liver Cancer Group; CP:Child-Pugh.

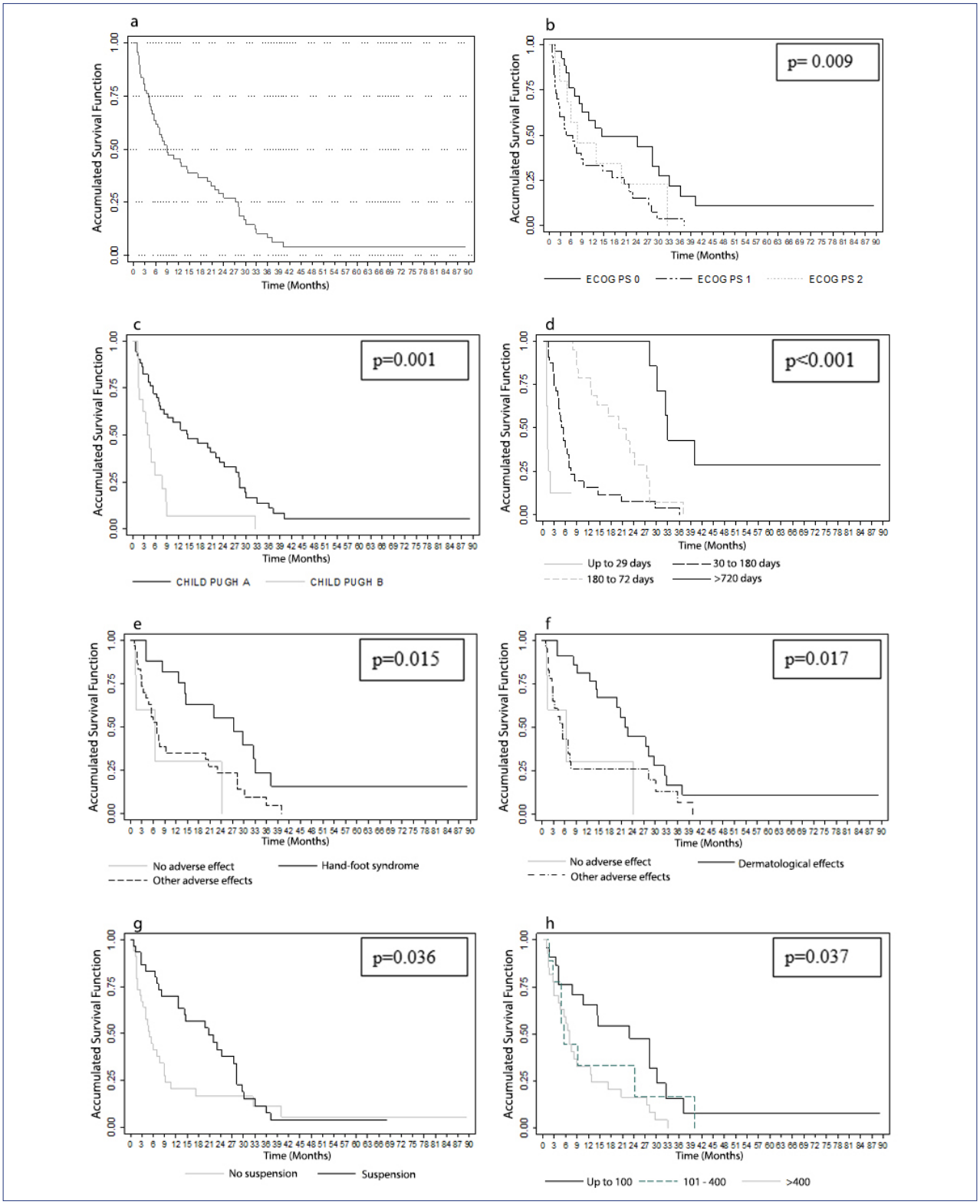

FIGURE 1.(A): GLOBAL SURVIVAL FUNCTION (SF) OF PATIENTS TREATED WITH SORAFENIB; (B): SF BY ECOG PS; (C): SF BY CP; (D): SF BY TIME OF USE OF MEDICATION; (E): SF BY AE -HAND AND FOOT SYNDROME; (F): SF BY AE - DERMATOLOGICAL EFFECTS; (G): SF BY MEDICAL SUSPENTION; (H) SF BY AFP

Patients' survivals by categorical characteristics were analyzed also by Kaplan-Meier models. Figure 1 shows the functions of accumulated survival due to the variables that proved to be significant.

Table 2 shows the Cox regression model, with the variables 10% significant in UA. Variables associated with AE- Hand-foot syndrome and AE-dermatological effects and AFP were not considered due to the high

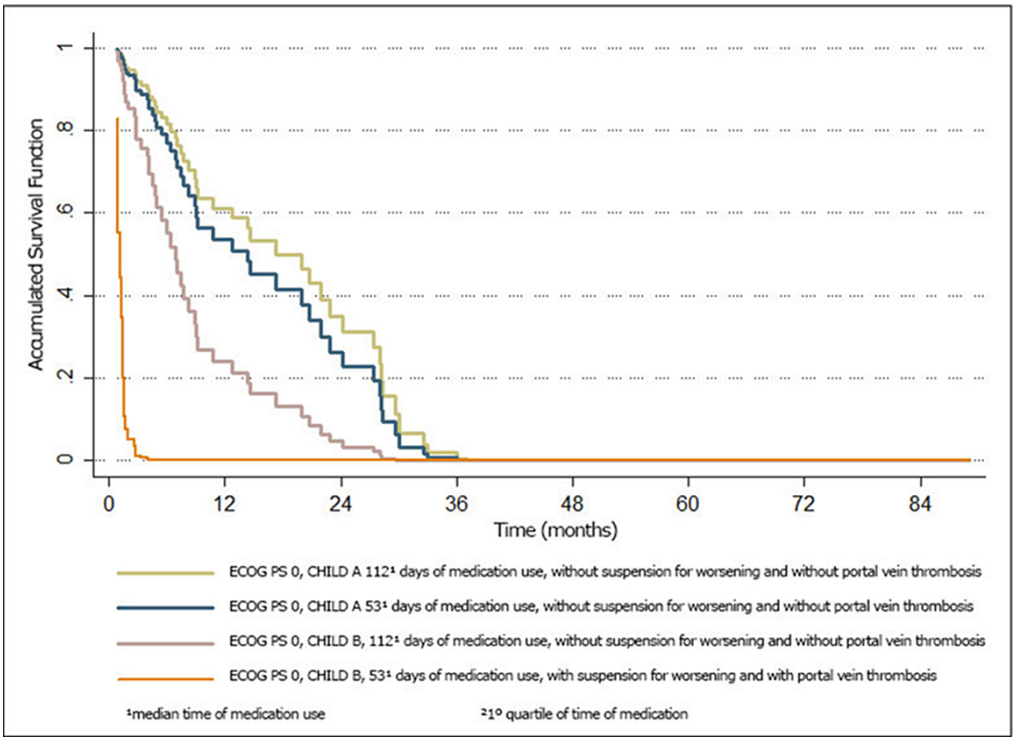

FIGURE 2. SURVIVAL FUNCTIONS ESTIMATED VIA FINAL COX MODEL FOR SOME PATIENT PROFILES

number of cases with missing information (16 cases (23.2%) and 9 cases (13.0%), respectively for adverse events and AFP. By including these two variables, the model estimation was not possible.)

According to table 2, the following variables remained significant in the final model: ECOG PS, Child-Pugh (CP), time of medication use, suspension – clinical worsening, and portal vein thrombosis.

Figure 2 presents the estimates of the survival functions of the final Cox model for some patients' profiles.

Survival by medication

A survival rate comparison was drawn between drug recipients and non-recipients (Figure 3).

It was observed that patients without medication had lower survival than patients receiving medication ($p < 0.001$). The median overall survival time in the group of non-recipient patients was 69.95 days. (95% CI: 46.12 - 93.78), about 2.3 months.

DISCUSSION

Of the 88 patients with an indication for the medication, 78 (4%) received sorafenib, but 21.6% did not receive the medication despite having the indication; patients died before the medication was available by the State Secretariat of Health or lost eligibility during the wait for medication.

Sorafenib is released by SES (Secretaria Estadual de Saúde) for patients after medical indication. The documentation comes from the ISCMSP central pharmacy and is sent to SES. As soon as the SES bureaucratic process is completed and the medication dispensed, a telegram is sent to the patient's residence, who can then retrieve the drug from the SES building. The mean time between indication and reception of medication was 32.53 (SD = 7.86), and the median was 27.5 days.

The mean time of therapy with sorafenib was 9.7 months, a similar value was presented in another Brazilian study (8.23 months)[13]. In general, the meantime of overall survival was 504.74 days (95% CI: 355.13 – 654.35), around 16.8 months, higher than in previous studies such as the SHARP (10.7 months) and Asia-Pacific (6.5 months)[6,7].

A recent French study established a new scoring system for BCLC C stratification using five independent prognostic elements: CP, performance status, AFP levels, number of nodules, and infiltrative nature of the tumor[14].

Another Korean study proposed establishing the sub-classification of stage C into three groups according to the scores established by five prognostic factors (CP, AFP, type of tumor (nodular versus diffuse/infiltrative), extrahepatic metastasis and portal invasion): low-risk, medium-risk and high-risk group, with

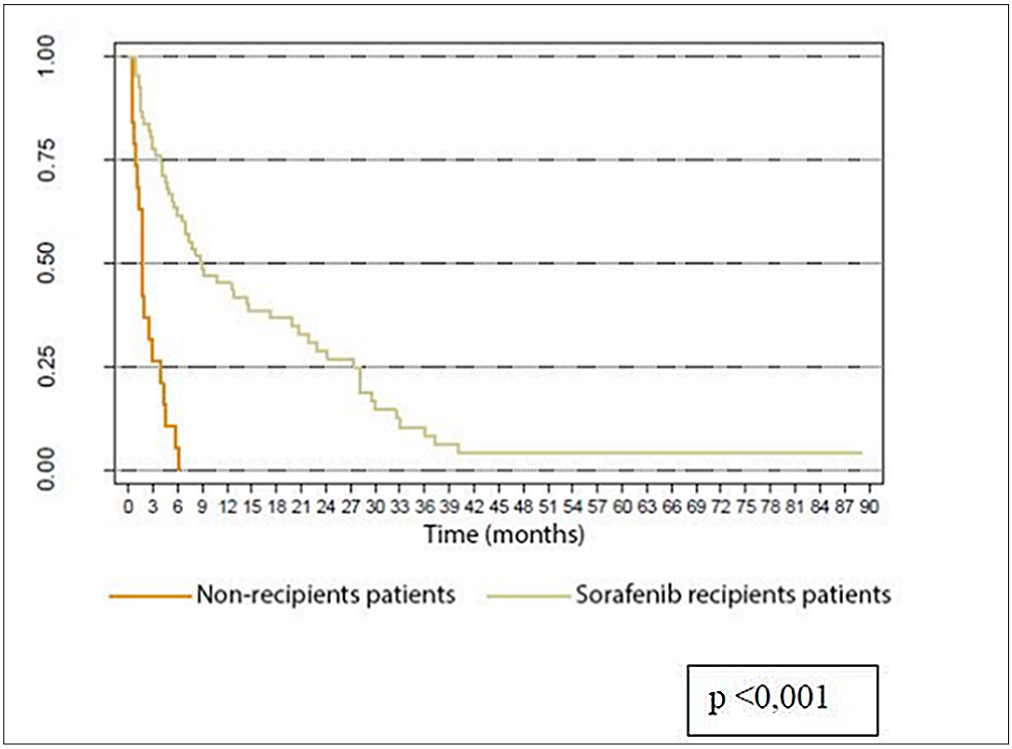

FIGURE 3.
KAPLAN - MEIER ACCUMULATED SURVIVAL FUNCTION BY USE OF MEDICATION

expected survival of 16.7 months, 9.6 months, and 4.5 months, respectively, in ECOG PS 0 and 1[14].

Although the BCLC algorithm for HCC treatment includes only advanced BCLC C hepatocellular carcinoma, early or intermediate HCC with contraindication for loco-regional treatment, and intermediate HCC with progressive disease post-TACE (without indication of new TACE) are also indications for this drug. In real-life observational studies, patients who use sorafenib are not always BCLC C[13,15,16].

Due to the high number of cases without information on the AFP value and presence of adverse effects, it was not possible to create a mathematical formula that estimates the survival time. It was only possible to estimate survival functions through the final Cox model for some patients' profiles.

In the multivariate analysis, the variables portal vein thrombosis (p=0.010), Child-Pugh (p=0.013), time of medication use (p<0.001), ECOG PS (p=0.024), and suspension for clinical worsening (p=0.031), remained statistically significant.

There was no statistically significant difference in overall survival between patients using sorafenib alone (advanced-stage diagnosis - BCLC C) and patients with previous therapy (early or intermediate stage diagnosis), despite a tendency for better survival in the group that had received another type of therapy previously (p: 0.067).

In our study, patients with vascular thrombosis had a risk 2.6 times higher of death than those without thrombosis. In the sub-analysis of the study SHARP, worse overall survival (8.1 *versus* 14.1 months) and lower time of disease progression (4.1 *versus* 7.3 months) were identified in the presence of vascular invasion, while in the presence of extrahepatic metastases, they identified worse overall survival (8.9 *versus* 14.1 months), with similar time of disease progression (5.3 *versus* 5.8 months)[17].

The presence of extrahepatic metastases had no statistical significance in our casuistry concerning OS; however, it is imperative to observe that lymph node metastases (38 patients) were quantified separately from distant metastases (35 patients), which may justify the non-significance.

Alencar et al.[13], in 2016, identified three variables associated with better OS: treatment duration longer than 6 months, presence of dermatological adverse effects, and AFP value lower than 100 ng/ml.

In our study, Child-Pugh was considered a predictor variable of a better OS, as well as in other studies[13,18]. Patients with CP B had a risk 2.9 times higher of death than those with CP A. The GIDEON study[15] found a mean survival of 13.6 months for Child A patients as compared to 5.2 in Child B patients, while Hollebecque et al.[16] found 13 *versus* 4.5 months, and Iavarone et al.[19] had 12.7 *versus* 7.7 months, respectively.

Still in the GIDEON study[15], a significant part of the patients could maintain sorafenib for more than 28 weeks, including 21% of patients with CP B, suggesting that those who can keep the treatment besides the initial period are able to continue subsequently for long periods, reinforcing the importance of the management of adverse effects in the first weeks of treatment. In our study, for every additional day of medication use, a 0.4% reduction in the risk of death was observed.

Similarly, a positive association between treatment duration and OS in the trials of Hsaio et al.[20] and Arizumi et al.[21] was also verified, which magnifies the importance of the duration of treatment with sorafenib.

Similarly to the results obtained for the CP scale (p=0.013), the functional status (p=0.024) showed a strong association with OS. Patients with ECOG PS 1 have a risk of death 2.18 times higher than those with ECOG PS 0, adjusted by the other variables of the final model. In the study INSIGHT[22], the baseline performance status had a significant effect on overall survival, with survival curves distinguishable for ECOG 0, 1, 2, and 3 (p <0.0001).

The serum AFP levels were stratified in values up to 100, from 101 to 400, and higher than 400 ng/ml. The value of 400 was used because it was the value informed in the medical report for the assessment of the request of oncological drugs of SES. Relative to the other subgroups, a Brazilian trial with the analysis of survival in patients with hepatocellular carcinoma who received sorafenib identified AFP values <100ng/ml as a possible predictor of better OS.[13]

The correlation between the presence of dermatological adverse effects and time to disease progression and overall survival has been suggested in some retrospective trials with patients with HCC undergoing treatment with sorafenib[18,23] and validated in prospective study[24].

With regard to treatment interruption with the suspension of sorafenib, the reasons in our casuistry were: disease progression, clinical worsening, and the presence of important adverse effects.

In 45%, therapy with sorafenib was suspended. In these patients, radiological disease progression – according to the guideline Response Evaluation Criteria In Solid Tumors modified (RECISTm) - was the most common cause of discontinuation (48.4%). In the multivariate analysis, patients who had the medication suspended for clinical worsening had a risk of death 2.55 times higher than those without such condition.

Initial doses of sorafenib vary widely between countries. In the GIDEON study[15], in the Korean and Japanese arms, respectively, 67% and 45.5% of the patients received the standard dose 800mg / day initially. Although some authors suggest starting with half the dose to prevent the development of side effects, this approach is not a consensus. Reig believes that the low-dose onset strategy to increase tolerance may not trigger the mechanism associated with the development of dermatological adverse events with the associated loss of survival improvement[24].

An interesting feature addressed in this study was that all patients who had an indication for sorafenib treatment were evaluated regardless they received the drug or not. Despite not having the statistical value of Intention to Treat (a statistical concept used in randomized control studies where patients are analyzed with the group that was previously randomized), it is worth noting that about 20% of patients who have medical indication of sorafenib –and prescription– do not receive treatment.

Due to its observational character, this study is limited for data analysis for several reasons, which include: the absence of a control group, selection bias, and limited data from medical reports many times not completed carefully. However, a non-interventionist trial creates space for observing the actual clinical practice, identifying the most critical points in the daily assessment of patients.

The proportion of missing data was 4.5% in relation to the presence of cirrhosis, 13% regarding AFP value, 13.6% for portal hypertension, 23% for the presence or absence of adverse effects, and 7.2% in relation to the suspension or continuation of the medication.

From this study, it was possible to assess our results, and in an indirect manner, the quality of the care provided, showing the need for better training of resident physicians and assistant physicians in order to make a better management of these patients possible, which may implicate better results.

CONCLUSIONS

With regard to the results obtained in the treatment of the patients included in this study, we can conclude that the absence of portal vein thrombosis, Child-Pugh A, ECOG PS 0, longer time of medication use, and absence of suspension for clinical worsening

are predictor factors of better overall survival. The indication of the medication is in accordance with the BCLC recommendations in 94% of the patients.

Abbreviation List

AASLD: Associação Americana do Estudo das doenças hepáticas

AE: Adverse effects

AFP: Alpha-fetoprotein

BCLC: Barcelona Clinic Liver Cancer Group

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status

HCC: Hepatocellular carcinoma

ISCMSP: Irmandade da Santa Casa de Misericórdia de São Paulo

OS: Overall survival

SD: Standard Deviation

SUS: Sistema Único de Saúde

UA: Univariate analysis

Acknowledgment

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Author's contribution

Ferreira CPC performed the research, analyzed the data and wrote the paper. Ribeiro MA conceived the original idea and contributed to the interpretation of the results. Szutan LA guided and reviewed the research. All authors provided critical feedback and contributed to the final manuscript.

RESUMO

Tumores malignos do fígado são a quarta maior causa de morte por câncer, sendo que o carcinoma hepatocelular (CHC) corresponde a 85-90% desses casos. A maioria dos doentes apresenta-se, ao diagnóstico, sem possibilidade de tratamento curativo, restando apenas as opções paliativas (quimioembolização e sorafenibe). Há poucos estudos nacionais acerca do sorafenibe.

OBJETIVO: *Avaliar fatores preditivos de sobrevida em pacientes com CHC que tiveram indicação de tratamento com sorafenibe na Irmandade da Santa Casa de Misericórdia de São Paulo (ISCMSP) e avaliação da conformidade da indicação da medicação em relação às recomendações do BCLC.*

MÉTODOS: *Foram analisados retrospectivamente os dados de 88 pacientes que tiveram indicação de tratamento com sorafenibe no período de 2010 a 2017 na ISCMSP. Análises univariada e multivariada foram realizadas na busca de preditores de sobrevida global nos pacientes que receberam a medicação.*

RESULTADOS: *Idade média de 61,2 anos, sendo 70,5% homens. A maioria (69,3%) foi classificada como Child Pugh A e BCLC C (94,3%). A cirrose esteve presente em 84,6% e a hipertensão portal em 55,7% desses. O vírus da hepatite C foi a etiologia mais comum (40,9%) do CHC. Sessenta e nove (78,4%) pacientes receberam a medicação, sendo o tempo médio de duração do tratamento 9,7 meses e a sobrevida global média, 16,8 meses. Diferenças significativas foram observadas na análise multivariada: Ecog PS (p=0,024), CP (p=0,013), tempo de uso de medicação (p<0,001), suspensão por piora clínica (p=0,031) e trombose portal (p=0,010).*

CONCLUSÃO: *Ausência de trombose portal, Child Pugh A, Ecog PS 0, tempo maior de uso de medicação e ausência de suspensão por piora clínica foram fatores preditores de melhor sobrevida global e a indicação da medicação esteve em conformidade com as orientações do BCLC em 94% dos pacientes.*

PALAVRAS-CHAVE: *Neoplasias hepáticas. Carcinoma hepatocelular. Sorafenibe. Inibidores de proteínas quinases.*

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ORIGINAL ARTICLE

Challenges on participation in a cooperative group of childhood renal tumors in Brasil

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SUMMARY

OBJECTIVE: *Children with renal tumors included in clinical trials have significantly better outcomes. In Brasil, the enrollment of patients in clinical trials remains challenging. Here we aimed to describe participation accrual in the Brazilian Wilms Tumor Study Group (BWTSG) and to identify barriers to trial registration of children with renal tumors.*

METHODS: *We determined the numbers of renal tumor diagnoses in 105 hospital-based cancer registries from 2001-2009. We then compared these totals with the numbers of renal tumor cases registered in the BWTSG from the same hospitals during the same time period. We also invited members of the Brazilian Pediatric Oncology Society to complete a 5-point Likert-type scale questionnaire regarding their opinions of the importance of participation in cooperative group trials.*

RESULTS: *The accrual rate of patient participation per hospital varied from 25% to 76%, and was highest in the South region. The accrual rate of hospital participation also varied according to the region (20-31%) and was highest in the Southeast region. For the questionnaire regarding the importance of participation in cooperative groups, the responses showed an agreement of >75% on 10 of the 13 statements.*

CONCLUSION: *Our results demonstrated low accrual of participation in a cooperative group trial in Brasil. We identified variations in registration rates according to geographic region and hospital, which may help targeted efforts to increase registration rates. The survey responses demonstrated that colleagues understand the importance of trial participation.*

KEYWORDS: *Kidney neoplasms. Child. Neoplasms. Brasil.*

INTRODUCTION

Centralized multidisciplinary treatment is the gold standard for childhood cancer. Pediatric clinical trials lead to increased survival rates and represent a unique resource for expanded investigations of the treatment, biology, and etiology of childhood cancer worldwide[1]. In particular, collaborative group trials have yielded significant therapeutic advances. For example, clinical trials for Wilms tumor treatment

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have supported increased cure rates and continued refinement of therapy[2,3].

More complete registration of pediatric cancer patients in clinical trials improves outcome and quality of life and provides opportunities for translational research[4]. Cooperative group protocols for children undergoing cancer treatment have been widely available and successful around the world[5-7]. Uniform treatment facilitates the comparison of outcome data around the country. Importantly, identifying barriers to registration in cooperative groups can improve participant accrual rates and thus lead to improved survival.

In the present study, our aim was to describe participation accrual in the Brazilian Wilms Tumor Study Group (BWTSG) and to identify barriers to trial registration of children with renal tumors in Brasil.

METHODS

To assess the registration accrual of children with renal tumors in the BWTSG, we determined the number of renal tumor cases in each hospital-based cancer registry (HBCR) and compared these totals with the number of renal tumor cases registered in the BWTSG from each hospital during the same time period (2001-2009). Since 2001, the BWTSG has been merged with the SIOP-2001 study and has registered all cases in the SIOP-2001 database. HBCRs cover about 90% of the Brazilian public health system, comprising hospitals with oncological services located in the Federal District and 25 of Brasil's 26 states. We identified the HBCR dataset using the website Integrator System (http://www.inca.gov.br). Data were compiled into a single Excel database to compare the numbers of participating hospitals and cases registered in the BWTSG with the available HBCR information.

We additionally sought to assess our colleagues' opinions regarding the importance of participation in a cooperative group trial. To this end, 289 members of the Brazilian Pediatric Oncology Society (SOBOPE) were sent questionnaires that included 13 statements to rate using a 5-point Likert-type scale, where 1 indicated strongly agree, 2 agree, 3 neutral, 4 moderately disagree, and 5 completely disagree (Table 1).

RESULTS

A total of 1497 patients were diagnosed with childhood (0-14 years of age) renal tumors and registered in 105 HBCRs from 22 Brazilian states and the Federal District between 2001-2009. During the same period, 498 cases were enrolled in the BWTSG (Figure 1). Among the 105 HBCRs, 27 hospitals (26%)

TABLE 1. STATEMENTS AND RESULTS OF THE LIKERT QUESTIONNAIRE

Statement	number of participants	median score (IQR)	% of agreement *	Agreement reached reached
1) To participate in a cooperative group it is necessary extra time on daily activities.	89	1(1-2)	87,7	yes
2) To participate in a cooperative group it is necessary financial support.	89	3(3-4)	39,3	no
3) Complete registry of all cases is essential to participate on a cooperative group.	89	1(1-1)	98,9	yes
4) The participation on a cooperative group is benefit to the institution.	89	1(1-1)	95,5	yes
5) A task to participate is to obtain the inform consent from children/parents.	89	4(4-5)	28,1	no
6) To participate on a cooperative group is necessary a multidisciplinary team participating to fill in the forms.	89	2(2-2)	92,1	yes
7) The participation in a cooperative group is important for treatment sucess and overall survival of children with cancer.	89	1(1-2)	95,5	yes
8) Health system improves with the participation on a cooperative group.	89	1(1-2)	96,6	yes
9) The major benefit to participate in a cooperative group is the scientific contribution.	89	2(2-2)	87,6	yes
10) Extra time in filling the forms jeopardize the participation on a cooperative group.	89	2(2-4)	69,6	no
11) Despite the extra time it is worth to participate on a cooperative group.	89	1(1-2)	96,6	yes
12) To follow strictly the treatment protocol is essential to participate on a cooperative group.	89	1(1-2)	97,7	yes
13) The participation on a cooperative group is benefit to all participants' colleagues.	89	1(1-2)	93,2	yes

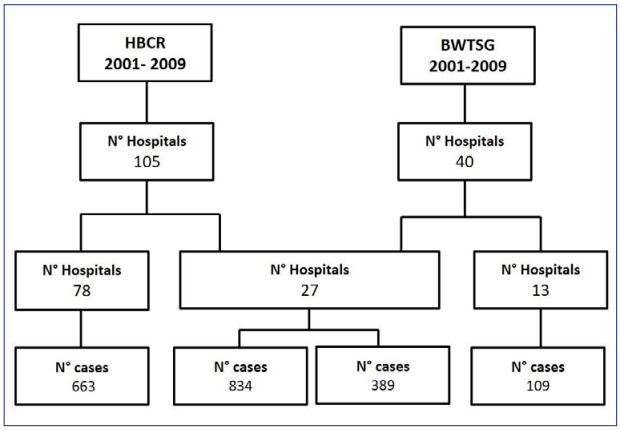
* Agreement was defined as scores of 1 or 2 (1=strongly agree;2=agree, 3=neither agree or disagree, 4=disagree, 5=strongly disagree.

participated in the BWTSG (Figure 2). Among these 27 hospitals, 834 renal tumor cases were registered in the HBCRs, and 389 renal tumor cases were registered in the BWTSG (47%) (Table 2). Thirteen hospitals that participated in the BWTSG (with 109 cases) had no data available from HBCRs (Figure 1).

The accrual rate of patient participation per hospital varied from 25% to 76% and was higher in the South region. The accrual rate of hospital participation varied according to the region (20-31%) and was highest in the Southeast region. Registration rates varied according to geographic region, with the accrual rate of patient participation per hospital being higher in the Northeast (67.4%) and South (76.2%) (Table 2).

Among the 289 SOBOPE members contacted, 89 (30%) completed the Likert questionnaire. The answers revealed a greater than 75% consensus for 10 of the 13 statements in the questionnaire. The statement regarding the "need for financial support to participate" showed low agreement (39.3%) and a median score of "neither agree nor disagree". Additionally, the "task of informed consent" had a median score of "disagreement". No agreement was achieved regarding the effect of the time needed to complete forms, and the median response was "agreement". However, there was a high rate of agreement that participation was worth the extra time required (Table 1).

FIGURE 1. FLOW DIAGRAM OF PATIENTS INCLUDED IN HOSPITAL-BASED CANCER REGISTRIES (HBCRS) AND THE BRAZILIAN WILMS TUMOR STUDY GROUP (BWTSG) DURING THE PERIOD FROM 2001-2009



DISCUSSION

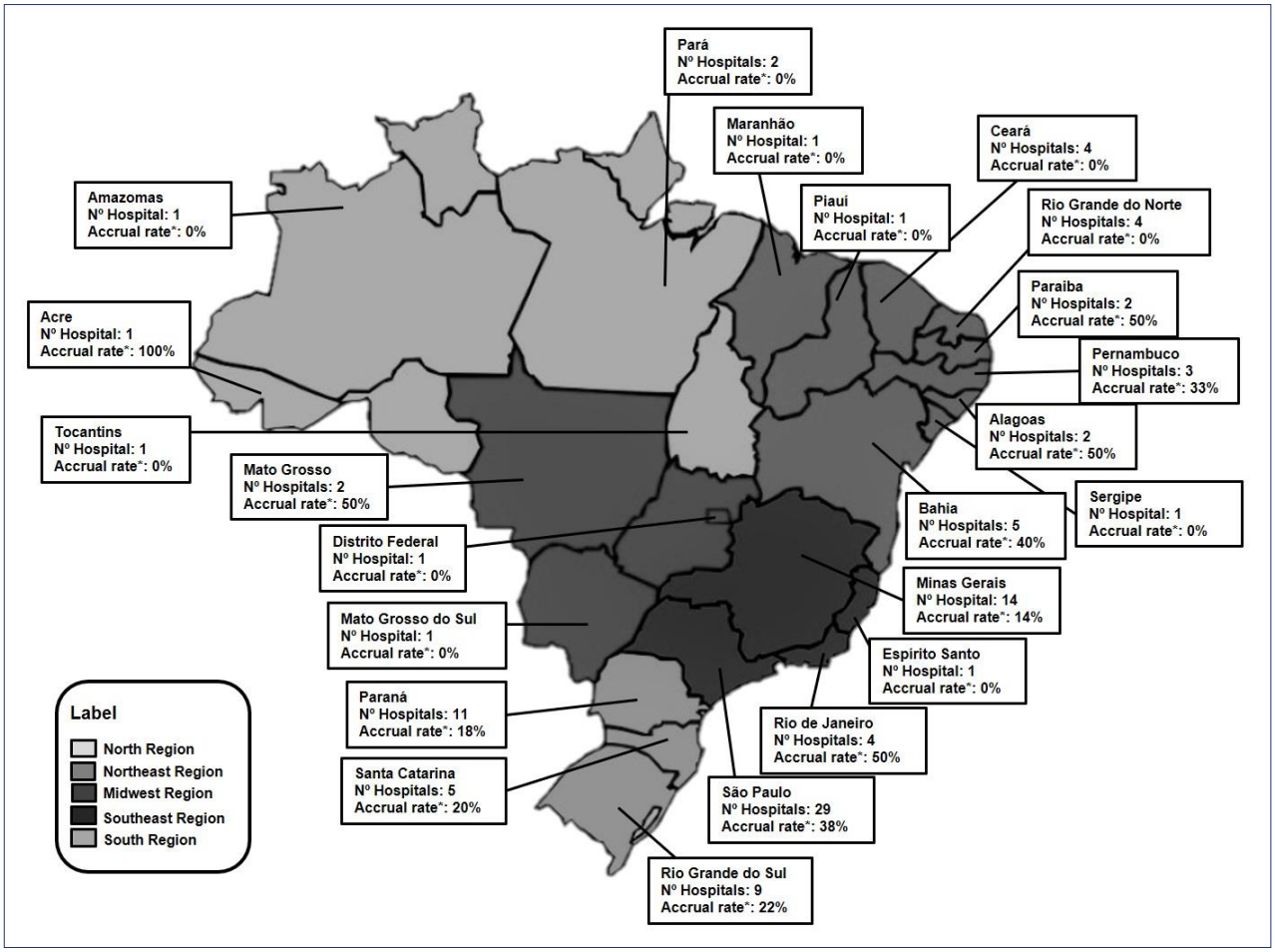
The goal of this study was to estimate the proportion of pediatric renal tumor patients in Brasil who were registered in the BWTSG. Our results indicated that compared with the numbers of renal tumor cases in HBCRs, substantially fewer patients were enrolled in the BWTSG.

Registration rates varied among geographic regions, which may reflect patterns of registration by physicians. Although the BWTSG aims to register all childhood renal cancer patients, the process relies on the physician providing information to the cooperative group data center, which requires knowledge and time. In Brasil, the BWTSG was created in 1986 and merged with the SIOP-2001 study in 2001[6,8]. The Brazilian Population-Based Cancer Registry (PBCR) is limited to capitals. In 13 Brazilian PBCRs, the median age-adjusted incidence rate of Wilms tumor was 9.5 per million, showing regional variations, with the lowest rate in Natal located in the Northeast region (5.2 per million) and the highest rate in Goiania in the Midwest region (18 per million)[9]. The estimated numbers of renal tumors in Brasil is around 600 new cases annually, and only 10% of children with renal tumors are registered in the BWTSG. During the first study of the Brazilian group, it was estimated that 25% of cases were registered[10]. One possible explanation for this difference may be that the first cooperative group trial guided the physicians to follow a treatment protocol and informed them of the necessity of registering in a study. Nowadays, Wilms tumor treatment is better known, and more oncology centers have been established throughout the country. The reduced imperative to join a trial, combined

TABLE 2. ACCRUAL RATES OF PATIENT AND HOSPITAL PARTICIPATION ACCORDING TO BRAZILIAN REGION

Brazilian geographic regions	N° Hospitals		Accrual rate	N° patients		Accrual rate
	BWTSG	HBCR	%	BWTSG	HBCR	%
North	1	5	20.0	1	4	25.0
Northeast	5	23	21.7	62	92	67.4
Midwest	1	4	25.0	7	13	53.8
Southeast	15	48	31.3	255	641	39.8
South	5	25	20.0	64	84	76.2
BRASIL	27	105	25.7	389	834	46.6

FIGURE 2. ACCRUAL RATE OF HOSPITAL PARTICIPATION IN BWTSG



with the substantial time needed to participate in a study, are likely major factors reducing participation. However, with high cure rates, large numbers of patients are needed to demonstrate small incremental improvements, which can only be achieved through a cooperative group.

In our present study, we compared the numbers of cases registered in HBCR and BWTSG during the same period. We described the disparity between the numbers of renal tumors treated at the hospitals versus the enrollment of renal tumors in the BWTSG, and evaluated the representativeness of the registered renal tumors. Our results revealed variations among different geographic regions in Brasil. The accrual rate of cases registered in the BWTSG was highest in the South region, and the accrual rate of participating hospitals was highest in the Southeast. The North region had the lowest accrual rate of hospitals, as well as the second-lowest number of cases registered per hospital, exceeding only the Midwest region.

Pediatric clinical trial groups represent a unique resource to define the best treatment for pediatric cancers and to conduct clinical and biological research. Participation in cooperative groups improves survival, as well as facilitates the identification of possible associations and causes of childhood cancer[1,5,11,12]. Our present study documented the accrual rate of participation in the BWTSG and helped us identify hospitals that treat children with renal tumors and do not register all children. Despite the low accrual rate of participation, the BWTSG has been able to collaborate with the randomized SIOP-2001 study, bringing 126 randomized cases to this study to help answer important questions regarding the treatment of Wilms tumor[8].

Participation in a cooperative group is considered the gold standard of treatment for childhood cancer. No single hospital has a sufficient number of patients to conduct a definitive, randomized, controlled trial. Participation in cooperative trials also has significant educational benefits with

regards to the dissemination of standards of care, which extend across institutions and regions[4]. In the United States and Europe, 90-95% of all children under age 15 with a newly diagnosed malignancy are treated within a cooperative group following a clinical trial protocol[12,13]. One successful example is the treatment of Wilms tumor through the creation of the National Wilms Tumor Group in 1969 in the United States. Five consecutive studies (1969-2002) demonstrate that multidisciplinary cooperation significantly improves the outcomes of children with Wilms tumor[14-17]. This collaboration contributed to the elucidation of the nature and clinical characteristics of various childhood malignant kidney tumors and enabled the completion of randomized trials of comparative treatment regimens. More recently, the Children's Oncology Group (COG) performed clinical trials[18]. The European group SIOP has conducted 6 clinical trials for Wilms tumor since 1971[19-22]. In 2001, several groups outside Europe joined the group, and the SIOP-2001 Wilms tumor study had patients enrolled from additional countries[8].

The BWTSG has now changed its name to Brazilian Renal Tumors Group (BRTG) to include all renal tumors. The group has made efforts to improve participation through the development of a website (www.gbtr.com.br) to facilitate participation, case discussions, radiology and pathology review, improving diagnosis and treatment in this heterogeneous country. We have provided feedback to all hospitals regarding accrual rates of participation, and we believe physicians saw this as very positive feedback.

The present study has several limitations, mainly due to the analysis of secondary data collected at 105 different cancer treatment centers. We did not have information regarding the clinical epidemiologic aspects, such as stage distribution, histology, outcome, and treatment compliance, and we were unable to determine whether there was a selection bias in patient registration. One hospital provided additional information that they register only randomized cases (personal communication). Our results suggest that renal tumor cases are under-reported to the BWTSG in certain regions of Brasil, especially in the North. Even with its limitations, the present analysis of the accrual rates of participation by hospitals was valid, and we hope the findings will support improved participation accrual.

The questionnaire sent to all members of the SOBOPE served to highlight common problems among centers. From the results, we concluded that physicians understand the importance of trial participation, and that lack of time is the most important issue hindering registration. The major barrier to participation was lack of time to complete the forms. Physicians understand and agree that participation is important for better outcomes, improves knowledge, and has benefits for patients, multidisciplinary teams, and the hospital. Importantly, physicians did not report that they lack the financial support to participate, and they agree that participation is worth the required extra time. Notably, data from a Likert scale must be interpreted with caution, and further research is necessary.

We believe that the data from our present study will improve knowledge and participation, facilitating the exchange of information and research regarding renal tumors, not only around Brasil but globally, and will encourage collaboration at national and international levels. Strategies to increase participation have been suggested, and an online registration system is presently being implemented (www.gbtr.com.br).

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Authors disclosures and conflicts of interest

All authors have no relationship to disclose

Author contributions

Lucian S. Viana: Data collection, analysis, and interpretation; final approval of the manuscript.

Rejane de Souza Reis, Marceli de Oliveira Santos, Neimar de Paula Silva, Nathalie V. Balmant, Paulo A. Faria, Beatriz de Camargo: Study conception and design; data analysis and interpretation; final approval of the manuscript.

RESUMO

OBJETIVO: *Crianças com tumores renais incluídas em ensaios clínicos apresentam melhora significativa na sobrevida. No entanto, o envolvimento desses pacientes em ensaios clínicos continua sendo um desafio no Brasil. Nosso objetivo neste estudo é descrever a taxa de aderência e adesão no Grupo Cooperativo Brasileiro para tratamento de Tumor de Wilms (GCBTTW) e identificar barreiras na participação ao protocolo.*

MÉTODOS: *Identificamos o número de casos de tumores renais diagnosticados em 105 registros hospitalares de câncer no período de 2001 a 2009. O número total desses casos foi então comparado ao número de casos de tumores renais registrados no GCBTTW provenientes das mesmas unidades hospitalares e durante o mesmo período. Os membros da Sociedade Brasileira de Oncologia Pediátrica foram convidados para completar um questionário com escala do tipo likert com o objetivo de conhecer suas opiniões sobre a importância e as dificuldades na participação em ensaios clínicos de grupos cooperativos.*

RESULTADOS: *A aderência de pacientes por hospital variou de 25% a 76% e foi maior na região Sul. A adesão da participação do hospital também variou de acordo com a região (20-31%) e foi maior na região Sudeste. Com relação ao questionário referente à importância da participação em grupos cooperativos, as respostas mostraram concordância de mais de 75% em 10 das 13 afirmações.*

CONCLUSÃO: *Nossos resultados demonstraram uma baixa participação em grupos cooperativos no Brasil. Houve variações nas taxas de adesão e aderência de acordo com a região geográfica e unidade hospitalar, o que pode auxiliar em futuros esforços para a melhora dessas taxas. As respostas ao questionário demonstraram que os profissionais entendem a importância da participação em grupos cooperativos.*

PALAVRAS-CHAVE: *Neoplasias renais. Criança. Neoplasias. Brasil.*

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ORIGINAL ARTICLE

Factors related to adherence to antiretroviral treatment in a specialized care facility

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SUMMARY

The objective of this study was to verify the level of adherence to antiretroviral treatment and its associated factors. This is a descriptive cross-sectional study based on data retrieved from medical records. To achieve this, we used a questionnaire composed of sociodemographic and clinical information recorded from patients aged between thirteen and fifty-nine years who attended a specialized service from 2007 to 2014. The chi-square test was performed to verify the association of the outcome with the categorical variables. Continuous variables were compared through the Student t-test. Thirteen variables were analyzed in the bivariate model, resulting in the selection of the following variables to the multivariate model (p<0.20) age of discovery (p=0.12), age (p=0.14), skin color (p=0.12), level of education (p=0.03), time since HIV diagnosis (p<0.001) and AIDS case (p<0.001). Among the six variables selected for the multivariate model, cases of aids (p<0.001) remained significant. We concluded that having aids decreases the probability of non-adherence to antiretroviral treatment by 92%. These results indicate that symptomatic patients have better adherence to therapy.

KEYWORDS: *HIV. Acquired immunodeficiency syndrome. Anti-retroviral agents. Medication adherence. Therapeutics. Health services.*

INTRODUCTION

Antiretroviral therapy (ART) emerged in the 1990s, resulting in an increase in survival rates. Nowadays, the term 'survival' is no longer used because ART has eliminated the prospect of short-term death, ensuring a life expectancy similar to that of non-infected individuals, provided there is proper adherence to therapy[1].

Brasil has been a pioneer in adopting a public policy of universal free access to antiretroviral treatment, even at an international level. In 1996, Brasil implemented high-efficacy antiretroviral therapy, whose greatest success was adopting a regime of three antiretroviral medications (triple therapy)[2]. The universal access to these drugs in Brasil resulted in a change in the characteristic of acquired immunodeficiency syndrome (AIDS), from a disease of high lethality to a controllable chronic disease[3].

The quality of life provided by the universal access to therapy is evidenced by statistical data reproduced by the Global Report of the Joint United Nations Program on Human Immunodeficiency Virus (HIV)/AIDS (UNAIDS)[4], which proved a significant decline in mortality due to aids, not only in Brasil but in all

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other countries. In 2013, there was a reduction of 800,000 deaths[5].

In 2015, UNAIDS established ambitious goals for HIV through a protocol that aims to chart new directions for the treatment of the virus. The goals for 2020 include the knowledge of their seropositive status by 90% of all people living with HIV, uninterrupted antiretroviral therapy for 90% of all people diagnosed with HIV infection, and viral suppression in 90% of all people receiving antiretroviral therapy[4].

Currently, in Brasil, it is estimated that 83% of those infected know their diagnosis, 62% are undergoing medical treatment, and 88% have an undetectable viral load. Thus, in order to achieve the goal established by UNAIDS, it is necessary that those affected by the disease have continued medical monitoring[6].

Considering the above, the objective of this study was to determine the levels of adherence to antiretroviral treatment and the factors related to it by evaluating patients with HIV/Aids in the aged between 13 and 59 years old and treated in a Specialized Care Service (SAE), located in the municipality of Vitória, Espírito Santo (ES), between 2007 and 2014.

METHODS

This is a descriptive, cross-sectional study based on a quantitative approach to identify and assess patients from 13 to 59 years old treated in the Center of Reference for Sexually Transmitted Diseases (STD/AIDS), located in the municipality of Vitória, ES, between 2007 and 2014.

All information was obtained by using a structured form for data collection. The form was divided into two stages, one containing questions related to sociodemographic aspects and the other to the clinical aspects.

We considered a minimum frequency of poor adherence of 5% for any of the categories present among the participants. To obtain a population estimate, considering a confidence interval of 95%, a sample of 102 individuals would be required to discriminate a five-times-higher frequency of poor adherence in a risk category, with 80% of power. Since there were 20 adolescents aged between 13 and 19 years old recorded in the SAE, we decided to include all of them plus a sample of 100 adults, which, in a direct comparison of age ranges, resulted in a ratio of 1:5.

Data were collected from patients' medical records, and we selected those aged from 13 to 59 years. We randomly drew 100 records from the 849 of patients aged between 19 and 59 years, since all adolescents aged between 13 and 19 years were included. The collection period lasted from November 2015 to March 2016.

Regarding the treatment adherence criterion, we classified as adherent members who continued ART without interruptions from the time of diagnosis until the day of data collection, i.e., the criterion used was medication pick-up from the SAE pharmacy. Those who abandoned therapy for any period or permanently were classified as non-adherent.

The categorical variables were represented by their absolute and relative frequencies. The continuous quantitative variables were represented by their central position and variability. Since all fit the Gauss model, we used mean and standard deviation. The bivariate analysis considered a dichotomous outcome (adherence or not), assessing its possible association with several variables. The association of the outcome with the categorical variables was verified by the Chi-square test, except when expected frequencies found were lower than five, in which case the maximum likelihood ratio (more than two categories) was used. Continuous variables were compared by Student's t-test (two groups). To measure the effect, we used the odds ratio with their respective confidence intervals of 95%.

Variables with a p-value of less than 0.2 in the bivariate analysis were included in the multivariate model, which comprised binomial logistic regression. The data were analyzed using Statistical Package for Social Sciences (SPSS), version 17.0, and presented in simple frequency tables.

This study was preceded by the approval of the Research Ethics Committee of the Federal University of Espírito Santo (UFES) (CAAE No. 46032915.9.0000.5060).

RESULTS

Of the 120 forms filled out, 79 (65.8%) belonged to male individuals, and their average age until the day of the collection was 36.3 years. There were 41 females (34.2% of the collected data), with an average age of 38.2 years. The distribution according to skin color revealed that 77 (64.2%) were brown, 22 (18.3%) were white, and 21 (17.5%) were black. Regarding formal education aspects, considering valid records, 27 (27.3%) had not completed primary education, and 24 (24.2%) had completed secondary education (Figure 1). With respect to occupations, we decided to categorize

patients between those who exercise (87 - 76.3%) or not (27 - 23.7%) a profession and then into jobs that require secondary education, corresponding to 66 individuals (57.9%), those that require an university degree, with a total of 21 individuals (18.4%), and those that do not apply, which included 27 individuals (23.7%) who were students, unemployed, or homemakers.

Regarding the distribution of people living with HIV/aids, according to the clinical variables, we found that the main source of infection by the virus was through sex, corresponding to 111 people (97.4%). We observed that the time for the diagnosis of HIV was an average of 63.6 months and 77 individuals (67%) progressed to AIDS. The Viral Load (VL) was undetectable in 67 patients (75.3%). The CD4 lymphocyte count had an average of 608.53 cells/mm3. Regarding a previous history of opportunistic infections, we observed that 66.7% had no history, as shown in Table 1.

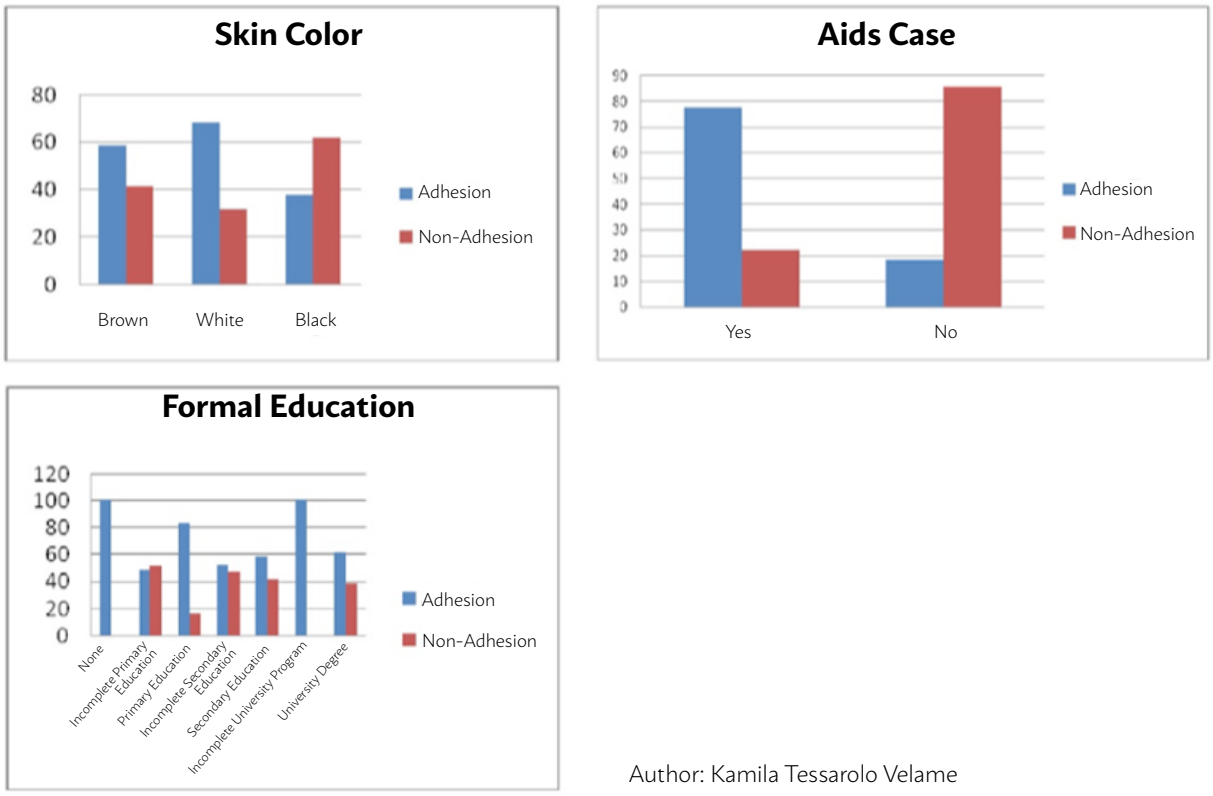
Initially, we searched for an association between the adherence or non-adherence and sociodemographic and clinical variables. There was a significant difference ($p<0.05$) concerning the age at the time of diagnosis. Regarding skin color, brown-skinned people showed better adherence when compared to blacks and whites. In relation to formal education, people with higher educational levels showed greater adherence, with statistical significance. As to the clinical variables, we found a significant difference in adherence among those with an AIDS diagnosis ($p<0.001$) (Figure 1). There was significance regarding viral load ($p=0.04$); however, it was not included in the multivariate model because its increased level is a natural consequence of non-adherence and could act as a confounding variable. The prevalence of non-adherence was 43.3% in the sample.

Among the 13 variables analyzed, six were included in the logistic regression model. The results of the analysis (Table 2) showed that an aids diagnosis is associated with better adherence to antiretroviral treatment.

DISCUSSION

In the present study, we observed that an aids diagnosis improves adherence to antiretroviral therapy. Other variables that are considered as potential risk factors for non-adherence, such as education and marital status, showed no significant association with the outcome of interest (adherence).

FIGURE 1. CATEGORICAL VARIABLES INCLUDED IN THE LOGISTIC REGRESSION MODEL



Author: Kamila Tessarolo Velame

TABLE 1. CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS OF A SAMPLE OF 120 INDIVIDUALS AGED BETWEEN 13 AND 59 YEARS IN FOLLOW-UP IN THE CENTER OF REFERENCE FOR STD/AIDS* OF VITÓRIA, ES, BRASIL, 2007 TO 2014.

Variables		Adherence n (%)	Non-adherence n (%)	Total n (%)	P-value ¥
Gender	Female	22 (53.2)	19(46.3)	41 (34.2)	0.63a
	Male	46 (58.2)	33 (41.8)	79 (65.8)	
Age (years) mean (SD)		38.2(11.7)	35.3 (9.3)		0.14b
Age of diagnosis (years) average (SD)		34.2(11.1)	29.4 (9.1)		0.12b
Skin color	Brown	45 (58.4)	32(41.6)	77 (64.2)	
	White	15(68.2)	7(31.8)	22(18.3)	0.12a
	Black	8(38.1)	13(61.9)	21 (17.5)	
Marital status	Single	51 (63.0)	30 (37.0)	81 (67.5)	
	Married	11 (45.8)	13 (54.2)	24 (20.0)	
	Divorced/separated	5 (55.6)	4 (44.4)	9 (7.5)	0.4a
	Widow(er)	1 (50.0)	1 (50.0)	2(1.7)	
	Stable union	0 (0.0)	1 (100.0)	1 (0.8)	
Formal education	None	3(100.0)	0 (0.0)	3(3.0)	
	Incomplete primary education	13(48.1)	14(51.9)	27 (27.3)	
	Primary education	5 (83.3)	1 (16.7)	6(6.1)	
	Incomplete secondary education	10(52.6)	9 (47.4)	19(19.2)	0.03a
	Secondary education	14 (58.3)	10(41.7)	24 (24.2)	
	Incomplete university program	7(100.0)	0 (0.0)	7(7.1)	
	University degree	8(61.5)	5 (38.5)	13(13.1)	
Occupation 1§	Yes	51 (58.6)	36(41.4)	87 (76.3)	0.8a
	No‖	15(53.6)	13 (46.4)	28 (24.6)	
Occupation 2^|	Until secondary education	37(56.1)	29 (43.9)	66 (57.9)	
	University degree	15(71.4)	6 (28.6)	21 (18.4)	0.35a
	Does not apply**	15(53.6)	13 (46.4)	28 (24.6)	
Source of	Sexual transmission	64 (57.7)	47 (42.3)	111 (97.4)	
infection	Use of injectable drugs	0 (0.0)	1 (100.0)	1 (0.9)	0.21a
	Occupational	0 (0.0)	1 (100.0)	1 (0.9)	
	Others	1 (100.0)	0 (0.0)	1 (0.9)	
Time of HIV diagnosis (months) average (SD)		54.6 (26)	75.3 (23.7)		<0.00 Ib
Aids case	Yes	60 (77.9)	17(22.1)	77 (67.0)	< 0.001a
	No	7(18.4)	31 (85.6)	38 (33.0)	
Viral load	<50 (undetectable)	55(82.1)	12(17.9)	67 (75.3)	
(copies/ml)	50 to 100,000	10(52.6)	9 (47.4)	19(21.3)	0.04a
	100,001 to 500,000	2 (66.7)	1 (33.3)	3 (3.4)	
Prior history	Yes	23 (57.5)	17(42.5)	40 (33.3)	
of infection	No	45 (56.2)	35 (43.8)	80 (66.7)	0.9a
Total				120/100	

[a]Chi-square test; [b]Student t-test. *STD- sexually transmitted diseases; ¥ - p - probability of significance; SD - standard deviation. Occupation 1§ - categorized as presence or absence of profession; ||No - unemployed, students, and homemakers; Occupation 2 - categorized according to the level of formal education; **Does not apply - unemployed, students, and homemakers. The frequencies were obtained from the record items that contained valid data.

Socioeconomic factors, such as formal education and marital status, have more influence only in situations of extreme poverty since this can make it more difficult to have access to treatment[7].

The results in relation to the variable "case of aids" indicate that the likelihood of non-adherence to antiretroviral treatment is reduced by approximately 92% among individuals who developed the disease. This indicates that symptomatic individuals adhere more often to treatment.

Probably, the presence of symptoms motivates the search for rigorous clinical monitoring due to the expectation of improvement, which, in turn, causes satisfactory adherence to treatment. The absence of symptoms and feeling of well-being are pointed out as causes for not taking their medicine, since patients

TABLE 2. RESULTS FROM THE REGRESSION ANALYSIS OF VARIABLES WITH P < 0.2 AFTER BIVARIATE ANALYSIS OF THE CHARACTERISTICS OF 120 INDIVIDUALS AGED BETWEEN 13 AND 59 YEARS IN FOLLOW-UP IN THE CENTER OF REFERENCE FOR STD/AIDS VITÓRIA, ES, BRASIL, 2007 TO 2014.

Variables	Coefficient (Beta)	Standard error (SE)	Significance (p-value) ¥	Odds ratio Exp (Beta)	Confidence interval (CI 95%)	
					Lower threshold	Upper threshold
Age of diagnosis	.452	.342	.187	1.571	.803	3.074
Age	-.382	.338	.259	.683	.352	1.324
Skin color	.038	.348	.913	1.039	.525	2.054
Formal education	.136	.159	.392	1.146	.839	1.565
Time of HIV diagnosis	-.007	.030	.807	.993	.936	1.053
Aids case	-2.527	.670	.000	.080	.022	.297

*STD - sexually transmitted diseases; ¥ - p - probability of significance; CI - Confidence Interval.

believed it was not necessary, and only resumed taking it once they started to feel bad again[8].

In Brasil, a study conducted in 55 health services specialized in the care for patients with HIV/aids showed large variations in the non-adherence rates throughout the country, ranging from 10.7% to 86.0%. Absenteeism in consultations was a factor that contributed even more to non-adherence and worsened values of CD4 lymphocytes and viral load[9].

The issue of the disease symptoms is highly emblematic in literature and incorporates several dimensions, even those attributed to the occurrence of adverse reactions to medications[10]. The patient cannot see the medication as a trial, just using it when they are symptomatic, believing there will be a spontaneous improvement and, at the same time, blame it for the onset of symptoms. This compromises the correct adherence to treatment[11].

Another important reason for low adherence or even the late start of ART is the stigma. Patients are afraid of being identified as infected by HIV; thus, they avoid care until very late when there are no more choices left, and weakness is inevitable. These aspects reflect a poor understanding of the chronic nature of the disease[12]. In Uganda, a study was conducted that confirms this hypothesis. In it, patients reported difficulties in taking medication when they were close to employers, colleagues, or friends who were not aware of their condition[13]. The irregular follow-up makes it more likely for them to develop symptoms of immunodeficiency. Thus, patients adhere to antiretroviral therapy aiming at a clinical improvement[14].

This study has limitations related to its cross-sectional design, which prevents a proper assessment of causality, and the fact that its sample was calculated to show large effects, thus limiting its ability to identify valid associations of smaller magnitude. In addition, it was not possible to retrieve information about patient behavioral data due to the scarcity of information in the records analyzed.

On the other hand, the importance of the study lies in the fact that it identifies the presence of symptoms as a potential factor that stimulates adherence. In a scenario of an early start of antiretroviral therapy in infected individuals, the results presented here highlight the importance of developing precise strategies to stimulate adherence, since such individuals are more probable of being asymptomatic[15].

CONCLUSION

The AIDS epidemic is currently characterized by the presence of many epidemiological changes in its profile, related to both socioeconomic and clinical aspects. This requires ongoing changes to patient care, which is provided through antiretroviral treatment and various professionals.

The present study fits into the context of the need to establish appropriate strategies to reduce the damages related to HIV infection in individuals. However, there is no intention to exhaust the theme and encompass the full range of issues inherent to a subject as important as the factors that can interfere with adherence to antiretroviral treatment.

Authors contributions

Kamila Tessarolo Velame - Participated in the conception of the study, its design, data collection, data analysis and drafting of the manuscript. Renata de Souza da Silva - Participated in data collection, data analysis, and critical reading of the first version of the manuscript. Crispim Cerutti Junior - Participated in the conception of the study, its design, data analysis, and drafting of the manuscript.

Conflict of interest

There are no conflicts of interest to be declared. Derived from the Master's thesis entitled "Fatores relacionados à adesão ao tratamento antirretroviral em serviço de atendimento especializado", submitted as part of the Graduate Program on Infectious Diseases, at the Federal University of Espírito Santo, Vitória, ES, Brasil.

RESUMO

O objetivo deste estudo foi verificar os níveis de adesão ao tratamento antirretroviral e os fatores associados a ela. Trata-se de um estudo descritivo de delineamento transversal baseado em levantamento de prontuários. Para tanto, foi utilizado um questionário composto de informações sociodemográficas e clínicas de pacientes com idade entre 13 e 59 anos atendidos em um serviço de atendimento especializado nos anos de 2007 a 2014. Foi realizado o teste do Qui-quadrado para verificar a associação do desfecho com as variáveis categóricas. As variáveis contínuas foram comparadas pelo teste t de "Student" (dois grupos). Treze variáveis foram analisadas no modelo bivariado, sendo selecionadas para o modelo multivariado (p<0,20): idade de descoberta (p=0,12), idade (p=0,14), cor da pele (p=0,12), escolaridade (p=0,03), tempo de diagnóstico do HIV (p<0,001) e caso de aids (p<0,001). Das seis variáveis selecionadas para o modelo multivariado, permaneceu significante o fato de o paciente ter aids (p<0,001). Concluiu-se que ter aids reduz a probabilidade de não adesão ao tratamento antirretroviral em cerca de 92%. Os resultados indicam que o indivíduo que é sintomático adere melhor à terapia.

PALAVRAS-CHAVE: *HIV. Síndrome da imunodeficiência adquirida. Antirretrovirais. Adesão à medicação. Terapêutica. Serviços de saúde.*

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ORIGINAL ARTICLE

Physical performance is associated with visual acuity in university students: results of a school-based study

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SUMMARY

OBJECTIVE: *The aim of our study is to explore the relationship between physical performance and visual acuity in university students in China.*

METHODS: *tests of standing long jump, 50-meter dash and pull-ups sit-ups were conducted. The visual acuity was measured using a logarithm of the minimum angle of resolution (logMAR) chart. Pearson correlation was used to test the correlation of physical performance with visual acuity in university students.*

RESULTS: *The number of pull-ups was negatively associated with visual acuity in the left eye for male students, while a negative correlation was found between the time of the 50-meter dash and visual acuity in the right eye for female students.*

CONCLUSIONS: *Our study identified that physical exercise might help improve visual acuity. University students should practice strength exercises to improve physical performance.*

KEYWORDS: *Physical functional performance. Visual acuity. Students.*

INTRODUCTION

Recently epidemiology studies have shown that most university students are not physically active[1]. Physical activity impacts health-related quality of life[2], social problem-solving ability[3], physical performance[4], and obesity[5]. There was a higher prevalence of reduction of visual acuity in students from a medical university in China[6]. A previous study found that children should remain the focus of detection and treatment of reduction of visual acuity[7]. However, little is known about the relationship between physical performance and visual acuity in university students.

In the present study, our objective was to evaluate the relationship between physical performance and visual acuity among university students from a university in China.

METHODS

Participants

This cross-sectional study was conducted in university students recruited for a physical-fitness test in 2012 – which was described in a previous study[8].

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A total of 2313 subjects (978 males and 1335 females) were recruited. All students agreed to provide their personal information related to the scope of this study. This study was also approved by the Wannan medical college ethics committee.

Criteria for inclusion and exclusion

Students who had a serious disease that influenced physical activity were excluded from this study.

Physical-fitness test

All students took part in standing long jump, 50-meter dash, and pull-ups/sit-ups tests. We recorded the time of the 50-meter dash and the number of pull-ups/sit-ups. For the standing long jump, students had three attempts, and the best result was recorded. We recorded the number of pull-ups for male students and the number of sit-ups for female students.

Visual acuity-test

The visual acuity was measured using a logarithm of the minimum angle of resolution (logMAR) chart by staff trained, which is the "gold standard" by which the outcomes of the vast majority of clinical trials or interventions were assessed, and each eye was measured separately (using the Standard for Logarithmic Visual Acuity Charts, GB 11533-1989, GB/T 11533-2011 of the Standardization Administration of the People's Republic of China)[9]. The uncorrected visual acuity was used in this study. The examination was performed under the condition of no direct sunlight and shadows.

Statistical analysis

R software was used to describe the physical performance and vision among university students. Pearson correlation was used to test the correlation of physical performance with visual acuity in university students. A P-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 2313 participants (978 males and 1335 females) aged from 19 to 23 years old were admitted into our study. The mean of visual acuity is shown in table 1. Table 2 shows the correlation between physical performance and visual acuity for male students. The results showed that the number of pull-ups was negatively associated with visual acuity in the left eye. However, the correlation between the time of the 50-meter dash and the distance of the standing long jump with visual acuity in the left eye was not significant, and no significant correlation was found between physical performance and visual acuity in the right eye. Table 3 shows the correlation between physical performance and visual acuity for female students. There was a negative correlation between the time of the 50-meter dash and visual acuity in the right eye, and a positive correlation between the number of sit-ups and visual acuity in the right eye, while no significant correlation was found between performance and visual acuity in the left eye.

TABLE 1. COMPARISON OF MEASUREMENT VALUES FOR VISUAL ACUITY BETWEEN MALE AND FEMALE STUDENTS

Variable	Male		Female		t	P
	Mean	SD	Mean	SD		
Left eye	5.52	0.42	4.57	0.39	2.57	0.010
Right eye	4.48	0.43	4.54	0.40	3.47	0.001

TABLE 2. CORRELATION BETWEEN PHYSICAL PERFORMANCE AND VISUAL ACUITY FOR MALE STUDENTS

		50-meter dash	standing long jump	pull-ups	Left eye	Right eye
50-meter dash	Pearson Correlation	1				
	Sig. (2-tailed)					
	N	1025				
standing long jump	Pearson Correlation	-.240**	1			
	Sig. (2-tailed)	.000				
	N	1024	1118			
pull-ups	Pearson Correlation	-.166**	.314**	1		
	Sig. (2-tailed)	.000	.000			
	N	1020	1112	1117		
Left eye	Pearson Correlation	-.045	.017	-.064*	1	
	Sig. (2-tailed)	.147	.568	.032		
	N	1025	1117	1116	1124	
Right eye	Pearson Correlation	-.058	.026	.034	.795**	1
	Sig. (2-tailed)	.065	.387	.251	.000	
	N	1025	1118	1117	1124	1125

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

TABLE 3. CORRELATION BETWEEN PHYSICAL PERFORMANCE AND VISUAL ACUITY FOR FEMALE STUDENTS

		50-meter dash	Standing long jump	Sit-up	Left eye	Right eye
50-meter dash	Pearson Correlation	1				
	Sig. (2-tailed)					
	N	1389				
Standing long jump	Pearson Correlation	-.223**	1			
	Sig. (2-tailed)	.000				
	N	1387	1474			
Sit-up	Pearson Correlation	-.179**	.187**	1		
	Sig. (2-tailed)	.000	.000			
	N	1384	1468	1470		
Left eye	Pearson Correlation	-.047	.005	.048	1	
	Sig. (2-tailed)	.083	.844	.065		
	N	1386	1471	1467	1481	
Right eye	Pearson Correlation	-.080**	-.019	.064*	.820**	1
	Sig. (2-tailed)	.003	.460	.014	.000	
	N	1386	1471	1467	1480	1481

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Our present study shows there are significant differences in visual acuity between male and female students. The results of our study are consistent with previous ones in which there were more females with poor vision than males[10]. The possible reason may be that female students work harder than male students in China, which leads to a reduction of visual acuity.

We also found that the number of pull-ups was negatively associated with visual acuity in the left eye for male students. While a negative correlation between the time of the 50-meter dash and visual acuity in the right eye was found for female students. A possible reason for this may be that there are differences in the choice of sports activities between male and female students. Our cross-sectional study found that physical performance was associated with visual acuity, which provides a possible strategy for preventing vision damage via strength training physical activity.

There are also some limitations to the present study. It is cross-sectional, which limits explanations for causal-results relationships. Additionally, some variables (dietary, economic factor) that may affect vision were not included.

CONCLUSION

Our study suggests that physical exercise is associated with visual acuity. However, cause-results relationships also need to be confirmed.

Author Contributions

Conceptualization, Koulong Wu and Liu Yang; formal analysis, Koulong Wu; writing—original draft preparation, Liu Yang; writing—review and editing, Lianping He; supervision, Tianhua Du; funding acquisition, Tianhua Du.

RESUMO

OBJETIVO: *O objetivo deste estudo é explorar a relação entre desempenho físico e acuidade visual em alunos universitários da China.*

MÉTODOS: *testes de salto em distância em pé, corrida de 50 metros, flexões e abdominais foram realizados. A acuidade visual foi medida através de um logaritmo do quadro de ângulo mínimo de resolução (logMAR). A correlação de Pearson foi utilizada para testar a correlação entre o desempenho físico e a acuidade visual em alunos universitários.*

RESULTADOS: *O número de flexões apresentou uma associação negativa com a acuidade visual do olho esquerdo em estudantes do sexo masculino e uma correlação negativa foi encontrada entre o tempo da corrida de 50 metros e a acuidade visual do olho direito em estudantes do sexo feminino.*

CONCLUSÃO: *O nosso estudo identificou que o exercício físico pode ajudar a aumentar a acuidade visual. Os estudantes universitários devem praticar musculação para melhorar o desempenho físico.*

PALAVRAS-CHAVE: *Desempenho físico funcional. Acuidade visual. Estudantes.*

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ORIGINAL ARTICLE

Analysis of the chemerin and resistin adipokines in children and adolescents

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SUMMARY

OBJECTIVES: *To compare the serum concentrations of adipokines resistin and chemerin in children and adolescents with eutrophic and overweight and to evaluate their relationship with anthropometric, biochemical, and blood pressure variables.*

METHODS: *a cross-sectional epidemiological study was conducted with 234 students enrolled in public elementary schools in the city of Juiz de Fora / MG. Anthropometric evaluation, biochemistry, and blood pressure measurement were performed. Statistical analyzes included the Student-t or Mann-Whitney tests, Pearson or Spearman correlation, used according to the distribution of the variables, and linear regression analysis, by means of the evaluation of the effect of the independent variables on the serum levels of chemerin and resistin, adjusted for age and sex. For the data analysis, SPSS® software version 21.0 and STATA® version 10.1 were used, assuming a significance level of 5%.*

RESULTS: *the concentrations of chemerin were higher in eutrophic individuals than in those with excess weight (p> 0.05). In contrast, levels of resistin were higher in the young with excess weight than in the eutrophic ones (p <0.05). In the multiple linear regression analysis, the levels of chemerin were associated with the values of resistin, systolic, and diastolic blood pressure. Resistance levels maintained association only with BMI and chemerin values.*

CONCLUSION: *the adipokines analyzed presented a distinct profile in the groups of children and adolescents with eutrophic and overweight.*

KEYWORDS: *Child. Adolescent. Adipokines. Risk factors. Chemokines. Resistin.*

INTRODUCTION

Although cardiovascular diseases (CVD) are rare in childhood, the atherosclerotic process begins during this stage and is characterized as an inflammatory disease of the blood vessel walls that triggers a series of responses, at the cellular and molecular level, which is intensified in individuals with obesity, since the adipose tissue is responsible for secreting numerous bioactive substances - the adipokines - that may have pro-inflammatory or anti-inflammatory action[1].

The unregulated production of these substances, fostered by the increase in fat mass, can contribute to the onset of metabolic disorders resulting from obesity[2,3]. Studies have reported that adipokines are related to excess weight, dyslipidemia, hypertension,

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and insulin resistance, both in adults and children and adolescents[4,5].

The marked presence of inflammatory markers associated with excess weight among children is worrying since long-term inflammation causes cumulative vascular damage, indicating a risk of future cardiovascular events[6].

In the face of the alarming prevalence of excess weight among children and adolescents and its possible consequences in adulthood, it is important to better understand the physiopathology of the adipose tissue and the substances its secretes, investigating their association with the inflammatory process and its metabolic and cardiovascular implications. However, the literature on the role of adipokines in the children and adolescent population and their association with comorbidities and cardiometabolic risk variables is still scarce. Therefore, the objective of this study is to compare the serum concentrations of the resistin and chemerin adipokines in children and adolescents with eutrophy and excess weight and assess its relationship with anthropometric and biochemical variables and blood pressure, traditionally used to evaluate cardiovascular risk.

METHODS

Study design and sampling process

This is a cross-sectional epidemiological study conducted in the municipality of Juiz de Fora, MG, and divided into two stages. In the first stage, we evaluated a probability sample of 708 students from 7 to 14 years old of both sexes, enrolled in public schools of elementary education. The second stage involved a subsample of 234 students, randomly selected and divided into two groups based on their BMI classification, according to their age: (a) children and adolescents with eutrophy and (b) children and adolescents with excess weight.

We did not include in the sampling process students who attended Special Education classes and the adolescents who reported pregnancy. For the subsample, we excluded students with low weight.

The sample was selected through a simple random sampling process, according to age and proportion in each school. The sample size calculation was based on the proportion of the population studied with the prevalence of overweight and obesity for the age group studied (8%), considering 20% of losses due to possible absences or refusals, a desired precision of 2%, and a significance level of 5%.

Anthropometric assessment and body composition

In the anthropometric analysis, we included weight, height, body fat percentage, and waist perimeter. The weight was measured by a digital electronic scale with bioelectrical impedance (Tanita Ironman®), and the height was measured using a portable stadiometer (Alturexata®).

The nutritional status of the students was determined by BMI, calculated by dividing the weight (kg) by the squared height (m^2) and classified according to the BMI curve per age. To calculate the data, we used AnthroPlus® software.

The waist perimeter was measured using a simple inelastic measuring tape at the midpoint between the iliac crest and the costal arch.

The assessment of body composition, using horizontal tetrapolar bioelectrical impedance equipment (Biodynamics®), was performed following the instructions of the equipment manufacturer. To determine the percentage of body fat, we used the equation by Deurenberg et al.[7] based on the resistance and reactance values in relation to age.

Measurement of pressure levels

The blood pressure levels were measured three times, alternately, on the right arm, using a digital oscillometric sphygmomanometer (Omron®), with a cuff adjustable to the width of the arm. The minimum interval between measurements was 5 minutes.

Biological samples and biochemical analyzes

Blood samples were collected by venous puncture from the antecubital region of patients after 12 hours of fasting. The following biochemical analyses were carried out: (a) total cholesterol and ratios; (b) triglycerides; (c) serum glucose; and (d) insulin. All were measured by the enzymatic colorimetric method and adapted to the automatic analyzer Cobas Mira Plus®.

Insulin resistance was determined by the HOMA-IR index (Homeostasis Model Assessment Insulin Resistance), using the formula Homa-IR= fasting insulin (IU/mL) *x* fasting glycemia (mmol/l)/22.5.

From the blood serum of the samples collected, three aliquots were obtained, which were placed in an amber tube, encoded, and stored at -80 ºC. The serum was used for the resistin and chemerin analyses by the immunoenzymatic ELISA method (Enzyme-Linked ImmunoSorbent Assay). For this purpose, commercial kits were used of the brands Sigma-Aldrich®

(RAB0419) and Abcam's® (ab155430), respectively, following the protocol established by the manufacturers.

Ethical aspects

The legal guardians and principals of the schools were previously informed about the objectives, the protocol, and study procedures, as well as the risks and benefits of participating in the present study.

The student participation was voluntary, upon authorization and signing of the Informed Consent by parents and/or guardians. The study was approved by the Human Research Ethics Committee of the Federal University of Juiz de Fora - the first stage by decision No 09/2010 and the second by decision No 789.725/2014.

Statistical analysis

Initially, we used the Kolmogorov-Smirnov test to verify if the distribution of the variables followed the assumptions of normality. In the descriptive analysis, we highlighted the measures of central tendency (mean or median) and their corresponding values of dispersion (standard deviation and interquartile range). Based on the distribution of the variables, we used the Student *t*-test or Mann-Whitney test to compare the mean values in each group and the Pearson or Spearman correlation tests for quantitative variables.

Multiple linear regression analysis was performed to assess the effect of independent variables on serum values of adipokines. The variables that presented $p < 0.20$ in the bivariate analysis and/or biological plausibility were included in the multiple linear regression model, which was adjusted for possible confounding factors. The variables were included in the model using the enter method, and those that lost significance were removed ($p<0.05$). We calculated the confidence interval of 95% (95).

For the data analysis, we used SPSS® version 21.0 and Stata® version 10.1, at a significance level of 5% ($p<0.05$).

RESULTS

Anthropometric, biochemical, and clinical characteristics of eutrophic and overweight young people

The study sample included 234 young people, classified into two groups: (a) eutrophic children and adolescents (134) and (b) children and adolescents with excess weight (100). The mean age was 10.52 ± 2.05 years. Among the students, 52.1% were female and 66.5%, adolescents. Of those classified as eutrophic, 53.7% were female, and 68.7% were adolescents. In relation to the group with excess weight, 50.0% were female, and 64.0% were adolescents.

The anthropometric, biochemical, and clinical characteristics of the participants, according to their BMI classification per age, can be found in Table 1. The group with excess weight presented higher values for

TABLE 1. ANTHROPOMETRIC, CLINICAL, AND BIOCHEMICAL VARIABLES CHARACTERIZED BY BMI PER AGE.

Variables	Eutrophy (n=134)		Excess weight (n=100)	
	Mean or median	SD or IQR	Mean or median	SD or IQR
Age (years)	10.69	2.02	10.41	2.1
Height (cm)	145.4	13.54	147.67	12.95
WC (cm)	60.29	5.85	74.04	8.93**
BF (%)	18.89	6.08	31.69	5.88**
SBP (mm Hg)	103.48	9.66	110.36	8.37**
DBP (mm Hg)	64.15	7.05	69.39	6.15**
Chemerin (ng/mL)	220.29	103.17	213.08	119.75
Resistin (pg/mL)	773.96	479.63-1,160.25	942.22	606.77 -1,461.08*
Total cholesterol (mg/dL)	153.0	136.0-178.0	160.5	144.5-182.25
HDL (mg/dL)	49.0	43.5-57.0	44.0	38.75 - 49.25**
LDL (mg/dL)	94.49	25.44	99.7	23.73
TG (mg/dL)	56.5	43.0-79.25	68.5	52.0 - 94.75**
Serum glucose (mg/dL)	80.17	9.09	83.81	8.51**
Fasting insulin (μUl/mL)	4.0	2.73-6.38	7.3	4.35 - 9.25**
Homa- IR	0.81	0.51-1.35	1.46	0.81 - 2.0**

Note: BMI - body mass index; WC - waist circumference; BF - body fat; SBP - systolic blood pressure; DBP - diastolic blood pressure; LDL - low-density lipoprotein cholesterol; HDL - high-density lipoprotein; TG - triglycerides; Homa-IR, homeostatic model assessment insulin resistance. Data are expressed as mean ± standard deviation or median (interquartile range) in cases of non-Gaussian data. *p<0.05. **p<0.01

the following variables: waist circumference, body fat percentage, systolic and diastolic arterial pressure, triglycerides, serum glucose, fasting insulin, and Homa-IR index. On the other hand, they had lower values of HDL-cholesterol, although the values were low in both groups.

The chemerin adipokine presented a reduction in serum values in the group with excess weight [213.08 ± 119.75 ng/mL] compared to the eutrophic group [220.29 ± 103.17 ng/mL], however, without a significant difference (Figure 1). The opposite profile was observed for resistin values, with 869.35 ± 515.37 pg/mL in the eutrophic group and 1,078.31 ± 668.49 pg/mL in the group with excess weight ($p<0.05$).

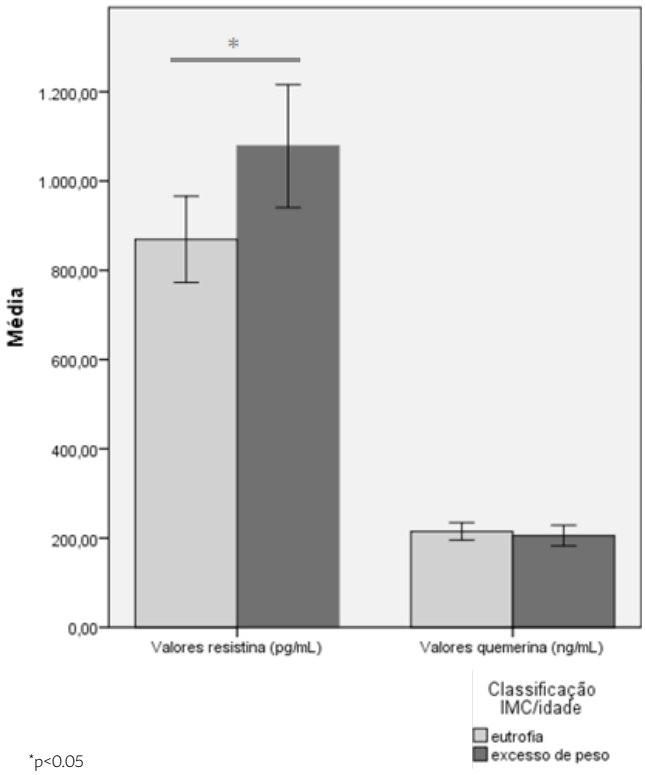
Analysis of correlation and linear regression

The chemerin adipokine was correlated with diastolic blood pressure and resistin. All correlations were weak and negative. Regarding resistin, we observed a correlation with the values for weight, waist circumference, systolic, and diastolic blood pressure, LDL-c, and chemerin. All correlations proved to be weak and, with the exception of chemerin, were positive.

We included in the multiple linear regression model the variables that presented $p < 0.20$ in the bivariate analysis. Thus, in the chemerin model, we included diastolic blood pressure and resistin. Whereas in the model of resistin, we included weight, BMI, waist circumference, body fat percentage, systolic and diastolic arterial pressure, LDL-c, and chemerin. In addition to the parameters that presented $p < 0.20$ in the bivariate analysis, variables of biological plausibility were added to the model. Thus, to the chemerin model, we included weight, BMI, waist circumference, systolic blood pressure, and Homa-IR and to the resistin model, BMI, and Homa-IR.

In the multiple linear regression analysis, the values of chemerin showed an association with the resistin values (p=0.004, 95% CI: -0.06 - 0.01), systolic blood pressure (p=0.01, 95% CI: 0.64 - 4.66) and diastolic blood pressure (p=0.001, 95% CI: -7.39 – -1.99). The resistin values maintained an association only with the values of BMI (p=0.02, 95% CI: 3.52 - 45.75) and chemerin (p=0.003, 95% CI: -1.86 – -0.38). We observed that 8.5% of the variation of chemerin values could be explained by resistin, systolic and diastolic arterial pressure (Table 2), and 5.8% of the variation of the resistin concentrations could be explained by BMI and chemerin. The final model is presented in Table 3.

FIGURE 1. PLASMA LEVELS OF RESISTIN AND CHEMERIN IN EUTROPHIC AND OVERWEIGHT YOUNG INDIVIDUALS.



*p<0.05

TABLE 2. LINEAR REGRESSION OF ANTHROPOMETRIC, CLINICAL, AND BIOCHEMICAL VARIABLES WITH SERUM VALUES OF CHEMERIN.

Serum concentrations of chemerin			
Variables	β	CI 95%	p*
Resistin (pg/mL)	-0.04	-0.06 – -0.01	0.004
SBP (mm Hg)	2.65	0.64 – 4.66	0.01
DBP (mm Hg)	-4.69	-7.39 – -1.99	0.001

Note: SBP - systolic blood pressure; DBP - diastolic blood pressure. $R^2 = 0.085$. *adjusted for sex and age.

TABLE 3. LINEAR REGRESSION OF ANTHROPOMETRIC, CLINICAL, AND BIOCHEMICAL VARIABLES WITH SERUM VALUES OF RESISTIN.

Serum concentrations of resistin			
Variables	β	CI 95%	p*
BMI (kg/m^2)	24.63	3.52 – 45.75	0.02
Chemerin (ng/mL)	-1.12	-1.86 – -0.38	0.003

Note: BMI - Body Mass Index. $R^2 = 0.058$. *adjusted for sex and age.

DISCUSSION

In recent years, it has been observed that changes in the adipokine profile may contribute to obesity and several related disorders, such as insulin resistance, hypertension, and CVD. Evidence suggests that the atherosclerotic process begins in childhood, progressing gradually until the onset of clinical manifestations; therefore, early identification of risk factors for CVD is indispensable[8].

In view of that, the present study evaluated the serum concentrations of two adipokines, which showed a distinct profile in groups of eutrophic and overweight children and adolescents. Resistin presented higher values in individuals with excess weight, while chemerin showed no differences between the groups, with a tendency of reduction in young patients with eutrophic nutritional status. In addition, some traditional risk factors for CVD, such as waist circumference, body fat percentage, systolic and diastolic arterial pressure, triglycerides, serum glucose, fasting insulin, and Homa-IR index, were higher in the group with excess weight when compared to the eutrophic group, as has been observed in several other studies[9].

Changes in traditional cardiovascular markers can be preceded by changes in the values of adipokines in obese children and adolescents[10]. Higher concentrations of pro-inflammatory adipokines in this population suggest that the inflammatory mechanisms involved in obesity and cardiometabolic complications are already activated[11]. However, there is still insufficient data in the literature to understand the behavior of adipokines in children and adolescents.

Although our findings did not observe any difference between the groups regarding the chemerin, young people with obesity have higher concentrations of this adipokine[11], with values about 30% higher than those of eutrophic individuals[2]. Chemerin is a chemoattractive protein that acts regulating the immune response in the process of adipogenesis and glucose metabolism in the liver, skeletal muscle, and adipose tissue[12]. In publications on children and adolescents, serum concentrations of chemerin are associated with obesity, diabetes, risk factors for CVD, and premature vascular inflammation[13].

We observed a negative correlation between diastolic blood pressure and chemerin values. Unlike what was found in this study, El Dayem et al.[14] found no correlation between chemerin values and blood pressure. However, Sledzińska et al.[15] identified a positive correlation between adipokine and systolic blood pressure. However, no explanation was found for this in the literature. The mechanisms of vasoconstriction that can be influenced by chemerin and how they work remain unknown[16].

In regard to findings on resistin, there is still a contradiction in its association with obesity among children and adolescents[17]. After comparing groups of eutrophic and overweight young people, different behaviors of adipokines were observed. In some studies, it has been observed that resistin values are similar among eutrophic and obese children[18].

However, like in the present study, Mantovani et al.[10] and Olza et al.[9] found higher values of resistin among overweight and obese young individuals. It is known that excess adipose tissue, especially in the abdominal cavities, promotes the secretion of pro-inflammatory adipokines while reducing the synthesis of anti-inflammatory properties[9].

In another study, by Codoñer-Franch et al.[19] no differences were found in the concentrations of resistin between eutrophic and obese groups; however, when stratifying them based on the values of insulin resistance, higher serum values of resistin were detected in obese children with insulin resistance in comparison to those who were eutrophic or obese without insulin resistance, which can be explained by the relationship between resistin and the inflammation that is characteristic of obesity and its comorbidities[20]. Resistin is considered a biomarker for insulin resistance, and its association with the Homa-IR index may indicate endothelial damage even in young people since adipokine has effects on vascular cell function[9].

In the same way, Rupérez et al.[21] found higher values of resistin between Spanish children with excess weight and those metabolically obese with normal weight.

Resistin is a protein produced in response to inflammatory stimuli[20] associated with chronic non-communicable diseases, such as obesity, and it may induce insulin resistance and vascular inflammation[17,19]. It is involved in glucose homeostasis, insulin action, and lipid metabolism[22]. The role of adipokine on metabolic syndrome, diabetes mellitus type II, and CVD has been previously described[20]. In the pediatric population, high values of resistin may precede comorbidities associated with obesity[10].

In this context, our results showed a correlation between the values of resistin and BMI, which was also demonstrated in the study by Lausten-Thomsen et al.[17]. However, other studies have found an association

of adipokine only with body fat, especially among girls aged between 12 and 16 years[23], and with the waist circumference, fat mass, and Homa-IR, suggesting it is associated with visceral adiposity[18]. Aeberli et al.[24] demonstrated that some indexes of adiposity, such as BMI, body fat percentage, and waist circumference, were not considered predictors of resistin.

Regarding the relationship between adipokine and blood glucose and insulin values, Gerber et al.[25] found no correlation. However, Olza et al.[9] found a correlation between resistin and the Homa-IR index. In addition, adipokine was positively correlated with inflammatory markers such as IL-6, TNF-α, C-reactive protein, and leptin, with an unfavorable lipid profile[20].

Among the limitations of this study is the relatively small sample size. However, the inclusion criteria were well established, and the assessment protocol was conducted in a rigorous fashion. Furthermore, the study brings as contributions the analysis of adipokines in a population of children and adolescents; it is the first study conducted on this population that seeks to analyze chemerin in Brasil.

Thus, we found that the adipokines analyzed presented a distinct profile in groups of eutrophic overweight children and adolescents and were correlated with some variables traditionally established for assessing CVD risk.

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RESUMO

OBJETIVOS: *Comparar as concentrações séricas das adipocinas resistina e quemerina em crianças e adolescentes com eutrofia e excesso de peso e avaliar sua relação com as variáveis antropométricas, bioquímicas e a pressão arterial.*

MÉTODOS: *Estudo epidemiológico transversal realizado com 234 estudantes matriculados em escolas públicas do ensino fundamental no município de Juiz de Fora/MG. Realizou-se avaliação antropométrica, bioquímica e aferição da pressão arterial. As análises estatísticas compreenderam os testes t de Student ou Mann-Whitney, correlação de Pearson ou Spearman, utilizados de acordo com a distribuição das variáveis, e análise de regressão linear, realizada por meio da avaliação do efeito das variáveis independentes nos níveis séricos de quemerina e resistina, ajustado por idade e sexo. Para a análise dos dados foram utilizados os softwares SPSS® versão 21.0 e Stata® versão 10.1, admitindo-se nível de significância de 5%.*

RESULTADOS: *As concentrações de quemerina foram maiores nos indivíduos eutróficos do que nos com excesso de peso (p>0,05). Em contrapartida, os níveis de resistina estiveram maiores nos jovens com excesso ponderal do que nos eutróficos (p<0,05). Na análise de regressão linear múltipla, os níveis de quemerina apresentaram associação com os valores de resistina, pressão arterial sistólica e diastólica. Os níveis de resistina mantiveram associação apenas com os valores de IMC e quemerina.*

CONCLUSÃO: *As adipocinas analisadas apresentaram perfil distinto nos grupos de crianças e adolescentes com eutrofia e com excesso de peso.*

PALAVRAS-CHAVE: *Criança. Adolescente. Adipocinas. Fatores de risco. Quimiocinas. Resistina.*

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ORIGINAL ARTICLE

Alcohol use, abuse and dependence among elderly in outpatient treatment through the application of AUDIT

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SUMMARY

OBJECTIVE: *To identify or use alcohol abuse and abuse in the IAMSPE elderly, through the application of AUDIT, socioeconomic characterization of the elderly, and problems associated with drinking and weight, if there is a relationship between depression and alcohol abuse.*

METHODS: *This is a cross-sectional, exploratory, and descriptive study with a quantitative approach. One hundred elderly patients were interviewed to apply a socioeconomic form and to assess alcohol consumption from AUDIT.*

RESULTS: *correlation between alcohol consumption and female gender (p = 0.021). Most of the participants were between 60 and 79 years old, were female, had a partner, had completed elementary school, had income and selected house, were retired and unemployed.*

CONCLUSION: *In the present study, we found no correlation between alcohol abuse and depression; Only one correlation was found between male gender and higher alcohol abuse. However, a significant prevalence of moderate use of high alcohol was found (3.9% in women and 21.7% in men), i.e., it poses a risk to the health of the elderly.*

KEYWORDS: *Health of the elderly. Alcoholism. Alcohol-related disorders.*

INTRODUCTION

According to the World Health Organization (WHO), all individuals aged 60 years or more are considered elderly. However, for public policymaking, there may be variations in the limit proposed by the WHO according to the characteristics and conditions of each country. It is worth noting that the minimum age adopted does not serve exclusively as a marker for the changes that accompany aging; there can be large variations in the level of participation in society, health, and independence among the elderly in different scenarios[1].

Aging is a natural physiological process that starts at birth and culminates with death. Regarding its physiological aspect, the elderly have reduced the capacity of homeostatic adaptation according to situations in which the body feels a functional overload. In addition,

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it includes changes in professional and social roles, as well as losses of psychological, emotional, and motor nature[2].

The Brazilian Institute of Geography and Statistics (IBGE)[3] highlights that the Brazilian population will continue to grow until 2042, reaching 228.4 million people, and, from the following year, will decrease gradually, reaching around 218.2 million in 2060. Life expectancy at birth should reach 80 years in 2041, reaching 81.2 years in 2060. Regarding gender, life expectancy at birth in 2013 reached 71.3 years for males and 78.5 years for females, and, for 2060, the projection indicates 78.0 and 84.4 years, respectively[3].

However, individual variables, such as lifestyle, socioeconomic conditions, chronic diseases, smoking, alcoholism, family and social role, and presence of support by family members and friends, among others related to the aging process, contribute to healthy aging or with the emergence of chronic-degenerative diseases[4].

Functional independence and autonomy are currently considered as the real indicators of the health conditions of the elderly, which may or may not present aggravating factors. Postural instability is one example because, in addition to causing a risk of falls, it can also cause emotional damage, such as depression[5].

Discussions on the consumption of alcohol usually refer to young people due to the damage caused to this group, such as violent deaths and accidents. However, the elderly have resorted to the use of this substance as a "escape valve" to face the changes during aging. The loss of loved ones, absence of an important role in society and within the family, a dependency of others to perform activities of daily living (ADLs), or even the financial dependence for food and shelter can generate frustrations, resulting in stimuli for dependency[6,7].

Regarding the effects and consequences of alcohol, there are no clear boundaries between use, abuse, and dependence. However, use is defined as the consumption of any substance sporadically; abuse is when, as a result of consumption, there is some kind of injury (biological, psychological, or social); and dependence is when there is a loss of control, usually associated with serious problems for the user[8].

The levels and patterns of alcohol consumption, as well as the magnitude of the problems related to its use by various populations, are influenced by both individual factors (age, sex, health condition, among others) and social (economic development, culture, availability of alcohol, among others), associated with the quality of the product, context, and the motivations for consumption, besides the individuals personal vulnerability, indicating a multi-factor interaction[9].

Several countries have adopted, due to the harmful effects of alcohol, clear definitions of low-risk consumption, and the standard dose of alcohol. The "standard dose" refers to the measurement of the amount of pure ethanol contained in alcoholic beverages. For the WHO, this dose is approximately 10-12 grams of ethanol (corresponding to a 330 ml beer can, or a 100 ml glass of wine, or 30 ml of a distilled drink). As for "low risk", it is considered when two doses are not consumed per day, and the individual spends at least two days without drinking. This recommendation is for both sexes[10].

Considering the above about the aging process, vulnerabilities and the use of alcohol by the elderly, specifically, is described as a complex, multifactorial, and misunderstood problem, like an invisible epidemic since it is underestimated and poorly identified, either for reasons arising from the elderly themselves, such as guilt and fear, by a stereotypical perspective of health professionals or even due to the lack of technical skills[11-13].

Nevertheless, the management of care for the elderly must comprise all spheres of life because when individuals live in social isolation or even alone, with losses in social, occupational, or leisure activities due to the use of alcohol, their existence and habits go unnoticed, and, sometimes, the person is ignored or neglected[14].

It is worth mentioning that biological and physiological changes related to aging affect the absorption, metabolism, and elimination of alcohol, causing a decline in the liver and renal functions, and even in drug interactions, causing various problems[15].

It is important to emphasize that the presence of depression is also considered a strong risk factor for other health problems, such as the use/abuse of alcohol and other drugs. This psychopathology is characterized by negative symptoms, such as mood predominantly depressed and/or irritable, anhedonia, tiredness, fatigue, disinterest, slowing, pessimistic thoughts and ideas of ruin, in addition to poor sleep quality, changes in appetite, among others, which predispose depressed patients to make use of alcohol to reduce the discomfort of symptoms[16,17].

Still, sometimes depression is underdiagnosed and undertreated, possibly due to the criteria used by the professional or due to the professional's difficulty in recognizing depressive symptoms in relation to the aging process, or even due to the lack of management during anamnesis[18].

As in any pathology, early diagnosis is essential for its prognosis. In the case of alcoholism, the instrument *Alcohol Use Disorders Identification Test* (AUDIT), developed by WHO and already validated for the Brazilian population, is used for the assessment with the purpose of identifying drinkers at risk; measure consumption, symptoms, and the personal and social consequences of drinking; identify the alcohol experience both in the previous year as over the course of life, applicable in various scenarios, as well as to identify risk levels, suggesting their respective interventions[19].

The AUDIT instrument is a questionnaire consisting of 10 questions that evaluate the behavior of the individual in relation to alcohol consumption. Three of the questions assess the amount and frequency of use, three investigate the symptoms related to dependence, and four refer to problems resulting from alcohol consumption that occurred in the previous year. Therefore, four different patterns of consumption can be identified: low-risk use (which probably does not lead to problems), risk use (which may lead to problems), harmful use (consumption that probably already has led to problems), and probable dependency[9,19].

Thus, the aim of this study was to identify the use, abuse, and dependence of alcohol in elderly patients from an outpatient clinic - Iamspe - through AUDIT, considering the socioeconomic characterization of the elderly population and the problems associated with consumption and whether there is a relationship between depression and abusive use or alcohol dependence.

METHODS

It is a cross-sectional, exploratory, and descriptive field study with a quantitative approach[20].

The research was carried out in outpatient clinics of Geriatrics and Psychiatry of the Institute of Medical Assistance to the Public Servants of the State of São Paulo (- Iamspe), located in São Paulo/SP. The data collection took place between June and August of 2015.

The study population consisted of patients treated in those outpatient clinics. We included patients of both sexes, treated in outpatient clinics of Geriatrics (without a diagnosis of depression) and Psychiatry (with a diagnosis of depression), with age greater than or equal to 60 years, presenting good cognitive level, i.e., with the ability to understand and respond the form and the questionnaire clearly, and to agree and sign the Informed Consent Form (ICF). We excluded patients who did not meet the above criteria established by the groups, or who did not have a minimum cognitive capacity.

The data collection occurred randomly, once or twice a week, during the morning and before the individual's medical appointment. Since this was in an outpatient clinic, patients, in their majority, arrived before the time scheduled, and their records were already separated by the collaborators of the sector. Once the records were available, the diagnosis was read and identified. The patients at the Geriatrics outpatient clinic were selected based on the inclusion criteria and without a diagnosis of depression; this same selection dynamic was used in the Psychiatry outpatient clinic, but patients needed to have a diagnosis of depression. At this stage, the goal was only to separate and select records. Individually, we invited the subjects to participate in the research, explaining its objectives and the subsequent stages. After they agreed to participate, they were asked to sign the informed consent form. After collection, the data were tabulated using *Statistical Package for the Social Sciences* (SPSS), version 17.0, and analyzed later. We observed the need for increasing our sample, initially of 60 patients, so it was increased to 100. Of these, 50 patients were from the Geriatrics outpatient clinic without a diagnosis of depression, and the other 50 from the Psychiatric outpatient clinic with a diagnosis of depression. The new data collection took place in the same outpatient clinics from October to December 2015.

The first step after the agreement was signed was the collection of data from a form that aimed to characterize the sociodemographic characteristics of the study population (age, marital status, formal education, occupation, family income, and residence/housing situation). In the second stage, we recorded the score obtained from the Audit, aiming to identify the potential risk drinkers, the dynamics of consumption, symptoms of dependence, and the personal and social consequences of drinking in the elderly's life. Since this instrument is simple, its format allowed it to be applied both as an interview or as a self-administered questionnaire. However, despite the preserved cognition, for most of the subjects, the interview format was

used due to difficulties such as a deficit of vision or due to the interviewee's preference, among others. This scale is composed of 10 questions, and each question has a margin of 0 to 4, allowing for a final score of 0 to 40 points. The result is given by the following scores: 0 points: nondrinkers; 1 to 7 points: low-risk consumption; from 8 to 15 points: low to moderate; 16 to 19 points: moderate; 20 to 40 points: likely dependency.

According to the standards of Resolution no. 466/2012 by the National Health Council (CNS), who is responsible for standards on research with human beings, the study was performed after approval by the Research Ethics Committee (RET) of Iamspe under the decision no. 1,105,338 and the signing of an ICF by all participants. It should be emphasized that the study did not expose participants to risks of physical, moral, or psychological nature.

For the data analysis, we used the *Statistical Package For The Social Sciences* (SPSS) version 17.0 and the chi-square test to check the association of the pattern of alcohol consumption in each group. The significance level adopted was 5% ($p<0.05$).

RESULTS

According to the first part of the research, which addressed the socioeconomic aspects of participants, of the 100 elderly respondents, there was a greater number of elderly individuals between the ages of 60 and 79 years (72%); 43.1% of elderly people who did not consume alcoholic drinks, and 48.6% who consumed little of it; 64.3% of the elderly people over 80 years presented a low-risk consumption. There was a predominance of females, with 77%, of which 54.5% presented low alcohol consumption. However, a positive correlation was found between male sex and moderate to high alcohol use. Regarding the marital status, 51% shared their life with a companion, without any

TABLE 1. THE DISTRIBUTION OF THE INTERVIEWEES ACCORDING TO THEIR SOCIODEMOGRAPHIC CHARACTERISTICS AND ALCOHOL CONSUMPTION. SÃO PAULO, 2015.

	Alcohol consumption							
	None (0 points)		Low (1 to 7 points)		Moderate/high (8 to 24 points)		Total	p-value (χ^2)
	N	%	N	%	N	%		
Total	**39**	**39.0**	**53**	**53.0**	**8**	**8.0**	**100**	
Age								
60 to 79 years	31	43.1	35	48.6	6	8.3	72	0.358
80 years and older	8	28.6	18	64.3	2	7.1	28	
Sex								
Women	32	41.6	42	54.5	3	3.9	77	0.021
Men	7	30.4	11	47.8	5	21.7	23	
Marital status								
With a spouse	18	35.3	26	51.0	7	13.7	51	0.095
Without a spouse	21	42.9	27	55.1	1	2.0	49	
Formal education								
Complete elementary school	27	39.7	34	50.0	7	10.3	68	0.409
Medium	12	37.5	19	59.4	1	3.1	32	
Occupation								
No occupation (retired/unemployed)	30	36.6	45	54.9	7	8.5	82	0.563
With occupation (works / homemaker / other)	9	50.0	8	44.4	1	5.6	18	
Income (in MS)								
With income	33	37.5	47	53.4	8	9.1	88	0.290
Without income	2	28.6	5	71.4	0	0.0	7	
Does not know	4	80.0	1	20.0	0	0.0	5	
Housing Condition								
Rented	0	0.0	3	75.0	1	25.0	4	0.190
Others	3	23.1	8	61.5	2	15.4	13	
Owned	36	43.4	41	49.4	6	7.2	83	

correlation with the use of alcohol. Another important point is the lack of occupation, i.e., idle time as a risk factor (54.9% of low risk). In the other variables, there was no correlation with alcohol.

After applying the Audit instrument, it was possible to establish a relationship, according to sex, depression, and alcohol consumption. It is possible to note that the presence of women, with 54% (N=77), was higher in relation to men, 21.7% (N=23), although men presented 21.7% of alcohol consumption of moderate/high risk and 54.5% of low-risk alcohol consumption. However, the female population, according to the statistics, presented greater significance (0.021) regarding alcohol consumption in relation to the male population, with no association between use exclusively and depression.

In relation to the score from the Audit instrument, we found that 53% of the participants, without distinction of sex, presented low-risk consumption, so the recommendation was to intervene with guidance and education, as appears in Table 1.

DISCUSSION

The research sample is significant for females. This finding corroborates the data from a study carried out in Manaus with 317 elderly individuals that aimed to assess the risk of alcohol consumption,

TABLE 2. DISTRIBUTION OF INTERVIEWEES ACCORDING TO SEX, DEPRESSION, AND ALCOHOL CONSUMPTION. SÃO PAULO, 2015.

	Alcohol consumption							
	None (0 points)		Low (1 to 7 points)		Moderate/high (8 to 24 points)		Total	p-value (χ^2)
	N	%	N	%	N	%		
Total	39	39.0	53	53.0	8	8.0	100	
Depression								
No	19	38.0	26	52.0	5	10.0	50	0.762
Yes	20	40.0	27	54.0	3	6.0	50	
Gender								
Women	32	41.6	42	54.5	3	3.9	77	0.021
Men	7	30.4	11	47.8	5	21.7	23	

TABLE 1. CORRECTION BETWEEN SCORE X FREQUENCY X RISK LEVELS AND RECOMMENDED INTERVENTION. SÃO PAULO, 2015

Relationship between score x frequency, risk levels (classification) and their respective interventions in the context of the Audit					
Score	Frequency (total = 100)	Classification	Zone	Suggestion of classification for the analysis	Recommended intervention
0	39	0 points 39 individuals (390%) Nondrinkers	I	0 points 39 individuals (390%) Nondrinkers	Information and education
1	29	1 to 7 points 53 individuals (53.0%) low-risk consumption	I	1 to 7 points 53 individuals (53.0%) low-risk consumption	Information and education
2	6				
3	11				
4	4				
6	1				
7	2				
9	1	8 to 15 points 5 individuals (5.0%) low-moderate	II	8 to 24 points 8 individuals (8.0%) moderate probable dependency	Guidance / intervention / referral for specialist care
11	1				
12	1				
13	2				
16	1	16 to 19 points 2 individuals (2.0%) moderate	III		
18	1				
24	1	20 to 40 points 1 individual (1.0%) probable dependency	IV		

given the prevalence of females, with 63.05%[21]. Still, in similar data, we can see the prevalence of women in health services, which demonstrates a concern in caring for their health, despite social non-acceptance and prejudice[22,23]. On the other hand, elderly women who stay at home, usually widows and alone, socially isolate themselves and make use of alcohol, which also pushes them further away from family members due to fear of judgment[24]. The study also pointed out that the female population has a greater statistical significance (0.021) regarding alcohol consumption in relation to the male population, with no association between use exclusively and depression.

In relation to age and alcohol use, the range of greater representativeness was between 60 and 79 years, ranging in 43.1% for no consumption and 48.6% for low consumption. In contrast, males presented 21.7% of moderate/high risk for alcohol consumption, whereas women presented 3.9%. In a similar study in the region of Braga, Portugal, with 210 elderly, in which 57.6% were women, although men presented 56.2%, they found a significant association between male sex and risk consumption of alcohol[25]. Age and formal education were not associated with risk consumption. No significant difference was found between alcohol use in patients with and without depression, as well as in the use of alcohol when patients were classified according to the socioeconomic variables (age, marital status, formal education, income, housing conditions).

In relation to the socioeconomic condition, the lack of occupation was a risk factor (54.9% of low-risk); however, the occupation in another study can be seen as a protector of functional capacity[26]. In addition, idleness causes low self-esteem or greater depressive feeling because it projects a negative self-image. Therefore, work can be considered an important factor in the protection and maintenance of mental health[27].

In relation to the frequency (Table 1) of the use of alcoholic beverages, according to the criterion of Audit, most elderly people (53%) present low-risk consumption (1 to 7 points) against 39% of non-drinkers (0 points), both considered as zone I. In comparison with a study from Manaus that aimed to apply the Audit in an elderly population in 2013, most subjects were also characterized as zone I, with 273 elderly patients (86.12%), out of 317 respondents, followed by 34 (10.73%) in zone II, nine (2.84%) in zone III, and one (0.32%) in zone IV. The focus of traceability of alcohol use/risk among the elderly may not always take into account only the amount consumed but also its association with medications, clinical conditions, and the very aging process[28].

CONCLUSION

With the analysis of the results, it was possible to verify that elderly individuals aged between 60 and 79 years have a greater possibility of exposure to low-risk alcohol consumption. Another important fact is the presence of elderly women in the range of low alcohol consumption, but with no relationship with depression. However, the female presence is expressive in health care services; however, the issue in question is still permeated by prejudices and paradigms and, on the contrary, we found a positive correlation between elderly men and moderate to high use of alcohol, but with little presence in these same spaces of care, which makes us reflect on the importance of public strategies and policies targeted at this population. The lack of occupation, i.e., idle time as a risk factor, also contributes to the use of alcohol. In relation to the Audit, even though it is considered an instrument of traceability in the investigation of alcohol use and can be used in several scenarios, more research is needed to confirm its viability in the elderly population due to the aging process, chronic pathologies, and psychosocial issues, in addition to the paradigms that underlie the act of drinking, making it more difficult to reach an assertive diagnosis. In view of the integral assistance to the individual, as recommended by the Ministry of Health (MOH) by means of the doctrinal principles of the Single Health System(SUS), health professionals should have a holistic approach. Thus, the importance of training professionals is highlighted so they can be prepared to meet this demand, which requires specific care. We expected that the present study could arouse clinical and academic interest that leads to new research, testing new instruments, and aiming for a more efficient and reliable diagnosis so as to establish plans for treatment and care and provide elderly patients an active aging and quality end of life.

Contribution of the authors

DPB and FCGP, advisors; PCOG, research, and text.

RESUMO

OBJETIVO: *Identificar o uso, abuso e dependência de álcool em idosos do ambulatório do Iamspe, por meio da aplicação do Audit, através da caracterização socioeconômica dos idosos e dos problemas associados pelo consumo e pesar se há relação entre depressão e uso abusivo ou dependência de álcool.*

MÉTODOS: *Trata-se de um estudo de corte transversal, exploratório e descritivo de abordagem quantitativa. Foram entrevistados cem pacientes idosos para aplicação de um formulário socioeconômico e de avaliação do consumo de álcool, a partir da Audit.*

RESULTADOS: *Verificou-se correlação entre o consumo de álcool e sexo feminino (p=0,021). A maioria dos participantes estava na faixa etária entre 60 e 79 anos, era do sexo feminino, tinha companheiro(a), com ensino fundamental completo, renda e casa próprias, era aposentada e desocupada.*

CONCLUSÃO: *No presente estudo não verificamos correlação entre abuso de álcool e depressão; somente foi encontrada a correlação entre sexo masculino e maior uso abusivo de álcool. No entanto, encontrou-se prevalência significativa de uso moderado a alto de álcool (3,9% em mulheres e 21,7% em homens), o que, por si, traz risco para a saúde de idosos.*

PALAVRAS-CHAVE: *Saúde do idoso. Alcoolismo. Transtornos relacionados ao uso de álcool.*

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ORIGINAL ARTICLE

Sedentary behavior, physical activity and body composition in adults

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SUMMARY

OBJECTIVE: *We investigated the associations between objectively assessed sedentary behavior (SB) and moderate-to-vigorous physical activity (MVPA) and body composition variables among a representative sample of Brazilian adults.*

METHODS: *Using an accelerometer, SB and MVPA were monitored for at least 5 days in 524 participants (261 men; age, 18-65 years). Each minute epoch was classified as sedentary or spent in light, moderate, or vigorous physical activity (LPA, MPA, and VPA, respectively). The measured body composition variables included abdominal perimeter (AP) and neck circumference (NC).*

RESULTS: *Men accumulated significantly more min/day of MPA (37.82 versus 27.28), VPA (1.10 versus 0.31), MVPA (39.02 versus 27.61), and steps/day (14,978 versus 13,443) than women (p<.001). In men, MPA, VPA, MVPA, and steps/day were negatively associated with AP (p<.05) independently of SB. Only VPA was significantly associated with NC (β= 0.113; p=.002). In women, only SB was significantly associated with AP (β= 0.003; p=.031). There were no significant associations between physical activity intensities and body composition in women.*

CONCLUSIONS: *Our findings on the unequal association of physical activity with body composition variables between sexes can help inform future intervention strategies in Brasil.*

KEYWORDS: *Accelerometry. Obesity. Anthropometry.*

INTRODUCTION

Physical activity (PA), a pillar in the prevention and treatment of obesity and cardiovascular diseases (CVD), is inversely associated with excess weight[1]. Whereas a high level of sedentary behavior (SB) probably favors obesity[2]. In general, 50.1% of Brazilian men and 48% of women have excess weight, and 12.4% and 16.9%, respectively, are obese[3]. In addition, only 60.2% of men and 51.5% of the women follow the recommendations of moderate to vigorous physical activity (MVPA)[4,5]. Although population studies have

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revealed that the association between PA and obesity varies according to sex, the relationships between the intensities of PA and health outcomes have not been sufficiently studied. The understanding of these associations is important for the development of public policies and interventions aimed at behavioral changes.

Objective measures of time spent in SB, in different intensities of PA, and the number of steps/day may help to understand the human movement behavior related to obesity. Objective evaluations using accelerometers are commonly included in studies from high-income countries[6]. In contrast, relatively few studies have applied this technology to research in low- and middle-income countries, such as Brasil[6]. The present study investigated the association between SB and MVPA, both objectively assessed, with body composition variables in Brazilian adults according to the intensity of the PA.

METHODS

Brazilian Study on Nutrition and Health

The present study was part of the Latin American study on Nutrition and Health (*Estudio Latinoamericano de Nutrición y Salud*, Elans)[7], conducted in eight countries of Latin America: Argentina, Brasil, Chile, Colombia, Costa Rica, Ecuador, Peru, and Venezuela. The study included data of the Brazilian Study on Nutrition and Health (Ebans)[8]. The Ebans is a cross-sectional, populational, household-based survey. The participants were stratified by geographic location (urban areas only), sex, age, and socioeconomic level (SEL). The data were collected between November 2014 and August 2015. The sample included subjects of both genders, aged between 15 and 65 years, who belonged to various regions and cities[8]. All participants signed the Informed Consent Form, and the comprehensive Elans protocol (60953716.4.0000.5505) was approved by the Federal University of São Paulo, Brasil.

Participants

In total, 1,436 people who participated in the Ebans did not use an accelerometer or had less than five days of valid data, yielding a final sample of 524 participants. In general, we found no significant differences between the participants who did not use accelerometers and those who had valid data in groups stratified by sex (p=0.644), level of formal education (p=0.110), and body mass index (BMI) (p=0.813).

We excluded from the study: pregnant women and infants, individuals with major physical or cognitive disabilities, which could affect food intake and physical activity, individuals aged <18 or >65 years, who lived in any residential environment that was not a household, and those unable to read.

Accelerometer

To monitor SB and MVPA objectively, participants were asked to wear a triaxial accelerometer (model GT3X +, ActiGraph, Pensacola) on an elastic band at hip-height, on the right midaxillary line, for seven days. In addition, they were was asked to put on the device as soon as they woke up and removed it when sleeping, bathing, or swimming. Verbal and written instructions on how to use the accelerometer were provided. Participants completed a diary indicating the start and end time of use of the device and were encouraged to wear it for 12 hours/day, including on both weekend days. Data from at least five days (including at least one weekend day) from the use of the accelerometer were considered acceptable, with at least 10 hours/day of use after excluding sleep time[9,10]. After removing the nocturnal sleep period, the time of non-use was defined as any period of at least 60 consecutive minutes in a zero-count activity.

On the eighth day of data collection, the research team visited the homes of participants to collect the accelerometers. Data were compiled using the latest version of ActiLife (version 6.0; ActiGraph), collected at a sampling rate of 30 Hz, and downloaded in periods of 60 seconds[11].

Based on the time accumulated, SB was defined as ≤100 counts/min, mild PA (MIPA) as ≥101-1951 counts/min, moderate PA (MOPA) as ≥1,952-5,724 counts/min, vigorous PA (VPA) as ≥5,725 counts/min, and MVPA as ≥1,952 counts/min[12]. The participants were classified as having fulfilled or not the recommendations of MVPA[5].

Body Composition

Bodyweight was measured with a precision of 0.1 kg using a portable scale (Seca®, Hamburg, Germany) up to 200 kg after removing all heavy clothing items, items in pockets, and shoes[13]. Two measurements were obtained, and the mean was calculated for analysis.

The body height was measured using a portable stadiometer (Seca 213®, Hamburg, Germany) with a measuring range of 0 to 205 cm. After assembling the

stadiometer, the subject's height was measured without shoes on[13]. The subject was positioned under the stadiometer, standing in an upright position with their backs against the wall and their heads positioned on the Frankfurt plane[13]. The measurement, taken while inhaling, was repeated, and the average was used for analysis. The BMI (kg/m^2) was calculated based on reference data for adults[14,15].

The abdominal perimeter (AC) was measured to the nearest centimeter, between the last rib and the iliac crest after exhaling, with participants standing up, in accordance with the recommendations by the World Health Organization (WHO)[15,16]. The measurement was taken on exposed skin with non-elastic tape after removing accessories such as belts and girdles in the abdominal region. Each individual stood with their feet together, and arms relaxed on the side of their bodies. The AC (kg/m2) was classified based on reference data for adults[17].

The NC has recently been used to identify obesity and is correlated with age, weight, and BMI in both sexes[18]. The NC (cm) was measured using a non-elastic tape placed right below the larynx, perpendicular to the long axis of the neck, with the tape, on the front and back of the neck, at the same height[19]. The adults were categorized as NC >39 cm for men and NC >5 cm for women[20]. Each measurement was taken twice to ensure accuracy, and the average was used for the analyses.

Sociodemographic variables

A questionnaire was used to collect demographic information such as age, gender, years of education, race, and marital status. The SEL was also assessed using a questionnaire whose format was based on the national indices used in Brasil[7]. The SEL data were divided into three strata (high, medium, and low).

Statistical analysis

Descriptive statistics included averages, standard deviations, and frequencies, as appropriate. The Kolmogorov-Smirnov tests were applied to evaluate data distributions. To check for differences between sexes, we used the t-test for independent samples and the chi-square test. The Pearson correlation test was used to evaluate the association between SB, different intensities of PA, steps/day, and body composition variables.

Multiple linear regression models were used to examine the independent associations between SB, PA, steps/day, and body composition variables. Our first model was adjusted by region (to allow the grouping of the regional level), age, race, educational level, marital status, and employment situation. The second model was added to the MVPA as an adjustment. When considering PA as a dependent variable, we also made adjustments for SB. The calculations were done using SPSS, version 20.0, with a level of significance of $p < 0.05$.

RESULTS

There were significant differences between men and women regarding race, marital status, and employment situation, but not in age and educational level. Men used the accelerometer for significantly more time than women; however, there was no significant difference in the number of valid days of monitoring between the sexes. There were no significant differences between the sexes regarding SB and MIPA. Men accumulated significantly more minutes of MOPA (10.5 min/day), VPA (0.8 min/day), MVPA (11.4 min/day), and steps (1,535 steps/day) than women. In general, 60.9% of the participants met the guidelines for MVPA (Table 1).

There were significant differences between men and women in body weight and height, BMI (kg/m^2), AC (categorical), and NC (cm); however, there were no significant differences in the classification of the BMI, AC (cm), or NC (categorical) between them (Table 1).

Tables 2 and 3 show the results of the multiple linear regression analysis describing the independent association between variables from the accelerometer with body composition (AC and NC) according to sex. There were no significant associations of the SB and MIPA with the AC in men. MOPA, VPA, MVPA, and steps/day were significantly negatively associated with the AC. In women, only SB was significantly associated with the AC, regardless of region, age, race, educational level, marital status, employment situation, and MVPA. On the other hand, MIPA, MOPA, VPA, MVPA, and steps/day were not associated with the AC (Table 2).

In men, there were no significant associations between SB, MIPA, MOPA, MVPA, and steps/day with the NC. Only VPA was negatively associated with the NC, regardless of region, age, race, educational level, marital status, employment situation, and MVPA. In women, there were no significant associations between any variables from the accelerometer and the NC (Table 3).

DISCUSSION

This study investigated the association between SB and PA, both objectively assessed, with body composition variables in Brazilian adults. In men, VPA proved to have the greatest potential to influence body composition (mainly regarding AC) than MPA, even after adjusting for SB. In contrast, we found no significant association between SB and body composition variables. In women, only SB was significantly associated with the AC.

TABLE 1. DESCRIPTIVE ANALYSIS (MEAN AND STANDARD DEVIATION, OR FREQUENCY AND PERCENTAGE) OF THE VARIABLES FROM THE ACCELEROMETER AND BODY COMPOSITION IN BRAZILIAN ADULTS

Variables	Men (n=231)	Women (n=293)	p-value*
Age (years)	38.44 (13.08)	39.68 (13.44)	0.269
Ethnicity			
White	87 (38.8)	125 (44.6)	0.014
Black	47 (21.0)	56 (20.0)	
Mixed	37 (16.5)	59 (21.1)	
Others	60 (23.7)	53 (14.3)	
Educational level			
Basic/Primary Education	96 (41.6)	122 (41.6)	0.683
Secondary Education	117 (50.6)	142 (48.5)	
Higher Education	18 (7.8)	29 (9.9)	
Marital status			
Single	83 (35.9)	91 (31.1)	<0.001
Married	133 (57.6)	157 (53.6)	
Widow(er)	1 (0.4)	22 (7.5)	
Divorced	14 (6.1)	23 (7.8)	
Employment Status			
Does not work	120 (51.9)	232 (79.1)	<0.001
Active Worker	111 (48.1)	61 (20.9)	
Time of Vigil (min/day)	925.59 (123.05)	902.32 (116.76)	0.028
Number of days	6.43 (0.66)	6.36 (0.67)	0.205
SB (min/day)	565.84 (130.70)	550.59 (119.87)	0.166
MIPA (min/day)	322.72 (95.89)	324.73 (91.76)	0.116
MOPA (min/day)	37.82 (14.18)	27.28 (19.20)	<0.001
VPA (min/day)	1.10 (0.18)	0.31 (0.14)	<0.001
MVPA (min/day)	39.02 (16.29)	27.61 (19.31)	<0.001
Steps/day	14.978 (5.721)	13.443 (4.610)	<0.001
Meet the recommendations for MVPA	160 (69.3)	159 (54.3)	<0.001
Bodyweight (kg)	79.26 (16.53)	70.87 (14.94)	<0.001
Height (cm)	171.67 (7.00)	159.28 (7.07)	<0.001
BMI (Kg/m2)	26.91 (5.43)	27.95 (5.63)	0.003
BMI Classification			
Underweight	7 (3.0)	7 (2.4)	0.380
Normal weight	81 (35.1)	84 (28.7)	
Excess weight	85 (36.8)	108 (36.9)	
Obesity	58 (25.1)	94 (32.0)	
Abdominal circumference (cm)	90.21 (14.07)	88.02 (13.79)	0.590
Bellow the threshold	196 (84.8)	154 (52.6)	<0.001
Neck circumference (cm)	36.88 (4.18)	32.99 (4.23)	<0.001
Bellow the threshold	171 (74.0)	210 (71.7)	0.548

*Significance value of the Student t-test.

All measurements were calculated from the time of vigil.

SB: sedentary behavior; MIPA: mild physical activity; MOPA: moderate physical activity; VPA: vigorous physical activity; MVPA: moderate to vigorous physical activity; Min: minutes; BMI: Body Mass Index.

Our results corroborate previous studies that showed a negative relationship between MVPA and body composition variables and risk factors, regardless of SB[21]. The study by Van Dyck et al.[21] showed a curvilinear relationship of MVPA with the BMI and a probability of excess weight/obesity in adults. In men, MOPA and VPA seem to be worthy of behavioral targets associated with body composition variables. In the present study, VPA was the best predictor of body fat estimates. Similar to the previous findings, our results support the hypothesis that VPA has a potentially greater influence in the AC and NC than MOPA, even after adjusting for SB. Regarding public health, it is suggested that efforts should focus more

TABLE 2. ADJUSTED ANALYSES BETWEEN THE ACCELEROMETER VARIABLES AND THE ABDOMINAL CIRCUMFERENCE IN BRAZILIAN ADULTS

Accelerometer variables	Men			Women		
	β coefficient	95% IC	p-value	β coefficient	95% IC	p-value
SB (min/day)[a]	0.002	−0.024, 0.075	0.353	0.002	0.011, 0.038	0.031
SB (min/day)[b]	0.095	0.064, 0.188	0.257	0.003	0.002, 0.006	0.042
MIPA (min/day)[a]	-0.032	-0.021, 0.014	0.609	0.043	-0.011, 0.026	0.456
MIPA (min/day)[c]	-0.058	-0.027, 0.010	0.351	-0.006	-0.020, 0.018	0.913
MOPA (min/day)[a]	-0.047	-0.087, -0.018	0.032	-0.002	-0.038, 0.041	0.951
MOPA (min/day)[c]	-0.005	-0.112, -0.020	0.039	-0.002	-0.048, 0.055	0.398
VPA (min/day)[a]	-0.114	-0.358, -0.104	<0.001	-0.079	-0.379, 0.371	0.074
VPA (min/day)[c]	-0.126	-0.373, -0.107	<0.001	-0.074	-0.425, 0.299	0.083
AFMV (min/day)[a]	-0.055	-0.067, -0.045	0.035	-0.036	-0.074, 0.058	0.914
AFMV (min/day)[c]	-0.076	-0.094, -0.059	0.021	-0.047	-0.086, 0.042	0.377
Steps/day[a]	-0.002	-0.006, -0.001	<0.001	-0.001	-0.001, 0.002	0.465
Steps/day[c]	-0.005	-0.011 -0.005	0.035	-0.002	-0.006, 0.004	0.062

Note: All measurements were calculated from the time of vigil.

SB: sedentary behavior; MIPA: mild physical activity; MOPA: moderate physical activity; VPA: vigorous physical activity; MVPA: moderate to vigorous physical activity; min: minutes; 95% IC: 95% confidence intervals, p<0.05.

a Basic adjustment: region, age, ethnicity, level of education, marital status, and employment status.

b Full adjustment: region, age, ethnicity, level of education, marital status, employment status, and moderate to vigorous physical activity.

c Total adjustment: region, age, ethnicity, level of education, marital status, employment status, and sedentary behavior.

TABLE 3. ADJUSTED ANALYSES BETWEEN THE ACCELEROMETER VARIABLES AND THE NECK CIRCUMFERENCE IN BRAZILIAN ADULTS

Accelerometer variables	Men			Women		
	β coefficient	95% IC	p-value	β coefficient	95% IC	p-value
SB (min/day)[a]	-0.093	-0.006, 0.003	0.123	-0.079	-0.007, 0.001	0.146
SB (min/day)[b]	-0.117	-0.007, 0.002	0.062	-0.095	-0.008, 0.002	0.134
MIPA (min/day)[a]	0.061	-0.003, 0.021	0.331	-0.024	-0.002, 0.008	0.746
MIPA (min/day)[c]	0.205	-0.005, 0.317	0.518	-0.023	-0.007, 0.004	0.735
MOPA (min/day)[a]	-0.082	-0.016, 0.012	0.280	-0.018	-0.028, 0.022	0.163
MOPA (min/day)[c]	-0.083	-0.012, 0.005	0.174	-0.048	-0.067, 0.016	0.101
VPA (min/day)[a]	-0.116	-0.260, -0.041	<0.001	-0.109	-0.382, 0.072	0.054
VPA (min/day)[c]	-0.113	-0.273, -0.032	0.002	-0.074	-0.422, 0.008	0.052
AFMV (min/day)[a]	-0.057	-0.030, 0.014	0.131	-0.280	-0.029, 0.022	0.290
AFMV (min/day)[c]	-0.083	-0.031, 0.008	0.090	-0.043	-0.036, 0.017	0.113
Steps/day[a]	-0.036	0.000, 0.001	0.581	-0.046	0.000, 0.001	0.425
Steps/day[c]	-0.073	0.000, 0.001	0.235	-0.090	0.001, 0.002	0.143

Note: All measurements were calculated from the time of vigil.

SB: sedentary behavior; MIPA: mild physical activity; MOPA: moderate physical activity; VPA: vigorous physical activity; MVPA: moderate to vigorous physical activity; min: minutes; 95% IC: 95% confidence intervals, p<0.05.

a Basic adjustment: region, age, ethnicity, level of education, marital status, and employment status.

b Full adjustment: region, age, ethnicity, level of education, marital status, employment status, and moderate to vigorous physical activity.

c Total adjustment: region, age, ethnicity, level of education, marital status, employment status, and sedentary behavior.

on the promotion of MOPA than in VPA since MOPA can be achieved by walking and is more likely to be practiced by the population through appropriate promotion strategies.

MIPA was not significantly associated with any body composition variable, a finding consistent with most previous findings, showing no significant associations [22]. It is, therefore, plausible that there is a intensity threshold in PA for body composition benefits. At least 250 min/week of MOPA (≥3 metabolic units [METs]) are required if the primary goals are to reduce body mass and fat[23]. There is no recommendation regarding the time necessary of MIPA to achieve weight loss; however, the amount of MIPA necessary to improve body composition is possibly much greater than that of MVPA, given the reduced level of intensity[22]. In addition, evidence suggests that the total volume of PA is a key factor in achieving weight loss[24]. MIPA can help improve individuals' metabolic profile; however, there is a lack of evidence to support the effect of MIPA on the positive effects for CVD in adults[22].

In our study, SB in women was significantly associated with the AC after adjustments for MVPA. This finding is consistent with a previous study[25]. Campbell et al.[25] found that 1 hour/day in SB causes, on average, during a period of five years, changes in body weight and AC of ≤0.19 kg, and ≤0.02 mm, respectively. In addition, previous studies that reported a significant association between sedentary time and weight used mainly questionnaires that included questions about television time as a tool to measure sedentary time and did not report findings on general sedentary time.

On average, men spent more time in MVPA, MOPA, and VPA than women, which suggests that women had a higher prevalence of physical inactivity compared to men. Although the variability was high in each sex, women spent less time in MPA, VPA, and MVPA and had fewer steps/day. Increasing women's participation in MVPA is essential not only for health and quality of life, but also for the potential positive impacts on economic development in different geographical, cultural, and political contexts. We recommend, therefore, that Brazilian policymakers develop initiatives to promote PA among women.

The strengths of this study include the objective measurement of PA using techniques and approaches that are rare in countries like Brasil, unlike most of the previous studies that used questionnaires for indirect measurement of PA[4]. As far as we know, this is the first study that investigated the associations between accelerometry data with NC in Brasil. However, this study has several limitations: 1) Ebans had a cross-sectional design, preventing inferences on causality; 2) the MVPA estimates may not be representative of the total population of Brasil since participants were recruited based only on an urban residence, sex, age, and SEL; 3) only PA was examined in relation to the weight results; a more complete perspective could have been provided if measures related to diet, sleep, and more accurate measures of body fat had been included.

CONCLUSION

The present study provided evidence for significant associations between MOPA, VPA, MVPA, and steps/day with the AC. In this study, only VPA was associated with the NC. We found a strong association between MVPA (specifically VPA) and the AC, regardless of SB. VPA had a greater influence on the AC and NC than MOPA. In women, only SB was positively associated with the AC, regardless of MVPA. Our results are informative for the development of public policies and health programs intended to reduce the levels of physical inactivity and obesity, particularly in women.

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Author's contribution

G. L. M. Ferrari was responsible for the concept of the manuscript, conducted the statistical analyses, interpreted the data, and drafted the manuscript. E. R. Victo contributed to the drafting and critical revision of the manuscript. I. Kovalskys contributed in part to the concept of the study, provided statistical knowledge and critical review. A. V. Mello interpreted the data and drafted the discussion of the manuscript. A. N. Previdelli contributed to the data analysis and interpretation and provided critical revision of the manuscript. D. Solé provided critical revision of the manuscript. M. Fisberg contributed to the concept and design of the project and provided critical revision of the manuscript. All authors provided critical reviews, read, and approved the final manuscript.

RESUMO

OBJETIVO: *Investigar a associação do comportamento sedentário (CS) e da atividade física de moderada a vigorosa (AFMV), avaliados objetivamente, com variáveis de composição corporal em uma amostra de adultos brasileiros.*

MÉTODOS: *CS e AFMV foram monitorados por meio de acelerômetros no mínimo por cinco dias, em 524 participantes (231 homens; 18-65 anos). Cada período de epoch de um minuto foi classificado como sedentário, atividade física leve (AFL), moderada (AFM) ou vigorosa (AFV). As variáveis de composição corporal medidas foram: perímetro abdominal (PA) e circunferência do pescoço (CP).*

RESULTADOS: *Os homens acumularam significativamente (p<0,001) mais min/dia em AFM (37,82 versus 27,28), AFV (1,10 versus 0,31), AFMV (39,02 versus 27,61), e passos/dia (14.978 versus 13.443) do que as mulheres. Nos homens, AFM, AFV, AFMV e passos/dia associaram-se (p<0,05) negativamente com PA, independentemente do CS. Somente AFV associou-se significativamente (β= −0,113; p=0,002) com CP. Já nas mulheres, apenas CS associou-se significativamente com o PA (β= 0,003; p=0,031). Não houve associações significativas entre as intensidades de atividade física com a composição corporal nas mulheres.*

CONCLUSÕES: *Nossos achados sobre a associação desigual da atividade física com composição corporal entre os sexos aumentam a base de evidências e podem ajudar a informar futuras estratégias de intervenção no Brasil.*

PALAVRAS-CHAVE: *Acelerometria. Obesidade. Antropometria.*

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ORIGINAL ARTICLE

More Doctors Program: health work process and socioeconomic indicators

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SUMMARY

OBJECTIVE: *To analyze the working process of the professionals of the More Doctors Program and its relationship with socioeconomic indicators. It is a quantitative study, in which secondary data from supervision reports of PMM were used. The dependent variable was the quality of work processes in Primary Care facilities, and the independent ones were the type of municipality, education, Gini index, Primary Health Care investments, and health facilities coverage. Data were analyzed with multiple modeling based on Poisson regression with robust variance.*

RESULTS: *16,000 doctors within 3816 municipalities were analyzed. Variables related to the working process the remained significant in the final model were the investments in Primary Health Care and the health facilities coverage. The results expressed the equity principle, as those municipalities with more vulnerable conditions and with higher coverage are prone to perform more activities in their working process.*

CONCLUSIONS: *The implementation of the More Doctors Program and hence the provision of doctors in deprived regions promoted the consolidation of three main aspects, namely the health working process, primary health care and equity, making it possible to carry out a health working process focused on PHC. This implies performing a greater number of activities that are inherent to PHC, which were not carried out due to the absence of doctors. The More Doctors Program fulfills its role in the combat of inequalities, particularly regarding more vulnerable municipalities.*

KEYWORDS: *Health Status Indicators. Primary Health Care. Health Services Coverage.*

INTRODUCTION

Brasil is currently fighting for the survival of the Unified Health System (SUS). Among the many challenges, is the replacement of 8 thousand Cuban doctors who left the country in 2018 due to the end of the technical cooperation between Brasil and Cuba, putting at risk the access to assistance of 23 million people in 2,800 vulnerablemunicipalities[1].

In the international context, several countries have adopted measures to tackle the shortcomings of human resources, in particular, of doctors, with emphasis on Canada, England, Holland, Portugal, Australia, the United States, and Chile[1-5].

In 2013, Brasil presented a density of 1.85 doctors per thousand inhabitants. Five years later, in 2018,

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that figure rose to 2.24, below that of countries such as Canada (2.54 in 2015); the United Kingdom (2.83 in 2016), and Australia (3.5 in 2015). It should be emphasized that currently, in Brasil, only 823 municipalities have one or more doctors per thousand inhabitants and that there are 374 municipalities with one doctor for a thousand inhabitants[6-9].

In this context, we had the *Programa Mais Médicos* (PMM - More Doctors Program), which was launched in July 2013, through Law No 12,871, to train human resources in the medical area of SUS in order to meet the rights provided for in the Constitution. This policy is structured around three strategic axes: training for the Single Health System (SUS); infrastructure improvement for Basic Health Units (UBS), and provision of emergency physicians[10].

The PMM aims to reduce the shortage of doctors in priority regions, reduce inequalities in access to health care, strengthen Basic Health Care (ABS), improve medical training, expand the inclusion of training physicians in ABS, strengthen the policy of continuing education on service, promote the exchange of knowledge and experiences among Brazilian health professionals and doctors trained abroad, improve the training of doctors to work on SUS public policies and, finally, stimulate SUS-related research[11].

In the face of the enormous demand for medical professionals, the program recruited Brazilian and foreign doctors. Initially, a small portion of the vacancies was occupied by Brazilian physicians trained in Brasil, followed by Brazilian physicians trained abroad, and, only then, by foreign doctors, with a preponderance of Cuban professionals, who occupied nearly 85% of the vacancies. In 2015, 100% of the vacancies were occupied by Cuban doctors. In 2018, the cooperation between Brasil and Cuba was interrupted, which culminated with 8 thousand Cuban doctors leaving the project. There was enormous difficulty in finding Brazilian physicians to fill out this new vacancies[1].

Added to this situation, the PMM is currently experiencing several challenges related to the perspective of its continuity. Thus, the ruptures in the work process caused by the replacement of the preexisting medical teams, the regional inequalities in the distribution of physicians, the instability for the permanent establishment of professionals, the deficiency in the management of work and education, the fragility of regional and hierarchical networks of health care, the absence of transformation in models of care/management, and the lack of quality assistance to the population represent the main challenges noted by the literature for the consolidation of the PMM[6,11,12].

Faced with this reality, it seems clear there is a need to investigate the work process associated with the PMM, mainly regarding the provision of professionals in remote and vulnerable areas. Therefore, seeking associations between socioeconomic indicators and the work process of the program, in different realities, represents an important tool for planning and drafting policies capable of contributing to overcoming these challenges, particularly in order to justify the continuation of such a policy.

Thus, the present study aims to analyze the relationship between the work process of the physicians who participated in the Cuban cooperation with the PMM and some contextual socioeconomic indicators.

METHODS

It is a quantitative and observational study, in which we used secondary data from the first supervision visit report (2015) of the PMM, conducted in 3,816 Brazilian municipalities and involving 15,397 professionals.

The pedagogic supervision reports were filled out by the PPM supervisors and are available *online*, hosted on the website of the Ministry of Education. There are stored in a Webportfólio System/UNA-SUS.

The report is composed of personal data of the supervisor, the physician supervised, the work location of the supervised physician, health units, work process, health care, health care network, and continuing education. The database refers to physicians who participate in the Cuban cooperation, aiming to analyze the specific work process of the participating professionals.

In this study the work process was represented by a set of dependent variables, namely: (a) team meetings, (b) team acceptance, (c) physician participation in the acceptance, (d) discussion of the therapeutic project, (and) physician participation in home visits, (f) team planning, and (g) health indicators.

Were used, also, independent socioeconomic variables, selected from an exploratory study, in order to verify the viability of the model to be tested. Then we sought correlations between those and the main dependent variable (represented by the sum of all dependent variables cited previously). From these

correlations, we excluded those that presented the greatest colinearity between themselves, in addition to being supported by the literature. In the end, we selected the following independent variables to compose the model: type of municipality, expectation of years of study, income inequality (Gini index), resources of basic care, and health units coverage.

Still in relation to the statistical analysis, we performed a descriptive analysis of the variables studied, followed by a grouping of the variables that constitute the work process, forming the main dependent variable with three categories: "performs all activities", "does not perform up to 2 activities", and "does not perform 3 or more activities". Subsequently, a bivariate analysis was performed by Pearson chi-square test ($p < 0.05$), to check the variables that were candidates to multiple regression. Then, we performed a Poisson regression with robust variance considering as the outcome the "number of activities not performed".

Finally, it is worth noting that this study involved secondary data; thus, it was not necessary to obtain any approval from the Research Ethics Committee.

RESULTS

We analyzed data from the reports of the first supervision visit of 3,816 municipalities, covering 15,397 professionals in Brasil. For the purposes of analysis, we excluded some municipalities that were not yet covered by the program.

The results revealed that some socioeconomic variables explain the work process model of the PMM, as shown in Tables 1 and 2.

Table 1 showed, from the bivariate analysis, that all variables had a significance level below 0.2 and, therefore, were included in the Poisson multiple regression model. The variable "expectation of years of study" was the only one not associated with the work process hours of the PMM physicians.

The results showed that the performance of a greater number of activities inherent to the work process of physicians in Primary Health Care occurred in the state capitals (41.8%), in municipalities that had an average formal education of up to 9.16 years (37.5%), with a higher Gini index (40.2%), and lower Human Development Index (HDI) (40.2%). It should be emphasized that the performance of all work process

TABLE 1. DESCRIPTIVE ANALYSIS OF THE VARIABLE RELATING TO THE WORK PROCESS IN RELATION TO THE SOCIOECONOMIC INDEPENDENT VARIABLES. BRASIL, 2019

	Performs all activities		Does not perform 1 to 2 activities		Does not perform 3 or more activities		
	n	%	n	%	n	%	p
Type of Municipality							
Capital	839	41.8	729	36.3	438	21.8	<0.001
Interior	5,289	35.7	5,192	35.0	4,338	29.3	
Expectation of years of study							
Over 9.94	1,973	35.6	1,930	34.8	1,640	29.6	0.058
From 9.16 to 9.94	2,021	36.1	2,018	36.1	1,556	27.8	
Up to 9.16	2,134	37.5	1,973	34.7	1,580	27.8	
Gini Index							
Up to 0.49	1,724	30.7	2,015	35.9	1,871	33.4	<0.001
From 0.491 to 0.550	2,189	38.4	1,936	33.9	1,578	27.7	
Over 0.550	2,215	40.2	1,970	35.7	1,327	24.1	
HDI							
Over 0.737	1,938	35.3	1,947	35.4	1,610	29.3	<0.001
From 0.643 to 0.37	1,929	35.4	2,066	36.2	1,713	30.0	
Up to 0.643	2,261	40.2	1,908	33.9	1,453	25.8	
Per capita investment in APS							
Over 43.3	2,196	39.2	1,994	35.6	1,412	25.2	<0.001
From 28.3 to 43.3	2,027	35.6	2,048	36.6	1,523	27.2	
Up to 28.3	1,905	33.9	1,879	33.4	1,841	32.7	
Health Units Coverage							
Over 1.76	2,068	37.0	2,056	36.8	1,460	26.1	<0.001
From 0.69 to 1.76	1,989	35.6	2,006	35.9	1,589	28.5	
Up to 0.69	2,038	36.5	1,841	33.0	1,708	30.6	

activities occurred in municipalities with higher per capita investment in APS (39.2%), associated to greater coverage of Basic Health Units (367%).

In relation to municipalities that did not perform three or more activities related to the work process, the data showed that these were concentrated in the interior (29.3%), in municipalities that had a higher expectation of years of study (29.3%). It also occurred in cities with the lower Gini indexes (40.2%), more developed (HDI, 25.8%), lower per capita investment in APS (25.2%), and with lower coverage of Health Units (26.1%).

Table 2 presents the results of the multiple regression, in which the HDI variable lost significance. With the multiple regression, the municipalities with an expectation of up to 9.16 years of study began to show a direct relationship with the prevalence of activities not performed. The same occurred for municipalities with per capita investment in APS of up to R$ 28.30.

DISCUSSION

The research evidences the three pillars in health: equity, work process, and primary health care, and showed that the most vulnerable municipalities performed a greater number of activities inherent to the work process of APS. However, the activities analyzed in this study (which make up the work process) are not on the sphere of innovation or invention but are inherent to the routine of Primary Health Care and the production of health care.

Santos et al.[9] highlight the activities provided for in the National Policy of Basic Care (Pnab), for example, regular meetings for the planning of health actions, home visits, and educational activities that became routine only after the deployment of the PMM.

In relation to the type of municipality, the study found there was the consolidation of a greater number of activities in capitals due to the existence of more appropriate infrastructure and greater ease of access in comparison with the interior. This is a counterpoint to the study conducted by Carneiro et al.[13] and Santos et al.[9], who aimed to evaluate the performance of the Family Health Strategy (ESF) after the implementation of the PMM in the territory of Marajó-PA, noting that the PMM fulfilled its role with greater effectiveness in coastal regions, areas of difficult access on the island of Marajó[13].

The data found in this study show there is a link between the three variables - coverage, per capita health investment, and the Gini index - which are considered strategic in the analysis of public policy, indicating that the allocation of resources, in the perspective of the PMM, occurs in municipalities that

TABLE 2. POISSON REGRESSION MODELING TO CHECK THE RELATIONSHIP BETWEEN THE INDEPENDENT AND DEPENDENT VARIABLES (N=16,825). BRASIL, 2019

	Activities not performed	Prevalence Ratios (PR) by Poisson Regression			
Variables	Mean (95% CI)	Unadjusted		Adjusted	
Type of Municipality		PR(95%CI)	P	PR(95%CI)	p
Capital	1.44 (1.36-1.51)	1		1	
Interior	1.80 (1.77-1.83)	1.25 (1.20-1.30)	<0.001	1.30 (1.24-1.36)	<0.001
Expectation of years of study					
Over 9.94	1.82 (1.77-1.87)	1		1	
From 8.16 to 9.94	1.75 (1.69-1.80)	0.96 (0.93-0.99)	0.005	1.03 (1.00-1.06)	0.028
Up to 9.16	1.71 (1.66-1.76)	0.94 (0.91-0.96)	<0.001	1.04 (1.01-1.08)	0.007
Gini Index					
Up to 0.49	2.02 (1.97-2.08)	1		1	
From 0.491 to 0.550	1.70 (1.64-1.74)	0.83 (0.81-0.85)	<0.001	0.86 (0.84-0.89)	<0.001
Over 0.550	1.56 (1.51-1.61)	0.77 (0.75-0.79)	<0.001	0.84 (0.81-0.87)	<0.001
Per capita investment in APS in reais					
Over R$ 43.3	1.58 (1.53-1.63)	1		1	
From R$ 28.3 to R$ 43.3	1.71 (1.66-1.76)	1.08 (1.04-1.1)	<0.001	1.10 (1.07-1.13)	<0.001
Up to R$ 28.3	1.98 (1.92-2.03)	0.89 (0.86-0.91)	<0.001	1.28 (1.23-1.32)	<0.001
Coverage of Health Units (UBS/10,000 inhabitants)					
Over 1.76	1.65 (1.60-1.70)	1		1	
From 0.69 to 1.76	1.80 (1.72-1.82)	1.07 (1.04-1.10)	<0.001	1.04 (1.00-1.07)	0.011
Up to 0.69	1.85 (1.80-1.91)	1.12 (1.09-1.15)	<0.001	1.07 (1.04-1.12)	<0.001

are more vulnerable, have more UBS coverage, and greater health inequality[11].

Coverage is a relevant indicator in the assessment of APS and the performance of Family Health Teams in Brasil since it provided better access to health services and systems. The results demonstrate that municipalities with a smaller population have greater coverage by the ESF, which does not necessarily translate into greater geographical or organizational accessibility[10,11].

Kemper et al.[14] highlight that with the implementation of the PMM there was an expansion of coverage. Currently, Brasil has more than 40,000 Family Health Teams deployed, responsible for the coverage of 130 million people. The PMM has contributed to the reduction of the shortage of physicians in priority and vulnerable areas, such as the North and Northeast regions, reaffirming the principle of fairness that was stressed in this research[12].

In relation to investments in primary health care, it was found that the more resources allocated to vulnerable areas, the further the development of APS. Research conducted by Mendonça et al.[15] aimed at evaluating primary health care based on the methodology by Starfield and Shy concluded that municipalities with very low per capita expenditures are associated with worse APS scores, which is in line with those of European countries, which related the improvement of primary care with better populational health status, lower rates of hospitalization, and lower socioeconomic inequality, and the overall expenditure in health is better in countries with better APS.

However, in the context of SUS, APS has been marked by a trajectory of reduction of resources due to the underfinancing of the system structure[16]. By the end of 2017, Brasil experienced a downsizing of Basic Care, not only regarding resources but in its conception and financing. We face a scenario of health "de-financing", which may culminate in the annihilation of the attempts of building a universal system and, particularly, of Primary Health Care. Indeed, there were drastic cuts in public spending, justified by an attempt to achieve fiscal balance. The Constitutional Amendment (EC) 95/2016 limited public spending (primary expenditure) for 20 years. There was a loss of R$ 9.2 billion in the budget of the Ministry of Health in 2016, which intensified the underfinancing of SUS[16].

FIGURE 1. DESCRIPTION OF THE DEPENDENT AND INDEPENDENT VARIABLES. BRASIL, 2019

Dependent Variables		
Variable	Description	Categories
Acceptance	Refers to the way one welcomes others or is welcomed.	Yes No
Physician acceptance	Refers to the presence of the physician in the act or way of welcoming others.	Yes No
Discussion of the therapeutic project by the team	It is a set of proposals and therapeutic conducts articulated to a individual and group as the result of a collective discussion by an interdisciplinary team.	Yes No
Home visit by a physician	It is a type of care targeted at a family or an individual provided in households or in partnership with local social resources, also with the presence of a physician.	Yes No
Team planning	Developing a team plan to reach a certain goal.	Yes No
Health indicators	Parameters used internationally to assess, from a health point of view, the healthiness of human groupings, as well as provide subsidies for health plans.	Yes No
Independent Variables		
Variable	Description	Categories
Type of Municipality	Classification of the municipality in relation to its representation in the state of which it is part.	Capital Interior
Expectation of years of study at age 18	Average number of years of study that a generation of children who enters school must complete by the age of 18 years, if current standards are maintained throughout the school life.	Years of formal education
Gini Index	Measures the degree of inequality in the distribution of individuals according to the per capita household income. It varies from 0, when there is no inequality (the per capita household income of all individuals is the same), to 1, indicating maximum inequality (a single individual is responsible for all the income). The universe of individuals is limited to those living in permanent private households.	0 a 1
HDI	Geometric average of the indices of income, education, and longevity dimensions, with equal weights.	0 a 1
Basic Care Resources	Amount invested in primary care, divided by the total population in 2010.	Reais *per capita*
Health Units Coverage	Number of primary care teams (Family Health Program) multiplied by 3,450, divided by the total population.	1:10,000

The authors add that the impacts are immediate and direct on work processes of health teams and the health conditions of the population, reflecting, crosswise, in the work process of the teams and the main health indicators, such as, increased infant mortality, decreased supply of vaccine coverage, thus, hindering hospital care and the development of actions and services of basic care[16].

CONCLUSIONS

It can be concluded that the provision of physicians in unassisted regions allowed for a work process with strong evidence of the principle of equity. With the implementation of the PMM, teams went on to perform a greater number of activities, improving the work process and bringing it closer to the attributes of APS.

Socioeconomic variables are fundamental to explain the work process with the deployment of the PMM in Brazilian municipalities. In our study, the pillar of financing and coverage of basic care stand out for accomplishing a work process that is consistent with the actual needs of the population, considering that the allocation of resources to the most vulnerable regions can enable an improvement in the infrastructure of units, a greater number of human resources, inputs, and equipment, which are essential for a better quality of care.

As discussed, in order to strengthen Primary Health Care and to achieve an effective work process, it is essential to invest in and increase coverage in unassisted and vulnerable areas. However, it is also necessary that medical professionals display sensitivity and flexibility in a health team in order to effectively carry out the activities that are already part of the work process in Primary Health Care.

Authors Contribution

All authors contributed equally to this study.

RESUMO

OBJETIVO: *Analisar a relação entre o processo de trabalho dos médicos do Programa Mais Médicos (PMM) no Brasil e alguns indicadores socioeconômicos no período de 2015.*

MÉTODO: *Trata-se de uma pesquisa quantitativa que utilizou dados secundários dos relatórios de supervisão do PMM. A variável dependente foi a qualidade do processo de trabalho e as variáveis independentes foram o tipo de município, expectativa de anos de estudo, índice de Gini, investimento em Atenção Primária à Saúde (APS) e cobertura de unidades de saúde. Na análise dos dados foi realizada a modelagem múltipla por regressão de Poisson com variância robusta.*

RESULTADOS: *Foram analisados dados de 3.816 municípios, abrangendo 1.537 profissionais. Destacam-se como variáveis socioeconômicas estratégicas e que explicam o modelo do processo de trabalho do PMM: o investimento e a cobertura da atenção básica. Tornou-se bastante evidente o princípio da equidade, pois os municípios mais vulneráveis e de maior cobertura realizam maior número de atividades em seu processo de trabalho.*

CONCLUSÕES: *Com a implantação do PMM e o provimento de médicos em regiões desassistidas ocorreu a consolidação do tripé processo de trabalho em saúde, atenção básica e equidade, tornando possível a efetivação de um processo de trabalho focado na APS. Isso implica a realização de maior número de atividades inerentes à APS, as quais não eram realizadas em função da ausência do profissional médico. Nesse sentido, o programa cumpre o seu papel de combater as desigualdades em municípios mais vulneráveis.*

PALAVRAS-CHAVE: *Indicadores básicos de saúde. Atenção Primária à Saúde. Cobertura de serviços de saúde.*

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ORIGINAL ARTICLE

Validation of the Objective Structured Assessment of Technical Skill in Brasil

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SUMMARY

BACKGROUND: *The aim of this study was to perform a cross-cultural adaptation of the Objective Structured Assessment of Technical Skill (OSATS) tool into Brazilian Portuguese and to determine its reproducibility and validity in Brasil.*

METHODS: *A Brazilian Portuguese version of OSATS was created through a process of translation, back-translation, expert panel evaluation, pilot testing, and then its validation. For the construct and the concurrent validities, twelve participants were divided into a group of six experts and six novices, who had to perform tasks on a simulation model using human placentas. Each participant was filmed, and two blinded raters would then evaluate their performance using the traditional subjective method and then the Brazilian Portuguese version of OSATS.*

RESULTS: *The Brazilian Portuguese version of OSATS had the face, content, construct, and concurrent validities achieved. The average experts' score and standard deviations were 34 and 0.894, respectively, for Judge 1 and 34.33 and 0.816 for Judge 2. In the case of novices, it was 13.33 and 2.388 for Judge 1 and 13.33 and 3.204 for Judge 2. The concordance between the judges was evident, with the Correlation Coefficient (Pearson) of 0.9944 with CI 95% between 0.9797 and 0.9985, with p < 10-10, evidencing the excellent reproducibility of the instrument.*

CONCLUSION: *This preliminary study suggests that the Brazilian Portuguese version of OSATS can reliably and validly assess surgical skills in Brasil.*

KEYWORDS: *Educational measurement. Simulation. Training. Surgical procedures, operative/education. Surveys and questionnaires.*

INTRODUCTION

Traditionally, the proficiency of surgical residents is based on case records that measure their operational experience but do not assess their performance[1,2]. In addition, the performance assessment of residents is often carried out based on subjective criteria, which have low reliability and hinder the feedback to the learner[3].

In recent years, there has been a shift in paradigm regarding surgical education and the profile of the residents[4-6]. A systematic procedure has been increasingly used to assess operative performance objectively[7,8]. For this purpose, the instrument most used worldwide is the Objective Structured Assessment of Technical Skills (OSATS)[9,10]. It is composed of a global rating scale (GRS-OSATS) with seven assessment items scored on a Likert scale of 5 points. Therefore, the total score of

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the GRS-OSATS varies from 7 to 35, with higher scores indicating a greater technical ability of the surgeon[11].

The GRS-OSATS was originally developed in English at the University of Toronto, and surgical researchers who wish to use this tool in a country in a language other than English have to carry out a process of transcultural adaptation and validation[12-14]. As far as we know, no validation study for the scale has been published in Brasil yet. Thus, the objective of this work was to cross-culturally adapt the GRS-OSATS for Brazilian Portuguese and validate it in Brasil.

METHODS

This cross-sectional observational study was approved by the Research Ethics Committee (Coep - CAAE Decision No: 0364.0.203.000-11), Federal University of Minas Gerais (UFMG), Brasil. All participants consented in writing to participating in this work.

We collected 12 human placentas from the obstetrics department of the Hospital das Clínicas of the Federal University of Minas Gerais (HC-UFMG). The pregnant women were submitted to a pre-natal infection assessment and signed the consent for the placenta donation for the practice of surgical techniques. The placentas were returned in their entirety to the Pathology Department of the UFMG five days after they were obtained, and their partial or total use for other purposes was forbidden.

The research was divided into two stages: first, the GRS-OSATS was transculturally adapted for Brazilian Portuguese; then, a validation study was conducted to determine its reproducibility, validity, and reliability in Brasil.

Transcultural adaptation

The cross-cultural adaptation of the original version of the GRS-OSATS was divided into five stages: the initial translation, translation synthesis, back-translation, consensual version, and pre-test[15].

The first stage was the initial translation of the original version of the GRS-OSATS from English into Brazilian Portuguese by two bilingual translators. These produced two different versions of the translation, T1 and T2.

The second stage was the translation synthesis. The T1 and T2 versions were discussed with both translators, thereby producing a single version in Brazilian Portuguese, i.e., version T1-2.

In the third stage, two bilingual translators, who had no previous contact with the original instrument, back-translated separately the T1-2 version into English, which resulted in versions BT1 and BT2. These new versions in English allowed the identification of possible translation errors and grammar inconsistencies in comparison with the original version.

The fourth stage consisted of the assessment of all versions by a committee composed by the authors of this study. The objective of this stage was to review all translations to get a final single version in Brazilian Portuguese (FV-GRS-OSATS). Thus, we evaluated the semantic equivalence with respect to the meanings of words with attention to idiomatic expressions and colloquialisms; the experimental equivalence, comparing the realities of different countries and cultures; and the conceptual equivalence, ensuring that words have the same definition.

The last stage was the pre-test for adjustments and detection of inconsistencies and to allow the validation of the instrument. In the pre-testing, the FV-GRS-OSATS was presented to 20 surgeons. After examining it, the surgeons were asked about the difficulty in interpreting or understanding the instrument. They were then requested to assess the clarity of the items using a Likert scale of 5 points (1, not clear at all; 2, not very clear; 3, somewhat clear; 4, clear; and 5, very clear).

Validation

After the pre-test, we started the validation stage, in which we handed out to 20 participants a questionnaire on the ability of an instrument to measure the residents' technical skills in a general way for face validity and specifically for content validation of each item. A Likert scale of 5 points was also used (1, not capable; 2, barely capable; 3, moderately capable; 4, capable; and 5, very capable. The reliability, i.e., the consistency between evaluators, was measured by calculating Cronbach's coefficient alpha, whereas a value above 0.70 was acceptable.

For the construct validation (ability to differentiate the performance between experts and beginners) and the concurrent validation (comparison of the traditional subjective method with the proposed one), we recruited 12 participants, divided into two groups: six experts in surgery for the Expert Group (EG), which comprised surgeons with over ten years of experience, and six beginners for the Novice Group (NG), which comprised 1st-year surgical residents with little or no surgical experience.

As seen in Figure 1, a total of 12 human placentas were prepared, according to Oliveira Magaldi et al.[16]. Then, a standardized explanation of basic surgical techniques exercises in these models of training was presented to both groups. These consisted of dissecting a blood vessel, sectioning it with surgical scissors, and performing a hemostatic suture. Thus, we began the practice rounds using surgical simulation models.

Each training session was filmed, with special attention so that the camera framing captured only the hands of the participant during the exercises. The videos were then seen separately watched at two distinct moments by two experts in surgical education chosen as judges and who were not present during the training sessions. They were unaware of the participants' experience levels. Initially, the two judges evaluated the videos in the traditional subjective way and graded them from A to D (A, excellent; B, good; C, regular; D, bad. After 15 days, both evaluated the participants' videos again; however, this time, using the FV-GRS-OSATS. The grades were distributed as follows: A for scores from 28 to 35, B for scores from 21 to 27, C for scores from 14 to 20, and D for scores from 7 to 13. The Correlation Coefficient (Pearson) between both judges was calculated with the help of Stata version 11.0, and we considered a CI of 95% and $p<0.05$.

RESULTS

In the first stage of the GRS-OSATS transcultural adaptation, there was a difference in the translation of certain words. However, since the meanings were preserved, the translation synthesis and back-translation stages were carried out without questions. In

TABLE 1. FINAL VERSION OF THE GRS-OSATS IN BRAZILIAN PORTUGUESE

Escala de Classificação Global de Instrumento de Avaliação Objetiva e Estruturada de Habilidades Técnicas Operatórias (Global Rating Scale of Objective Structured Assessment of Technical Skills)					
Cuidados com o Tecido (Respect for tissue)	**1.** Utilizou frequentemente de força desnecessária sobre o tecido ou causou danos ao mesmo pelo uso inapropriado dos instrumentos. (Frequently used unnecessary force on tissue or caused damage by inappropriate use of instruments.)	**2**	**3.** Manipulou cuidadosamente o tecido, mas ocasionalmente, causou danos inadvertidos. (Careful handling of tissue but occasionally caused inadvertent damage.)	**4**	**5.** Consistentemente manipulou o tecido de forma apropriada, causando danos mínimos. (Consistently handled tissues appropriately with minimal damage.)
Economia de Tempo e Movimentos (Time and motion)	**1.** Muitos movimentos desnecessários. (Many unnecessary moves.)	**2**	**3.** Movimentos eficientes, mas alguns desnecessários. (Efficient time/motion but some unnecessary moves)	**4**	**5.** Evidente economia de movimentos e máxima eficiência. (Economy of movement and maximum efficiency.)
Manuseio dos Instrumentos (Instrument handling)	**1.** Constantemente faz movimentos hesitantes ou desajeitados com os instrumentos. (Repeatedly makes tentative or awkward moves with instruments.)	2	**3.** Uso competente dos instrumentos, embora, ocasionalmente, apresenta-se travado ou desajeitado. (Competent use of instruments although occasionally appeared stiff or awkward.)	**4**	**5.** Movimentos ajustados e fluidos com os instrumentos. (Fluid moves with instruments and no awkwardness.)
Conhecimento dos Instrumentos (Knowledge of instruments)	**1.** Frequentemente usou ou solicitou instrumentos inapropriados. (Frequently asked for the wrong instrument or used an inappropriate instrument.)	**2**	**3.** Conhecia o nome da maioria dos instrumentos e os utilizou adequadamente para a tarefa. (knew the names of most instruments and use appropriate instrument for the task.)	**4**	**5.** Evidentemente familiarizado com os instrumentos requisitados e com os seus respectivos nomes. (Obviously familiar with the instruments required and their names.)
Fluxo operatório e antecipação no planejamento cirúrgico (Flow of operation and forward planning)	**1.** Frequentemente interrompeu o procedimento operatório ou necessitou discutir sobre o próximo passo. (Frequently stopped operating or needed to discuss next move.)	**2**	**3.** Demonstrou capacidade de antecipação no planejamento operatório com progressão contínua do procedimento. (Demonstrate ability for forward planning with steady progression of operative procedure.)	**4**	**5.** Evidentemente planejou o curso da operação, sem esforços para avançar no passo-a-passo da cirurgia. (Obviously planned course of operation with effortless flow from one move to the next.)
Uso de Auxiliares (Use of assistants)	**1.** Consistentemente alocou mal os auxiliares ou falhou ao utilizá-los. (Consistently placed assistants poorly or failed to use assistants.)	**2**	**3.** Bom uso dos auxiliares na maior parte do tempo. (Good use of assistants most of the time.)	**4**	**5.** Utilizou os auxiliares estrategicamente, com o máximo proveito durante todo o tempo. (Strategically used assistant to the best advantage at all times.)
Conhecimento do Procedimento Operatório Específico (Knowledge of specific procedure)	**1.** Conhecimento deficiente. Necessitou de instrução específica na maioria dos passos operatórios. (Deficient knowledge. Needed specific instruction at most operative steps.)	**2**	**3.** Conhecia todos os aspectos importantes da operação. (Knew all important aspects of the operation.)	**4**	**5.** Demonstrou familiaridade em todos os aspectos da operação. (Demonstrate familiarity with all aspects of the operation.)

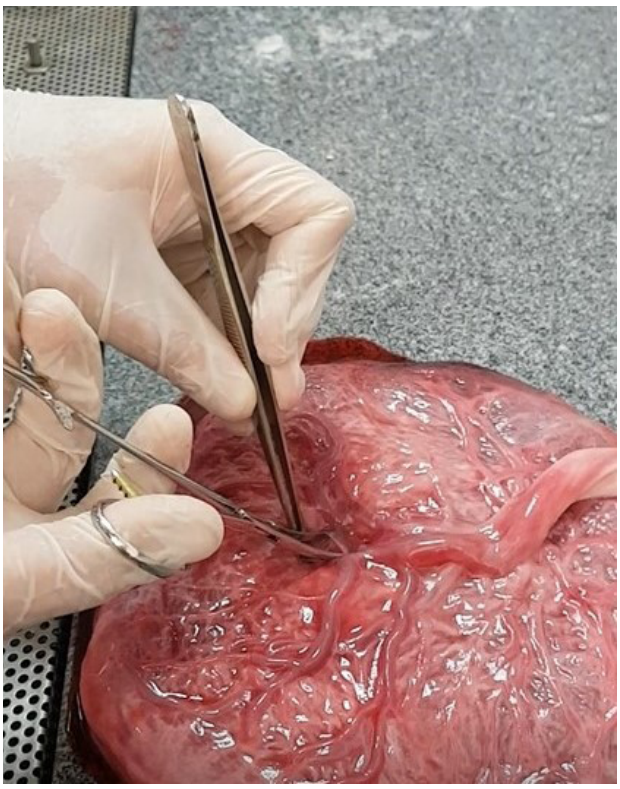

FIGURE 1.

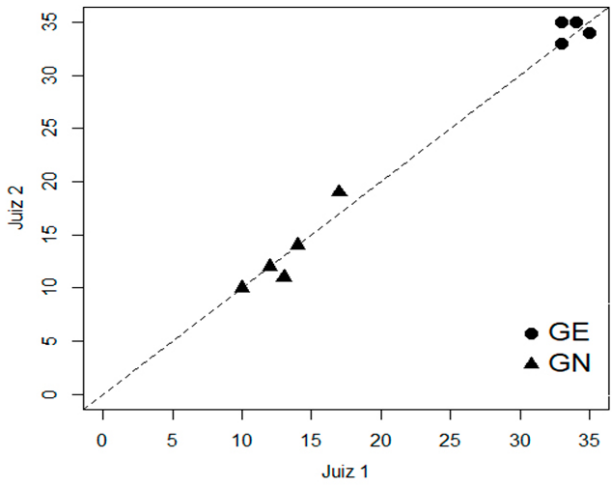

FIGURE 2.

the stage of the committee's consensual version, grammatical errors and were corrected, and some items of version T1-2 were modified by the authors. In Table 1, it is possible to see the final version of the adapted evaluation instrument.

During the pre-test, all participants found it easy to interpret and understand the instrument. Only the item "Surgery Flow and Anticipation in Surgical Planning" was not considered very clear by all surgeons. However, the three surgeons who did not give the maximum score to this item gave it a 4 (clear), which was also acceptable.

During the face validity process, in which the instrument was assessed in general, the percentage of agreement between grades 5 (very capable) among the participants was 85%. During the content validation, in which each item of the instrument was assessed individually, only the items "Knowledge of the Instruments" and "Use of Assistants" received a grade 3 (moderately capable) from one surgeon. All others receive grades 4 or 5 (capable or very capable). Still, the item "Knowledge of the Instruments" had an agreement of grades 5 of 70% and 65% for the item "Use of Assistants" The consistency between evaluators was excellent, with a Cronbach's Coefficient Alpha of 0.954.

The experts received considerably higher grades than the novices, evidencing clear discrimination between the two groups and resulting in construct validity. The mean and standard deviation of the scores assigned to experts were, respectively, 34 and 0.894 for Judge 1 and 34.33 and 0.816 for Judge 2. As for the novices, these statistics were 13.33 and 2.338 for Judge 1 and 13.33 and 3.204 for Judge 2. Figure 2 compares the scores given by each judge to each individual evaluated. The correlation coefficient (Pearson) between the two judges was 0.9944, with a CI of 95% between 0.9797 and 0.9985 and $p<10^{-10}$, demonstrating the excellent reproducibility of the instrument.

In initial traditional subjective evaluation, the grades attributed by the judges dissented in three videos, while, in the second moment, after the use of the FV-GRS-OSATS, both judges agreed in all assessments. In addition, the first judge evaluated two videos differently in both stages. In the subjective evaluation, the judge considered that two participants should receive grade D, while in the objective assessment, their grades were C. The ratings of the second judge differed three times between the two stages, and, in the subjective evaluation, an expert was given grades equivalent to those of a novice, i.e., both received B.

DISCUSSION

This is the first study to cross-culturally adapt the Osats to Brazilian Portuguese and validate it for use in Brasil. Santos & Salles[17] described the validation of specific checklists for assessing performance in some surgical procedures but did not use the global classification scale of the Osats. Few authors have published

studies in which the Osats was used in Brasil, but did not bother with its previous transcultural adaptation and validation for our country[18,19].

To fulfill its purposes, an instrument that was developed in one culture and will be used in another must be, first, subjected to a test of cultural equivalence[20,21]. In addition, the assessment must have validity and reliability, which is related to the consistency and accuracy of the results of the measurement process[22].

During the process of transcultural adaptation of the GRS-OSATS to Brazilian Portuguese, changes were necessary to adapt it, such as was the case with the idiomatic expression "Time and Motion", which was adapted as "Economia de Tempo e Movimentos". These adjustments were made because, when the committee met, it was observed that the understanding of the items varied. For this reason, the adaptation of an instrument into another language is a complex process, which cannot be done by just a simple translation. For Beaton et al.[23], the Committee plays a fundamental role in cross-cultural adaptation. In our study, the Committee evaluation showed that, although no radical change in the items was required, the adjustments provided homogenization of their understanding by the evaluators and allowed for the next step of the study: validation.

After the transcultural adaptation was completed, the face and content validity were considered appropriate for the instrument's ability to measure what it proposes to measure. During the content validation, two items stood out for, although having achieved a high rate of agreement of grades 5, receiving smaller grades in relation to the others: "Knowledge of the Instruments" and "Use of Assistants". In the specific case of the item "Knowledge of the Instruments", the measurement of operative technical skills can be underestimated. Sometimes, the resident might know when and how to use the instrument, but not its name. In addition, he can also use an instrument considered inadequate and achieve the expected result.

Another item that received smaller grades was "Use of Assistants," which might be justified by the fact that the resident assessment of the use of assistants does not depend only on their technical capabilities. It also depends on the surgical assistants themselves. In this case, for example, the measurement of the operative technical skills of residents may be overestimated if the assistants are very good and familiar with all aspects of the operation. The proactivity of the assistants, so desired in surgical practice, may compromise the ability to assess the resident since it is not possible to know where the ability of the assessed individual begins and ends. The maintenance of the surgical team, with the same assistants in all operations, could solve this limitation.

The construct and concurrent validities were considered appropriate since the evaluations using the GRS-OSATS allowed for clear discrimination between the experts and novices and were more reliable and consistent than the subjective evaluation. Although this is the best tool researched so far, and the results of our study have proven the effectiveness of an objective evaluation in relation to a subjective one, the Judge's personal opinion is still prevalent over the instrument, which makes its application more difficult. In this context, the judges must be trained to standardize their assessment and reduce their subjectivity.

With that regard, it is worth reflecting on what is intended with this type of instrument. Its most important role perhaps is for individual feedback since it enables residents to follow their own evolution in a systematized way. Due to the influence of context, the comparison of performance evaluations, using the GRS-OSATS, between residents is not trustworthy; therefore, this instrument should not be used for ranking. It is important that the residents' activities are not reduced to standardized items that engender their actions. More important than measuring is improving the performance of surgeons, aiming for the development of health care.

The sampling used in the instrument validation process was of convenience in a public university hospital. The evaluation of operative performance in a single reference center and the reduced sample are the main limitations of this study.

The Brazilian Portuguese version of the GRS-OSATS maintained semantic, experimental, and conceptual equivalence with the original instrument. Face, content, construct, and concurrent validities were achieved. Thus, the instrument proved to be reproducible and reliable for use in Brasil.

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Conflicts of interest

The authors have no conflict of interest for the present study.

Contribution of the authors

Marcelo Esteves Chaves Campos (design, structuring, planning, analysis, interpretation, writing). Marcelo Magaldi Ribeiro de Oliveira (advice, interpretation, revision). Lilian Bambirra de Assis (structuring, writing, revision). Augusto Barbosa Reis (coordination, data collection, revision). Flávio Bambirra Gonçalves (analysis, methodology, interpretation).

RESUMO

OBJETIVOS: *Objetivou-se com este trabalho adaptar transculturalmente o instrumento Objective Structured Assessment of Technical Skill (Osats) para o português-brasileiro e validá-lo no Brasil.*

MÉTODOS: *Uma versão em português-brasileiro do Osats foi criada por meio de um processo de tradução, retrotradução, versão consensual por um comitê de especialistas e pré-teste, seguido da etapa de validação. Para validades de constructo e concorrente, foram recrutados 12 participantes da Universidade Federal de Minas Gerais, divididos em um grupo de seis especialistas e um grupo de seis novatos, que tiveram de realizar tarefas em modelos de simulação utilizando placentas humanas. Cada participante foi filmado em anonimato e dois examinadores avaliaram os seus desempenhos usando o método tradicional subjetivo e depois a versão em português-brasileiro do Osats.*

RESULTADOS: *A versão em português-brasileiro do Osats alcançou as validades de face, de conteúdo, de constructo e concorrente. A média e o desvio padrão das pontuações atribuídas aos especialistas foram, respectivamente, 34 e 0,894, para o Juiz 1 e 34,33 e 0,816 para o Juiz 2. No caso dos novatos, foram 13,33 e 2,338 para o Juiz 1 e 13,33 e 3,204 para o Juiz 2. O Coeficiente de Correlação (de Pearson) entre os dois juízes foi de 0,9944 com IC 95% entre 0,9797 e 0,9985, com p<10-10, evidenciando a excelente reprodutibilidade do instrumento.*

CONCLUSÃO: *A versão em português-brasileiro do Osats manteve-se equivalente ao instrumento original e foi validada. Assim, pode ser usada para avaliar a performance operatória dos residentes em cirurgia no Brasil.*

PALAVRAS-CHAVE: *Avaliação educacional. Simulação. Capacitação. Treinamento. Procedimentos cirúrgicos operatórios/educação. Inquéritos e questionários.*

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ORIGINAL ARTICLE

Underutilization of insulin and better metabolic control. A NOVA clinic experience

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SUMMARY

OBJECTIVE: *To present the results of metabolic control in patients with type 2 Diabetes Mellitus from a private clinic in Northern Mexico,*

METHODS: *This cross-sectional study used retrospective data obtained from electronic records from a private outpatient clinic at the end of 2018. Inclusion criteria were a diagnosis of T2DM and age ≥ 18 years. Baseline characteristics (age, gender, drug use) were reported. The achievement of glycated hemoglobin goals was established as <7%.*

RESULTS: *A total of 3820 patients were evaluated. Their mean age was 59.86 years (+/-15.01). Of the population, 46.72% were men, and 53.28% were women. Glycated hemoglobin goals were adequate in 1872 (54%) patients. There were 3247 patients (85%) treated with oral medications, of which 1948 (60%) reported glycated hemoglobin less than 7%. Insulin use was reported in 573 (15%) patients, with 115 (20%) reporting glycated hemoglobin less than 7%. The most frequently used basal insulin was glargine in 401 (70%) patients.*

CONCLUSIONS: *Our findings are clearly higher than the control rate reported by our national health surveys of 25% with glycated hemoglobin < 7%, but similar to that reported in other countries. The most commonly used therapeutic scheme was the combination of oral hypoglycemic agents. The percentage of cases that include insulin in their treatment was lower. Clinical inertia to insulin initiation and intensification has been defined as an important cause of this problem.*

KEYWORDS: *Diabetes mellitus. Insulin. Hypoglycemic agents.*

INTRODUCTION

As the prevalence of type 2 diabetes (T2DM) globally increases, the need for improved disease prevention and management strategies becomes urgent. The International Diabetes Federation estimates that 415 million (1 in 11 persons) individuals have DM, and this will increase to 642 million or almost 10% of the general population by 2040[1]. There are great individual, societal, and economic costs associated with DM, which can be heightened by microvascular complications, such as retinopathy and neuropathy, conditions that have been attenuated by better glycemic control. Macrovascular complications are relatively better abated by lipid and blood pressure control[2]. However, for individuals with DM, cardiovascular disease (CVD) remains the most prevalent cause of morbidity and mortality in both men and women[3]. Studies show that insulin initiation

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is often delayed until after multiple oral antidiabetic drug failures and deterioration of glycemic control well beyond recommended guidelines[4,5]. Clinical inertia to insulin initiation and intensification has been defined as an important cause of this problem in Mexico[6,7].

The objective of this report is to present the results of the metabolic control of patients with T2DM from a private clinic in Northern Mexico, emphasizing the proportion of patients that achieve target goals.

METHODS

This cross-sectional study used patient data obtained during 2018 from electronic records from the private outpatient clinic of the Hospital Clinica Nova in San Nicolas de los Garza, Mexico, where all diagnostic procedures and treatments were free of charge to patients, given by general internists. Inclusion criteria were a diagnosis of T2DM and age ≥ 18 years. We excluded pregnant patients, patients with type 1 DM, and patients with acute metabolic complications, such as diabetic ketoacidosis and hyperglycemic hyperosmolar state. Baseline characteristics, including age, gender, and drug use, were reported. Hemoglobin A1c (A1c) goal was established as < 7% following ADA 2018 recommendations[8]. The study was approved by the local research ethics committee. Statistics were reported as frequencies, percentages, and central tendency. When comparing different treatments to the therapeutic goal, $p < 0.05$ was considered significant.

RESULTS

A total of 3820 patients were evaluated. The mean age was 59.86 years (15.01); 46.72% were men, and 53.28% were women. A1c goals were adequate in 2063 (54%) of patients.

Of the 3247 patients (85%) treated with oral medications, 1948 (60%) had an A1c less than 7%. In most cases, treatment was combined using 2 to 4 drugs, including metformin (66.34%). Insulin use was reported in 573 (15%) patients, either with insulin alone or insulin combined with oral agents. The most frequently used insulin was glargine, reported in 401 (70%) patients; premixed insulin in 115 (20%); and other types of insulin (NPH, determir, degludec) in 57 (10%). In patients with insulin treatment, the A1c target was met in 115 (20%). There is a significant difference in glycemic control in favor of oral medication compared to insulin (x^2=31.68, p<0.00001). Other measures to treat cardiovascular risk factors, such as statins and acetylsalicylic acid, were used by a small percentage of patients (< 20%).

TABLE 1.

	A1c <7% (n,%)	A1c >7% (n,%)
N= 3820	2063(54)	1757(46)
Oral Treatment (n=3247)*	1948(60)	1299(40)
Insulin (n=573)	115(20)	458(80)

*Differences between oral and insulin metabolic control: P < 0.00001

DISCUSSION

The control of T2DM in our clinic was 54%. Our findings are clearly higher than the control rate reported in the national health survey in Mexico of 25% with A1c < 7%[6,7], although similar to results reported by primary care doctors of the Spanish healthcare system[9]. Other recent publications from the United States reported that overall glycemic control has not improved and remains poor among nearly a quarter of younger patients[10].

The most frequent therapeutic scheme was the combination of oral hypoglycemic agents with metformin in a large proportion with good glycemic control. This is similar to previous studies, in which up to 80% of patients with DM were taking oral treatment, along with a tendency to reduce the use of sulfonylureas[11,12]. New treatment schemes that include glycosuric or GLP agonist drugs have yet to represent a significant proportion in our studies, due to them being just recently added to our therapeutic tools[13]. It is very important to establish appropriate guidelines for the selection of OHAs. We use metformin as monotherapy and combination therapy, and its association with other drugs will depend on the patient's clinical characteristics and the efficacy, side effects, mechanism of action, risk of hypoglycemia, the effect on body weight, patient preference, and combined comorbidity. Interestingly, newer antihyperglycemic medications such as the GLP-1 RAs and SGLT-2 inhibitors showed significant promise in recent clinical trials in terms of providing CV benefit via their favorable effect on traditional CV-risk factors. GLP-1 agonists provided more benefits in terms of improving vascular risk factors and atherosclerosis, whereas SGLT-2 inhibitors improved HF outcomes and CV mortality[14,15]. Real-world data evaluating SGLT-2 inhibitors use in T2DM patients confirmed the findings of EMPA-REG OUTCOME study and also showed that SGLT-2 inhibition could have CV benefit in patients with low CV risk[14].

We have recently published our findings in relation to one of these classes of medications[13]. More detailed studies, perhaps using patient and physician questionnaires, should attempt to establish the reasons for a delay in intensification, particularly among older people with DM and those with comorbidities.

The percentage of cases that included insulin in their treatment was lower than that reported in other countries where it is greater than 30 %[16]; however, it is similar to the 13% in the national survey[6], despite the low rate of insulin use, the control measured by A1c is similar to that of developed countries[10], perhaps due to the option of combining two or more non-insulin drugs, or the significant delay in the initiation of insulin treatment after glycemic failure with oral antidiabetic drugs[11,12]. Initiation of insulin treatment with basal analogs insulin is often a preferred option for primary care physicians for its relatively low risk of hypoglycemia or in patients with a history of hypoglycemia with human insulins[11,12,17]; however, there is no fixed standard for intensification of insulin treatment in patients who continue to have poor glycemic control after insulin initiation. However, the use of other schemes is infrequent[18]. Moreover, it is important that studies on clinical inertia be carried out regularly to keep up with the changes in patient demographics, therapy options, and clinical guidelines[19]. We speculate that these patients may have been on very low doses of insulin and have low adherence to medical treatment. This hypothesis could be the basis for further research.

In our country, age, a high body mass index, stress in a private setting, and longer duration of DM and insulin use have been found as the main cause of chronic poor control. Fasting blood glucose is the method frequently used to assess glycemic control and A1c, considered the gold standard, is used in less than 10% of cases[6,7].

The strengths of the present analysis include cohort size, which corresponds to a private clinic where the first level of care are internists, with institutional coverage of all antidiabetic drugs approved in our country and a multidisciplinary team for the care of patients with DM.

We are also developing a multidisciplinary coaching strategy in outpatient "problem" patients under both oral and insulin medications, using all clinical evaluation and biomarkers as determinations of peptide C in the decision making, personalizing of diabetes care ranking the following aspects: Pathophysiology (insulin resistance or insulin deficiency), Potency (effectiveness), Precaution (security), Perks (non-glycemic effects), Practicalities (consistency with the treatment), and Price (our clinic provides coverage), all this in addition to personalized goals according to age and comorbidities. The main limitation of our cross-sectional study is its design: an electronic database with unidentified data variables such as body mass index, insulin dose, time of evolution of chronic poor control, dose intensification or titrations, treatment adherence, among others, selection bias because the population is from a secondary-care hospital clinic. No subanalysis of results that could modify these data was performed; for example, for geriatric patients whose therapeutic goals are more flexible. Also, no pharmacodynamic study was performed. Our goals are to continue increased medical education including structured programs in DM both for patients and physicians and to try to create preventive, predictive, personalized and precise care, along with informing about and prescribing medication for cardiovascular risk factors, such as the use of statins and aspirin, which is low in our clinic. We will also continue promoting independent medical education for the attending physician as a strategy for improving clinical inertia and providing personalized care.

CONCLUSION

Our patients' glycemic control is similar to that reported around the world, but higher than that reported in our country. The use of oral hypoglycemics in combination is the most frequently used therapeutic strategy. Insulin treatment represents only a small percentage with insufficient control. The prescription of drugs for cardiovascular risk factors, like statin and aspirin, is an area of opportunity due to its infrequent indication. The management of T2DM calls for employing a holistic risk factor control approach with conventional T2DM medications and adequate control of additional cardiovascular risk factors.

Conflict of interest

None

Sources of funding

None

Author contributions

All authors contributed to the study design, data analysis, data interpretation, and writing of the manuscript

RESUMO

OBJETIVO: *Apresentar os resultados do controle metabólico de pacientes com Diabetes Mellitus tipo 2 em uma clínica privada no norte do México,*

MÉTODOS: *Este estudo transversal utilizou dados retrospectivos obtidos em prontuários eletrônicos de um ambulatório privado no final de 2018. Os critérios de inclusão foram o diagnóstico de DM2 e idade ≥ 18 anos. Características basais (idade, sexo, uso de drogas) foram relatadas. A realização de metas de hemoglobina glicada foi estabelecida como <7%.*

RESULTADOS: *Um total de 3820 pacientes foram avaliados. A média de idade foi de 59,86 anos (+/- 15,01). Da população, 46,72% eram homens e 53,28% eram mulheres. Objetivos de hemoglobina glicada foram adequados em 1872 (54%) pacientes. Havia 3247 pacientes (85%) tratados com medicamentos orais relatando em 1948 (60%) menos de 7%. O uso de insulina foi relatado em 573 (15%) pacientes, com 115 (20%) relatando menos de 7%. A insulina basal mais utilizada foi a glargina, em 401 (70%) pacientes.*

CONCLUSÕES: *Nossos resultados são claramente mais altos do que a taxa de controle relatada por nossos levantamentos nacionais de saúde de 25% com hemoglobina glicada <7%, mas semelhante à relatada em outros países. O esquema terapêutico mais utilizado foi a combinação de hipoglicemiantes orais. A porcentagem de casos que incluem insulina no tratamento foi menor. A inércia clínica à iniciação e intensificação da insulina tem sido definida como uma importante causa desse problema.*

PALAVRAS-CHAVES: *Diabetes mellitus. Insulina. Hipoglicemiantes*

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ORIGINAL ARTICLE

Oncology practice during COVID-19 pandemic: a fast response is the best response

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SUMMARY

The first confirmed case of coronavirus disease 2019 (COVID-19) in Brasil was reported on February 25th, 2020, and by April 3rd, 8076 were confirmed in the country. As COVID-19 disease incidence escalates in Brasil, management of cancer patients requires immediate action and oncology clinics are urged to establish a contingency plan. We have installed a COVID-19 Management Committee to elaborate and implement best practices to assist cancer outpatients as well as to provide a safe environment for clinical staff and other employees at the outpatient clinics. The challenges of cancer treatment in the midst of COVID-19 global pandemic highlight the importance of a rapid response by institutions, where organizational structure, strategic planning, agility in guidelines implementation and alternative ways to protect and support clinical staff, employees and patients may be the key to mitigate pandemic effects.

KEYWORDS: *COVID-19. Coronavirus. Medical oncology. Public Health. Pandemics*

INTRODUCTION:

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is rapidly spreading all over the world, affecting 180 countries and threatening the health of all mankind, leading the World Health Organization (WHO) to classify Coronavirus Disease (COVID-19) as a pandemic on March 12th, /2020 and its risk as *very high* at global level[1].

By April 3rd, 1.039.166 cases were confirmed worldwide, among which 55.092 patients (5,3%) died. Updated statistics for Brasil have shown 8076

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confirmed cases and 329 (4%) COVID-19 associated deaths[2]. Nonetheless, as testing for SARS-CoV-2 is restricted to severe cases and health professionals, these numbers are likely to be underestimated[3].

Clinical experience in other countries has shown that early recognition of infected individuals is crucial. Since the severity of disease is highly related to its prognosis, the essential strategies to improve outcomes remain the early detection of high-risk patients and early intervention guided by intensivists. As there has been no effective antiviral treatments for COVID-19, reduced mortality is achieved by early and strong intervention to prevent contamination and disease progression[4-6].

Management of cancer patients during COVID-19 disease outbreak requires immediate action and oncology clinics are urged to establish a contingency plan, as mortality among these at risk individuals reaches 28,6%[7], contrasting to 5,3% in the general population[2]. The immunosuppressive state caused by either anticancer treatments and/or surgery renders cancer patients more susceptible to infections. A recent study has shown that these patients have a statistically significant higher risk of developing severe events associated to SARS-CoV-2 infection, with a hazard ratio of 3.56[8]. This study enrolled a small number of patients, but nonetheless, it reflects the general position undertaken by most hospitals and clinics around the world, where adjuvant chemotherapy or elective surgery for less aggressive cancers is being postponed and personal protection should be reinforced for patients with cancer or cancer survivors. Intensive surveillance or treatment should be considered for those cancer patients with active disease who are infected with SARS-CoV-2 virus, as mortality can be as high as 28% among these individuals. As COVID-19 disease incidence escalates in Brasil, it poses a challenge to medical practice and presses for a crisis management plan. AMO is a network of outpatient clinics currently operational in 6 cities in 2 states. In 2019, our 247 physicians assisted 41.429 patients on a total of 97.110 medical visits and 3917 patients underwent 33.524 chemotherapy sessions. As the largest oncology group in the Bahia state, we undertook the task to install a COVID-19 Management Committee to elaborate and implement best practices to assist cancer outpatients as well as to provide a safe environment for clinical staff and other employees at the outpatient clinics.

COVID-19 MANAGEMENT COMMITTEE INSTALMENT AND INITIAL CONTINGENCY PLAN

WHO declared COVID-19 outbreak as a Public Health Emergency of International Concern on January 30th, raising general awareness on timing and pattern of virus spreading from China to other countries. The first positive case in Latin America was registered on February 25th in São Paulo[9], Brasil. Thus, the Committee was installed on March 11th and the 1st version of the contingency plan was elaborated in this meeting and implemented on March 12th, the very same day that COVID-19 was declared as pandemic by WHO. The timeline of subsequent resolutions and actions of the Committee are detailed in Figure 1.

The COVID-19 Management Committee is composed by staff from the AMO Clinic, as follows: Medical Director (Hematologist), Medical Manager (Pulmonologist), Director of Assistance and Reception, Director of Pharmacy and Logistics, Quality and Safety Manager, two Risk Management and Ambulatory Health Care Infection Prevention and Control Service (SCIA) Nurses, Nursing Coordinator and Coordinator of Communication and Marketing and an *ad hoc* Infectologist. The Committee meetings are held daily or on-demand and any modifications in the protocol to manage suspected and/or confirmed cases of COVID-19 are communicated to staff immediately. Updated literature was used as source of information/best practice (see References) and all protocols are adjusted according to data updates.

The Initial Contingency Plan, implemented on March 12th, had as main objective to instruct employees on how to identify suspected cases of COVID-19 among patients and employees, to instruct patients, family members, clinical staff and employees about prevention and adequate hygienic/decontamination procedures of themselves as well as working areas, and how to proceed upon occurrence of unexpected events. The plan defined the roles of those professionals involved in its execution, as well as the communication procedures (both internal and external) to ensure access to information, guaranteeing the continuation of the activities developed by employees, prioritizing safety and adequate care for patients, avoiding financial losses and customer dissatisfaction. Also, a triage procedure was adopted and performed by the call center using a scripted approach. Follow up appointment of patients

reporting suspected COVID-19 symptoms where postponed and for those symptomatic patients scheduled to undergo infusion treatment, the assistant physician was contacted and upon decision to maintain the infusion, patients would be listed at the reception hall as required to wear a mask at all times while at the clinic. Infusion treatment would only proceed if after clinical examination the suspicion of COVID-19 was discarded or rejected/dismissed. Objectives and topics covered in the contingency plan were modified according to subsequent deliberations of the Committee and grouped into recommendations for oncology practice (elaborated and validated in collaboration with clinical oncologists staff) , monitoring and managing of outpatient/clinical research patients, clinical staff /employees safety and well-being, telemedicine implementation and observational data collection of COVID-19 pandemic consequences upon clinical outcome of cancer patients.

RECOMMENDATIONS FOR THE MANAGEMENT OF ONCOLOGY PRACTICE DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has imposed a scenario of resource contingency and reassessment of the benefit of exposing patients to treatments that will increase the risk of severe complications. In order to facilitate decision-making and patient management, the COVID-19 Management Committee postulated the following general recommendations for oncology practice[6,8,10-12]:

1. Provide guidance about the importance of vaccination against influenza (strain 2020) except when acute fever is detected. In order to avoid agglomerations, patients are suggested to undergo vaccination in a drive-thru vaccination facility, by scheduled appointment or to undertake it at home, depending on availability.

2. Maintain adjuvant chemotherapy with curative intent for those patients who are already in treatment.

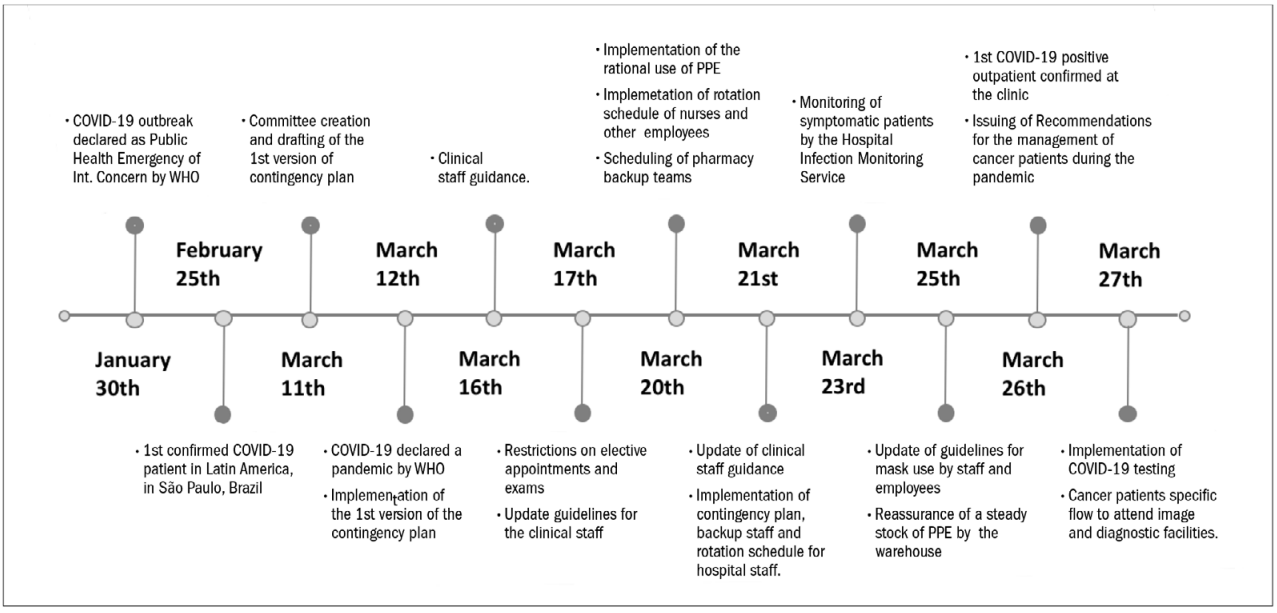
3. Consider reducing adjuvant duration for those who have already started treatment, when the benefit is not impaired (e.g. patients with low risk stage III colon cancer, early ovarian or breast cancer)

4. In non-indolent tumors, with indication for curative surgical treatment, prioritize surgery. If the situation evolves to a shortage of hospital beds, consider neoadjuvant therapy in tumors where literature evidence supports equivalence to adjuvant therapy (e.g. stage II-IIIA non-small cell lung cancer, T2N0M0 gastric cancer, EC I-III breast cancer).

5. Do not delay or postpone chemotherapy in high-risk tumors with a clear indication of adjuvancy. As far as possible, choose the least toxic and /or oral schemes when equivalents in terms of clinical benefit.

6. Consider not performing adjuvant chemotherapy in situations where a small benefit is expected (e.g.

FIGURE 1. TIMELINE OF EVENTS LEADING TO THE CREATION OF THE COVID-19 MANAGEMENT COMMITTEE AND ITS SUBSEQUENTE ACTIONS. WHO: WORLD HEALTH ORGANIZATION; COVID-19: CORONAVIRUS DISEASE 2019; PPE: PERSONAL PROTECTION EQUIPMENT.



stage Ib lung cancer, stage II colon cancer) or in those tumors where a non-immunosuppressive treatment is an option (e.g. ER-positive early-stage breast cancer).

7. Consider the use of prophylactic G-CSF in protocols with a higher risk of neutropenia and allow more permissive use in cases of previously verified neutropenia.

8. For patients with metastatic disease undergoing chemotherapy:

- Do not interrupt treatment in symptomatic patients with active disease or in those at high risk of progression

- Consider interrupting maintenance therapy if the disease shows improved remission. Share the decision with the patient, weighing risks of progression and/or infections.

- Switch intravenous medications to oral medications when possible (e.g. 5-FU, vinorelbine, anticoagulants).

9. Radiotherapy should be maintained to:

- Treatment with curative intent of fast-growing tumors.

- Treatment of oncological emergencies. Ex: spinal cord compression, bleeding, etc.

- When radiotherapy, combined or not with chemotherapy, is the standard of treatment (e.g. anal, cervix, esophagus and head and neck tumors.

- In those patients who have already started treatment.

Note: Whenever possible, give preference to hypofractionation schemes (shorter duration).

10. Consider delaying radiation therapy for indolent tumors

11. Postpone supportive medications or reconcile with chemotherapy days (e.g. denosumab and zoledronic acid, except in cases of hypercalcemia)

12.Patients on cancer follow-up, without active treatment and asymptomatic may have their appointments postponed.

MANAGING AND MONITORING OUTPATIENTS

Our outpatient clinic assists the population of a large urban area, and concerns for exposing patients to COVID-19 grew as SARS-CoV-2 spread in the country. Outpatients are allowed in with only one companion, which are advised to join the appointment only when patients are underage or non-self-sufficient.

The Call Center contacts each patient the day before its appointment and through a scripted questionnaire, accesses if patients display respiratory symptoms and are suspected of COVID-19 infection, as well as screens for non-urgent follow up appointments that are rescheduled within 15 days (see Telemedicine Service Implementation) (Figure 2).

Asymptomatic outpatients whose appointment should not be rescheduled proceed through regular patient flow but within longer intermission between appointments and assigned to specific seats in the waiting room (2 meters apart from each other). Suspected COVID-19 infected patients (here forward referred to as "Symptomatic") outpatients on follow-up are rescheduled, but suspicion of COVID-19 infection is reported to SCIA and subsequently monitored (see Cancer Patients Monitoring during COVID-19 Pandemic). Initially, Front Desk received a daily report of the patients required to wear masks upon arrival at the clinic (all symptomatic patients), however, following a recent recommendation of the Ministry of Health, all patients are required to wear it now (compliance ensued as soon as clinic warehouse reassured adequate mask supply).

Patients undergoing infusion treatments are classified as asymptomatic or symptomatic – the former will follow the regular pre-infusion workup and treatment plan. The latter will undergo clinical triage and its management will be determined by prescribing Physician or Physician on Duty, either cleared to proceed treatment or put on hold and requested to be tested for COVID-19. Either way, SCIA is notified and patient monitoring proceeds (see Cancer Patients Monitoring during COVID-19 Pandemic).

Accrual of patients for clinical trials and monitoring visits of ongoing protocols were brought to a halt, while on protocol patients were scheduled for visits/procedures in off-peak hours. Clinical trials staff was divided on shifts, drug and/or sample kits delivery by sponsors was all concentrated in one day of the week and when feasible, already providing a 4-months supply.

Access to COVID-19 testing is guaranteed through a commercial agreement between the Clinic and a private laboratory to assure adequate sample collection and analysis. Furthermore, a specific protocol was adopted for patients required to perform imaging and/or other tests in our diagnostic facility located in another facility, where a specific flow dictates access at exclusive schedules, at large and patient density-controlled waiting rooms and private parking.

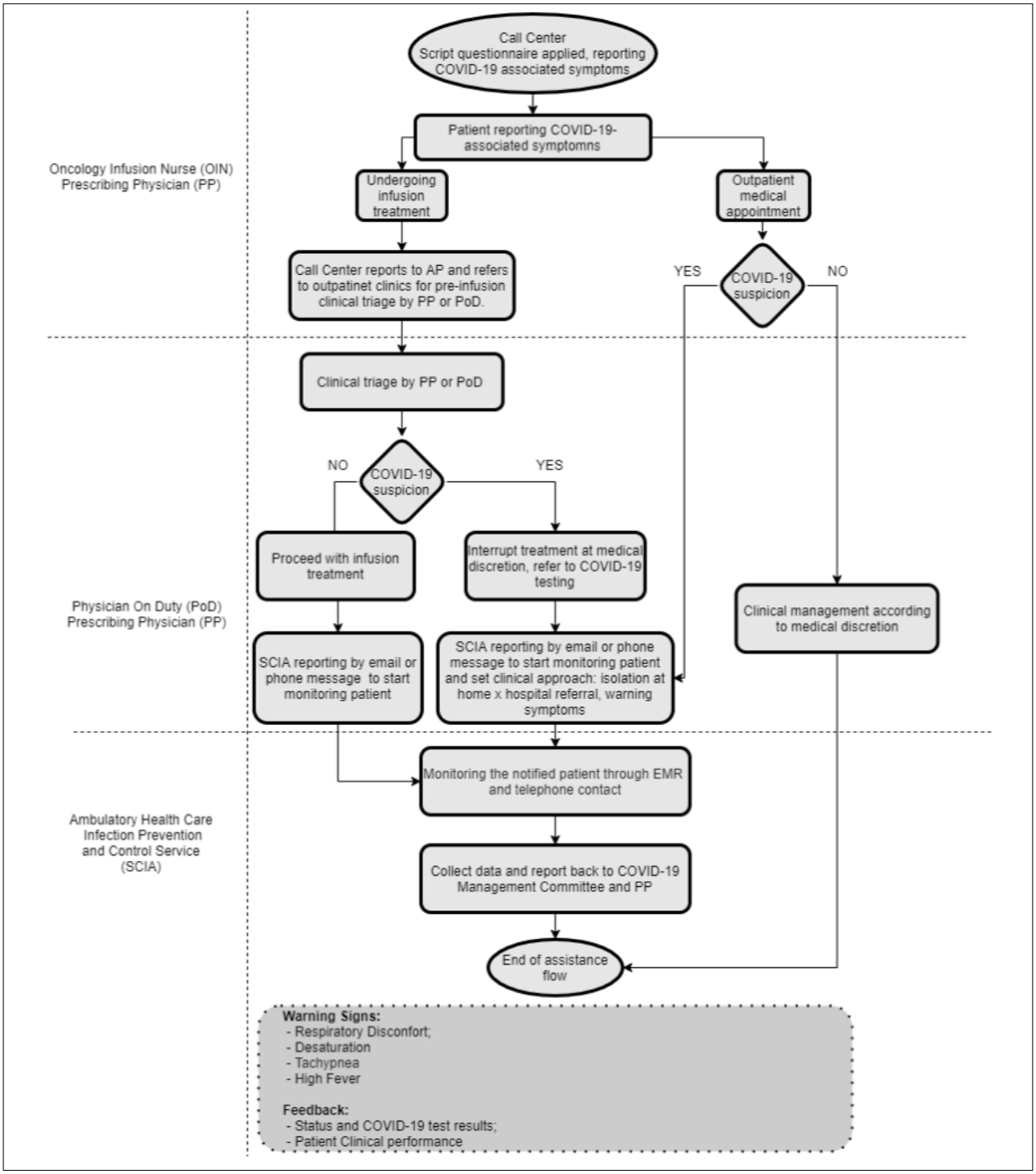


FIGURE 2. FLOWCHART FOR MANAGING AND MONITORING OUTPATIENTS. PP: PRESCRIBING PHYSICIAN; POD: PHYSICIAN ON DUTY; SCIA: AMBULATORY HEALTH CARE INFECTION PREVENTION AND CONTROL SERVICE, EMR: ELETRONIC MEDICAL RECORD.

EMPLOYEE AND LEADERSHIP SAFETY AND WELL-BEING

Psychological and physical well-being of clinical staff and employees is crucial to avoid the anticipated burnout imprinted by COVID-19 Pandemic and, therefore, clinics should abide by guidelines of best practice to ensure a safe work environment. We have provided training on prevention, personal protection and decontamination of working areas to all clinical staff and employees. Staff who are immunocompromised, have significant comorbidities, > than 60yo or are at any high-risk category were withdrawn from clinical practice.

As the number of outpatient appointments were

reduced, we have temporarily closed one of our Clinics branches and redesign the schedule of shifts, reducing working hours. Clinical staff was either assigned to practice at the outpatient clinics or at the hospital, reducing risks of cross-contamination. Hospital attending staff is considered to be at higher exposure to SARS-CoV-2 infection and, therefore, were scheduled to one week working/one week off shifts.

Staff shortage is expected due to several anticipated limitations, such as school closings and the need to quarantine staff on short notice, thus Human Resources reached out to our database to create a backup labor pool and started the hiring process of a temporary taskforce for subsequent training.

Personal Protection Equipment (disposable mask, gloves and gown) was provided at first for all staff in contact/attending symptomatic patients, later on the use of masks became mandatory to all staff and patients once the clinic warehouse reassured a steady supply of PPE. Recently, the Brazilian Ministry of Health recommended mask use for all health care providers, and because we took an early action upon it, we will be likely to fully comply with this recommendation in the near future.

Clinicians that also undertake administrative duties were advised to do it remotely, laptops were provided for those who needed it, and any other professional gatherings, such as scientific meetings and educational sessions were either canceled or postponed from March 12th on, and all weekly tumor boards are being held online.

TELEMEDICINE SERVICE IMPLEMENTATION

To ensure continuity of oncology assistance to our patients, our clinic has put forward Telemedicine Practice as a follow up option. On March 19th, the Federal Council of Medicine issued a statement[13] authorizing Telemedicine Practice during COVID-19 pandemic, based on following terms:

-Teleguidance: medical professionals can remotely carry out guidance and referral of patients in isolation

-Telemonitoring: performed under medical supervision, for remote monitoring or enforcement of health and/or disease parameters.

-Teleinterconsulting: exclusively for the exchange of information and opinions among doctors, for diagnostic or therapeutic assistance.

From April 6nd, the Call Center Triage will offer telemedicine-based assistance to eligible patients upon remote informed consent signature. The Telemedicine Assistance can be contracted as out of pocket or reimbursed from health care providers, as authorized by the National Health Agency (ANS)[14] on March 30th.

CANCER PATIENTS MONITORING DURING COVID-19 PANDEMIC

All symptomatic patients (confirmed or not) undergoing infusion therapy during the COVID-19 pandemics are going to be closely monitored by the Ambulatory Health Care Infection Prevention and Control Service. Clinical data of these patients will be collected for assistance purposes and after COVID-19 pandemic resolution, data will be released as a scientific report, accounting for the impact of infection and/or mandatory changes in oncology practice during the pandemic.

CLOSING REMARKS

COVID-19 pandemic called for a fast response from Oncology Care Professionals to provide proper prevention, guidance and appropriate identification and treatment of critical cases, including decisions on whether to postpone or interrupt treatment. The effects of these compulsory modifications in cancer patient management and their clinical outcomes are yet to be known. Nonetheless, promotion of prevention, monitoring and early intervention are key to avoid or lessen the effects of COVID-19 pandemic upon this very high-risk group. Our oncology outpatient clinic (AMO Clinic, Bahia) staff responded very early to the warning of an upcoming epidemic, so when COVID-19 pandemic was announced by WHO, all the strategy and structure to face the challenge of providing cancer care on such conditions was already in place. We expect that the fast implementation of an early contingency plan and all the subsequent and continuous recommendations elaborated by our COVID-19 Management Committee will contribute to lessen the pandemic burden brought upon patients and staff/employees, as well as avoid infection, clinical complications and preventable deaths associated to SARS-CoV-2.

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Clínica SIM, Ética Pesquisa Clínica and Hospital da Bahia, who have been working countless hours to provide safe patient care during the COVID-19 pandemic.

Special thanks are due to all the professionals that collaborated discussing and reviewing COVID-19 Management Committee resolutions and contributed to implement the contingency plan and subsequent necessary modifications in routines. We would like to thank Dr. Carlos Sampaio for critically reviewing the manuscript and offering valuable insights. Last, but not least, we would like to thank patients and their families, who have been extremely understanding and abiding by routine changes in treatment and staff interaction.

Authors Contribution

CS: Data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version. TL: Conception or design of the work, data analysis and interpretation, critical revision of the article, final approval of the version. APGAVN: Data analysis and interpretation, final approval of the version to be published. BVF; APLF; CDA; ABA; LOH; SSND Data collection, final approval of the version. PN: Data collection, data analysis and interpretation, critical revision of the article, final approval of the version. AC: AKC Data collection, critical revision of the article, final approval of the version. AP: Conception or design of the work, data analysis and interpretation, critical revision of the article, Final approval of the version.

RESUMO

O primeiro caso confirmado de Doença Associada ao Coronavírus 2019 (COVID-19) no Brasil foi confirmado em 25 de fevereiro de 2020 e em 3 de abril já haviam 8076 casos confirmados no país. A medida que a incidência de COVID-19 aumenta no Brasil, o tratamento de pacientes com câncer exige ação imediata e as clínicas oncológicas são instadas a estabelecer um plano de contingência. Instalamos um Comitê de Manejo de COVID-19 para elaborar e implementar as melhores práticas para ajudar pacientes ambulatoriais com câncer, bem como proporcionar um ambiente seguro para a equipe clínica e outros funcionários das clínicas ambulatoriais. Os desafios do tratamento do câncer em meio à pandemia global do COVID-19 destacam a importância de uma resposta rápida das instituições, onde a estrutura organizacional, o planejamento estratégico, a agilidade na implementação de diretrizes e formas alternativas de proteger e apoiar a equipe clínica, funcionários e pacientes podem ser a chave para mitigar os efeitos da pandemia.

PALAVRAS-CHAVE: *COVID-19. Coronavirus. Oncologia. Saúde Pública. Pandemias*

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REVIEW ARTICLE

Cardiac amyloidosis: non-invasive diagnosis

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SUMMARY

Cardiac amyloidosis is an infiltrative disease which requires a high degree of clinical suspicion for appropriate diagnosis. Early diagnosis and the definition of the type of amyloidosis play a key role in the early treatment and prognosis of this disease. In this context, the use of cardiac biomarkers such as troponins and NT-proBNT associated with analysis by multimodality imaging methods like echocardiographic techniques such as strain, nuclear medicine, and cardiovascular resonance imaging have an increasing role in patients with cardiac amyloidosis. This article details the role of non-invasive diagnostic methods in patients with cardiac amyloidosis.

KEYWORDS: *Amyloidosis. Echocardiography. Magnetic resonance spectroscopy. Nuclear medicine. Biomarkers.*

INTRODUCTION

Amyloidosis is a systemic disease resulting from tissue deposition of an amyloid substance. Although the heart is one of the organs most frequently affected in systemic amyloidosis, cardiac involvement is not a rule. Regardless, it is essential to identify it, since the presence of cardiac amyloidosis (CA) significantly affects the prognosis of the disease[1-4].

Clinically, it can be classified as:

1. AL amyloidosis is the most severe and common form of systemic amyloidosis. It results from the deposition of protein derived from fragments of the immunoglobulin light chain (AL amyloid). The heart is affected in up to 90% of the patients, and only 5% have isolated heart disease[4].

2. The hereditary amyloidosis (familial) is an autosomal dominant inheritance disease caused by tissue deposition of mutant amyloid protein derived from genetic variants of transthyretin (TTR), apolipoprotein A-I, lysozyme or fibrinogen alpha chain. The heart is most commonly involved with the mutation of TTR (ATTR amyloidosis)[5].

3. The senile systemic amyloidosis (or *wild type*) results from the deposition of amyloid proteins derived from wild type transthyretin (TTR wt). It occurs more

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frequently among men with a mean age of 78 years, and its prognosis is better than those of the AL and ATTR presentations.

4. AA amyloidosis results from the excessive production of a non-immunoglobulin protein known as AA. Kidney disease is frequent in this subtype, while clinically significant involvement of the heart is rare.

This paper details the use of noninvasive methods for the diagnosis of patients with cardiac amyloidosis.

CLINICAL PRESENTATION

The degree of cardiac involvement is variable and depends on the different types of amyloidosis; it is frequent in senile, AL, and ATTR amyloidosis, but rare in AA amyloidosis. CA includes a subclinical stage characterized by discrete and unspecific symptoms. Patients may present signs of heart failure (HF); however, with preserved ejection fraction (HFpEF) secondary to diastolic dysfunction and increased left ventricular filling pressures[6].

Orthostatic hypotension occurs in approximately 10% of patients due to amyloid infiltration into the autonomous nervous system and/or blood vessels. Angina may occur due to amyloid infiltration into the intramyocardial vessels. Syncope is a common symptom secondary to dysautonomia and arrhythmias[4-6].

The prognosis is related to a particular subtype of cardiac amyloidosis. Senile amyloidosis presents less cardiac involvement and has a good prognosis when compared to ATTR. AL amyloidosis, on the other hand, presents a very reserved prognosis[1-6].

DIAGNOSIS

The clinical diagnosis should be suspected in patients with HF symptoms associated with unexplained weight loss, peripheral (such as carpal tunnel syndrome) or autonomic (postural hypotension and syncope) neuropathy, nephrotic syndrome, and hepatomegaly[1-6].

Electrocardiogram

The ECG is usually abnormal, and the most characteristic finding is the presence of QRS complexes of low voltage or decreased progression of the R wave in the precordial derivations (Figure 1A). Low voltage is more common in the AL type and less common in the TTR and senile presentations of the disease. Other findings include the presence of a pseudo infarction pattern, bundle branch blocks, and axis deviation. Among arrhythmias, atrial fibrillation or flutter is common and may be related to atrial amyloid deposition[7]. The presence of low voltage on the ECG has also been associated with a worse prognosis in all types of the disease, including hospitalization, death, or orthotopic heart transplantation[8].

Symptomatic conduction system disease requiring permanent pacemaker implantation is an uncommon manifestation of cardiac amyloidosis, al-though it is likely that a number of sudden cardiac deaths occurring in patients with amyloidosis may be due to bradyarrhythmias. Isolated conductiondisease appears to be most often associated with senile amyloidosis, although survival after the onset of clinically significant conduction disease was not different in patients with senile amyloidosis when compared with those with primary amyloid-osis. In patients with conduction disease due toprimary amyloidosis in whom the underlying disease cannot be modified, the prognosis is poor[9].

Biomarkers

The dosage of serum biomarkers, such as BNP and NT-pro BNP and troponin levels (cTnT or cTnI), allows an early diagnosis of myocardial involvement and its elevation is indicative of a worse prognosis[10].

Two prognostic models were designed using cutoff values for NT-pro BNP and cTnT or cTnI in patients with the AL presentation[10.11]. Based on their increased levels of troponins and/or BNP, the patients were classified as stage I, II, or III. In stages I, II, and III, the survival rate was 26.4, 10.5, and 3.5 months, respectively. In patients with the ATTR presentation, heart biomarkers were abnormal in a substantial percentage of patients, and BNP/NT-pro BNP were independent predictors of survival[10.11].

Echocardiography

There can be thickening of the atrial walls, atrioventricular valves, left ventricular intramural deposition with an increase in the myocardial thickness, signs of diastolic dysfunction, and reduction of longitudinal LV function in a subclinical stage[12-14].

It is important to note that these echocardiographic findings are nonspecific and often absent in early stages, besides being more frequent in the ATTR presentation. Differential diagnoses include hypertrophic cardiomyopathy, aortic valve stenosis, advanced chronic renal insufficiency, and other infiltrative cardiomyopathies.

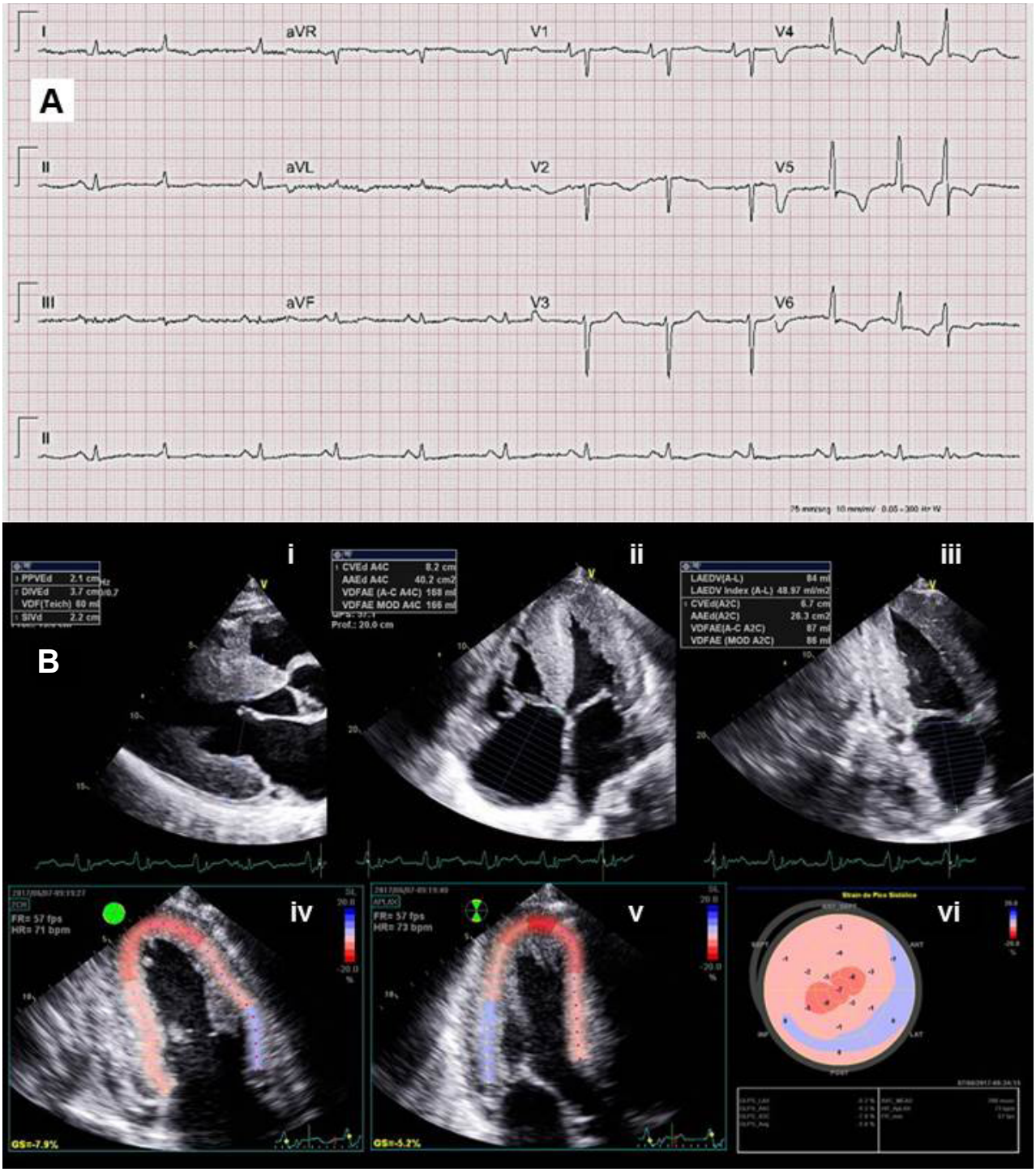

FIGURE 1. A. Electrocardiogram (ECG) of a patient with TTR amyloidosis showing low QRS complex voltage in the frontal plane, in addition to signs of an electrically inactive area in the anterior wall ("pseudo infarction"). B. Typical echocardiographic findings of a patient with AC: thickening of the left ventricular walls with a shiny and granular appearance in parasternal longitudinal view (i), Apical 4-chambers (ii) and Apical 2-Chambers (iii); global and segmental longitudinal myocardial deformation impairment (strain) (iv to vi). There is less involvement of the apical strain in relation to the basal and midsections (apical sparing pattern) (vi).

The progression of the disease causes a significant increase in left ventricular wall thickness (>15 mm) of granular aspect, resulting in signs and symptoms of HFpEF (Figure 1B)[6]. The presence of a restrictive pattern to the mitral Doppler indicates significant diastolic dysfunction and is indicative of a poor prognosis[15].

The thickening of the ventricular wall sometimes can be local and may be confused with hypertrophic cardiomyopathy. A recent study showed that 5% of

patients with hypertrophic cardiomyopathy had a diagnosis of real TTR amyloidosis[16].

LVEF is often preserved even in the presence of HF and in more advanced stages. In some patients, systolic dysfunction can be observed as a result of significant necrosis of cardiomyocytes and extensive fibrosis.

An atrial thrombus can be found, even in the presence of sinus rhythm in patients with AL presentation[17].

Current echocardiographic techniques, such as the analysis of myocardial deformation (strain) by speckle tracking, also play an important role in patients with cardiac amyloidosis. The evaluation of the longitudinal strain is a sensitive method for the early detection of cardiac amyloidosis before the onset of symptoms and the increase in the myocardial thickness, and it is correlated with the prognosis[18,19]. The involvement of the LV longitudinal strain is present in different subtypes of amyloidosis, and these abnormalities are correlated with other echocardiographic parameters[19].

Phelan et al.[20] described a pattern with relative preservation, or relatively normal values of deformation of the apical segments (apical sparing). The presence of this pattern has prognostic implications; it is a predictor of lower rates of cardiac events (Figure 1B)[19]. This pattern has been useful in the differentiation of cardiac amyloidosis from other causes of LV hypertrophy, such as in patients with aortic stenosis and hypertrophic myocardiopathy.

Recent studies have demonstrated the efficacy of three-dimensional echocardiography in differentiating cardiac amyloidosis from other types of LV hypertrophy[21]. The left atrial function is also often reduced in patients with cardiac amyloidosis, even in patients in sinus rhythm[22].

Finally, measurements of right ventricular function have also been considered important predictors of prognosis in cardiac amyloidosis[23].

NUCLEAR MEDICINE

From the early 1970s, it has been found that some diphosphonates and sodium pyrophosphate derivates labeled with technetium-99m (PYP), which are radiopharmaceutical agents commonly used for bone scintigraphy, may present uptake in the heart and, eventually, in other organs (especially the liver and peripheral muscles) in patients with amyloidosis[24]. In addition to PYP, available in the United States and in Brasil, DPD (3,3-diphosphono-1,2-propanodicarboxylic acid) has been used with similar results in Europe. The mechanism by which the uptake happens is not entirely clear, but it has been found that these substances bind to calcium mainly on areas where this ion is actively deposited.

TTR amyloidosis often presents a higher number of microcalcifications, which could justify the increased uptake of these radiopharmaceutical agents (Figure 2A). The greater microcalcification found in TTR amyloidosis can be explained by the more advanced age of patients and a longer time of disease evolution.

In the absence of cloned immunoglobulins produced by plasma cells, the intense cardiac uptake of PYP is highly suggestive of a TTR presentation; thus, a biopsy may eventually not be necessary for a diagnosis. However, other types of amyloidosis can also present varying degrees of microcalcification and eventually show a small degree of the uptake of these tracer agents.

Using a visual score (0= absence of uptake, 1= uptake smaller than the costal arches, 2= uptake equal to the costal arches, and 3= high uptake - more intense than bone uptake) for the evaluation of cardiac PYP uptake, it is possible to differentiate between TTR and other types of cardiac amyloidosis[25].

It is also possible to use a semiquantitative analysis considering the count rate per pixel in the projection of the cardiac area and in the contralateral chest. Values lower than 1: do not suggest ATTR; above 1.5: highly suggestive of ATTR; values between 1 and <1.5: may be associated with AL amyloidosis or early ATTR[25]. Values above 1.6 have been associated with a worse prognosis, regardless of the disease presentation[26].

Positron emission tomography also allows detecting amyloid deposition in the heart, as occurs in the brain[27,28]. Some substances, such as the florbetapir and florbetaben marked with fluorine-18, are being investigated for this purpose. Due to its characteristics of allowing for better anatomical definition than conventional scintigraphy and absolute quantification of process activity, this technique seems to be promising for cardiac amyloidosis assessment.

Cardiovascular magnetic resonance (CMR)

CMR provides an accurate evaluation of myocardial mass and thickness, in addition to the differential diagnosis between CA and other cardiomyopathies. However, in patients with proteinuria and renal failure,

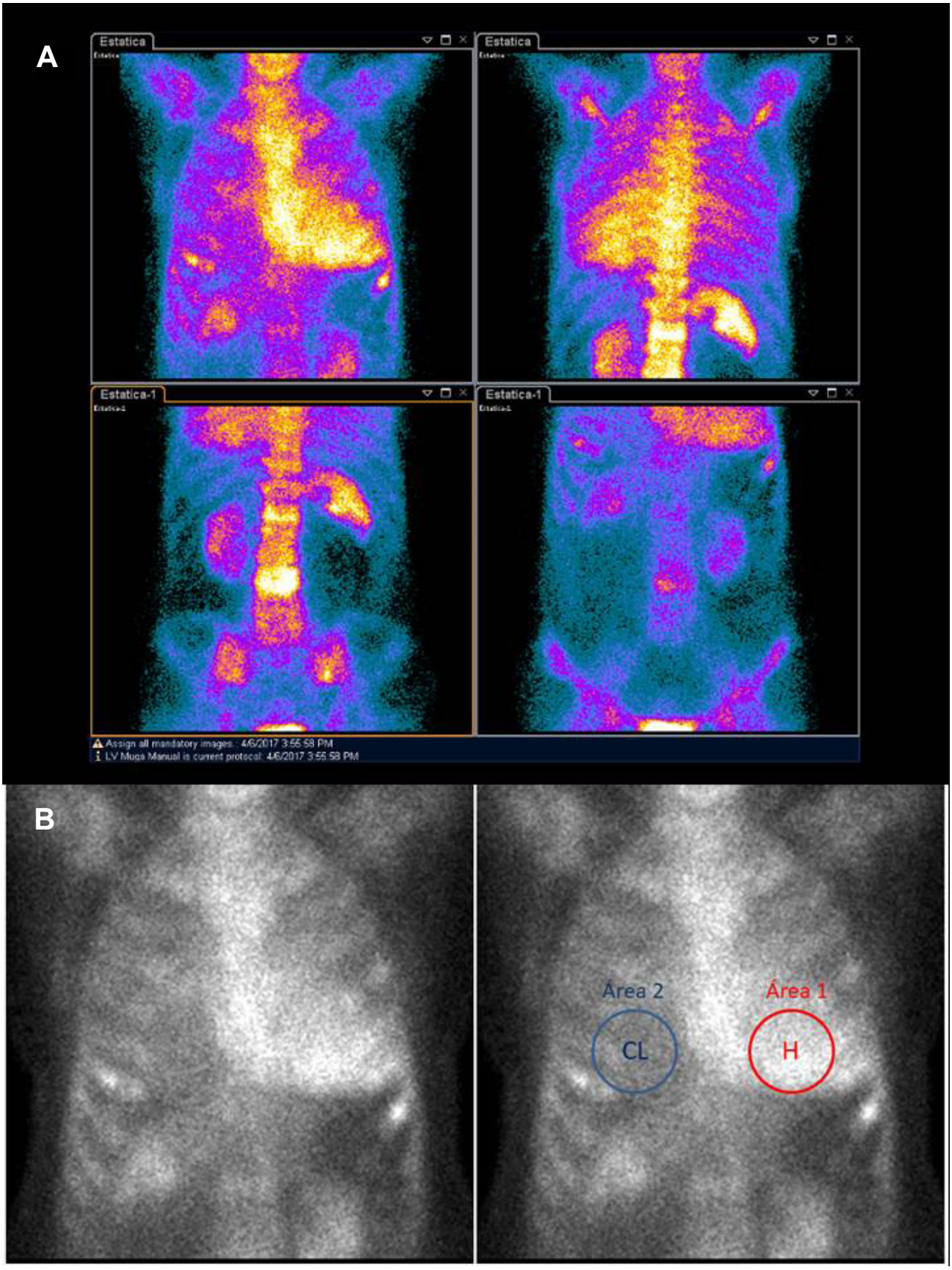

FIGURE 2. A. 85-year-old patient with TTR amyloidosis. The images were acquired three hours after the administration of 20 mCi of pyrophosphate labelled with technetium 99m and show intense increased uptake in the projection of the entire cardiac area. B. Area 1: considers the average counts in the heart area (H = 66.1 counts per pixel). Area 2: considers the average counts in the contralateral thoracic area (CL = 40.5 counts per pixel). Heart/contralateral thoracic area ratio H/CL = 1.63.

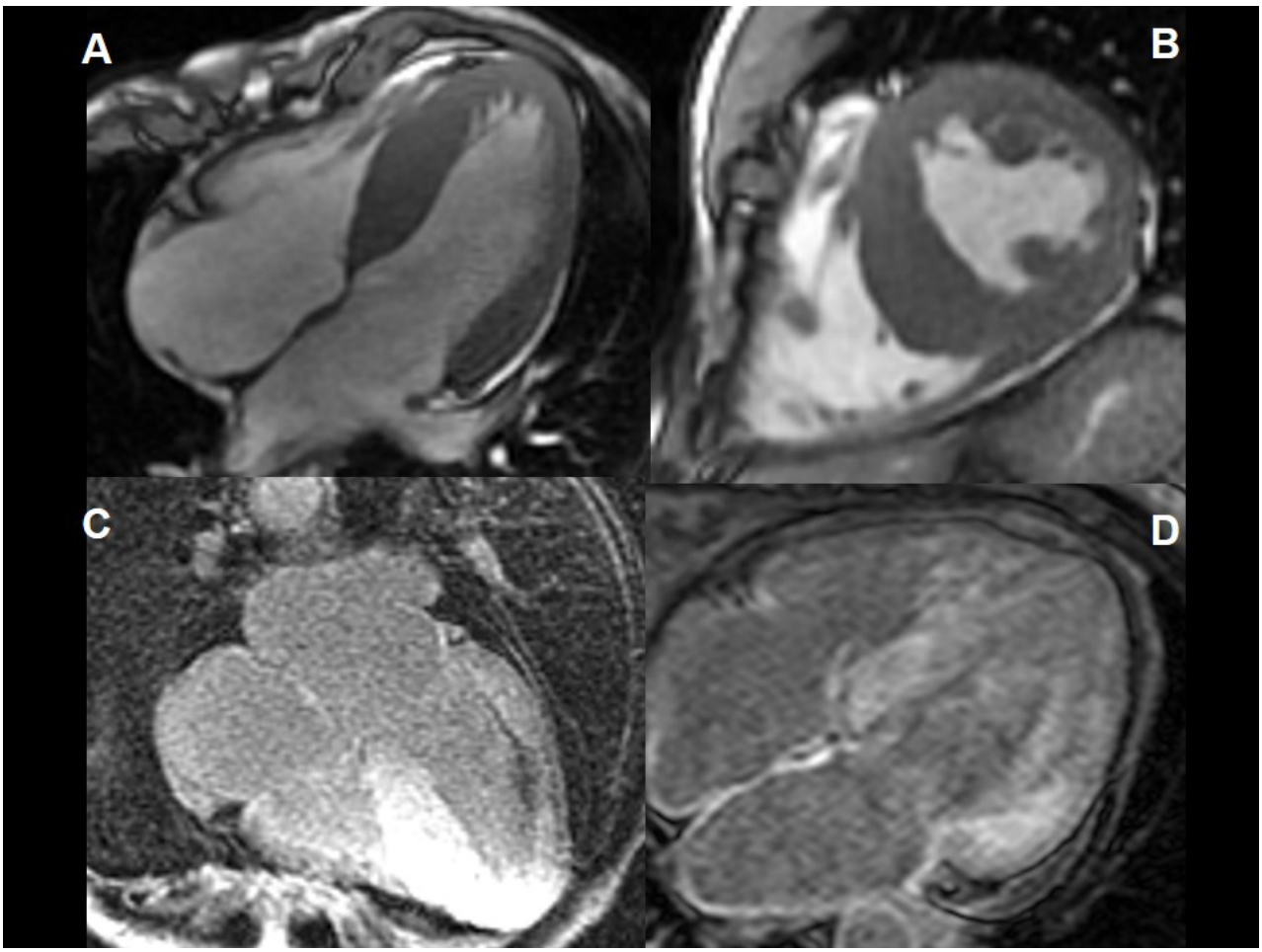

FIGURE 3. CMR images of four chambers (A) and transversal (B), demonstrating an increase in the thickness of the myocardial wall. In C and D, the CMR images show late gadolinium enhancement in four chambers. There is a diffuse increase of myocardial signal despite the use of multiple inversion times.

gadolinium injections are contraindicated due to the risk of nephrogenic systemic fibrosis. The sensitivity of CMR for the diagnosis of cardiac amyloidosis is described to be around 80% with 94% specificity, according to Takeda et al.[29].

CMR provides non-invasive information on tissue disease, which has been associated with relevant cardiovascular outcomes. Patients with ATTR and AL amyloidosis present longer values of T1 consistently when compared to normal volunteers[30,31] and patients with aortic stenosis[32]. However, despite the great usefulness of T1 mapping, its use alone for CA diagnosis presents some limitations, such as the need for standardization of T1 mapping acquisition parameters, in addition to the standardization of values between different brands.

Thus, the CMR technique most often used in CA patients consists of analyzing late enhancement (LGE - Late Gadolinium Enhancement). Gadolinium is a contrast agent that migrates rapidly to the extravascular compartment. However, its molecule is too large to penetrate intact cell membranes. Thus, in CA patients, the extracellular volume (ECV) presents progressive expansion due to the deposition of amyloid protein, resulting in a progressively larger reservoir for gadolinium accumulation. In patients with established CA, the ECV often exceeds 40%, a level rarely reached unless in cases of extensive scarring fibrosis [33]. In patients with AL amyloidosis, there is a diffuse subendocardial impairment pattern, while patients with ATTR can present a transmural enhancement pattern (Figure 3)[33]. In addition, delayed enhancement in ATTR saves the apex, which is the same phenomenon that can be observed in the speckle tracking technique, making this finding is suggestive of ATTR[34].

A potential incremental diagnostic application can be obtained from the derivation of the respective ECV fractions versus the intracellular volume (ICV). In patients with a definite diagnosis of amyloidosis, calculating the ECV versus the ICV can allow the subclassification into AL or TTR, the latter group

presenting high cell volumes suggestive of concomitant hypertrophy[35].

Thus, CMR techniques are very useful in identifying patients with cardiac amyloidosis and those with a high risk of future adverse events. Thus, currently, CMR must be regarded as the first-line preferred diagnostic method to assess patients with cardiac amyloidosis and to differentiate subtypes of cardiac amyloidosis.

CONCLUSIONS

Cardiac involvement in this disease has been detected with greater frequency in patients with amyloidosis. However, diagnosis is often late, which implies a very reserved prognosis. Although no noninvasive test alone is pathognomonic of cardiac amyloidosis, the use of integrated noninvasive techniques in a context of high clinical suspicion may be enough for proper diagnosis.

RESUMO

A amiloidose cardíaca é uma doença infiltrativa que exige um alto grau de suspeição clínica para o diagnóstico apropriado. O diagnóstico precoce e a definição do subtipo de amiloidose têm um papel fundamental para a terapêutica e prognóstico desta doença. Nesse contexto, o emprego de biomarcadores cardíacos como as troponinas e NT-proBNT associados à análise por métodos de imagem multimodalidade por técnicas ecocardiográficas atuais como o strain, medicina nuclear e a ressonância magnética cardíaca têm papel crescente em pacientes com amiloidose. Este artigo detalha a utilização dos métodos não invasivos para a avaliação de pacientes com amiloidose cardíaca.

PALAVRAS-CHAVE: *Amiloidose. Ecocardiografia. Espectroscopia de ressonância magnética. Medicina nuclear. Biomarcadores.*

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REVIEW ARTICLE

Melatonin and organ transplantation: what is the relationship?

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SUMMARY

Melatonin has anti-inflammatory and antioxidant properties that can influence tissue growth and apoptosis. This aspect may influence the success of organ transplantation.

OBJECTIVE: *To evaluate the relationship between melatonin and organ transplantation.*

METHODS: *A systematic review was performed in PubMed databases using the search terms: "melatonin physiology" or "melatonin therapy" and "transplant pharmacology" or "transplant physiology" or "transplant therapy" or "Transplant therapy". Experiments on the organs of the reproductive system were not included. After analysis, five articles were selected after reading the title and abstract of 50 manuscripts. The works were divided into two aspects: a) analysis of the influence of the organ transplantation procedure on melatonin production; b) action of melatonin on organ transplantation.*

RESULTS: *The cardiac transplantation surgical procedure, immunosuppression, and graft did not influence melatonin secretion in rodents, but there was a significant reduction of melatonin in the renal transplantation procedure in patients with renal insufficiency. Melatonin administration in experimental models decreased rejection and improved transplant success.*

CONCLUSION: *Studies show that melatonin can reduce organ and species dependence, and the use of melatonin decreases graft rejection.*

KEYWORDS: *Melatonin. Oxidative stress. Transplants.*

INTRODUCTION

Melatonin is an indolamine produced mainly by pineal gland[1,2], which has a potent activity to neutralize free radicals due to its antioxidant and antiapoptotic functions[1,3,4]. Due to its hydrophilic and lipophilic affinity, melatonin can diffuse widely in various cellular compartments such as membranes, cytoplasm, nucleus, and mitochondria[1,4]. Thus, it can perform its antioxidant action quickly and effectively, soon after the production of these agents, which are harmful to the viability of tissues[5].

Some studies point out that one of the main challenges to achieving a successful transplant with less graft loss is the reduction of free radicals produced by the procedure[6], especially caused by

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ischemia-reperfusion stress[5]. Therefore, melatonin may block fatty acid uptake and would have multiple antioxidant actions, such as the removal of pro-oxidative enzymes, prevention of calcium overload and mitochondrial damage, and inhibition of cyclooxygenase[4-6]. Thus, it may reject grafts, promoting cellular repair, and removing reactive oxygen species[7]. Also, melatonin has immunological and antiapoptotic properties that are necessary for successful organ transplantation[5]. In the reproductive system, Shiroma et al.[8] showed that melatonin increases the success of ovarian transplantation. Therefore, this systematic review aims to evaluate the connection between melatonin and non-reproductive organ transplantation (uterus and ovary).

METHODS

The systematic review of studies that show the relationship between melatonin and organ transplantation, excluding those of the reproductive system (uterus and ovary) was conducted according to the recommendations established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[9]. For the identification of relevant studies, Medline primary database queries were conducted from January 1992 to May 2019, without restriction on the year of publication.

PICO was elaborated as follows: P (patient or experimental model): patients or animals that underwent organ transplantation, I (intervention): a) impact of the transplantation procedure on melatonin production; b) administration of melatonin on transplantation success; C (comparison): control group, and O (outcome): the relationship between melatonin and organ transplantation. The retrieval of articles was conducted through the search strategies described in Figure 1. The bibliographic references of the articles surveyed were also searched (data retrieval).

The selection of studies, the evaluation of titles and abstracts obtained from the search strategies in the consulted databases were conducted by two researchers (C.F.H. and R.S.S.) independently and blindly, strictly following the inclusion and exclusion criteria. After this step, the original article was critically evaluated to decide whether to include it or not in the review. When there was disagreement about study selection among investigators, a third reviewer was consulted (J.M.S.J).

The following inclusion criteria were used to identify relevant sources: (a) full text available; (b) articles in Portuguese, English, Spanish, or French; and (c) studies that used objective instruments to evaluate the relationship between melatonin and organ transplantation. Reproductive system manuscripts such as "ovary" and "uterus" were excluded, as well as duplicate manuscripts or narrative or systematic reviews.

The information obtained from the articles that make up the systematic review were shown in Tables 1 and 2, grouping: authors' name and year of publication, species, groups, objective, method, and outcome.

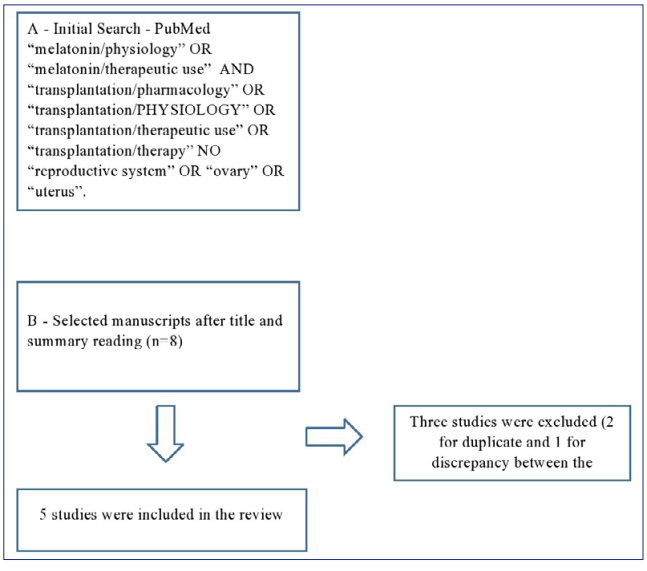
The analysis followed the PRISMA statement for systematic reviews[15]. Eight studies were identified by this research. After a detailed analysis of the manuscript contents, three were excluded: a) duplicate (n = 2); b) discrepancy about the analyzed subject (n = 1) (Fig. 1). Meta-analysis could not be performed due to the small number of studies.

RESULTS

Data on 126 rats and 210 patients were analyzed. In the studies, three rats were reported killed in one experimental study. In the remainder, there were no other complications or mortality. Two studies[10,11] aimed to evaluate the effects of organ transplantation procedure on melatonin production, while the other three[12-14] analyzed the effects of melatonin administration on heart or lung transplantation.

Regarding the first evaluation (impact of the transplantation procedure on melatonin production), as can

FIGURE 1. A) SEARCH STRATEGY AND B) SYSTEMATIC REVIEW ALGORITHM



be seen in Table 1, both manuscripts analyzed the relationship between organ transplantation and serum melatonin concentration. Viljoen et al.[10] showed a decrease in serum melatonin concentration after renal transplantation in patients with chronic renal failure. Cardell et al.[11] did not show significant changes in serum melatonin concentration after cardiac transplantation in rats.

The effects of melatonin on transplanted organs are summarized in Table 2. The beneficial effect of melatonin on short-term graft transplantation success (acute effect) is due to decreased oxidative stress, inflammatory process, and decreased apoptosis. The result is lower graft rejection in experimental studies.

Inci et al.[12] used a 10mg/kg dose of melatonin and observed a decrease in tissue damage after lung transplantation: a) smaller area of ischemia; b) reduced lipid peroxidation rate compared to the control; c) drop in lipid infiltration; d) reduction of tissue levels of glutathione oxidase and myeloperoxidase (MPO) activity; e) increased glutathione. Thus, some elements that suggest increased protection of the transplanted lung from the deleterious effects of reperfusion after ischemia.

Jung et al.[13] reported longer survival with reduced cellular and humoral immune response in rats treated with melatonin. This effect was dose-dependent. The lowest concentration of indolamine used was 20 mg/kg and the highest 200 mg/kg. There was a marked decrease in IgM concentration, proliferation, and graft rejection at the highest dose compared to the lowest dose and vehicle.

Santana-Rodríguez et al.[14] showed that melatonin (10 mg/kg) would improve radiological signs of severe respiratory failure in rats and longer graft survival. In this study, a group of animals was treated with estradiol (25mg / kg) and had the worst results: a) severe respiratory failure; b) increased inflammatory process; c) greater rejection; d) shorter survival with a high mortality rate of around 60%.

DISCUSSION

Melatonin has properties that reduce graft rejection, such as its anti-inflammatory and antioxidant effect[1-7]. This action had already been described for ovarian grafts[7]. Our studies have proven these actions in heart and lung transplantation in experimental models. Therefore, melatonin could be beneficial in reducing graft rejection. Regarding the influence of the transplantation procedure on melatonin production, it was shown that the serum reduction of this indolamine might be dependent on the species or tissue type[10,11]. However, the number of works is small, requiring further research in this field.

In a study that included 210 patients with chronic renal failure who underwent kidney transplantation[10],

TABLE 1. EFFECTS OF ORGAN TRANSPLANTATION PROCEDURE ON SERUM MELATONIN LEVEL

Author/year	Species	Groups	Objective	Method	Results
Viljoen et al.[10], 1992	Humans (n=210)	Control group (n = 35); Experimental group (n=175)	Determine melatonin concentration after transplantation.	RIA Method	Drop in serum melatonin levels after transplantation
Cardell et al.[11], 2008	Rats	Control group (n=6); Experimental group 1 (n=6); Experimental group 2 (n=6); Experimental group 3 (n=6)	Determine melatonin concentration after transplantation.	RIA Method	Transplant exposure did not affect serum melatonin concentration.

TABLE 2. EFFECTS OF MELATONIN ON THE TRANSPLANTED GRAFT

Author/Year	Species	Groups	Objective	Method	Results
Inci et al.[12], 2002	Rats	Control group (n=10); Experimental group (n=10)	To evaluate the protective effect of melatonin on transplantation	Biochemical and morphological analysis	Oxidative stress reduction
Jung et al.[13], 2004	Rats	Control group (n=12); Experimental group 1 (n=12); Experimental group 2 (n=8)	To evaluate the action of melatonin on acute transplant rejection.	RIA Method	Improved transplant
Santana-Rodríguez et al.[14], 2011	Rats	Donar group (n=25); Receiving Group (n=25); Control group (n=10); Experimental group 1 (n=5); Experimental group 2 (n=5); Experimental group 3 (n=5)	To evaluate the effect of melatonin on lung transplantation	Radiological, histological and inflammatory analysis	Improved transplant

this reduction was significant. In contrast, in the second study[11] conducted on rats, the authors observed that serum melatonin levels did not change significantly after the procedure of heart transplant in rats. The effect of surgical stress on melatonin reduction has been reported in other studies[16] and reinforces the result found in patients with renal failure[10]. Besides, the very clinical conditions of patients with renal failure and transplantation may have influenced an increase in melatonin clearance[10]. Therefore, greater elimination could occur than a fall in production. Regarding the second study, the number of animals employed is small, which would be the major limitation of this study[11].

Melatonin has a circadian cycle, regulated by the suprachiasmatic nucleus that receives information about the luminosity of the retinohypothalamic tract. Thus, melatonin production is higher at night and lower during the day[17]. Therefore, the time of blood collection may influence the interpretation of data[10,11]. Neither of the selected studies evaluated the melatonin curve, ie, several collections for 24 hours. This fact may have limited the studies.

Also, melatonin is produced in leukocytes and other tissues[18] that may have interference from immunomodulatory substances or suppressors employed in kidney transplantation. Two immunosuppressants were used in the renal transplant study: calcineurin inhibitor and rapamycin blocker (mTOR). The first drug increased serum melatonin levels, and the second led to a reduction in melatonin levels. Therefore, besides the stress of the surgical procedure, the type of immunosuppressant can negatively impact melatonin production[10].

In general, studies on the effects of melatonin on organ transplants had a positive effect on graft: a) reduction of oxidative stress; b) fall of the inflammatory process; c) decreased apoptosis; d) less rejection; e) longer survival of animals[12-14]. However, the concentration of melatonin employed was high in all studies[12-14], which may result in a serum concentration of this supraphysiological hormone[19], which may be a limitation in the interpretation of the data. It seems that the effect of melatonin may be dose-dependent, according to the study by Jung et al.[13].

The study by Santana-Rodríguez et al.[14] compared the effects of melatonin with those of estrogens, which may have a proliferative effect on tissues. In this study, the authors found the highest survival of animals using melatonin and the lowest with estradiol. Possibly, the properties of melatonin may help slow the graft rejection process, which has a direct impact on animal survival. In in vitro studies, estradiol may decrease melatonin receptor expression[20,21]. This fact may explain the result of greater graft rejection in the estrogen-treated group.

The limitations of this systematic review are the small number of studies with adequate methods to evaluate the relationship between melatonin and organ transplantation. This fact made the meta-analysis impossible. Also, there is a need for studies on the long-term effect of grafts in animal models. The strongest point of this review is the fact that melatonin may decrease graft rejection in animal models. This may be the future clinical application of melatonin. However, further studies are needed, especially in patients undergoing organ transplantation to assess their safety.

CONCLUSION

Our results suggest that serum melatonin concentration may be affected by the surgical procedure of kidney transplantation, as well as by the type of immunosuppressive therapy employed. In addition, the use of high-dose melatonin decreases graft rejection due to melatonin's antioxidant and anti-inflammatory properties.

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The authors do not have any conflict of interest.

Author's contributions

CFH - Made substantial contributions to the concept and design of the study, and definition of intellectual content; was involved in literature search, data analysis, statistical analysis, and manuscript preparation; in drafting the article or revising it critically for important intellectual content; gave final approval to the version to be published.

JMH - Made substantial contributions to the concept, design of the study, and definition of intellectual content; was involved in literature search, data analysis, statistical analysis, and manuscript preparation; in drafting the article or revising it critically for

important intellectual content; and gave final approval to the version to be published.

ECAV - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

ICES - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

RSS - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

RCC - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

ECB - Made substantial contributions to the concept, design of the study, and definition of intellectual content; was involved in the manuscript preparation; drafting the article or revising it critically for important intellectual content, and gave final approval of the version to be published.

JMSJ - Made substantial contributions to the concept, design of the study and definition of intellectual content; was involved in manuscript preparation; drafting the article or revising it critically for important intellectual content, and gave final approval of the version to be published.

RESUMO

A melatonina tem propriedades anti-inflamatórias e antioxidantes que podem influenciar o crescimento e a apoptose dos tecidos. Esse aspecto pode influenciar o sucesso do transplante de órgãos.

OBJETIVO: *Avaliar a relação entre a melatonina e o transplante de órgãos.*

MÉTODO: *A revisão sistemática foi realizada nas bases de dados do PubMed, usando os termos de pesquisa: "fisiologia da melatonina" ou "terapêutica da melatonina" e "farmacologia do transplante" ou "fisiologia do transplante" ou "terapêutica do transplante" ou "terapia do transplante". Não foram incluídos os experimentos sobre os órgãos do sistema reprodutivo. Após análise, cinco artigos foram selecionados após a leitura do título e do resumo de 50 manuscritos. Os trabalhos foram divididos em duas vertentes: a) análise da influência do procedimento de transplante de órgão na produção de melatonina; b) ação da melatonina sobre o transplante de órgãos.*

RESULTADOS: *O procedimento cirúrgico do transplante cardíaco, a imunossupressão e o enxerto não influenciaram a secreção de melatonina em roedores, mas houve redução significante da melatonina nos casos do procedimento de transplante renal em pacientes com insuficiência renal. A ministração de melatonina em modelos experimentais diminuiu a rejeição e melhorou o sucesso de transplante.*

CONCLUSÃO: *Os estudos mostram que a melatonina pode reduzir a dependência da espécie e do órgão e que o emprego da melatonina diminui a rejeição do órgão.*

PALAVRAS-CHAVE: *Melatonina. Estresse oxidativo. Transplantes.*

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REVIEW ARTICLE

Recommendations for radiotherapy during the novel coronavirus pandemic

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SUMMARY

KEYWORDS: *Radiotherapy. Neoplasms. Coronavirus. COVID-19. SARS-CoV-2, Pandemics*

The Coronavirus 2019 (COVID-19) pandemic requires swift and assertive health actions. The coronavirus is part of a family of RNA virus common in humans and other animal species. Symptoms include those of common colds but can evolve with complications, such as Severe Acute Respiratory Syndrome (SARS)[1].

Some types of cancer and their respective treatments can weaken the immune system, increasing the risk of infection by COVID-19, especially during chemotherapy or radiotherapy. In addition, this subgroup of patients may develop more severe complications and have a higher risk of respiratory disease that requires hospital admission, treatment in intensive therapy unit with ventilatory support, and a greater probability of unfavorable outcomes[2].

The first interpersonal transmission in Brasil occurred on 13 March 2020, leading to an exponential spread that has yet to peak. Thus, oncology services have a crucial role in preventing and controlling infection in treatment centers and drawing up a plan to be adopted in this pandemic scenario[3,4].

In radiotherapy services, in particular, it is important to consider shorter treatments, as well as avoid interruptions to the greatest extent possible. Given the large volume of publications involving this concerning subject and its many uncertainties, this article compiles information, advice, and experiences from different centers, in addition to suggesting alternative therapies that can be adopted during this period.

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GENERAL RECOMMENDATIONS FOR CANCER PATIENTS

In cancer patients, it is important to strengthen the existing preventive measures to minimize contact with COVID-19. It is important to mention there is a more vulnerable[5] subgroup comprising:

- Patients under active chemotherapy or radiotherapy treatment.
- Patients with hematological neoplasms, such as leukemia, lymphoma, myeloma, regardless of the treatment stage.
- Patients undergoing immunotherapy or continuous treatment with antibodies.
- Patients undergoing targeted therapy that affects the immune system, such as protein kinase inhibitors or PARP inhibitors.
- Patients who underwent bone marrow or stem cell transplant in the last 6 months or in use of immunosuppressant.
- Patients aged over 60 years.
- Patients with a history of cardiovascular disease.
- Patients with a history of respiratory disease.

Transmission occurs by exhaled droplets and contaminated surfaces, and the preventive measures are the same as those valid for the general population[3,4,6-8]. Thus, it is key to instruct cancer patients and their medical staff on the following topics:

Preventive Measures

- Avoid social agglomerations and close contact with sick people;
- Avoids interpersonal contact;
- Avoid touching the eyes, nose, and mouth;
- Wash hands often, for at least 20 seconds, especially after using the bathroom, before meals, after blowing the nose, coughing, or sneezing and before contact with other people;
- Clean and disinfect areas often touched daily. If the surface is dirty, use detergent or soap and then disinfect it.
- Get a flu shot;
- Stay home as much as possible;
- Ensure access to medication and supplies for several weeks, in the event it is necessary to self-isolate;
- Avoid traveling longer distances.

Symptoms

- Incubation period: 2 to 15 days after exposure - an average of 5.2 days.
- The most common symptoms are fever, dry cough, and fatigue. Some patients have reported a runny nose, nasal congestion, sore throat, and diarrhea, though the latter is less frequent.
- According to the World Health Organization[7], based on a study that included 56,000 patients, 81% of those infected develop mild symptoms (fever, cough and, in some cases, pneumonia), 14% severe symptoms (difficulty breathing, shortness of breath), requiring hospitalization for oxygen therapy, and 5% become critically ill (respiratory failure, septic shock, organ failure, and risk of death).
- Symptoms of urgency:
- Difficulty breathing or shortness of breath.
- Persistent pain or pressure in the chest.
- Confusion or inability to remain alert.
- Bluish lips or face.

SPECIFIC RECOMMENDATIONS[3-18] REGARDING TREATMENT

It is critical to categorize patients according to priority levels to assist in the decision-making process, which should always include the entire multidisciplinary team involved in cancer care and be discussed with the patient. The risks/benefits should be weighed in for each case individually[5].

Priority level 1:

- Patients with tumors of rapid proliferation treated with radio-chemotherapy or radical radiotherapy with curative intent. Intervals with subsequent compensation can be detrimental to the curative outcome.
- Patients with tumors of rapid proliferation whose treatment plan is external radiotherapy combined with brachytherapy and external radiotherapy is already being carried out.
- Patients with tumors of rapid proliferation who have yet to start treatment.

Priority level 2:

- Urgent palliative treatment in patients with spinal cord compression with recoverable neurological function.

Priority level 3:

- Radical radiotherapy for patients with less aggressive tumors, with radiotherapy as the first line of radical treatment.

- Postoperative adjuvant radiotherapy with proven residual disease in tumors with aggressive biology.

Priority level 4:

- Palliative radiotherapy when there is a relief of symptoms that may reduce the demand for hospitalization, such as hemostatic radiotherapy in hemoptysis patients.

Priority level 5:

- Adjuvant radiotherapy after complete tumor resection when the risk of recurrence in 10 years is lower than 20%.

REGARDING NEOPLASMS[10-17]

Based on the priority levels above, the radio-oncologist can evaluate the interruption of adjuvant therapies with low risk of recurrence, weighing in the risks and benefits, and discussing the situation with the patient, in addition to postponing non-urgent palliative cases and benign cases. In all cases, only hypofractionated schemes of radiotherapy should be considered clinically appropriate.

Breast cancer[14,15]

In early cases (*in situ neoplasia*, small invasive carcinomas, luminal tumors), the following considerations are possible:

a. Delay the start of radiotherapy for up to 2 months after the surgery.

b. If available in the center, consider intra-operative radiotherapy or other forms of accelerated partial breast radiotherapy

c. If the whole is being treated (with or without lymph nodes), use hypofractionated therapy (3 weeks).

d. Propose a concomitant boost when there is an indisputable indication for a boost.

In patients with breast cancer and age over 65 years, with T1/T2N0 luminal tumors, who will receive endocrine therapy, depending on the risks and benefits, the omission of adjuvant radiotherapy can be considered.

Patients with a formal indication for lymph node irradiation must have their indication maintained. However, it is important to consider hypofractionated therapy in these patients.

In cases of breast cancer with the possibility of conservative surgery, it is recommended to conduct a multidisciplinary discussion with the entire medical staff and the patient about the realization of mastectomy, with the purpose of reducing indications for adjuvant radiotherapy in times of pandemic.

Consider hypofractionated therapy for all patients. There are ultra hypofractionation schemes (5 fractions) performed within 1 week that could represent an alternative for the rapid treatment of patients[16].

Patients who underwent chemotherapy before radiation therapy: comply with the interval of up to 8 weeks between the end of the chemotherapy and the start of radiotherapy. Patients who underwent chemotherapy neoadjuvant to surgery should follow the same interval.

Prostate cancer[17,18]

In patients with low-risk and intermediate-to-low-risk prostate cancer, active surveillance with a follow-up visit in 6 months should be strongly considered.

For those with intermediate-to-high and high risk, postponed neoadjuvant hormonotherapy with delayed radiotherapy should be considered. If it is not possible to perform hormone therapy or if the cancer risk is greater than the risk of infection with unfavorable outcomes due to COVID-19, hypofractionated schemes should be strongly considered.

Current level 1 evidence converges to the equivalence of moderate hypofractionation compared to traditional fractioning. Thus, hypofractionation into 20 fractions of 3 Gy is strongly recommended.

If the treatment center has access to the image-guided radiotherapy technology required (*cone-beam* TC or fiducial markers), 7 fractions of 6 Gy, or 6 fractions of 6 Gy, or 5 fractions of 7.25 Gy can also be considered, all in line with the NCCN 2020 Guidelines[19].

Based on the evidence presented recently from RAVES[20] and RADICALS[21], early salvage after prostatectomy should be considered in all cases in the pandemic scenario. Consider postponing the beginning of salvage radiotherapy in up to one month for patients with an indication for such.

For oligometastatic patients (low-volume M1) with an indication for local radiotherapy, consider postponing radiotherapy while the patient is undergoing hormonotherapy. If radiotherapy is chosen, consider schemes with 6 fractions of 6 Gy, used in one of the arms of the STAMPEDE[22] study, and considered safe and acceptable.

Rectal cancer

Start, if possible, induction chemotherapy. The use of short-course preoperative radiotherapy in 5 fractions of 5 Gy is recommended[23].

Lung cancer

Patients with lung cancer may have a history of pulmonary dysfunction that increases the risk of severe respiratory complications. Thus, this group presents a particularly increased risk for radiotherapy in this pandemic scenario. Consider postponing the treatment:

- Early-stage lung cancer, especially those non-biopsied, with slow growth, advanced age, or comorbidities.
- Oligometastatic patients.
- Consolidation radiotherapy or prophylactic cranial irradiation in patients with small-cell lung cancer with extensive disease.
- Prophylactic cranial irradiation in patients with small-cell lung cancer with limited disease.

Gliomas

Low-grade glioma: postpone the start of radiotherapy as much as possible.

High-grade glioma: treatment should be individualized. Consider hypofractionation using 15 fractions of 2,7Gy or 5 fractions of 5 Gy. If possible, consider using temozolomide with subsequent reassessment for radiotherapy in patients with low-performance status and age over 65 years.

Palliative treatment

In cases of patients with spinal cord compression, metastatic bone pain irresponsive to other treatments (after attempted optimization), or microvascular bleeding, treatment in a single fraction is recommended.

Schemes that may be adopted: 1 fraction of 8 Gy to 10 Gy.

Cancer of the head, neck, anal canal, and cervix

It is not recommended to postpone or change the fractionation scheme.

Others

In sarcomas of the extremities, the hypofractionation is recommended whenever possible, both in neoadjuvant and adjuvant scenarios.

Strongly consider postponing the treatment of benign tumors, such as schwannomas and asymptomatic meningiomas.

Surgeries for keloids with an indication for radiotherapy should be postponed.

RECOMMENDATIONS TO RADIOTHERAPY DEPARTMENTS

- Remote screening (1 to 2 days before the initial consultations and daily before going to the center of treatment) of all patients through a questionnaire, sent by e-mail or phone message, aiming to identify any sign of infection by COVID-19.
- Upon arriving at the radiotherapy center, screen the patient again by measuring their temperature and asking about new symptoms. In case of a positive assessment, isolate the patient in a room reserved for such purposes until the time of treatment; ensure they do not come into contact with other patients and properly sanitize the equipment after the treatment. After the patient treatment is completed, recommend a confirmatory test, and transfer the patient to the last time slots of the day.
- Provide a hydroalcoholic solution for disinfecting hands at the entrance of the sector.
- Arrange treatment schedules in order to increase the interval between treatments and thus reduce the number of patients in waiting rooms.
- Increase the frequency of sanitization of common areas and equipment.
- In case of personnel infection that causes a severe reduction that may affect the functioning of the department, make decisions along with the hospital structure involved if this is the case (consider hiring new employees or contacting other radiotherapy centers; evaluate the use of external professionals).
- For the electronics of the console, it is recommended to often use alcohol wipes or sprays containing at least soft cloth that has been moistened with isopropyl alcohol with a concentration of 70%. To facilitate the cleaning of devices, consider using plastic wrap, which must be changed daily.

RECOMMENDATIONS TO DEPARTMENT EMPLOYEES

- Formally instruct department personnel through a bulletin about the symptoms and prevention of COVID-19.
- Stimulate remote activities, such as design, planning, and clinical meetings.

- Minimum scale of all employees.
- Avoid agglomerations, keeping a one-meter physical distance, if possible.
- Among technicians of radiotherapy, reinforce the need for hand hygiene with soap and water or alcoholic preparations before and after the use of computers and radiotherapy equipment after each application.
- Require the use of surgical masks throughout the working hours for all employees in contact with patients, such as nursing professionals, doctors, and radiotherapy technicians.
- If any staff members present any symptoms, this should be communicated, and they should be forwarded for evaluation and COVID-19 testing. If no test is available, consider a 10-day quarantine from the first day of symptoms.

RECOMMENDATIONS FOR CANCER PATIENTS UNDERGOING TREATMENT WITH SUSPECTED OR CONFIRMED INFECTION

- Assess the cancer risk involved in treatment interruption.
- The interruption of treatment has a greater impact on tumors of high cell replication, in which the total time of treatment has an impact on oncologic outcomes.
- The decision regarding the interruption must be made by the radio-oncologist along with the multidisciplinary team involved in patient care by weighing in the risks and benefits of this strategy.
- If it is impossible to interrupt the treatment, wait for clinical recovery and the mandatory quarantine of 10 to 14 days before restarting the treatment. Ideally, two tests performed 24 hours apart should come back negative.
- If the patient discontinues treatment, it is recommended to follow the unplanned interruption guide available on https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco191_radiotherapy-treatment-interruptions.pdf
- If it is impossible to interrupt treatment, organize the time of treatment in order to isolate cases, preferably in the last time slot of the day, grouping them.
- The infected patient should remain, from their arrival at the hospital or clinic, wearing a surgical mask, replacing it after two hours of use or when it becomes moist.
- During the patient treatment, the entire team in contact with them should wear N95 masks, gloves, eye protection, and a disposable protective apron. Everyone should be trained on the correct way to put on and take off the protective gear. If no N95 masks are available, the use of a surgical mask is recommended.
- Clean the room and treatment table after the treatment. The cleaning must be done wearing disposable gloves, and hands must be washed immediately after the procedure. If the surface was already dirty, use detergent or soapy water before disinfecting it.
- Never dry sweep surfaces because this favors the spread of micro-organisms transported by dust particles. Instead, wet sweep them with a mop or squeegee and cleaning cloths.
- For cleaning the floors, techniques of wet sweeping, lather, rinse, and dry should be used. Potential disinfectants for cleaning surfaces include those made of chlorine, alcohols, some phenols, and iodophors and quaternary ammonium compounds.
- All equipment should be cleaned at the end of the treatment of each patient with a suspected or confirmed case, even with the professionals are wearing PPE and avoiding contact with infected material.
- The use of kits for cleaning and disinfecting surfaces specific for patients in isolation is recommended.

REVIEW AND RETURN CONSULTATIONS

- For review consultations, telemedicine or consultations by phone are recommended. If a physical examination is necessary, it should be brief.
- Postpone return consultations and non-urgent follow-ups.

RECOMMENDATIONS FOR CANCER PATIENTS UNDERGOING TREATMENT

- Instruct patients that the oncologic treatment must not be interrupted.
- Patients undergoing treatment, at the first sign of respiratory infection, should contact their doctor for further instructions.
- It is recommended that an informed consent form is drafted for all patients informing about the

possibility of contamination during treatment.
- Patients must be instructed on handwashing, general hygiene, and preventive measures.
- Instruct patients to avoid physical contact with people who have influenza symptoms such as dry cough, shortness of breath, fever, or runny nose, as well as those with suspected infection by COVID-19.
- Encourage patients not to arrive early for their radiotherapy sessions.
- Restrict the number of companions, allowing them only in cases in which the patient is unable to go to the treatment center alone.
- Recommendations for the use of masks are the same as those valid for the general population[4,6].
  • Healthy individuals: no recommendation for the use of masks, except if:
  - Living with a sick individual who cannot wear a mask.
  - Is caring for a sick individual or suspects an infection by COVID-19.
  - Masks are only effective if used in combination with frequent hand washing using soap and water or alcohol gel.
  • People with symptoms or confirmed cases: wear a surgical mask, following the guidelines:
  - Before putting on the mask, sanitize hands properly.
  - Cover the mouth and nose, leaving no space between the face and the mask.
  - Avoid touching the mask during use.
  - Replace the mask when it gets moist and do not reuse single-use masks.
  - Remove the mask from the back to the front and discard it immediately in a closed bin. Sanitize hands afterward.

RECOMMENDATIONS FOR PATIENTS WHO HAVE ALREADY COMPLETED THEIR TREATMENT

- The same preventive measures that are valid for the general population apply to these patients and close contacts.
- Routine examinations should be avoided.
- Follow-up examinations should be conducted at the discretion of the clinical oncologist and radio-oncologist, but if possible and not detrimental to the patient, they should be postponed.

CONCLUSION

Hippocrates' principle of *primum non nocere* is of paramount importance in the global pandemic scenario, with a high risk of health care collapse in the Brazilian context. Flattening the curve of dissemination of COVID-19 by implementing the various measures mentioned above is fundamental for departments of radiotherapy to minimize disruptions to treatment without impacting the oncological outcomes of patients.

Always considering the risks and benefits for each individual cancer patient, the current scenario demands such interventions.

Contribution of the authors

MTMS; ARNSS; APAP; DRFEN; FCFR; LHB; TYTS - drafting of the text, literature review. SAH – text supervision and revision, literature review.

PALAVRAS-CHAVE: *Radioterapia. Neoplasias. Coronavírus. COVID-19. SARS-CoV-2. Pandemias.*

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REVIEW ARTICLE

Viral infections and atherothrombosis: Another caution in the wake of COVID-19?

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KEYWORDS: *COVID-19; Sars-COV-2; Atherosclerosis; Atherothrombotic.*

INTRODUCTION

The COVID-19 pandemic is caused by the novel coronavirus (Sars-COV-2), with global impact and leading to numerous hospitalizations and deaths in several countries. Data from 01 April 2020 show over 887,000 infected individuals and over 44,000 deaths.

Publications[1-4] show that the main risk factors for an unfavorable outcome are: hypertension 6-31% (SAH), diabetes 7.3-19% (DM), age, and presence of cardiovascular disease 8-15% (CVD); the main risk factor to date is age over 80 years. It should be noted, therefore, that patients with cardiovascular disease are at higher risk of complications. COVID-19 invades cells by binding to the of the angiotensin-converting enzyme (ACE-2), which has a greater expression in cardiac and pulmonary tissues[5].

Zhou, et al.,[2] has reported the clinical characteristics of 171 patients admitted with infections caused by COVID-19. Among the abnormal laboratory results found in multivariate analysis was the increase of D-dimer > 1ug/ml, which was related to worse prognosis, as were advanced age and increased SOFA score. Studies have also demonstrated that many patients can evolve with lymphopenia[1,4]. The presence of coagulopathy, evidenced by the increase of D-dimer, prothrombin time (PT), and disseminated intravascular coagulation (DIC), was also a marker of negative prognosis, regardless of its high levels during admission or at any time during hospitalization[2,6]. In a recent meta-analysis[7], high levels of troponin were also related to a worse prognosis.

In another publication on 416 hospitalized patients[8], there was an association between increased troponin and mortality; whereas the higher its value, the higher was the risk. Myocardial injury was identified in 19.7% of patients. These were older, had a higher number of comorbidities (including cardiovascular), and presented other increased inflammatory parameters in relation to the control group, such as increased leukocytes, C-reactive protein, and procalcitonin, as well as greater opacity on computed tomography scans of the chest. In addition, these patients had a longer period of mechanical

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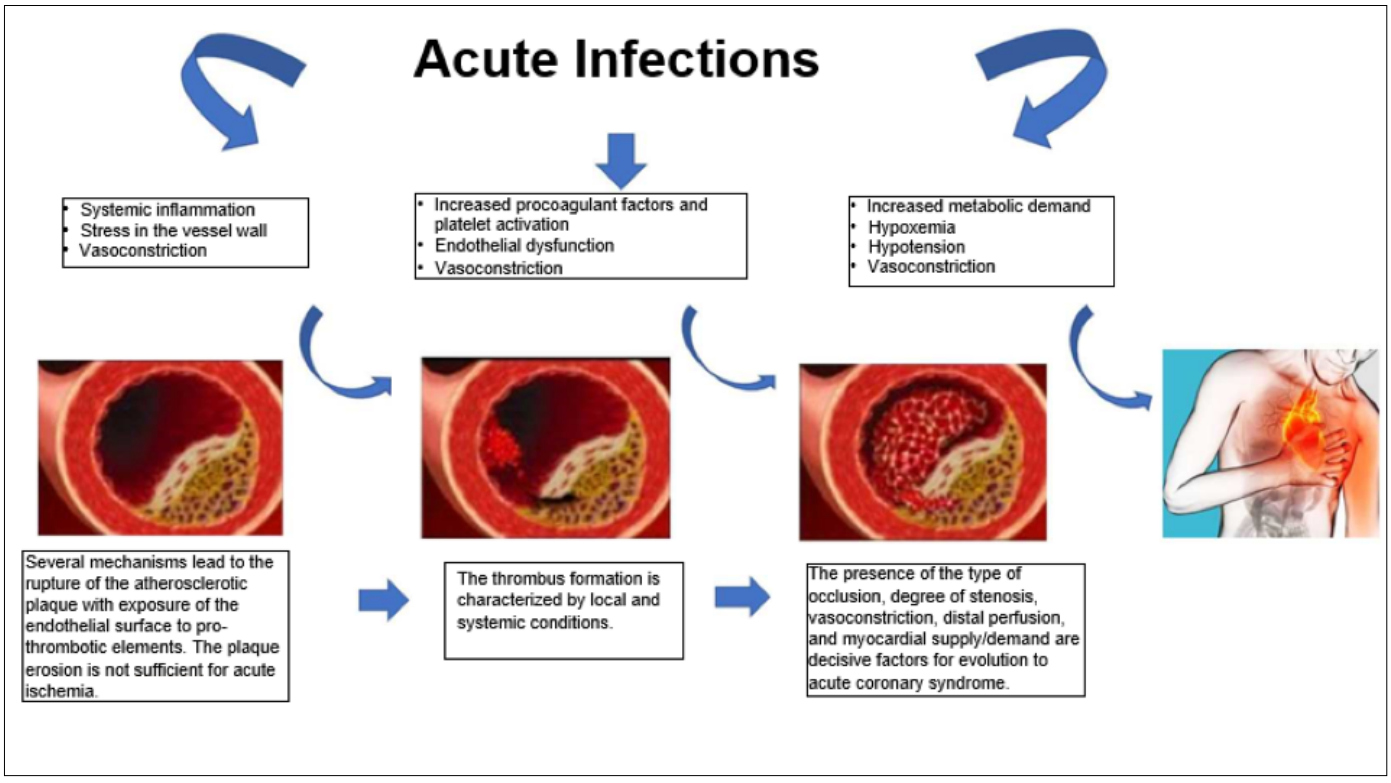
ventilation, renal dysfunction, and coagulation disorders. The difference in mortality was 51.2% vs. 4.5% (P<0.001). This inflammatory storm, with increased cytokines, troponin, D-dimer, among others, leads to a greater predisposition to cardiovascular events and death. In addition, data show that acute coronary events, arrhythmias, myocarditis, Takotsubo syndrome, and acute heart failure can occur related to COVID-19. In relation to acute heart complications, Wang[4] reported 16% of arrhythmia.

Preliminary evidence[9-12] demonstrates that infections, viral ones included, lead to systemic inflammatory conditions, including atheromatous plaques. As shown in Figure 1, during the inflammatory activity triggered by the infection, there is an infiltrate of cells in the atheromatous plaque (T cells, macrophages, and neutrophils), contributing to the production of cytokines, coagulation factors, oxygen radicals, and vasoactive molecules, leading to increased vascular permeability, endothelial damage, rupture of the fibrous layer, and exposure of thrombogenic elements (collagen, tissue factor, and platelet adhesion molecules), contributing to the formation of thrombus. The plaque erosion alone is not enough to cause coronary ischemic syndromes. Other important factors for the emergence of injury and ischemia are: the nature of the thrombus formation (partial vs. total), degree of stenosis, presence of vasoconstriction, distal perfusion, and an imbalance between supply and demand in the coronary bed evidenced by hypoxia, hypotension, tachycardia, and the increase of endogenous catecholamines leading to local vasoconstriction. Previous reviews[13-15] have demonstrated the role of platelets and the coagulation system in viral infections. It is suggested that platelets can bind to pathogens through receptors on their surface and help eradicate them. After the binding, there is a release of factors such as Thromboxane A2 and Adenosine Diphosphate (ADP), activating the coagulation and inflammatory cascade. There have been reports that this platelet activation results in thrombocytopenia, a common finding in viral infections (such as Influenza, Coronaviruses, and HIV). An endothelial lesion can lead to exposure of prothrombotic factors, such as the Von Willebrand factor, on the vessel wall, as well as to the decrease of endogenous anticoagulant factors, such as proteins C and S, and antithrombin. Previous data show that in infections caused by Influenza and SARS, there was

FIGURE 1. ACUTE INFECTIONS TRIGGERING MYOCARDIAL INJURY AND ACUTE CORONARY SYNDROMES. (ADAPTED FROM MEDINA ET, AL; ROLE OF ACUTE INFECTION IN TRIGGERING ACUTE CORONARY SYNDROMES; LANCET INFECT DIS 2010; 10: 83–92)



an increase of thrombi and fibrin deposits in the lungs, thus suggesting local microthrombosis.

There have also been descriptions of "shock-induced Endotheliopathy in critical patients"[12], which suggests that during shock there is sympathetic -adrenal hyperactivation, with an increase of circulating catecholamines, leading to endothelial and microcirculation damage due to capillary leak, with increased local inflammatory mediators, vascular edema, and tissue hypoxia, generating a vicious cycle of endothelial lesion. Thus, the endogenous anticoagulant system would be damaged, leading to microvascular occlusion, which can justify the increased D-dimer and troponin in more severe patients. In addition, in the final shock cascade, there can be coagulopathy and even DIC as a compensatory mechanism. Johansson et al. suggested that young people have less endotheliopathy (in patients with trauma-related shock) in comparison with the elderly. In addition, smokers, hypertensive, and diabetics patients have greater endothelial dysfunction, and the finding of endotheliopathy could be associated with the outcomes of death in the short and long term.

In a study published in 2018[16], viral infections by Influenza were associated with a higher rate of acute coronary events. It evaluated the diagnoses of acute myocardial infarction (AMI) during a 1-year period before and after a positive diagnosis for Influenza. In this study, there was a higher rate of AMI in up to 7 days after the diagnosis of Influenza in relation to the control group. According to the data presented, infections, among them, viral ones included, can lead to acute coronary conditions, as well as endothelial and microvascular lesions. Increased D-dimer and troponin suggest a worse prognosis and greater risk of mortality in COVID-19 positive patients, probably because they are associated with a greater inflammatory response, endothelial damage, and thrombotic events.

A Chinese study[17] that included 449 patients admitted for COVID-19 showed that the strategy of prescribing enoxaparin 40-60mg/day or non-fractionated heparin 10,000 to 15.000U/day brought benefits in mortality after 28 days in 2 subgroups. One of them comprised patients with criteria of coagulopathy induced by sepsis >= 4 (which uses the criteria of increase of PT, decreased platelet count, and increased SOFA score), with a difference of 40% vs. 64.2% (P = 0.029). The other subgroup was composed of patients with D-dimer > 6x the upper threshold of normality, with a difference of 32.8% vs. 52.4% (P = 0.017), demonstrating that the strategy of prescribing chemical prophylaxis for venous thromboembolism (VTE) should be considered in patients admitted with COVID-19, even if they present low/intermediate risk of VTE.

In relation to the therapeutic procedures for patients with CVD who are infected with COVID-19, the hypothesis has been raised that medications that interfere with the ACE can be harmful to the patient. Since there have been no studies demonstrating such association, most medical societies recommend not discontinuing angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), as well as any medications that were already in use, particularly those used with prognostic benefits [5,18]. Pro-thrombotic events, including acute coronary events, require increased attention, and there is no evidence that recommends the routine interruption of antiplatelet and anticoagulant drugs. In addition, the recommendations for influenza and pneumococcus vaccinations in patients with previous indications are maintained.

Contribution of the authors

a) Marcel de Paula Pereira: Author of the paper and literature review

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PALAVRAS CHAVES: *COVID-19; Sars-COV-2; Aterosclerose; Aterotrombótico.*

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REVIEW ARTICLE

Epidemiology, diagnosis, treatment, and future perspectives concerning SARS-COV-2: a review article

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SUMMARY

The present study aimed to review the epidemiology, clinical manifestation, laboratory diagnosis, treatment, and future perspectives related to COVID-19 infections. The following electronic databases were used searched: MEDLINE, SCIELO, and LILACS. It became clear that COVID-19 infections occur through exposure to the virus, and both the immunosuppressed and healthy population appear susceptible. The clinical course of COVID-19 is still not clear, although the SARS-CoV-2 infection seems to develop with mild, influenza-like symptoms in the vast majority of subjects, i.e., 10%–15% of COVID-19 patients. Since rRT-PCR tests serve as the gold standard method to confirm a SARS-CoV-2 infection, false-negative results could hinder the prevention and control of the epidemic, particularly considering the test plays a key role in the decision for continued isolated medical observation or discharge. Our findings also indicate that a radical increase in the identification and isolation of currently undocumented infections would be needed to fully control SARS-CoV2.

KEYWORDS: *Coronavirus. Epidemiology. Signs and symptoms. Diagnosis. Therapeutics.*

INTRODUCTION

The coronavirus was initially designated as the 2019-novel coronavirus (2019-nCoV) in January 2020 by the World Health Organization (WHO). The disease caused by it was named coronavirus disease 2019 (COVID-19). The Coronavirus Study Group of the International Committee suggested naming the new coronavirus as SARS-CoV-2, based on taxonomy, phylogeny, and established practice issued in February 2020[1]. In December 2019, several acute respiratory illnesses, now called COVID-19, occurred in Wuhan, Hubei Province, China. A total of 3,588,773 cases of COVID-19 have been confirmed including 247,503

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deaths as of May 06 2020. The pathogen of this disease was confirmed as a novel coronavirus by molecular methods, and to date, COVID-19 has affected people in more than 189 countries and has become a global pandemic[2].

Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, hepatic, enteric asymptomatic carrier, pneumonia of varying degrees of severity and neurological symptoms[3,4].

There are relevant factors associated with COVID-19; therefore, the present study aimed to review the epidemiology, clinical manifestation, laboratory diagnosis, treatment, and future perspectives related to the COVID-19 infection epidemiology.

METHODS

The following electronic databases were included in this review: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed (1966 to January 2020), available through the following link: https://www.ncbi.nlm.nih.gov/pubmed/; Scientific Electronic Library Online (SCIELO), available at https://www.scielo.org/ and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), available through the following link: https://bvsalud.org/; (1982 to January 2020). The electronic search resulted in 908 articles. Among them, thirteen were duplicates. After selecting the title and abstract, 74 articles were identified for a complete evaluation of the text. From those, 24 were used for the final review. There was no date and language restriction. Records were managed by EndNote X 9.0 software.

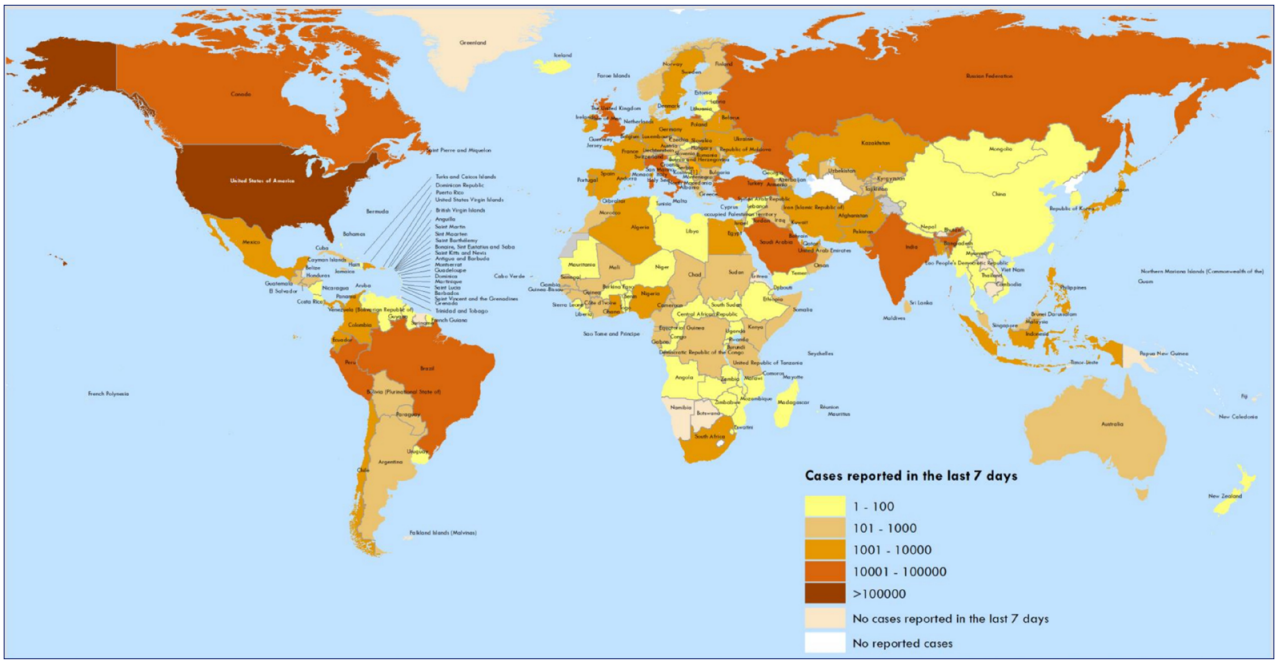
Epidemiology

It became evident that the COVID-19 infection occurs through exposure to coronavirus, and both the immunosuppressed and healthy population appear to be susceptible. Some studies have documented an age distribution of adult patients between 25 and 89 years old. Most adult patients were between 35 and 55 years old[5]. A study on early transmission dynamics of the virus reported the average age of patients to be 59 years old, ranging from 15 to 89 years, with the majority (59%) being male. It was suggested that the population most at risk might be people with a poor immune function, such as older people and those with renal and hepatic dysfunction[6].

Figure 1 shows the number of confirmed COVID-19 cases reported by country, territory or area, 30 April to 6 May, in accordance with WHO.

The epidemic of unknown acute respiratory tract

FIGURE 1. NUMBER OF CONFIRMED COVID-19 CASES REPORTED BY COUNTRY, TERRITORY OR AREA, 30 APRIL TO 6 MAY, 2020, IN ACCORDANCE WITH WHO.



Source: World Health Organization, 2020.

infections broke out first in Wuhan, China, in December 2019. This is possibly linked to the seafood market. Several studies suggested that bats may be the potential source of SARS-CoV-2. However, there is no evidence to date that the origin of SARS-CoV-2 is from the seafood market[7].

Currently, person to person transmission from patients with pneumonia or asymptomatic patients during the incubation period is the main source for the spread of the virus. Respiratory droplets are the main route of transmission, but the virus can also be transmitted through interpersonal contact or through the fecal-oral route based on a study that demonstrates the presence of the virus in rectal swabs[8,9]. Prevention and control strategies and methods are reported at three levels: national level, case-related population level, and general population level[10].

Airborne precautions and other protective measures have been discussed and proposed for prevention. Infection preventive and control measures that may reduce the risk of exposure include the following: use of face masks; covering coughs and sneezes with tissues that are then safely discarded[11].

Presently, there are four endemic coronavirus strains currently circulating in human populations: 229E, HKU1, NL63, OC43. If the novel coronavirus follows the pattern of the 2009 H1N1 pandemic influenza, it will also spread globally and become a fifth coronavirus pandemic in the human population[12]. Table 1 shows data as reported by national authorities on 6 May 2020.

TABLE 1. DATA AS REPORTED BY NATIONAL AUTHORITIES ABOUT SARS-COV-2 ON 6 MAY 2020

	Confirmed	Deaths
Western Pacific Region	154 884	6327
European Region	1 593 828	147 780
South-East Asia Region	76 998	2821
Eastern Mediterranean Region	221 230	8290
Region of the Americas	1 507 148	81 070
African Region	33 973	1202
Globally	3 588 773	247 503

Source: World Health Organization, 2020

Clinical manifestation

The clinical course of COVID-19 is still unclear. Although the SARS-CoV-2 infection seems to occur with mild, influenza-like symptoms in the vast majority of subjects, i.e., 10%–15% of COVID-19 patients (especially older ones and those with relevant comorbidities), the disease may progress to severe interstitial pneumonia, which may then evolve to acute respiratory distress syndrome and death in 2%–5% of cases[13].

Reliable evidence suggests that the incubation period of SARS-CoV-2 is approximately 6 days and that the average period between symptom onset and hospitalization is 7 days, while the average period of symptom duration is approximately 13 days, or slightly longer in patients with severe disease (16 days)[14].

In a study involving 108 patients (38 men, 70 women; age range, 21–90 years old), the manifestations observed were fever in 94 of 108 patients (87%), dry cough in 65 of 108 (60%), and fatigue in 42 of 108 (39%). The laboratory results were normal white blood cells (WBC) count in 97 of 108 patients (90%) and normal or reduced lymphocyte count in 65 of 108 (60%). High-sensitivity C-reactive protein level was elevated in 107 of 108 patients (99%). Most patients have lymphopenia and bilateral ground-glass opacity changes on chest computed tomography (CT) scans[15].

Laboratorial diagnosis

The nucleic acid test or genetic sequencing for SARS-CoV-2 was considered the gold standard method for confirmation of infection. Since rRT-PCR tests serve as the gold standard method to confirm a SARS-CoV-2 infection, false-negative results could hinder the prevention and control of the pandemic, especially since the test plays a key role in the decision for the need of continued isolated medical observation or discharge. The accuracy of RT-PCR can be substantially affected by the lack of harmonization of primers and probes, as well as by a variety of technical and analytical errors[16].

Studies on COVID-19 have generally been limited to the description of the epidemiology characteristics, initial clinical, hematological, and radiological findings. Laboratory results also found that SARS-CoV-2 is similar to some of the beta (β) coronaviruses generally identified in bats[17], which are part of a group of SARS/SARS-like CoV viruses. Case definition guidelines mention the following symptoms: decreased lymphocytes and white blood cells, new pulmonary infiltrates on chest radiography, and lack of improvement of symptoms after 3 days of antibiotic treatment[6]. For patients with a suspected infection, the following procedures have been suggested for diagnosis: real-time fluorescence RT-PCR to detect the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples[18].

In the advanced phase of SARS-CoV infection, rapid reduction of lymphocytes in peripheral blood, mainly T lymphocytes, was observed, and both CD4 and CD8 T lymphocytes decreased. The loss of lymphocytes precedes even the abnormal changes on the chest X-ray. SARS-specific IgG antibodies are produced in the late advanced stages (about 2 weeks) and gradually increase with the course of the disease. The sustainable existence of IgG makes the patients acquire immune function after the infection. The IgG level of mild patients was significantly higher than that of severely infected patients[19].

Treatment and futures perspectives

Suspected and confirmed cases need to be treated in designated hospitals under effective quarantine conditions. Suspected cases need to be treated separately in a single room, with confirmed cases admitted to the same ward, and critical cases should be admitted to ICU as soon as possible[20].

Unfortunately, there is no known specific treatment against COVID-19. Because of this, identifying effective antiviral agents to combat the disease is urgently necessary. However, chloroquine phosphate has shown apparent effectiveness in the treatment of COVID-19 associated pneumonia in clinical studies. Chloroquine is a 9-aminoquinoline discovered in 1934; it is used to prevent and treat malaria and is effective as an anti-inflammatory agent for the treatment of rheumatoid arthritis and lupus erythematosus. The drug also has many interesting biochemical properties, including an antiviral effect. Studies revealed that it also has potential against viral infection. Moreover, chloroquine was also found to be a potent inhibitor of SARS coronavirus infection by interfering with ACE2, one of cell surface binding sites for S protein of SARS-CoV[21].

The development of attenuated-virus vaccines is also possible by carefully screening the serially propagated SARS-CoV-2 with reduced pathogenesis such as induced minimal lung injury, diminished limited neutrophil influx, and increased anti-inflammatory cytokine expressions compared with the wild-type virus[22].

At least five vaccine technologies will be reviewed: inactivated vaccine, subunit protein vaccine, nucleic acid vaccine, adenoviral vector vaccine, and recombinant influenza viral vector vaccine[23]. Traditional vaccine technologies have been improved, and a wide variety of new technologies have emerged in the past two decades[24].

CONCLUSION

Our findings also indicate that a radical increase in the identification and isolation of currently undocumented infections would be necessary to control SARS-CoV2 fully. An estimation of the prevalence and contagiousness of undocumented novel coronavirus (SARS-CoV2) infections is critical for understanding the overall prevalence and pandemic potential of this disease. These findings explain the rapid geographic spread of SARS-CoV2 and indicate containment of this virus will be particularly challenging. No specific antiviral treatments or vaccines are available because it is a new and emerging viral disease. The development of SARS-CoV-2-based vaccines is urgently required.

Conflicts of interest

The authors declare there are no conflicts of interest that may have influenced this work.

Authors' contributions

ARVSC, MLCF, PCPA, and RNSF searched the databases. TJMR, CFSR, FTB, and FWSR selected the articles to be included in the research. FWSR corrected the writing in English. All authors performed the other parts of the research in an equally. All authors have reviewed and approved the final text of this article and are responsible for its content.

RESUMO

O presente estudo teve como objetivo realizar uma revisão sobre epidemiologia, manifestações clínicas, diagnóstico laboratorial, tratamento e perspectivas futuras relacionados à infecção pelo COVID-19. As seguintes bases de dados eletrônicas foram utilizadas MEDLINE, SCIELO e LILACS. Ficou claro que a infecção pelo COVID-19 ocorre por exposição ao vírus, e tanto a população imunossupressora quanto a normal parecem suscetíveis. O curso clínico do COVID-19 ainda não está claro, embora a infecção por SARS-CoV-2 pareça ocorrer com sintomas leves e semelhantes à gripe na grande maioria dos indivíduos, em 10%-15% dos pacientes com COVID-19. Uma vez que os testes rRT-PCR servem como o método padrão-ouro para confirmar a infecção do SARS-CoV-2, os resultados falso-negativos podem dificultar a prevenção e o controle da epidemia, particularmente quando este teste desempenha um papel de referência fundamental na decisão da necessidade de observação médica isolada ou alta. Nossos achados também indicam que seria necessário um aumento radical na identificação e isolamento de infecções não documentadas atualmente para controlar totalmente o SARS-CoV2.

PALAVRAS-CHAVE: *Coronavirus. Epidemiologia. Sinais e sintomas. Diagnóstico. Terapêutica.*

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REVIEW ARTICLE

Severe Cerebellar Degeneration and Chiari I Malformation - Speculative pathophysiology based on a systematic review

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SUMMARY

BACKGROUND: *Symptomatic Chiari Type I Malformation (CM) is treated with posterior fossa decompression with or without duroplasty. We have noticed some cases with concomitant severe cerebellar ataxia due to cerebellar atrophy. The aim of this study is to review the literature of CM associated with severe cerebellar atrophy and discuss its potential physiopathology.*

METHODS: *A systematic literature review in the Pubmed Database was performed using the following key-terms: "cerebellar atrophy Chiari", and "cerebellar degeneration Chiari". Articles reporting the presence of cerebellar degeneration/atrophy associated with CM were included.*

RESULTS: *We found only six studies directly discussing the association of cerebellar atrophy with CM, with a total of seven cases. We added one case of our own practice for additional discussion. Only speculative causes were described to justify cerebellar atrophy. The potential causes of cerebellar atrophy were diffuse cerebellar ischemia from chronic compression of small vessels (the most mentioned speculative cause), chronic raised intracranial pressure due to CSF block, chronic venous hypertension, and association with platybasia with ventral compression of the brainstem resulting in injury of the inferior olivary nuclei leading to mutual trophic effects in the cerebellum. Additionally, it is not impossible to rule out a degenerative cause for cerebellar atrophy without a causative reason.*

CONCLUSIONS: *Severe cerebellar atrophy is found in some patients with CM. Although chronic ischemia due to compression is the most presumed cause, other etiologies were proposed. The real reasons for cerebellar degeneration are not known. Further studies are necessary.*

KEYWORDS: *Arnold-Chiari Malformation. Cerebellum/abnormalities. Cerebellar diseases. Systematic review.*

INTRODUCTION

Chiari malformation (CM) is characterized by a congenital malformation of the posterior cranial fossa with cerebellar tonsils herniation through the foramen magnum, probably due to the underdevelopment of the posterior bony skeleton (exo-occipital and supraoccipital bones)[1,2]. Symptoms may have a wide range of clinical presentations, such as motor and sensory deficits, cranial nerve palsies, as well as cerebellar symptoms (ataxia, dysmetria, among others)[1-4]. When symptomatic, surgical treatment is well accepted, consisting of posterior fossa decompression, with or without duroplasty[1-4].

In our clinical experience, we have noticed that some patients present severe cerebellar ataxia, even after surgical treatment, due to severe atrophy, with cerebellar substance degeneration. The aim of this study is to review the potential causes of cerebellar atrophy in patients with symptomatic CM, before or even after surgical treatment.

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METHODS

In an attempt to study the relationship between cerebellar atrophy and CM, two electronic searches were conducted on PubMed (MEDLINE) in July 2019. We used the following search terms: "cerebellar atrophy Chiari" obtaining 40 articles titles. Another search was performed using the following search terms: "cerebellar degeneration Chiari" obtaining 16 titles. From the 56 revised titles with their respective abstracts, four case reports were included from the first search and two from the second one, with a total of six articles reporting cerebellar degeneration associated with CM. An illustrative case treated by the author was also included.

Since only case reports were evaluated, our review was classified by the Oxford Centre of Evidence-Based Medicine[5] as evidence level 4 (case series of poor quality).

RESULTS

We found six studies in our literature search, all of which were case reports, with a total of seven patients discussed (one case report had two illustrative cases)[6-11]. They were all described in detail. The majority of the authors rule out other causes of cerebellar degeneration, such as infections, inflammatory diseases, and medications/drugs.

Gebarski and Greenberg[6] reported the first case, in the CT scan era, (1984) of loss of cerebellar substance in a patient with CM. A 40-year-old woman with gait instability and visual blurring was diagnosed with olivopontocerebellar degeneration. She underwent clivomyelography with iophendylate demonstrating herniation of the cerebellar tonsils to the level of the axis. She also had a cerebral angiography demonstrating displacement of the tonsillohemispheric branches of the posterior inferior cerebellar arteries (PICA). She then underwent a suboccipital craniectomy with laminectomy of C1 and C2 and dural grafting, reestablishing normal gait and vision two months after the surgery. Authors proposed that the diffuse cerebellar ischemia from chronic compression of the small vessels was the cause of loss of cerebellar substance, although no arterial occlusions were noted in the limits of the subtraction angiography and no supratentorial ischemia or atrophy was documented. They emphasized that the loss of cerebellar substance should not be considered evidence enough to exclude the diagnosis of CM.

Goel et al.[7], almost 18 years after the first description of the association of cerebellar atrophy and CM, reported two cases of Basilar Invagination (BI) associated with CM in patients with severe cerebellar atrophy. It was the first report in the MR era. The first patient was a 24-year-old woman with gait impairment in the previous three years, associated with hoarseness of voice, dysphagia, and nasal regurgitation. She also had BI with CM, atlas occipitalization, and marked atrophy of the cerebellum. Digital angiography showed a "bulbar hump" but a normal filling of all posterior cranial fossa blood vessels. One year after the surgery, there was a marked improvement in her speech, swallowing, and her gait was normal. The other patient was a 38year-old man with complaints of imbalance, vertigo, and difficulty in swallowing for one month. He also had an MR with CM and BI with assimilation of the atlas and severe cerebellar atrophy. The angiography showed normal filling of posterior circulation with some stretching of the PICA. After bone decompression at the posterior fossa, marked improvement was reported. The authors reported that both patients did not have cerebral atrophy. Explanations included continuous insufficiency of blood supply to the brainstem and cerebellum, once infarction was not plausible due to the normal angiography exam. Interestingly, in both cases, there were marked BI with platybasia and a concavity of the brainstem, with normal tonsils morphology in an abnormal cerebellum.

Kempster and Pullar[8], in 2003, published a letter about the publication of Goel et al.[7]. In it, they also reported a 57-year-old man who had severe gait complaints, as well as speech slurring and swallowing difficulties. Although they did not publish images, the description of the MR reported a marked indented ventral surface of the upper medulla without signs of cerebellar or brainstem infarction and a dolicho-ectatic left vertebral artery. The cerebellar atrophy was more evident in the vermis. They proposed that a potential mechanism of cerebellar atrophy was due to some sort of trans-synaptic neuronal degeneration – with ventral compression at the level of the inferior olivary nuclei, a major source of cerebellar afferents, which resulted in trophic effects in the cerebellum due to the connections with the cerebellar Purkinje cells. Damage to one group of these neurons potentially may lead to degeneration of the others, according to animal studies (in rats).

Maurya and Singh[9], in 2003, reported a 34-year-old man with the diagnosis of cerebellar degeneration

from a CT scan, who subsequently had a diagnosis of CM after an MR. The patient had had gait unbalance in the previous three years, mild dysarthria with normal motor and sensory system exams. There was downbeat nystagmus, which was associated with cervicomedullary junction diseases. The CT showed marked cerebellar atrophy with asymmetry (the left side was more affected than the right one). Then, the MR showed tonsillar herniation below the foramen magnum without syringomyelia. Although the MR did not show any evidence of acute or subacute ischemic brain injury, they also speculated that diffuse cerebellar ischemia from chronic compression was the cause of cerebellar atrophy. The authors proposed that CM should be considered as a differential diagnosis of loss of cerebellar substance.

Petracca et al.[10], in 2013, reported a 33-year-old woman who had had previous surgery (posterior fossa decompression) for CM with complete resolution of tonsillar herniation in an early postoperative MR, with an improvement of sensory symptoms and also some improvement in walking unsteadiness. Three years after the surgery, she returned with symptoms of a cerebellar syndrome (imbalance and speech impairment), dysphagia, diplopia, and dizziness. She also had scanning speech, gait instability, and nystagmus in all gaze directions, with bilateral dysmetria. A screening for ataxia was performed and also a neurophysiological study of the upper and lower limbs with analysis of sensory and motor conduction, with axonal neuropathy. A new MR was performed about six years after the first one, with a diagnosis of severe cerebellar atrophy and late-onset idiopathic cerebellar ataxia (ILOCA). ILOCA is characterized by a neurodegenerative disorder of adult-onset and unknown cause of progressive cerebellar ataxia and atrophy of the cerebellum (and sometimes, also the brainstem). The authors proposed that ILOCA did not seem to be linked to CM.

Moscote-Salazar et al.[11] reported the case of an 18-year-old woman with headaches in the previous six months, with an associated quadriparesis. An MR showed tonsillar herniation and syringomyelia. She underwent posterior fossa decompression with a laminectomy of C1 and had fully recovered from her symptoms after three years of follow-up. In the same MR, severe cerebellar atrophy was evident. No mechanism to explain the cerebellar changes were proposed by the authors.

We also added the illustrative case of a 58-year-old man with CM surgically treated with posterior fossa decompression ten years ago who had later worsening of cerebellar ataxia with severe cerebellar atrophy (Figure 1). This patient had severe ataxia, almost unable to walk (requires flares), severe dysarthria, and dysmetria, but did not have pain or motor symptoms. He did not undergo another surgical procedure once his symptoms were attributed to severe cerebellar degeneration. A BI secondary to clivus hypoplasia and some ventral brainstem compression was evident.

DISCUSSION

Since the first paper about cerebellar ectopia published by Hans Chiari in 1891, congenital

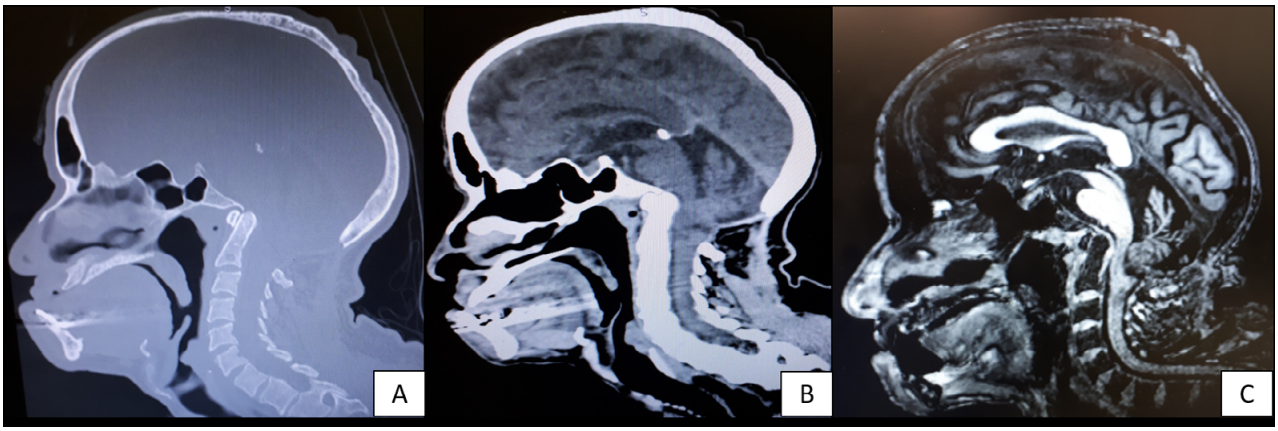

FIGURE 1. A) SAGITTAL BONE CT SCAN SHOWING CLIVUS HYPOPLASIA, PLATYBASIA, AND A POSTERIOR FOSSA DECOMPRESSION WITH A C1 LAMINECTOMY. B) SAGITTAL SOFT TISSUE CT SCAN SHOWING SOME VENTRAL COMPRESSION OF THE MEDULLA BY THE CLIVUS AND CEREBELLAR ATROPHY. C) SAGITTAL T1 MRI WITH SEVERE CEREBELLAR ATROPHY. ONCE THE PATIENT HAD ONLY ATAXIA ATTRIBUTED TO THE CEREBELLAR DEGENERATION, WE DID NOT INDICATE A NEW SURGICAL PROCEDURE.

craniocervical junction anomalies are still full of controversies[2,12]. The many different radiological presentations, which may include osseous components of the dysgenesis, such as atlantoaxial instability, BI, Klippel-Feil anomalies, atlas occipitalization, scoliosis, facet joints malformations, tethering cord, among many others, are extensively discussed in the literature[1,2,13-19]. When considering the neural components of CM, the association of CM with hydrocephalus, syringomyelia, and syringobulbia is also extensively found[13]. However, cerebellar atrophy has rarely been described, although we have noticed that this finding is not so rare.

In our review, we only found six studies discussing cerebellar atrophy associated with CM, with a total of seven patients, or eight patients, including our additional case. The images of the first case, date from 1984, and it is not possible to clearly elucidate if there is concomitant BI in the axial CT scan[6]. The two cases presented by Goel et al.[7] had severe BI with ventral brainstem compression. The fourth case, presented by Kempster and Pullar[8], did not have MR images available, but the authors reported that the patient had severe anterior brainstem compression without signs of cerebellar infarction. The fifth case reported by Maurya et al.[9] had only CM, without an evident BI and without ventral compression. The sixth case reported by Petracca et al.[10] also did not have evident BI. The seventh case reported by Moscote-Salazar et al.[11] had CM with important ventral brainstem compression, similarly to our illustrative case. Considering the eight cases reviewed, only two were "pure" CM, five had also BI with ventral brainstem compression, and one was inconclusive. It means that although ventral brainstem compression may play an important role in the development of cerebellar atrophy, it cannot be the only explanation for this finding.

The normal vascular flow documented in angiography of the posterior fossa performed in the cases of Gebarski and Greenberg[6], as well as in the Goel et al.[7] cases, suggested that infarction was not the reason for cerebellar atrophy, although the authors postulated that continuous insufficient blood supply might play a role in the physiopathology of cerebellar degeneration.

The theory proposed by Kempster et al.[8], based on animal studies (rats), that damage to the inferior olivary neurons may result in atrophy in the cerebellar Purkinje cells due to mutual trophic effects may be considered in cases with ventral brainstem compression[20]. However, as explained above, two patients had "pure" CM, without ventral brainstem compression in published images. For this reason, this explanation may also be questioned or does not explain atrophy in all cases.

Ito et al.[21] described a case of a 50-year-old woman who had a 40-year history of progressive sensorimotor deficits with CM with severe spinal cord atrophy below C12 (in the cervical, thoracic and lumbar spine, without tethering). She underwent foramen magnum decompression and C1 laminectomy with duraplasty, with progressive improvement. The authors speculated that spinal cord atrophy might be due to secondary retention of CSF at the spinal canal or spontaneous resolution of syringomyelia. We may also infer that CSF obstruction in the foramen magnum plays a role in cerebellar atrophy – with compartmental posterior fossa hypertension, the cerebellar tissue may be more sensitive to the higher pressure and degenerates. This local hypertension may result in direct compression of the cerebellum tissue in the bone of the posterior fossa – another potential mechanism of atrophy. This theory may be justified by venous hypertension and poor drainage of the posterior fossa in some patients with CM. We have observed some patients with severe BI with clivus hypoplasia that had important sinus bleeding when the dura of the posterior fossa was opened in decompressive procedures. To corroborate this theory, Saindane et al.[22] evaluated the severity of transverse sinus stenosis in contrast-enhanced brain MRIs of 30 patients who had surgery for CM and compared the findings with 76 controls subjects. Two different readers blinded to the diagnosis reported that CM patients had a higher rate of unilateral than bilateral transverse sinus stenosis. This finding may reflect associated intracranial hypertension due to an obstruction of the CSF flow or even poor venous drainage.

The main limitation of our study is the sparse literature about the association of cerebellar atrophy and CM. Additionally, we should also emphasize that many patients with CM may have some degree of cerebellar substance atrophy but did not present any symptoms related to it. However, this is the first study to review this problem and has raised many potential causes for cerebellar atrophy. Further studies are necessary to elucidate better the reasons for cerebellar degeneration in some patients with CM.

CONCLUSIONS

Although not common, severe cerebellar atrophy is found in some patients with CM, more commonly with associated BI. Many potential causes could justify this association, such as chronic ischemia, ventral brainstem compression, CSF hypertension, venous hypertension, or even an intrinsic degeneration. However, the reason for cerebellar degeneration in some patients with CM is not known. Further studies are necessary.

RESUMO

OBJETIVO: *A Malformação de Chiari (MC) tipo I sintomática é tratada através da descompressão da fossa posterior com ou sem duroplastia. Observamos alguns casos com ataxia cerebelar grave concomitante devido à atrofia cerebelar. O objetivo deste estudo é revisar a literatura sobre MC associada à atrofia cerebelar grave e discutir sua possível fisiopatologia.*

METODOLOGIA: *Conduzimos uma revisão sistemática da literatura no banco de dados Pubmed utilizando as seguintes palavras-chave: "cerebellar atrophy Chiari", e "cerebellar degeneration Chiari". Artigos sobre a presença de degeneração/atrofia cerebelar associada à MC foram incluídos.*

RESULTADOS: *Encontramos apenas seis estudos que discutiam diretamente a associação entre atrofia cerebelar e MC, com um total de sete casos. Nós adicionamos um caso da nossa própria prática para ampliar a discussão. Apenas causas especulativas foram descritas para justificar a atrofia cerebelar, entre elas: isquemia cerebelar difusa devido à compressão crônica de pequenos vasos (a causa especulativa mais citada), pressão intracraniana elevada crônica devido ao bloqueio de LCR, hipertensão venosa crônica e associação com platibasia com compressão ventral do tronco cerebral, resultando em lesão do núcleo olivar inferior e levando a efeitos tróficos mútuos no cerebelo. Além disso, não é possível descartar uma causa degenerativa para atrofia cerebelar sem motivos claros.*

CONCLUSÃO: *A atrofia cerebelar grave é encontrada em alguns pacientes com MC. A isquemia crônica causada por compressão é a causa mais apontada como suspeita, porém outras etiologias foram propostas. As reais causas da degeneração cerebelar não são conhecidas. Mais estudos são necessários.*

PALAVRAS-CHAVE: *Malformação de Arnold-Chiari. Cerebelo/anormalidades. Doenças*

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REVIEW ARTICLE

Timing factors as prognostic variables in patients with head and neck squamous cell carcinoma treated with adjuvant radiotherapy: a literature review

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SUMMARY

INTRODUCTION: *Radiotherapy (RT) plays an important role in the treatment of patients with head and neck neoplasia, and is frequently used as postoperative adjuvant therapy. This study aimed to review the literature about timing factors that may influence the clinical outcomes of patients with advanced head and neck neoplasia treated with adjuvant RT.*

RESULTS: *Timing factors such as total treatment time, length of adjuvant RT, and the absence of interruptions during RT may influence the clinical outcome of these patients.*

CONCLUSIONS: *In the same way that certain tumor factors can affect the prognosis of patients with squamous cell carcinoma of the head and neck, some therapeutic timing factors are also prognostic factors and therefore, must be carefully orchestrated in order to avoid loss at therapeutic outcomes for these patients.*

KEYWORDS: *Head and neck neoplasms. Radiotherapy. Carcinoma, squamous cell. Prognosis. Review literature as topic.*

INTRODUCTION

Tumors originated in the head and neck region represent 4% of all neoplasias worldwide, with 380,000 deaths and 560,000 new cases estimated yearly[1]. In about two-thirds of the cases, the diagnosis of these tumors is performed in advanced clinical stages, which usually determines a higher number of cases with guarded prognosis, in addition to the need of multidisciplinary treatment including surgeons, clinical oncologists, and radiation oncologists, as well as nurses, dentists, nutritionists, psychologists, speech therapists, and physical therapists[2].

Radiotherapy (RT) is often used in the treatment of patients with advanced the head and neck cancer as a postoperative adjuvant therapy with the objective of reducing the likelihood of local recurrence due to its ability to eradicate the remaining neoplastic cells that could evolve to a locoregional recurrence. Gilbert Fletcher introduced, in the 1950s, the concept of

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postoperative RT in squamous cell carcinoma of the head and neck after observing high rates of recurrence with surgical treatment alone[3]. Since then, the risk reduction of locoregional failure with the use of adjuvant RT has been repeatedly documented, confirming its ability to improve the rates of local control, progression-free survival, and overall survival[4] .

In 2004, two independent randomized clinical studies, one conducted by the European Organization for Research and Treatment of Cancer (EORTC 22931)[5] and another led by the Radiation Therapy Oncology Group (RTOG 9501)[6], published data with a high level of evidence justifying the use of concomitant adjuvant radio-chemotherapy due to the benefit of local control and progression-free survival in patients with a high risk of recurrence.

Although surgical resection followed by adjuvant RT, with or without chemotherapy, is the standard treatment for a good number of locally advanced tumors, it still presents unsatisfactory results, with rates of 30% of locoregional failure, 25% of distant metastases, and survival in five years around 40%-50%[7]. In addition to the clinical factors related to the tumor, some aspects related to the treatment, such as the total treatment time (TTT), the duration of RT, and the interval between surgery and the beginning of RT, also seem to have a prognostic impact on the clinical outcome of these patients since a delay to start the treatment seems to affect mainly patients with tumors of accelerated cell multiplication, such as squamous cell carcinoma of the head and neck. A delay to start the treatment seems to affect mainly patients with tumors of accelerated cell multiplication, such as squamous cell carcinoma of the head and neck, because their doubling time and speed of growth are directly related to the local control of the tumor[8]. In order to describe temporal factors that may impact the clinical outcomes of patients with advanced neoplasia of the head and neck treated with adjuvant RT, we propose this integrative literature review.

RADIOBIOLOGY AND TUMOR BIOLOGY OF HEAD AND NECK NEOPLASIAS

Adjuvant RT for the treatment of patients with head and neck cancer is usually administered daily, five times per week, for an average of five to seven weeks.

Cell death as a result of RT occurs by mechanisms at molecular levels and may happen through apoptosis or post-mitotic cell death (the predominant mechanism of radio-induced cell death). While apoptosis manifests rapidly after cell aggression, cell death after mitosis depends on the tumor tissue turnover time. In it, the chromosome damage caused by radiation only manifests when the cell tries, without success, to reproduce itself. Thus, there is a latent lag phase from the radio-induced chromosome damage to the manifestation of post-mitosis death. Furthermore, the depletion of tumor cells as a result of RT is a stimulus for accelerated clonogenic multiplication of the

remaining tumor cells, with increased number of cells to be eradicated, defining a phenomenon called accelerated repopulation, as illustrated in Figure 1. Thus, tumor cell repopulation increases with the duration of the radiotherapy treatment, with a higher rate after the first two weeks of treatment; being critical a therapeutic course interruption, especially at this stage. In this regard, Malaise and Tubiana[9] have demonstrated that the repopulation of fibrosarcoma transplanted into mice increased with the duration of treatment and was faster after a single fraction of RT than in non-irradiated tumors.

The radiobiological concepts that describe the rapid tumor repopulation after the start of RT give reason to expect the same with residual cells after surgical intervention. The surgical site is a favorable environment for cell proliferation since it is rich in growth factors that promote tumor cells, angiogenesis, and micrometastases, and the postoperative recovery period could be an opportunity for the tumor cells to become radio-resistant since its resistance increases with the number of cell multiplications[10]. What happens, however, is that different treatment techniques (radiotherapy or surgery) present different intervals for the onset of accelerated cell repopulation. According to the Gompertz model of volume-dependent

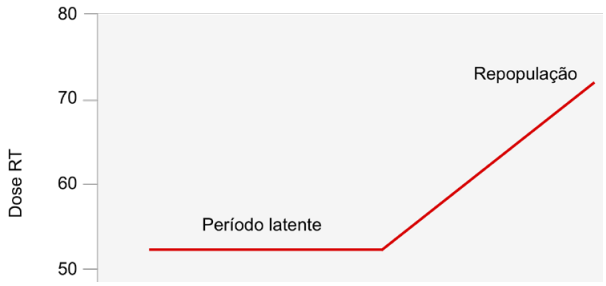

FIGURE 1. INITIAL LATENT STAGE AFTER RADIO-INDUCED CELL DAMAGE FOLLOWED BY AN ACCELERATED REPOPULATION PEAK FROM THE MANIFESTATION OF CELL DEATH AND DEPLETION CAUSED BY RT

tumor growth and cell repopulation, regeneration by means of effective growth of neoplastic cells after a surgical treatment is substantially lower (10^6 - 10^9 residual cells in the surgical site) than the growth tumor cells during RT (1 to 10^6 cells)[11]. Extended RT time may have an impact on the likelihood of tumor control, with a possible decrease of 1% to 2% for each additional day of treatment, while a extended interval between surgery and the beginning of RT has an impact of approximately 0.17%/day[12]. Thus, an extended interval between the surgical resection and the beginning of RT seems to be not as deleterious as extended radiotherapy treatment.

TREATMENT DURATION

Evidences indicates that the duration of postoperative RT, the absence of interruptions during radiotherapy, and the total treatment time (TTT) are determining factors for the final therapeutic results[13]. Withers et al.[14] have analyzed clinical information grouped from different institutions in order to identify the total RT dose needed to control 50% of the tumor cells in squamous cell carcinoma of the head and neck. This concept, known as Tumor Control Dose (TCD50) showed a marked increase in treatments that lasted more than four weeks, with need to increase the RT dose for each additional day of treatment, and the concept of accelerated repopulation justifing such a finding. By the same reasoning, when there are long intervals between fractions and a given dose is delivered in a longer period of time, the effectiveness of RT can be limited or compromised, with lower rates of tumor control and an increased likelihood of accelerated tumor growth of approximately 1.0%-1.5%

for each additional day of radiotherapy treatment[15]. Suwinski et al.[12] found a decrease of 10%-30% of

the locoregional control rate in five years when the treatment lasted for more than 10 days beyond the initially planned. It is estimated that the dose required to override accelerated tumor repopulation per additional day of treatment time is around 0.5 Gy/day-1.0 Gy/day, which may be administered as a second daily fraction, respecting the minimum interval of six hours between the fractions, without the extra dose generating even more additional days of treatment[14].

Thus, the treatment duration can be used as a the quality of care criteria. The recommendation, according to the treatment protocol used worldwide, the National Comprehensive Cancer Network (NCCN), regarding the time of treatment for patients with head and neck tumors, is that the interval between the surgical resection and the beginning of adjuvant RT should be preferably less than six weeks[16]. However, despite the NCCN recommendation, among the variables that compose the timeline of the adjuvant treatment (duration of RT, the interval between the surgery and the beginning of RT, or total time of treatment from the surgery to the conclusion of RT), one whose oncologic results are still unclear, with a lack of consensus in published studies, is the variation of time between the surgery and the beginning of adjuvant RT[17].

After analyzing the studies related to the subject published in the literature up to now, we found great heterogeneity of results, starting with the threshold of time established as safe between the surgery and the beginning of RT. The RTOG 95016 study established in its protocol that adjuvant RT should be initiated within eight weeks of the surgery, but other studies suggest intervals of six weeks at most, while others

Author	Year	Design	Cut-of	N	OS	LRC
Schiff et al.[19]	1990	Retrospective	0-6 weeks. *vs.* >6 weeks.	111	NM	5 years 88% *vs.* 73% (p=0.11)
Ang et al.[13]	2001	Analysis Retrospective	0-31 days *vs.* >31 days	151	5 years 47% *vs.* 20% (p=0.01)	5 years 72% *vs.* 48% (p=0.05)
Langendijk et al.[20]	2003	Retrospective	0-6 weeks. *vs.* 6-8 weeks. *vs.* >8 weeks.	217	3 years 79% *vs.* 73% *vs.* 73% p NS	3 years 57% *vs.* 57% *vs.* 60% p NS
Huang et al.[8]	2003	Systematic review	0-6 weeks. *vs.* >6 weeks.	851	5 years 61% *vs.* 39% (p=0.046)	OR 2.89 (95% IC 1.60-5.21) for an interval of >6.
Graboyes et al.[17]	2017	Retrospective	0-6 weeks. *vs.* >6 weeks.	41,291	5 years 69.4% *vs.* 64.3% (p<0.001)	NM

LRC = locoregional control; N = number of patients analyzed; NM = not mentioned; OS = overall survival; NS= not significative; OR= odds ratio

suggest seven weeks[18,19]. Regarding the oncological outcomes of locoregional control or survival, previous studies have also shown heterogeneous results, with some reporting influence in local control and survival[13.17], and others without the same finding[19,20]. This diversity demonstrates clearly that there is no consensus in determining the appropriate threshold of time until the beginning of postoperative RT, as seen in the table 1.

However, the TTT, defined as the period starting from the date of the surgery to the last day of RT, appears in published studies as a prognostic factor, with the more negative effects on the therapeutic outcome, the more extensive its duration. Parsons et al.[21] have evaluated the influence of intervals that make up the treatment of patients with tumors of the oral cavity who underwent surgical resection followed by adjuvant RT, detecting better rates of locoregional control when the total treatment did not exceed 100 days (14% versus 60%, p=0.04). Similarly, Rosenthal et al.[22] assessed the importance of the time variables that comprise the total treatment duration of patients with head and neck cancer submitted to surgery followed by adjuvant RT, detecting better rates of locoregional control and overall survival in patients who completed the TTT in 100 days.

For this reason, accelerated fractionation, reducing the TTT and decreasing the chance of tumor cell repopulation, is capable of producing better oncologic results when compared to usual radiotherapy fractionation, as documented by several authors[23.24]. A collaborative

Study between the UTMDACC, H Lee Moffitt Cancer Center, and Mayo Clinic randomized patients to receive 63 Gy in 35 fractions of 1.8 Gy administered for seven *versus* five weeks (five weekly fractions for three weeks and then two fractions daily for two weeks) with better rates of locoregional control and survival in the group of accelerated fractionation[13]. The study also showed that the prolonged interval between surgery and RT had a significant impact on the rates of locoregional control and survival of patients who received RT with conventional fractionation, but did not affect the patients who received RT with accelerated fractionation, demonstrating that the total duration of the combined treatment can significantly affect the rates of local control and survival. Thus, the authors recommendation was to aime the TTT as short as possible. Awwad et al.[25] randomized patients to receive 60 Gy in 30 fractions over 20 days *versus* 46.2 Gy in 33 fractions over 12 days in a postoperative scenario and noticed that the accelerated regime had higher rates of locoregional control; with the total treatment duration being the impacting factor for that outcome. They found no influence of the time between surgery and RT on the locoregional recurrence rates for both groups, and the best results were obtained when the total treatment time was less than or equal to 10 weeks (p=0.005).

A prolonged TTT can even override a possible benefit from the escalation of treatment dose, as demonstrated by a study conducted atUniversity of Texas, MD Anderson Cancer Center[26]. They presented the results of 20 years of follow-up of a prospective randomized study after randomizing 246 patients to receive a dose of 57.6 Gy/32 fractions *versus* 63 Gy/35 fractions for volumes considered as intermediate risk, and 63 Gy/35 fractions versus 68.4 Gy/38 fractions for high-risk volumes. The authors found no significant difference in the rates of locoregional control and overall survival between the different levels of dose, both intermediate and high-risk groups. However, they noted influence of the total duration of the treatment on the results, with prolonged treatment responsible for lower rates of tumor control, cancer specific survival, and overall survival. The authors speculated that the dose escalation was not successful due to cell regeneration during the extended time for greater delivery of the dose, with tumor repopulation nullifying any advantage gained by the increase of dose.

CONCLUSION

In the same way that certain tumor factors may affect the prognosis of patients with squamous cell carcinoma of the head and neck, some therapeutic factors, such as the total time of treatment, the duration of RT, and possible interruption of radiotherapy are also capable of impacting therapeutic results and, therefore, must be rigorously orchestrated in order to avoid overlapping losses for these patients.

The results found in this review can assist in the organization and dynamics of treatment centers, aiming to improve medical assistance to patients with head and neck cancer submitted to surgery and adjuvant RT in order to ensure that some treatment factors do not negatively influence the oncological outcomes of patients.

Contribution of the authors

Rejane Franco - Literature review and data compilation. Gustavo Nader Marta - Literature review, data compilation, and article revision.

RESUMO

INTRODUÇÃO: *A radioterapia (RT) tem importante papel no tratamento dos pacientes com neoplasia de cabeça e pescoço, sendo frequentemente utilizada como terapia adjuvante a fim de diminuir a probabilidade de recorrência local. O presente estudo tem o objetivo de realizar uma revisão da literatura para avaliar os fatores terapêuticos temporais que possam ter influência sobre os desfechos clínicos dos pacientes com neoplasia avançada de cabeça e pescoço tratados com RT adjuvante.*

RESULTADOS: *As variáveis terapêuticas, como o tempo total do tratamento, a duração da RT e a ausência de interrupções durante o tratamento radioterápico são capazes de impactar o resultado clínico dos pacientes.*

CONCLUSÕES: *Da mesma forma que determinados fatores tumorais podem afetar o prognóstico de pacientes com carcinoma de células escamosas de cabeça e pescoço, alguns fatores terapêuticos temporais também constituem fatores prognósticos e, portanto, devem ser rigorosamente orquestrados a fim de se evitarem prejuízos sobrepostos para esses pacientes.*

PALAVRAS-CHAVE: *Neoplasias de cabeça e pescoço. Radioterapia. Carcinoma de células escamosas. Prognóstico. Literatura de revisão como assunto.*

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Comments: "The use of high-resolution MRI to detect thrombosis and lipid-rich carotid artery plaques in a patient with homozygous familial hypercholesterolemia: a case report"

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Dear Editor,We read with great interest the study by Wang et al.[1] in which they demonstrated that high-resolution multi-contrast MRI played an excellent role in identifying carotid plaque components in a patient with homozygous familial hypercholesterolemia (HoFH). The authors indicate that data on carotid plaque burden may provide some information on patients with HoFH. In our opinion, we should combine a large number of relevant clinical cases to verify this.

Firstly, it is novel and innovative to use high-resolution MRI testing for plaque histology of patients with HoFH. Although the diagnostic accuracy of MRI is superior to CT in detecting thymomas, there is only one case included in present study[2]. Thus, more patients with HoFH should be recruited in future studies.

Secondly, high-resolution MRI has the ability to qualitatively and quantitatively evaluate the main components of advanced carotid atherosclerotic plaques. However, familial hypercholesterolemia is often perceived and described as underdiagnosed and undertreated[3]. In this kind of patient with major symptoms, CT would be treated directly with endarterectomy, with no change of the treatment given by the MRI.

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