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Practices and policies of health promotion in Brazil: context, challenges, and potentialities

Marcos Bagrichevsky[1]* ⓘ

Thinking about health and disease, consistently interpreting its multiple meanings – as phenomena connected to the social, economic, cultural events of everyday life – represents a challenging task, above all, from an interdisciplinary perspective. This is a permanent commitment of the multi-professional health teams that make up the "first level of care" in the Brazilian Unified Health System (SUS), also called the "gateway to the system" or "Primary Health Care (PHC)"[1].

The context of the peripheral territories in Brazil in which the PHC teams work is the feature of places almost always riddled with inequities, violence, and historically outside the reach of resolutive social policies. For obvious reasons, this situation needs to be considered, problematized and included in the *continuum* of "expanded therapeutic projects" in health that are aimed at the comprehensive and equitable care of people/populations linked to such territories[2].

The incorporation of this set of premises by PHC professionals (including family and community doctors) is one of the SUS guidelines. The regular adoption of this practice in the work process of the PHC teams has, for some time, shown to have significant implications in addressing local and regional health problems[2-4].

The implantation of SUS in the early 1990s leveraged the transformation of the health care model in the country. The development of a culture of 'other practices' in PHC, in tune with the dimension of the 'extended look' on the health-illness process, has come to give an increasing role to **health promotion** as a field inducing 'differentiated ways' of thinking and producing care in the daily experiences of services[5].

Critical currents of Brazilian thinkers and sanitarians have credited health promotion, the potential to become a valuable counterpoint to the hegemonic biomedical model of assistance and its medicalizing logic. Almeida-Filho[6], for example,

postulates that this is one of the great challenges to be faced by professionals and managers who work in the public health field.

For the services to be able to obtain **health promotion actions** appropriate to our conjuncture of micro-realities, it is necessary to attend and articulate two essential tasks in the PHC routine:

(i) to reflect on the ethical-political assumptions that guide such practices; and

(ii) to consider the need to reconfigure traditional pedagogical enterprises, which are still dominant in the 'health education' activities used along with population groups[7].

The **critical perspective of health promotion in Brazil**[5-7] calls for both actions, programs, and policies (inside and outside the health sector) to improve the structural conditions of society[8,9], and for opening up to the context of 'non-medicalized' life that requires a continuous production of strategies to value and enable listening, welcoming, and the subjects' singularities[10]. And both dimensions are not mutually exclusive, it is good to say. On the contrary, they converge and add up towards a politicizing project, socially relevant, but without the naive pretension of becoming the 'salvation' for all the 'evils' that affect our collectives.

Concerning this second facet, demedicalization and respect for human subjectivities, it is essential that the repertoire of devices used by PHC professionals contemplate/accept the aspects that give existential meaning to people, families, as the primacy of comprehensive health care processes concern and are intended for them. Their priorities and life aspirations must not be discarded or 'objectified', even in the face of extreme illness situations[11]. Sector managers also play a strategic role in this context and need to be committed to the same guidelines, developing them daily, *pari passu* with services.

[1]Universidade Regional de Blumenau – Blumenau (SC), Brazil.
*Corresponding author: marcos_bagrichevsky@yahoo.com.br

The challenges facing the Brazilian social and health scenario are complex and numerous. They require from the field of health promotion (and those who pass through it) the construction of 'operational' paths that privilege, at the same time, a sensitive and equitable view of reality. Equally important is the need to institutionalize these initiatives, which need to gain public visibility and be more prestigious/recognized in the services, as well as the professionals who plan and conduct these processes[11,12].

In this sense, I raise a question addressed to those who occupy positions in the formulation/management of health policies in our country: why not grant the health workers responsible for **health promotion groups/projec**ts[13] in the territories of PHC, the same "cash prizes"* formally allocated to health teams that obtain a reduction in epidemiological indicators of morbidity and mortality? In general terms, the structured proposals for health promotion are long-lasting, obtain long-term adherence from group/project goers, promote bonding, create spaces for listening, sociability, and politicization in communities. In other words, there are plenty of concrete and plausible reasons for them to be recognized and 'made official' by the administrative bodies of the health secretariats of Brazilian municipalities, as powerful and resolving actions. Despite being characterized as an old claim of professionals who work with health promotion in PHC, the question raised here also expresses a recurring dilemma from which managers cannot escape: how to define adequate choices (conceptual and methodological) for coping with different health problems present in the communities, wherein in the balance of 'objectivity *versus* subjectivity' only the first one mostly guides decision-making?

But, despite the existence of ethical-political aspects such as the one here highlighted and problematized briefly in the text (and which deserve to be discussed in depth!), it is worth saying that in the last decade and a half we have accumulated countless successful health promotion experiences conducted by health teams, across the country[13-15]. The record of its growing presence in the PHC territories indicates two aspects:

(i) the extent to which health promotion interventions can contribute to the well-being of local populations and mitigate the difficulties that they face and prevent full, continuous care; and

(ii) that we have reached an interesting status towards the consolidation of a recommended health care model and that we want for SUS[11,12].

The **counter-hegemonic health promotion approaches** shared in the PHC territories have as their primary guideline the ethical dimension of the subjects 'and collectivities' lives. They bring with them concepts that are essential to health care that presuppose the ability to dialogue between different knowledge and practices. Such understanding demands much more from the actors in the sector than the use of tools to map health problems; they expect an interdisciplinary interpretative analysis that also seeks to consider the complexity of the health-disease process and all the modes of subjectification that it mobilizes; that detaches from more immediate meanings (those traditionally expected by the biomedical model), and it is capable of expressing a more detailed, sensitive, and deep condition that each situation examined requires.

The final balance I make of these contemporary perspectives in Brazil points out dense and well-trodden paths. These are recent transformations; it is true but noteworthy! The permanent debate around the National Health Promotion Policy (NHPP)[5] evoked by different actors in society and the resulting repercussions illustrate my point of view: first published in 2006, NHPP has already undergone its second review in 2014, exhibiting since then, expressive textual changes in content and number[5]. Some of them have even 'officially' recognized the role of modes of subjectification in the composition of therapeutic care projects – a concern that did not exist in the first version of the NHPP (2006)[5]. Indeed, there is still much to do, what to fight for, in policies and services. Nonetheless, even in the face of the recent Brazilian situation that inspires a certain amount of pragmatism, we have marked advances that deserve our recognition!

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*At Brazilian Unified Health System (SUS), since 2011 there has been a government initiative called "Program for Improving Access and Quality in Primary Care" (PMAQ-AB, the initials into Portuguese) that pays cash bonuses to PHC health professionals/teams who achieve 'productivity goals' regarding improving epidemiological indicators recommended by the Ministry of Health. The recurring criticism is that there is nothing similar proposed to 'value likewise' the professionals who work continuously with "health promotion actions/groups" and/or with the subjective dimensions of care and who are also known to be successful through respective 'expanded therapeutic projects.

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COVID-19 and Hashimoto's Disease

Aydan Cevik Varol[1] , Uras Hatice[2]* , Selim Gorgun[3]

Dear Editor,

Hashimoto's thyroiditis is a common autoimmune disorder of the thyroid gland. Consequently, it has been linked to infections such as hepatitis C, EBV, HTLV-1, parvovirus B19, *Yersinia enterocolitica*, and coxsackie viruses. As COVID-19 has been associated with a few spectra of autoimmune diseases, we investigated the potential role of COVID-19 infection in inducing Hashimoto's thyroiditis[1].

A 36-year-old Turkish woman who worked as a laboratory assistant with no other chronic illnesses, and unknown COVID-19 exposure presented to the emergency department with a 2-day history of fatigue, loss in taste, and abdominal discomfort. She was afebrile and had a respiratory rate of 18 breaths per minute and oxygen saturation of 95% while she was breathing ambient air, the abdominal examination was normal. An oropharyngeal swab for COVID-19 testing was positive. After ten days, she reported complete resolution of her symptoms but complained of neck pain and constipation. Before the symptoms began, she was denied any personal or family history of autoimmune or thyroid disease.

On examination, the patient was afebrile and hemodynamically stable with no bradycardia or hypothermia. Cardiac, respiratory, abdominal, and neurological examinations were unremarkable, and the patient was clinically euthyroid with no goiter. Her thyroid function test (TFT) showed an elevated thyroid-stimulating hormone (TSH) reading of 0.012 mIU/mL (0.55–4.56), free T3 (fT3) level of 11.54 pg/ml (2–4.4) and a free T4 (fT4) level of 5.26 ng/L (0.78–1.76). Her TSH receptor antibodies were 2.71 IU/L (<1.75), her Anti-TPO level was 276 IU/mL (0.35), and her Anti Tiroglobulin level was 267.6 IU/ml (0–115). There was no anemia; her electrolyte levels, vitamin D, and B12 levels were normal. Her thyroid ultrasound showed her right thyroid

lobe as 16x20x33 mm, the left thyroid lobe was 16x21x29 mm, and Isthmus thickness was 7.5 mm. Both of her thyroid sizes are diffusely increased. Micronodular appearance and septal thickening were observed in the parenchyma. A hypoechoic nodular appearance of 9x4.5 mm was observed in the parathyroid region adjacent to the lower pole of the left lobe. One week later, when the patient's thyroid hormone levels were checked, her thyroid function test (TFT) showed a thyroid-stimulating hormone (TSH) level of 0.01 mIU/mL (0.55–4.56), free T3 (fT3) level of 3.13 pg/mL (2–4.4) and a free T4 (fT4) level of 1.12 ng/L (0.78–1.76). Our patient was diagnosed with Hashimoto thyroiditis due to clinical and laboratory findings and positive thyroid autoantibodies.

The patient was started on oral levothyroxine 25 mcg once a day and was counseled about her diagnosis of Hashimoto's thyroiditis. Four weeks later, the patient reported that she felt energized and had started running regularly. Her TFT was still deranged but had improved (fT3 4 pg/mL, fT4 1.7 ng/L; TSH 4.3 mIU/mL)

As the mounting evidence suggests a role of viral infection in the emergence of Hashimoto's thyroiditis, we have shown that there may be a positive correlation that COVID-19 infection is involved in the pathogenesis of some cases of Hashimoto's thyroiditis[2]. Ultimately, although the present study may demonstrate an association between COVID-19 and Hashimoto's thyroiditis, more detailed researches with a more specialized examination and precise consideration of COVID-19 species, and investigation of environmental factors are needed[3].

AUTHORS' CONTRIBUTIONS

VCA: Supervision. **UHB:** Writing – original draft. **GS:** Data curation, Formal Analysis, Supervision.

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[1]Ibn-i Sina Health Center – Tekirdag, Turkey.
[2]Erdem Hospital, Microbiology and Biochemistry Laboratories – Istanbul, Turkey.
[3]Samsun Training and Research Hospital, Microbiology and Biochemistry Laboratories – Samsun, Turkey.
*Corresponding author: busehaticeuras@gmail.com

Physical activity for health and use of face masks in the COVID-19 pandemic

Francisco José Gondim Pitanga[1,2]* (iD), Marcus Paulo Brito[2,3] (iD), Maguino Santos Silva[2,4] (iD),
Jorge Medeiros Gomes[2,4] (iD), Roque Aras Júnior[5] (iD), Carlos Fernando de Amorim Alves[2,3] (iD),
Alex Cleber Improta Caria[2,5] (iD)

INTRODUCTION

Since the appearance in December 2019 in the city of Wuhan, China, the new coronavirus (COVID-19) has been growing exponentially worldwide, to the point where the World Health Organization (WHO) declared in January 2020 that the outbreak of the disease constituted a public health emergency of international importance — the highest level of alert in the organization, as provided for in international health regulations[1].

On March 11, 2020, COVID-19 was characterized by WHO as a pandemic. The high infectivity of its etiological agent, the new coronavirus, combined with the activity of the attenuated immune system in many individuals and the lack of a vaccine, made the number of cases grow exponentially[2]. Worldwide, by December 10, 2020, 68.,165.877 cases of COVID-19 have been confirmed, with 1,557.385 deaths[1]. This situation has led several agencies and governments around the world to publish documents and decrees proposing social isolation, the closure of several commercial and leisure spaces, including in many cities, spaces for physical activity. In addition to these measures, care with personal hygiene such as constant hand washing, use of gel alcohol and more recently the use of masks, even for non-infected people, has become the new routine for a large part of the world population[2].

Until the discovery of a vaccine for COVID-19, and also as a protective factor for future pandemics, it seems to be very important to maintain habits that strengthen the immune system and mental health. In this regard, physical activity stands out and its broad scientific evidence shows its effectiveness in the prevention and treatment of cardiovascular, metabolic, and psychological events. Physical activity has an inverse association with blood pressure levels, diabetes, lipid changes, and risk of coronary artery disease and other cardiovascular events[3,4].

Another point observed concerns the impacts on mental health. People who, even in quarantine, remained physically active showed a protective factor for self-esteem, resilience to stress and depression[5].

According to this new reality, the practice of physical activity should undergo some adaptations, including the use of face protection masks outside the home environment. This situation raises questions about the safety, comfort, and efficiency of facial masks during the practice of physical activity. Physical exercise with face masks can reduce the available oxygen and increase air retention, preventing an efficient exchange of carbon dioxide, especially in higher intensity activities[6].

Thus, the objectives of this point of view are to highlight the importance of physical activity in strengthening the immune system and mental health, in addition to analyzing the necessary adaptations to its practice, taking into account the use of face protection masks during the pandemic COVID-19.

Benefits of physical activity and use of face masks during your practice

Regular practice of physical activities and/or physical exercises is an extremely important factor for maintaining or improving the structure and functionality of various organs and bodily

[1]Universidade Federal da Bahia, Instituto de Saúde Coletiva – Salvador (BA), Brazil.
[2]Sociedade Brasileira de Cardiologia Seção Bahia, Departamento de Educação Física – Salvador (BA), Brazil.
[3]Universidade Católica de Salvador – Salvador (BA), Brazil.
[4]Universidade Federal da Bahia, Departamento de Ortopedia e Traumatologia – Salvador (BA), Brazil.
[5]Universidade Federal da Bahia, Faculdade de Medicina da Bahia, Departamento de Medicina e Saúde – Salvador (BA), Brazil.
*Corresponding author: pitanga@lognet.com.br

systems, such as brain, inducing neuroplasticity[7] and neurogenesis[8], heart (modifying its phenotype, promoting hypertrophy beneficial eccentric, concentric or mixed, depending on the type of physical exercise)[9,10] and modulation of several genes that work to improve the cardiovascular, metabolic, neuroendocrine, respiratory, immune systems, among others[11].

Although several scientific pieces of evidence demonstrate the importance of physical activity and/or physical exercise as a protective factor for human health in general, there is still no evidence about its role in individuals infected with COVID-19. However, researchers point to the need to remain physically active and reduce sedentary behavior[12], in addition to suggesting that physical activity is recognized as essential during the pandemic period[13]. Thus, physical exercise becomes a potential therapy to combat physical and mental consequences of social isolation[14], as well as inhibit other comorbidities and diseases associated with physical inactivity, for example, overweight and obesity[15].

Thus, it is evident that the maintenance of regular practice of physical activities can be considered essential for asymptomatic individuals in this quarantine period, however, new conducts and precautions must be adopted to perform these activities[16], especially outdoors, such as hygiene of hands and use of facial masks[2].

The use of facial masks can be extremely unpleasant during physical activities or physical exercises, given that during the practice of these, oxygen consumption and gas exchange are increased, with the use of the mask, which can hinder these processes[17]. In this context, some doubts arose about the possible physiological changes that can occur in the human body during physical exercises using the face mask.

In this sense, for some time, and regardless of the current pandemic, some studies showed that the use of facial masks is beneficial for cardiovascular and pulmonary health during physical activity, since they reduce exposure to air pollution[18], although they also report that masks reduce human performance during physical effort, impairing breathing, thermal balance, among other psychological factors[19]. In these studies, highly efficient face mask filters were used (dust respirator 8812, 3M, St Paul USA18), while in the review study19 different types of filtration masks, quarter masks, full mask, respirators with an air-purifying filter, respirators with air supply, air-purifying respirators powered by a blower and self-contained breathing apparatus were used.

Researchers identified that performing aerobic physical exercise in light to moderate intensity, using the N95 type surgical face mask, does not increase the subjective perception of effort and neither the perception of heat in the group of individuals who were using the mask compared to a group without a mask, however, demonstrated that heart rate, respiratory rate, and transcutaneous carbon dioxide increased slightly in the group of individuals who performed exercises with the mask, and also observed a decrease in the temperature of the facial skin in the uncovered area, while the area covered by the mask showed an increase in temperature. Thus, the authors concluded that wearing a mask in low- to moderate-intensity physical activity is not associated with a clinically significant physiological impact or with significant subjective perceptions of effort or heat[20].

In another study, researchers compared a group of individuals who underwent strength training with an airflow restriction face mask and another group without a mask. In this study, it was evidenced that the use of the facial mask reduces muscular performance and increases the levels of perceived effort[21].

Therefore, despite being an indispensable material to minimize the risks of infection and transmission of COVID-19 more studies are needed to assess the impact of using facial masks during physical activities and/or physical exercises on neurological, psychological, cardiovascular, respiratory, and metabolic parameters.

Possible physiological responses to the use of facial masks during physical activity

With the scarcity of studies on the physiological effects of wearing a facial mask during physical activity, some hypotheses are suggested in this context. For example, the use of a face mask can induce a hypoxia environment [inadequate exchange of oxygen (O_2) and carbon dioxide (CO_2)], especially in higher intensity physical activities. In addition, this environment can become more acidic, both at the alveolar level and in the blood vessels, inducing numerous physiological changes, impairing muscle metabolism, cardiorespiratory, excretory system, modifying mechanisms of the immune system and the nervous system[6].

The face mask forms a closed circuit for inspired and exhaled air, although not completely airtight. The rebreathing of exhaled air would probably increase arterial CO_2 concentrations, increasing acidity in the environment. As a consequence, discomfort, fatigue, dizziness, headache, shortness of breath, muscle weakness and drowsiness can be generated[6].

The resistance offered to inspiratory and expiratory flow, for prolonged periods, can result in respiratory alkalosis, increased lactate levels, and early fatigue. In addition, there can also be an exponential increase in heart rate and blood pressure, with a consequent increase in aortic pressure and left ventricular pressure, causing an increase in cardiac overload and coronary demand. It is important to note that all of these hypotheses are more specifically related to higher intensity physical activity[6].

Recommendations for physical activity with the use of masks

Considering that the face mask is recognized as an important element to avoid contagion by COVID-19, it is suggested that physical activity outdoors or in any environment outside the home should be maintained, preferably at mild and moderate intensities, and with the use of masks, in addition to respect of social distance. It is noteworthy that low to moderate-intensity physical activity would be the most recommended to reduce the possible adverse effects of breathing with a mask. In addition, considering that there are several types of masks, it is suggested to use a model that is more comfortable considering, even, that double-sided masks cause greater difficulty in breathing. It is also suggested to change the mask whenever it is wet due to the practice of physical activity. When experiencing symptoms of dizziness, imbalance, excessive fatigue, and shortness of breath, it is advisable to stop or reduce the intensity of physical activity until the symptoms subside. In addition, it is recommended that people with heart disease choose to perform physical activity at home during the pandemic period.

CONCLUSIONS

According to the various articles that supported this point of view, the use of facial masks during a physical activity at light or moderate intensity, and when performed outdoors or in any environment outside the home seems to be an important strategy to avoid contagion by COVID-19.

AUTHORS' CONTRIBUTIONS

FJGP: Data curation, Supervision, Writing – original draft. Writing – review & editing. **MPB:** Data curation, Writing – original draft. **MSS:** Data curation, Writing – original draft. **JMG:** Data curation, Writing – original draft. **RAJ:** Supervision. **CFAA:** Supervision. **ACIC:** Data curation, Supervision, Writing – original draft. Writing – review & editing.

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Relationship between the intensive care unit beds and mortality by COVID-19 in Brazil

Carlos Dornels Freire de Souza[1]* (iD), Gibson Barros de Almeida Santana[1] (iD),
Thiago Cavalcanti Leal[1] (iD), João Paulo Silva de Paiva[1] (iD), Leonardo Feitosa da Silva[1] (iD),
Lucas Gomes Santos[1] (iD), Victor Santana Santos[2] (iD), Rodrigo Feliciano do Carmo[3] (iD)

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly infectious disease, which may progress rapidly to pneumonia or acute respiratory distress syndrome (ARDS), requiring mechanical ventilatory support in intensive care units (ICU)[1]. As the disease spreads rapidly and the fatality rate is high among patients with severe conditions, the availability of ICU beds has been considered as one of the strategies to face the disease and avoid deaths[1-3].

Globally, COVID-19 has affected more than 3 million people and caused more than 225,000 deaths in the first quarter of 2020[4]. The number of deaths has been high even in countries with well-structured health systems or having high number of ICU beds for severe cases[4]. As the disease spreads to low- and middle-income countries, we better understand the differential effects of COVID-19 according to socioeconomic positions.

Due to the community transmission of COVID-19, the number of cases and deaths increased exponentially and in April 4, 2020 more than 100,000 cases and 7,000 deaths had already been detected across Brazil. Brazil has 32,757 adult ICU beds, of which 45% of them allocated to the Unified Health System (Sistema Único de Saúde [SUS], in Portuguese), which are concentrated in states with better socioeconomic conditions[5].

Thus, this study described the distribution of ICU beds and its relationship with the mortality rate due to COVID-19 in Brazil until the pandemic stage.

METHODS

We conducted an ecological study referring to all COVID-19 deaths from March 17 to April 24, 2020 and their relationship with ICU bed availability indicators in Brazil.

Data were obtained from three different sources. Data on deaths were obtained from the Brazilian Ministry of Health on April 24, 2020. Information on the number of beds for each state was obtained from the National Registry of Health Establishments (CNES) and population data from the Brazilian Institute of Geography and Statistics (IBGE). From the data, we calculated for each state the mortality rate per 1 million population, the general rate of ICU beds for adults per 100,000 population, and the rate of ICU beds for adults per 100,000 population allocated in the public and private health systems. It is important to note that the case fatality rate was not analyzed since the low availability of the tests results in overestimated rates.

Moran's bivariate spatial correlation model and multivariate regression (ordinary least square) were used to verify the spatial relationship between the availability of ICU beds, the number of deaths, and the mortality rate of the states. In the regression analysis of the mortality rate, adjustment was made for the total number of deaths. A 95% confidence interval and a 5% significance level were adopted. This study did not require the approval of the Research Ethics Committee since we used public domain data.

[1]Universidade Federal de Alagoas, Department of Medicine – Arapiraca (AL), Brazil.
[2]Universidade Federal de Alagoas, Center for Epidemiology and Public Health – Arapiraca (AL), Brazil.
[3]Universidade Federal do Vale de São Francisco, Department of Pharmacy – Petrolina (PE), Brazil.
*Corresponding author: carlos.freire@arapiraca.ufal.br

RESULTS

Between Mach 17 and April 24, 2020, Brazil accounted for 3,670 deaths by COVID-19. The highest numbers of deaths were recorded in São Paulo (n=1.512), Rio de Janeiro (n=570), and Pernambuco (n=352) states, respectively. Amazonas state has the highest mortality rate (60.14 deaths/1 million; 255 deaths), followed by Pernambuco (36.47/1 million; 352 deaths), Rio de Janeiro (33.64/1 million; 570 deaths), São Paulo (32.82/1 million; 1512 deaths), and Ceará (30.94/1 million; 284 deaths).

Overall, the Federal District had the highest rate of adult ICU beds per 100,000 population (107.6/100,000) and Roraima state had the lowest rate (4.1/100,000). Considering only SUS adult ICU beds, Minas Gerais (12.5/100,000) and São Paulo (12.2/100,000) had the highest rates, while Amapá state had the lowest rate (1.5/100,000). In the private health network, the highest rates were observed in the Federal District (347.8/100,000 users) and Mato Grosso (66.3/100,000 users).

A significant correlation was observed between the number of deaths and the rate of ICU beds for adults per 100,000 population (Moran's I=0.157275; p=0.02) and the rate of ICU beds for adults per 100,000 population allocated in the private health system (Moran's I=0.157916; p=0.04). No significance was observed in the multivariate regression model (Figure 1).

An inverse correlation between the COVID-19 mortality rate and the rate of adult ICU beds in public health services was demonstrated in both bivariate (Moran's I= -0.136756; p=0.03) and multivariate (coefficient=-0.4073; p=0.035) analysis. There was no correlation between COVID-19 mortality and the rate of adult ICU beds available in private health services (Figure 2).
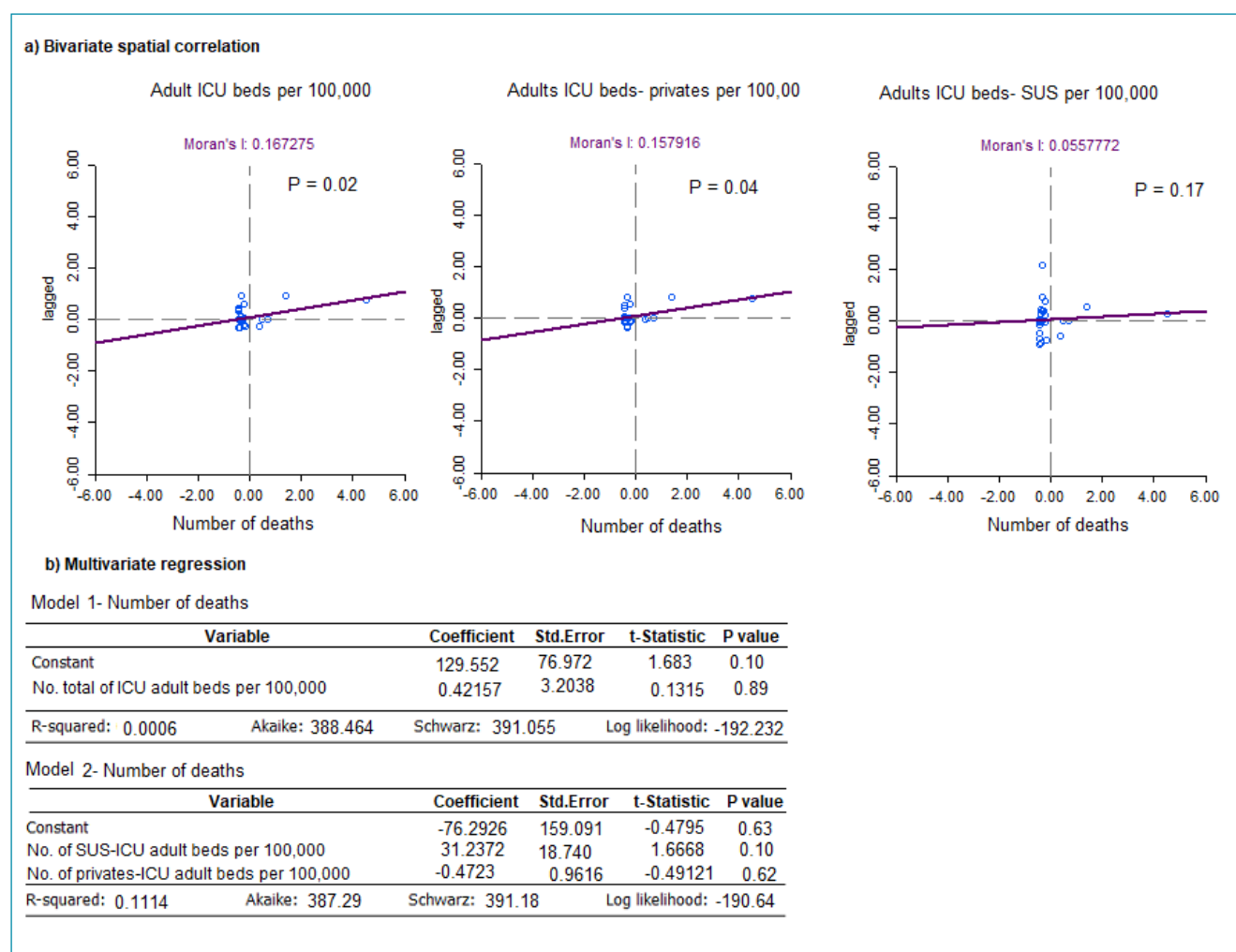
Figure 1. Bivariate spatial correlation and multivariate regression between the number of deaths by COVID-19 and the availability of intensive care units beds in Brazil, 2020. COVID-19, coronavirus disease 2019; intensive care units; SUS, Sistema Único de Saúde.
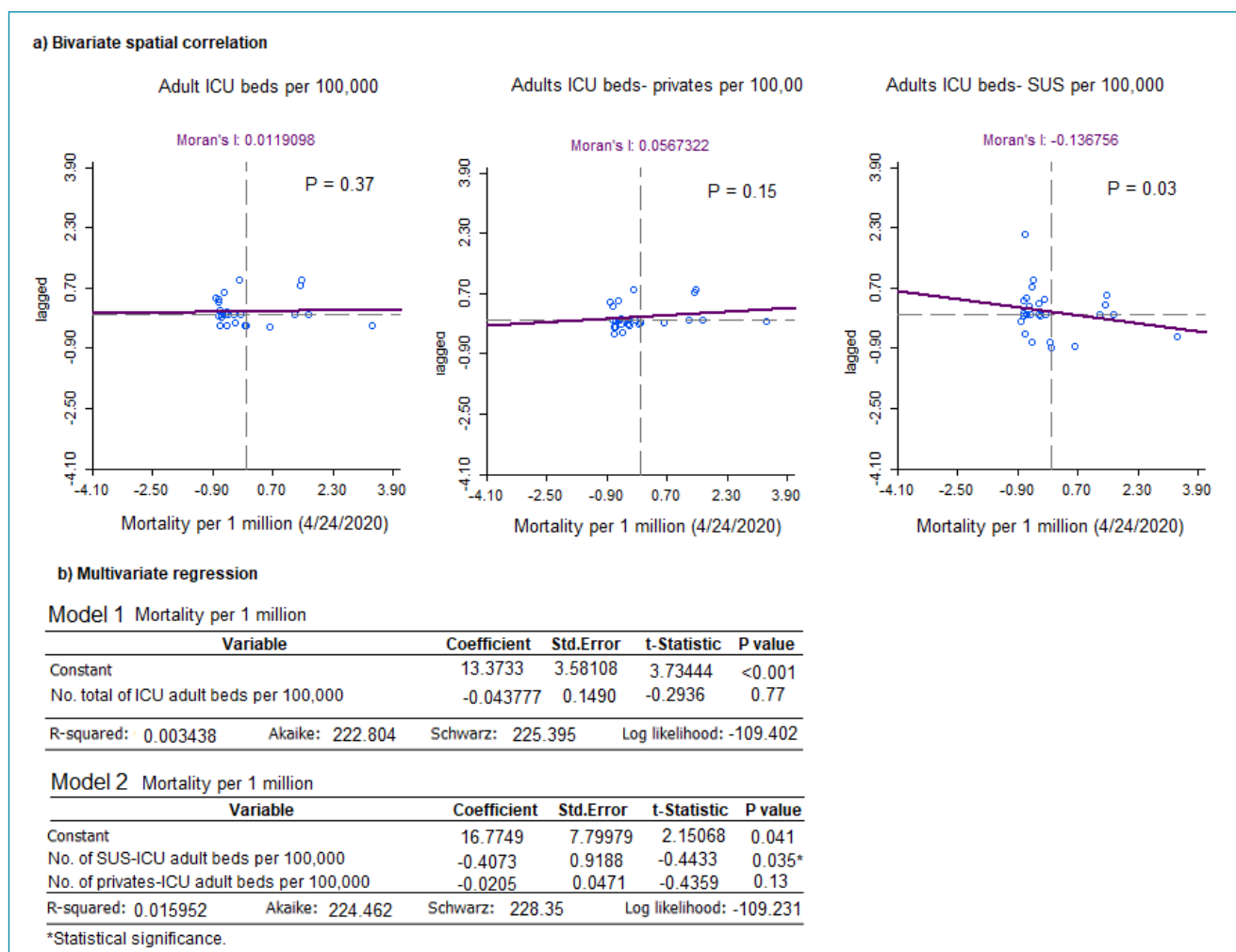
Figure 2. Bivariate spatial correlation and multivariate regression between the mortality rate by COVID-19 and the availability of intensive care unit beds in Brazil, 2020. COVID-19, coronavirus disease 2019; intensive care unit; SUS, Sistema Único de Saúde.

DISCUSSION

This study showed that the distribution of adult ICU beds in Brazil occurs heterogeneously among the Brazilian states. In addition, there was an inverse relationship between the mortality rate due to COVID-19 and the adult ICU rate in public services.

Brazil has considerable social, economic, and health resource disparities among the states. Despite the wide network of health services, which includes 5,922 hospitals and 563 public health laboratories[6,7], there are inequities in the distribution of these resources. States located in the North and Northeast regions historically had the highest inequalities regarding the provision of health services.

The North region presents one of the worst social and health conditions, including low human development in 46% of the municipalities, low number of physicians per 100,000 population,

and a pragmatic social vulnerability[8-10]. In addition, this study found that North region has the lowest number of ICU beds (n=1,331) and the lowest proportion of SUS beds per population (0.9 bed per 100,000 population). In Amazonas state–one of the states most affected by COVID-19 pandemic–the ratio of physicians working in municipalities distant from the capital Manus city is 0.2 per 100,000 inhabitants and Amazonas has only 271 ICU beds as reference to approximately 4.2 million people, resulting in a rate of 6.5/100,000 population. In addition, 182 of 271 adult ICU beds are available for SUS patients (5.0/100,000)[5,7].

Similar to the North region, the Northeast region has poor social and health conditions and the COVID-19 crisis has exacerbated the health problems[10]. For example, the states of Pernambuco, Ceará, and Piauí are already presenting a overcrowding of adult ICU beds. On April 30, Pernambuco

state–the state with the second largest number of adult ICU beds in the Northeast region (n=1,382)–already had 99% of the ICU beds in the public service occupied[11].

In Brazil, an estimated 80% of population depends exclusively on health services provided by SUS[8]. Thus, the significant increase in the number of COVID-19 cases, with a consequent increase in the number of critically ill people requiring intensive care, may overburden the public health system. This situation can be aggravated by the fact that 75% of health regions have insufficient numbers of ICUs to guarantee the care of the population before COVID-19[5]. Regardless of the COVID-19 pandemic, the expectation for ICU beds will certainly increase, as already observed in other countries[12], and this situation would cause more pressure on the public health system. Seriously, the lack of ICU beds would result in increased mortality from both COVID-19 and other diseases requiring hospitalization.

ICU care generates higher costs to the system, and in the case of COVID-19 the costs may be higher because of the long hospital stay of people in treatment for the disease. However, in recent years, the largest health service provider in Brazil has suffered from a lack of public investments; austerity policies, restrictions on public spending, underfunding, and the lack of political interest are obstacles to strengthen the SUS. The Constitutional Amendment No. 95, of December 15, 2016, is an example of this process of reducing the public health system. This amendment prevents the increase in health care costs for 20 years, starting in 2017, and represents the most serious threat to the principles that sustain SUS (Universality, Integrality, and Equity)[13]. In the face of the COVID-19 pandemic, the Brazilian response could be more effective if SUS had received the necessary investments.

Nevertheless, due to the epidemiological scenario installed in Brazil, some measures have been taken by the state authorities. As a strategy for coping with COVID-19, many Brazilian states, because of the low rate of ICU beds, have provisionally constructed field hospitals to exclusively treat COVID-19 patients, spawned a monthly national expense of 10.5 million[14]. However, it is important to note that these field hospitals are temporary structures, and after the pandemic, SUS will continue with the same structural problems as earlier. Therefore, it is of fundamental importance that investments in the public health system are continuous and guarantee the necessary support to its users even after the pandemic.

This study has some limitations. Underreporting may occur since our analyses were performed from secondary data, and they depend on the capacity of health and surveillance services. Another limitation is the lack of data on ICU beds for children. However, we believe that this does not compromise our findings due to the low mortality rate in this age group. In addition, the nonavailability of hospitalization rate represents an important limitation. Thus, the causal relationship cannot be established solely from ecological studies.

CONCLUSIONS

This study showed the importance of ICU beds as a determinant of mortality. It is urgent to expand the care network for patients with COVID-19 and to strengthen other measures that can reduce the transmission curve, relieving the health system. Monitoring of such measures is necessary to provide more information about how the COVID-19 pandemic behaves in a country with disparities in the allocation of health resources like Brazil.

AUTHORS' CONTRIBUTION

CDFS: Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **GBAS:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **TCL:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **JPSP:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **LFS:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **LGS** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **VSS:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing. **RFC:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft, Writing – Review and Editing.

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Imbalance between the cellular proliferation and death in harderian gland of female mice with hyperprolactinemia

Ariadne Stavare Leal Araújo[1] 🆔, Carina Verna[1] 🆔, Osvaldo Pereira Araújo Júnior[2] 🆔,
José Maria Soares Júnior[3] 🆔, Ricardo Santos Simões[3] 🆔, Edmund Chada Baracat[3] 🆔,
Manuel de Jesus Simões[1] 🆔, Regina Célia Teixeira Gomes[1,3]* 🆔

SUMMARY

OBJECTIVE: To assess the impact of the metoclopramide-induced hyperprolactinemia in cellular death and proliferation in the harderian gland of female mice.

METHODS: Twenty female mice were divided into two groups of 10 animals each and treated: 0.2 mL of saline solution (controls, Ctr) and 200 µg of metoclopramide (experimental, hyperprolactinemia), both for 50 consecutive days and at 12:00 a.m. On the 50th day, the female were euthanized, and the harderian glands were removed and processed for immunohistochemistry for detected ki67 and TUNEL method. Data were statistically analyzed by unpaired Student's t test (p<0.05).

RESULTS: The harderian gland of the hyperprolactinemia group showed increase in the immunoexpression of Ki67 and TUNEL compared to the Ctr group (p<0.05), and there was no significant difference in the amount of porphyrin in the HPrl group compared to the Ctr group.

CONCLUSION: The hyperprolactinemia led to increased cell death in the acini the harderian gland and cell proliferation in the stroma glandular, fact that suggesting a reduction process of cellular activity and fibrosis, which suggests impairment in the functioning of the lacrimal harderian.

KEYWORDS: Proliferation, cell. Harderian gland. Mice. Hyperprolactinemia.

INTRODUCTION

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary-gonadal axis[1] and may have physiological causes — pregnancy, nursing, sleep, stress, sexual dysfunctions, or even a pathological cause — a tumor called prolactinoma. Hyperprolactinemia is a condition similar to hypogonadism, since it acts negatively on ovarian function[2-5]. However, the relationship between hyperprolactinemia and the function of the lacrimal (LG) or the harderian glands (HG) is not well defined. Prolactin (PRL) is synthesized and secreted by the adenohypophysis lactotrophs with systemic action in humans[6] and rodents[7-9]. Understanding the endocrine changes in the glands responsible for the formation of the tear film, whether in human or animal models, is essential to understand the effects of hyperprolactinemia. The HG is a pigmented lacrimal gland found in vertebrates that have a nictitating membrane (translucent inner eyelid). The HG is in close association with the intra-orbital LG, and PRL and sex steroid hormones (estrogen

and progesterone) can affect this gland, as it contains receptors for these hormones.

PRL and ovarian hormones (estrogen and progesterone) have been investigated in the animal model (female) so as to provide data for researches with metoclopramide-induced hyperprolactinemia (HPrl). Histological study showed signs of a decreased intra-orbital LG cells activity due to changes in the cell volume of the acinar cells, as well as an increased number of collagen fibers in the connective tissue that supports the LG of female mice with HPrl[5,10]. Those studies are evidence that hyperprolactinemia could lead to processes of cell death or cell proliferation, as well as tissue fibrosis in LG and HG. Tissue homeostasis is an essential physiological phenomenon that ensures a dynamic balance between cell proliferation and cell death in the maintenance and regulation of healthy tissues. Thus, an imbalance in this homeostasis can lead to a decline in the LG and HG function, which consequently contributes to eye dryness, one of the main causes of tear film instability.

This study's main goal was to analyze the cellular proliferation (Ki67) and death (TUNEL method) in the HG of female mice with metoclopramide-induced HPrl.

METHODS

The experiments were carried out at the Histology Discipline of *Universidade Federal de São Paulo* (UNIFESP). The protocols were designed according to the Brazilian College of Animal Experimentation. They were approved by the Institutional Ethics Committee on Animal Experimentation of UNIFESP and Review Board (Report No. 84582409/15). A total of 20 virgin female adult mice, aged 3 months old, *Mus musculus*, and weighing 35–40g were given food and water *ad libitum* at room temperature (22°C) under artificial light with a 12:12 hour light:dark photoperiod (lights on from 7 a.m.–7 p.m.). Thereafter, they were adapted to the new environment for 2 weeks, vaginal smears were collected daily and stained by Harris-Shorr for cytological analysis for evidence of regular estrous cycles[5]. Initially, induction of HPrl was performed, 10 females received subcutaneous injections of 200 μg/day of metoclopramide dissolved in 0.2 mL of saline solution for 50 consecutive days (hyperprolactinemic group, HPrl), and 10 females received subcutaneous injections of 0.2 mL of saline solution for 50 consecutive days (control group, Ctr). The females were always treated at 12:00 p.m. Then, on the 50th day, 1 hour after the last injection, a colpocytological examination of vaginal smears was performed and all animals were euthanized by excessive exposure to an association of muscle relaxant and anesthetic (xylazine 20 mg/kg plus ketamine 100 mg/kg), subcutaneously and, finally, HG were removed (Figure 1) and fixed for 24 hours in 10% formaldehyde in phosphate-buffered saline (PBS) for the immunohistochemistry method (IHC).

Histological processing

After fixation, tissue samples were processed in the histotechnical equipment (Lupe Ltda, Brasil), according to the classic inclusion protocol: dehydration (ethanol), diaphanization (xylol), and impregnation with liquid paraffin, in a drying oven set at 60°C. The paraffin-embedded glands were cut into ten sections of 3μm on a Minot microtome LEICA – RM 2145 (Leica, Germany), adhered in silanized slides at 5%, and dried in an oven at 37°C for 24 hours for detection of the cell proliferation marker (Ki67) and cell death markers (TUNEL method) on HG by immunohistochemical analyses.

Immunohistochemical method

Immunohistochemical analysis was performed for the detection of the proteins: Ki-67 cell proliferation marker (M3064, 1:200, Spring, USA), and cell death marker (TUNEL, in Situ Cell Death Detection Kit, 11684817910 Roche). The paraffin-embedded glands sections were submitted to the classic deparaffinization protocol (three xylol baths for 5 min each), rehydrated (three absolute ethanol baths for 5 min each, and formic acid (one bath for 3 min), washed several times with running water, and then washed thrice with distilled water. Then, the sections were submitted to the IHC protocol: Fist protocol: three sections/animal were submitted to the IHC protocol for detection of Ki67: 1) antigenic recovery was performed with citrate buffer (pH 6.0) at 100°C, in a steam cooker, and sections were washed with PBS (pH 7.4) thrice for 5 min each (washing procedure); 2) endogenous peroxidase was blocked with a 3% H_2O_2 solution at 10 vol./methanol (1:1) for 25 min (washing procedure); 3) non-specific sites were blocked and the cell membrane was permeabilized with 0.5% Tween + 1% bovine serum albumin (BSA)/PBS (pH 7.4) (washing procedure); 4) sections were incubated with *primary antibody* diluted in PBS (pH7.4)/1% BSA for 18 hours in a humidity chamber at 4°C (washing procedure); 5) next, the sections were incubated with the post primary VECTASTAIN® Elite ABC anti-rabbit kits (PK-6101, Vector Laboratories, USA) (incubated with anti-rabbit IgG for 30 min at 37°C, and the same washing process), and again incubated with the avidi/biotin complex for 30 min at 37°C (plus washing process); 6) incubated with the chromogen, diaminobenzidine chromogen (DAB) (DAKO Cytomation, Denmark) for 3 min

(washing process); 7) counterstained with hematoxylin for two minutes, and the sections were washed several times with running water. Finally, the sections were submitted to the classic resin mounting protocol: all sections were immersed in three absolute ethanol baths for five minutes each, after three xylol baths for five minutes each, and then, the slides were covered using Entellan® (Merck, Germany) resin and cover slip. These methods consist of brown-brown staining in the nucleus. Negative controls were obtained by replacing the primary antibody with the respective concentration of non-immune IgG from a different species, Figure 2.

Second protocol: three sections/animal were submitted to the IHC protocol for detection of cell death by the TdT-mediated dUTP-biotin Nick End Labeling (TUNEL – In Situ Cell Death Detection Kit, Roche Diagnostics, 11684795910), carried out according to the manufacturer's instructions:

1) antigenic recovery: sections were subjected to enzymatic antigenic recovery with 20 µg/mL Proteinase K in 10 mM Tris-HCl, pH 7.6 (Gibco, Grand Island, NY, USA), for 20 min at 37°C, and washing procedure; 2) blocking of endogenous peroxidase with a 3% H_2O_2 solution at 10 vol./methanol (1:1) for 25 min (washing procedure); 3) the

sections were incubated with bromodeoxyuridine (BrdU), conjugated biotinylated nucleotides (TdTs), together with biotin/streptavidin conjugated rabbit anti-BrdU antibody, and then covered with parafilm for 60 min at 37°C, protected from light with aluminum foil, and washing procedure; 4) the sections were incubated with the antidigoxygenin peroxidase conjugate (DPC) and then covered with parafilm for 30 min at 37°C, plus washing procedure. Next, the incubation with the chromogen, the counterstaining, and the same assembly and immunostaining procedures were performed as explained above. In both methods, brown-brown staining in the nucleus associated with the histological characteristics of the cells was observed in the nucleus, in the cytoplasm or in the region bordering the cell membrane. Negative controls were obtained by replacing the primary antibody with the respective concentration of non-immune IgG from a different species, Figure 2.

Semiquantification

In this method, the presence of the brown-brown staining corresponds to a positive antigen-antibody-DAB reaction. Photomicrographs of the immunostaining sections were digitalized using a computerized system; sections were scanned
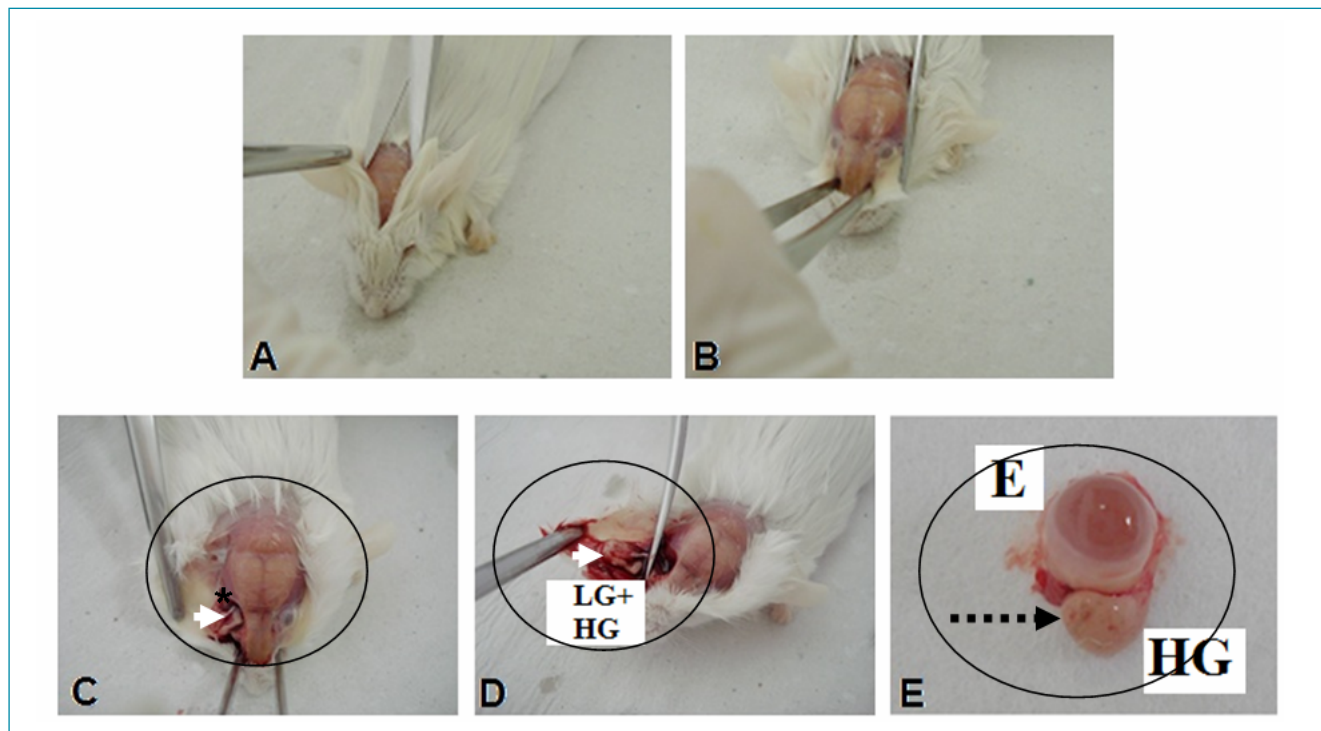
Figure 1. Procedure for the removal of intra-orbital harderian gland (HG). Before surgery, female mice were euthanized by deepening anesthetic and relaxing the muscle. Then, an incision was made in the skin (A and B), and the optic nerve (*), eyes (E), and lacrimal and harderian glands (white arrowhead) were exposed (D and E). Then, ophthalmic forceps was used to extract the lacrimal (LG) and harderian glands (HG) together (C and D) and then carefully separated (black arrow) (D).

with a Histech 3D scanner (Budapest, Hungary) and visualized by the Pannoramic Viewer software. Ten fields (areas in μm² with magnification from 100x to 400x) were selected in order to cover the entire length of the section, allowing for complete analyses of each gland. The Image Pro Plus7 software carried out an analysis (software of Media Cybernetics, USA) with a magnification from 100x to 400x. Results are expressed as % marked area/total area in μm². Analyses of the IHC photomicrographs were conducted by two blinded histologists.

Statistical Analysis

Measurements were submitted to the Student's t test to determine the differences between the groups studied. Data are presented as mean ± SD. All statistical tests were performed using GraphPad Prism software, version 7.0 for Windows (GraphPad Software). The significance level was set at $p<0.05$. All data were expressed as mean ± SD.

RESULTS

Morphological description and results of porphyrin quantification are summarized in Figure 2. The increased amount of porphyrin is not significant in the HPrl group compared to the Ctr one.

Semiquantification of the Immunohistochemistry

The results of the semiquantification of immunoexpression are summarized in Figure 2.

- the increase in the immunoexpression of the cell proliferation marker (Ki67) was significant in the HPrl group compared to the Ctr group: ($p<0.05$).
- the increase in the immunoexpression of the cell death marker by DNA fragmentation (TUNEL) was significant in the HPrl group compared to the Ctr group: ($p<0.05$).
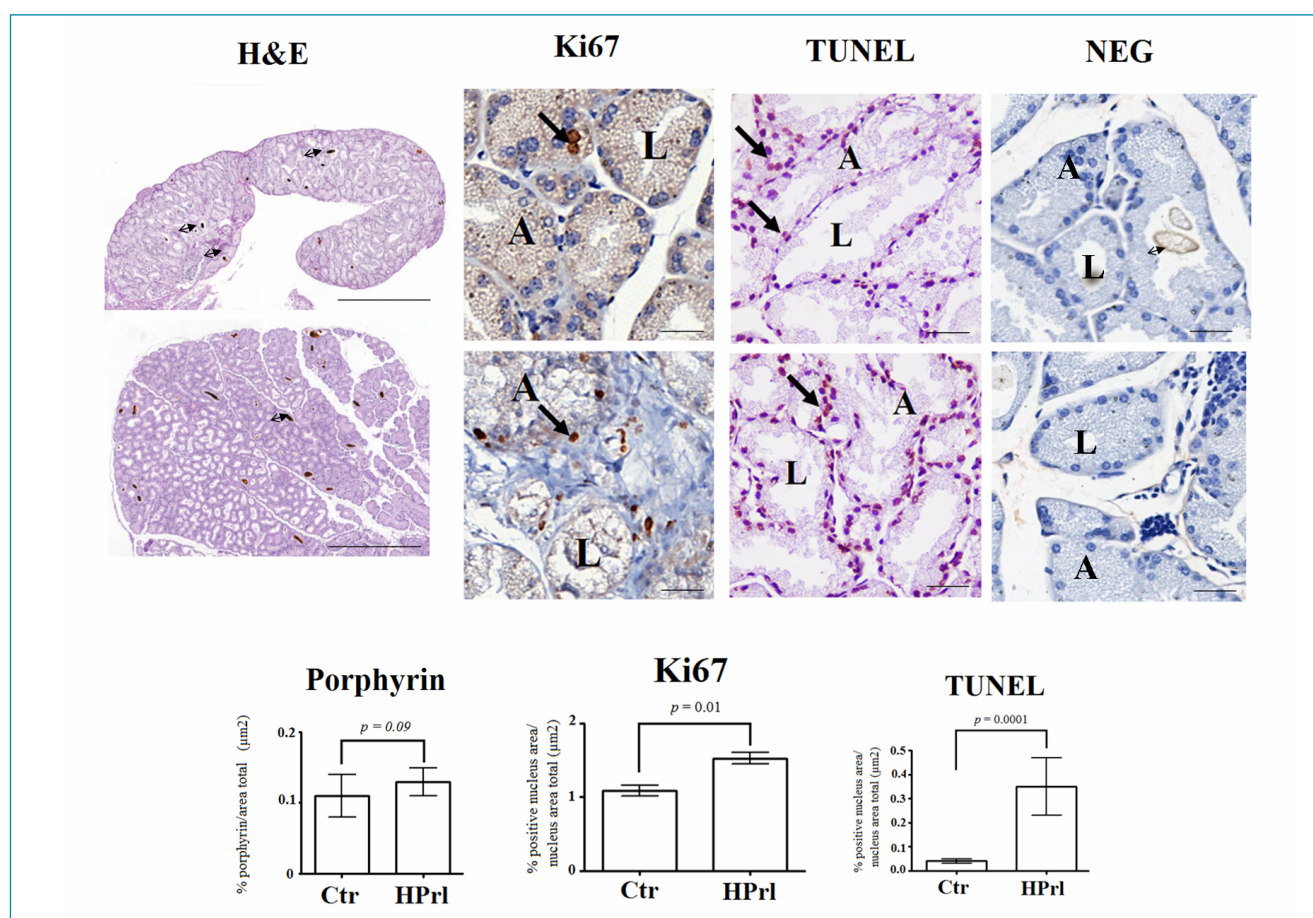
Figure 2. Representative photomicrographs of immunohistochemistry in the harderian gland of female mice of the control group and group with hyperprolactinemia. Note that the presence of brown nuclear reactivity identified ki67 and TUNEL positive cells. Additionally, it was observed in hematoxylin and eosin histology and porphyrin pigments in brownish-brown in the lumen of some acini. Therefore, the negative control (negative) was included in the figure. Observations were made in X100 and 400x magnification (Bar=50μm). The graphs represent the results expressed as mean ± standard deviation, number of animals (n=10). *Significant values, and statistical test: Student's t unpaired.

DISCUSSION

The present study's results show that hyperprolactinemia altered the proliferation and cell death of HG acini. It also indicates that morphological changes such as cellular disorganization, alteration in the volume of acinar cells, and the spacing between acini were similar to those found in LG. These cellular changes may be due to the direct effect of prolactin on LG and HG through prolactin receptors, or due to an imbalance in ovarian hormones.

Our morphological data on the action of HPrl in HG were similar to those found by Verna et al.[11] in intra-orbital LG (non-pregnant and pregnant). The same animal model was used for HPrl. The authors suggested that these results would indicate signs of decreased cellular activity. Our data show an increase in the TUNEL immunoexpression, a fact that results in higher death of acinar cells in the HG of females with HPrl.

Araujo et al.[5], in agreement with previous studies that used the same HPrl model[10,11], showed that serum PRL levels increased and that serum progesterone and estrogen levels decreased in all animals with HPrl when compared to control ones. Those findings suggest an impairment in LG function caused by increased serum PRL levels and decreased estrogen and progesterone. The primary condition related to the imbalance of sex hormones (estrogen/androgen) and PRL is Sjogren's syndrome, also known as dry eye syndrome. Carriers of the Sjogren's syndrome have high pro-inflammatory cytokines in the tear film and in the epithelium of the ocular surface[12,13]. Our data show an increase in Ki67 immunoexpression, which results in a higher proliferation of the acinar cells of HG and fibroblasts in the connective tissue around the acini of females with HPrl.

In humans, the LG is formed by an orbital portion, an eyelid portion (serous glands), and the meibomian glands (specialized sebaceous glands) that produce the oily components (meibum) of the outer lipid layer. Those components are responsible for preventing the overflow and evaporation of the tear. However, in murine, there is a third type of eye gland in the orbinal portion (intra-orbinal), the harderian glands (some authors consider HG to be a type of LG while others believe it to be an accessory gland in the LG). HG are found on vertebrates that have a nictitating membrane (translucent inner eyelid)[4-6,14].

Interestingly, the epithelial-derived HG consists of 2 types of secretory cells. The more numerous ones, type A cells, are responsible for the secretion of lipid droplets, while type B cells produce dark granules of multilamellar bodies (porphyrin pigments)[5].

Antolín et al. (1996)[17] show that HG of male hamsters present a very low rate of damaged cells that progressively increases after castration. This rise runs parallel to that of porphyrin synthesis and deposits, decreased Type B secretory cells, and finally concluded that this event is not a physiological cell death (apoptosis) but the consequence of the toxic accumulation of porphyrins (necrosis). Our data showed increased porphyrin in the HG of animals with HPrl, although not significant, leading us to believe in a relationship between cell death and increased porphyrin. Future studies are needed.

Most of the cells that make up the acini of the HG die from autophagy due to the secretion release mechanism, consisted of exocrine and holocrine glands. Thus, even though they may die from apoptosis[16], it is common to visualize remains of dead cells in the secretion product. Cells have developed biological mechanisms to control abnormal cell growth and maintain metabolic homeostasis. One of the known mechanisms is cell death due to autophagy or apoptosis[15,17]. Our results suggest that baseline levels of cell death, whether due to apoptosis or autophagy, are necessary to maintain the homeostasis of the HG. Histopathological studies of healthy subjects showed that, with aging, processes such as periductal and interacinar fibrosis and, ultimately, acinar atrophy are associated with the primary deficiency of the LG, leading to dry eye[18].

In summary, the data from this study showed that the hyperprolactinemic state could lead to an imbalance between cell death and proliferation, which can impair the functioning of the hardenian gland.

CONCLUSION

HPrl led to increased cell death in the acini the HG and cell proliferation in the stroma glandular, fact that suggesting a reduction process of cellular activity and fibrosis, which suggests impairment in the functioning of the lacrimal harderian.

AUTHORS' CONTRIBUTIONS

ASLA: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **CV:** Conceptualization, Data Curation, Formal Analysis. **OPAJ:** Writing – Original Draft, Writing – Review & Editing. **JMSJ:** Formal Analysis. **RSS:** Writing – Original Draft, Writing – Review & Editing. **ECB:** Writing – Original Draft, Writing – Review & Editing. **MJS:** Conceptualization, Data Curation, Formal Analysis. **RCTG:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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Nutritional aspects and cardiovascular risk in systemic lupus erythematosus

Joana Isabelli Calzza[1] (iD), Letícia Souza Muza[1]* (iD), Andrese Aline Gasparin[2] (iD),
Ricardo Machado Xavier[2] (iD), Odirlei André Monticielo[2] (iD)

SUMMARY

OBJECTIVE: Patients with systemic lupus erythematosus present with a higher number of classic risk factors for coronary diseases and a higher prevalence of metabolic syndrome resulting from the disease itself. To evaluate the nutritional indicators of the cardiovascular risk of patients with systemic lupus erythematosus by analyzing eating habits, anthropometry, laboratory data, and disease activity and to describe the prevalence of patients fulfilling the criteria for metabolic syndrome.

METHODS: Anthropometric measurements including waist circumference, food recall, and laboratory tests.

RESULTS: The population presented an insufficient daily intake of micronutrients. Anthropometry revealed that 37.5% of the patients were classified with degree II obesity by body mass index and 76.8% by abdominal obesity. Regarding metabolic syndrome, 18 patients (16%) fulfilled the diagnostic criteria.

CONCLUSIONS: Individuals with systemic lupus erythematosus presented with increased risk factors, as determined using anthropometric measurements and laboratory tests, for cardiovascular disease, indicating the need for nutritional guidance in this population to reduce cardiovascular risk, increase the quality of life, and increase survival of these patients.

KEYWORDS: Nutrition. Cardiovascular system. Systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune, chronic, multisystemic, relapsing-remitting autoimmune disease characterized by mucocutaneous lesions, hematological changes, and inflammation in joints, kidneys, serous membranes, and other organs associated with the presence of self-reactive antibodies and occurring predominantly in women. The Systemic Lupus International Collaborating Clinics Damage Index (SLICC) and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) are used to evaluate chronicity and disease activity. Cardiovascular disease (CVD) is an important cause of premature death in patients with SLE[1]. Compared to the general population, patients with SLE have a greater number of classic risk factors for CVD, such as obesity, dyslipidemia, and metabolic syndrome (MS), which are partly associated with nutritional aspects[1,2].

MS causes a 1.5-fold increase in overall mortality and a 2.5-fold increase in the risk for CVD[1,2], with a prevalence ranging from 20 to 28.4% in patients with SLE[2,3]. The prevalence of dyslipidemia in patients with SLE ranges from 36% at diagnosis to 60% or more after 3 years[4,5]. Its occurrence is specifically related to inflammatory disease activity and corticosteroid use[4]. The treatment of systemic inflammation with corticosteroids, in addition to disordered eating habits and reduced physical

activity, may increase the predisposition of accumulating body fat and of developing a coronary disease in patients with SLE. Abdominal obesity is commonly associated with the development of atheroma and CVD[6].

Regarding nutritional aspects in SLE, a review article showed that patients with SLE can benefit from a nutritionally balanced diet to maintain ideal body weight and from effective calorie control to avoid insulin resistance, by increasing high-density lipoprotein (HDL) and decreasing triglyceride levels[7].

In addition to dietary characteristics, the identification of anthropometric indicators helps in the early identification of nutritional aspects that increase the risk for CVD. The objective of this study was to evaluate the nutritional profile of patients with SLE by analyzing food intake, anthropometric indicators, and the association of disease activity and cardiovascular risk.

METHODS

Study design and population

This is a cross-sectional study with 112 patients diagnosed with SLE according to the diagnostic classification criteria described in 1982 and updated in 1997[8]. The studied population included random patients treated in an outpatient clinic created specifically for patients with SLE at the Rheumatology Service of the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil. The data were collected from May 2015 to February 2018. During routine consultations, patients were invited to participate in a study on the nutritional aspects of SLE to support the creation of future nutritional clinical strategies as treatment. All patients who agreed to participate signed an informed consent form. The exclusion criteria were the presence of metabolic modifying factors that could interfere with the nutritional evaluation, such as acquired immunodeficiency syndrome (AIDS) and being pregnant or breastfeeding at the time of evaluation.

Nutritional profile evaluation

The evaluation consisted of anthropometric, dietary, and laboratory measurements. Anthropometric data were measured according to the standards of the World Health Organization[9]. Body mass index (BMI) was calculated using the formula $BMI = weight/height^2$. Body fat percentage (BFP) was determined by body density using the equations proposed by Siri in 1961[10]. Abdominal obesity was determined by waist circumference (WC) using the cutoff points of ≥90 cm for men and ≥80 cm for women[11]. An anthropometric variable called metabolic

risk (MR) was created for the present study and defined as the group of participants concomitantly presenting all the anthropometric classifications of obesity.

Dietary indicators were evaluated using 24-hour dietary recall, which was subsequently processed in the DietWin Nutritional Analysis software version 2.0®.

The criteria for MS classification were based on the identification of three or more factors in the same person: abdominal obesity (≥90 cm in men and ≥80 cm in women); HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women; triglycerides ≥150 mg/dL; systemic blood pressure ≥135/85 mmHg or use of antihypertensive drugs; and, fasting glucose ≥110 mg/dL[12].

Laboratory measurements

The results of the following tests were collected directly from the patients' medical records: complete blood count; creatinine, glucose, total cholesterol, HDL, low-density protein (LDL), triglycerides, anti-double-stranded DNA, complement (C3 and C4) levels; and qualitative urine test.

Statistical analysis

The Statistical Package for Social Sciences software (SPSS) version 1.8.0 was used in the statistical analyses. The Fisher's exact test was used to determine the association between two or more qualitative random variables. The Pearson's Chi-square test was used to analyze probability in categorical data for unpaired samples. The Mann-Whitney test was used for independent samples. A $p < 0.05$ was considered statistically significant.

Ethical aspect

The identity of the study participants was kept confidential and all participants signed an informed consent form. The study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Sul under Certificado de Apresentação para Apreciação Ética (CAAE) no. 4338331 4.2.0000.5347.

RESULTS

The study population consisted of 112 patients, 106 (94.6%) of whom were women. Age ranged from 40 to 61 years for men and from 28 to 80 years for women. A total of 77 patients (68.8%) patients presented a score of 0 in the SLICC, similar to scores for disease activity, with 73 patients (62.5 %) presenting a score of 0 in the SLEDAI. The 25th to 75th percentiles of the medians were 0 to 1 for the SLICC and SLEDAI, as shown in Table 1.

Anthropometric data showed an obesity classification grade II according to BMI in 42 patients (37.5%), whereas 26 (23.2%) had grade I obesity, and 35 (31.3%) were overweight. The evaluation of adiposity according to BFP showed 48 patients (42.9%) and 25 patients (22.3%) being classified as very high and high risk, respectively, totaling 73 patients (65.2%) classified as having high body fat. Abdominal obesity was present in 86 patients (76.8%), as shown in Table 2. Regarding eating habits, there was an insufficient daily intake of micronutrients, mainly of potassium, copper, boron, and vitamin B1, with 100% of the participants consuming less than the daily quantity recommended.

MR was present in 58 patients (51.8%) who showed an association between MR and low dietary intake of vitamin B9, choline, and sulfur, as shown in Table 3. Regarding MS, 18 patients (16%) met the classification criteria. Laboratory tests showed that 31 patients (27.7%) had a high LDL level, 64 (57.1%) had a moderate or high-risk HDL level, seven (6.3%) had a high-risk cholesterol level, and 10 (8.9%) had triglyceride levels above the borderline cutoff.

Table 1. Descriptive data of the study population.

	n	%
Sex		
Female	106	94.6
Male	6	5,4
Total	112	100
Classification		
SLICC		
0	77	68.8
1	11	9.8
2	5	4.5
3	12	10.7
4	3	2.7
5	2	1.8
6	1	0.9
8	1	0.9
Total	112	100
SLEDAI		
0	70	62.8
1	5	4.5
2	11	9.8
3	2	1.8
4	15	12.4
5	2	1.8
6	4	3.6
8	2	1.8
9	1	0.9
Total	112	100

SLICC: Systemic Lupus International Collaborating Clinics Damage Index, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 2. Anthropometric data of the study population.

	n	%
BMI		
Obesity II	42	37.5
Obesity I	26	23.2
Overweight	35	31.3
Normal weight	7	6.3
Low weight	2	1.8
Total	112	100
BFP		
Very low	3	2.7
Low	17	15.2
Ideal	19	17
High	25	22.3
Very high	48	42.9
Total	112	100
WC		
High	86	76.8
Normal	26	23.2
Total	112	100

BMI: body mass index, BFP: body fat percentage, WC: waist circumference.

Table 3. Association of metabolic risk and insufficient micronutrient intake.

Micronutrients	n (%)	p
Choline	49 (84.5%)[a]	0.048
Sulfur	56 (96.6%)[b]	0.047
Vitamin B9	45 (77.6%)[a]	0.023

[a]Chi-square and continuity correction tests; [b]Chi-square and Fisher's exact tests.
Metabolic risk: concomitant classifications for obesity including body mass index, waist circumference, and percent body fat percentage.

DISCUSSION

The patients in this study had low SLICC and SLEDAI scores, which indicates little accumulated damage and controlled disease at the time of evaluation, possibly indicating more controlled disease in this population[1]. The anthropometric evaluation showed a high prevalence of high BMI, corroborating the literature. Some studies show a high prevalence of obesity and suggest that obesity is associated with disease activity[13,14]. There was a high BFP in 62.5% of the patients when high- and very-high-risk classifications were grouped. Some studies had similar results despite the use of other body adiposity measurement techniques. Borges et al.[15] used bioimpedance and reported that 59.2% of the study population had a BFP above the recommended range.

This study showed excess abdominal fat according to WC in 86 patients (76.8%), which represents a risk for CVD. A cohort study reported a high prevalence of abdominal obesity and a high incidence of cardiovascular risk in the SLE population[6]. Hormonal factors may be associated with increased weight and body fat in women with SLE, which were not addressed in the present study. However, they may be a topic for future research, as Li et al.[16] stated that menopause was associated with increased BMI and abdominal obesity in patients with SLE. The literature emphasizes the association between abdominal obesity and CVD in the general population[17]. An experimental study on SLE showed that a high-fat diet was associated with visceral obesity[18].

Regarding eating habits, although this study was limited to only one type of food survey, insufficient consumption of micronutrients was identified. Similar results were observed in the Mexican SLE population, regarding both the insufficient consumption of micronutrients and the excess weight[14].

In another study, low fruit and vegetable consumption and insufficient dietary calcium and iron intake were observed[15]. The literature reports low micronutrient intake in patients with SLE and its possible association with atherosclerosis in this population[19]. The present study found an association of insufficient intake of some micronutrients with MR; i.e., an insufficient intake of folic acid (vitamin B9), choline, and sulfur was associated with the grouping of anthropometric indicators for obesity.

To date, there are no studies in the literature in the SLE population reporting similar results, possibly owing to the diversity of methodologies, although a study demonstrated that a dietary folic acid deficiency in SLE may be associated with atherosclerosis[19], which in the present study was associated with MR. High micronutrient intake was reported as protective against excess weight in the Mexican SLE population[14].

General population studies show micronutrient deficiencies in obese people, mainly of fat-soluble vitamins, B vitamins, and folic acid[20]. An experimental study found an association of choline deficiency with obesity[21].

In the present study, 18 participants (16%) met the classification criteria for MS. A meta-analysis study reported an MS prevalence of 26% in patients with SLE[22]. Regarding the lipid profile of this population, there was a predominance of results above the normal range, and the literature shows that patients with SLE often present changed plasma lipids and decreased HDL-cholesterol levels[4,5]. Dietary intake of saturated fats is one of the factors associated with an increased lipid profile and can play an important role in increasing these levels, and there is evidence of excessive oil and fat consumption by patients with SLE[14,23]. In a study with 170 patients[15], 142 (83.8%) consumed excess fat according to a food frequency questionnaire not used in the present study. The present study shows the importance of controlling risk factors through nutritional monitoring, preventing overweight, and decreasing anthropometric values, especially WC, which is the most associated with CVD, in addition to controlling adequate nutrient consumption. Nutritional profile factors can be modified in this population, indicating that risk factors can be controlled and/or treated with early nutritional clinical care, thus improving their metabolic complication outcomes.

CONCLUSIONS

Patients with SLE had a nutritional profile that increases CVD risk factors, which could possibly be reduced with clinical nutritional monitoring.

AUTHORS' CONTRIBUTIONS

JIC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft. **LSM:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **AAG:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **RMX:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration; Validation; Visualization; Writing – review & editing. **OAM:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Study of the effects of kinesthetic motor imagery in patients with heart failure

Nélio Silva de Souza[1,2]* , Ana Carolina Gomes Martins[1] , Karoline Mello de Assis[1] ,
Lúcia Brandão de Oliveira[1] , Rosiane Fátima Silveira de Abreu[1] ,
Marco Antônio Araújo-Leite[2] , Marco Antônio Orsini Neves[2,3,4,5] ,
Nicolle dos Santos Moraes Nunes[3] , Victor Hugo do Vale Bastos[5] ,
Júlio Guilherme Silva[3,6] , Alba Barros Souza Fernandes[1]

SUMMARY

OBJECTIVE: The aim was to investigate the acute effect of kinesthetic motor imagery of the 2-minute walk test on hemodynamic and cardiopulmonary variables in patients with heart failure.

METHODS: Twenty participants were recruited for the analysis of these variables before and after the execution and imagination of the 2-minute walk test, with the number of laps executed and imagined being recorded.

RESULTS: The main results observed showed that (1) there was no difference in the number of laps executed and imagined (p=0.41), indicating that the participants actually imagined the test and (2) the motor imagery of the 2-minute walk test immediately increased (p<0.001) the heart and respiratory rates.

CONCLUSION: The motor imagery seems to have acute effects on the cardiopulmonary anticipatory responses of a patient with heart failure.

KEYWORDS: Heart failure. Imagery, psychotherapy. Heart rate. Respiratory frequency. Autonomic nervous system.

INTRODUCTION

Heart failure (HF) is defined as a complex clinical syndrome, characterized by functional or structural injury that compromises the ventricular filling or its ejection fraction[1]. These changes promote a decrease in the metabolic support of the tissue, resulting in a set of signs and symptoms, such as dyspnea, fatigue, and water retention[1,2]. The HF is categorized by the New York Heart Association (NYHA), according to the severity of symptoms related to the individual, in degrees of variation from I to IV, according to the functional impairment[2]. In this context, some patients with HF may have low tolerance to exercise associated with marked metabolic and/or respiratory responses. This condition can cause inactivity persistently

and a consequent decrease in cardiopulmonary function[1,3]. Cardiopulmonary physiotherapy is highly evidenced and recommended for the treatment of patients with HF[2,3]. However, some of these patients may have low tolerance to the exercises proposed in conventional physiotherapy[1-3].

Motor imagery (MI) is defined as the ability to mentally simulate a movement, without actually executing it[4,5]. The execution and imagination of the same movement are related phenomena and have an entirely voluntary motor control profile[6]. Different studies have shown that the temporal and biomechanical similarities between the execution and imagination of the same task[4,5], such as the time required for an individual to walk and imagine that he/she is walking the same fixed

distance, are similar (isochronous principle) without statistical difference[6]. The MI presents two distinct strategies: visual and kinesthetic. Specifically, in the kinesthetic MI, the individual "feels" performing the imagined movement[4,5], accessing somato-motor areas related to the perception of movement and part of the circuits related to the preparation and programming of the action[7].

Traditionally, the autonomic nervous system (ANS) regulates different visceral functions at the unconscious level. However, conscious modulations using kinesthetic MI are able to exert unconscious changes at the ANS level in healthy individuals or athletes, leading to, for example, an increase in heart rate (HR) and respiratory frequency (RF)[8-10]. These modulations occur due to the similarities in the brain areas that are responsible for the preparation and programming of the same task (dorsolateral prefrontal cortex, hypothalamus, cerebellum, basal ganglia, reticular formation, and supplementary motor area)[11]. Thus, these brain areas participate in the control of anticipatory cardiopulmonary responses (feed forward)[11] during both MI[12] and the execution of a physical activity[13]. Recently, our group published an editorial suggesting that some NYHA functional classes, which did not tolerate exercise, could benefit from the use of MI[14]. However, the effects of MI on HF patients are not known. Our hypothesis is that MI can modulate cardiopulmonary variables in HF patients in a way similar to healthy individuals. In this context, the aim of this study was to investigate the acute effect of kinesthetic MI of the 2-minute walk test (2MWT) on the hemodynamic and cardiopulmonary variables of patients with HF.

METHODS

Sample

Twenty participants were recruited with clinical and echocardiographic diagnosis of HF with preserved or reduced ejection fraction, in NYHA functional class II, as they have the tolerance to perform the test. All patients were followed up regularly at the outpatient clinic of the Clínica de Insuficiência Cardíaca (CLIC) of the Centro Universitário Serra dos Órgãos (UNFESO).

Ethics and consent form

The protocol was forwarded and approved by the Research Ethics Committee of UNIFESO through Brazil Platform (seem nº. 2,764,323). All participants signed a Free and Clarified Consent Term, in accordance with the resolution CNS 466/12 and the ethical standards established in the Declaration of Helsinki (2008).

Inclusion and exclusion criteria

This study included individuals diagnosed with HF in NYHA functional class II of both genders. Individuals with any limitation to walking and cognitive deficit in the Mini Mental State Exam (MMSE) were excluded[15].

Questionnaires

The Duke Activity Status Index (DASI) was used to assess the functional capacity profile of the research participants[16]. The volunteers' ability and vividness to perform MI were assessed using the Kinesthetic and Visual Imagery Questionnaire (KVIQ-10)[17].

Data collection strategies

The respiratory muscle strength was assessed by means of an analog and calibrated manovacuometer. The peak expiratory flow was quantified by the Peak Flow Meter®. Thoracic cirtometry was performed, and diameters were recorded at rest, maximum inspiration, and expiration. For the measurement of blood pressure (BP), a properly calibrated MISSOURI® sphygmomanometer was used and the peripheral oxygen saturation was verified with the Bioland® portable pulse oximeter. Experimental protocol

Initially, the MMSE[15], DASI[16], and KVIQ-10[17] questionnaires were applied. Then, the patients performed the 2MWT[18]. After performing the 2MWT, the participants were asked to sit in a chair for 10 min so that their cardiorespiratory parameters returned to the values close to the parameters at rest, establishing a baseline. Subsequently, the kinesthetic MI of the 2MWT was performed, with the patient sitting in a chair facing the track where the test was performed with his/her eyes closed and hands resting on his/her thighs. All participants were instructed to perform MI through the following instruction: "imagine that you are walking as you just did. You should feel like you are going as far as possible until you hear the end warning." The participants were instructed to count the number of completed laps during two min of the test (TC2M) executed and imagined with a digital numerical counter.

The variables recorded before and after the execution and imagination of the TC2M were RF, HR, recovery HR in the first minute (RHR1), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), peripheral oxygen saturation (SpO_2), subjective dyspnea scale (SDS), and fatigue using the Modified Borg Scale. The RF was recorded by the examiner, and HR was obtained by using a Polar FT1® frequency meter.

Data analysis

The normality of the data was previously verified using the Shapiro-Wilk test. The effect size (d) was estimated by partial eta-squared (η^2_p) and the statistical power in 80%. The hemodynamic

and cardiorespiratory parameters, evaluated before and after the execution and imagination of the 2MWT, were compared using the repeated analysis of variance (ANOVA) followed by the Bonferroni post-test. The paired Student's *t*-test was used to compare the number of runs executed and imaged on the 2MWT, as well as the other variables analyzed. The Spearman's correlation test was used to verify the degree of association between the cardiopulmonary variables after the MI. All the analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 20), assuming an alpha significance level of $p \leq 0.05$.

RESULTS

Sample characteristics

The following values are presented as mean±standard deviation (minimum–maximum). Ten volunteers of both sexes (n=20) were selected with the age of 59.1±7.5 (46–75) years and a body mass index (BMI) of 29.2±6.0 (23–44). Different levels of education were reported, with at least the completed fourth grade and at the most completed higher education. In the examination for cognitive impairment screening by the MMSE, the participants presented 24.7±2.0 (21–28). In general, the volunteers presented a functional capacity profile moderated by the DASI Questionnaire with 27.86±13.38 (9.95–50.95) points, which allowed them to participate in the proposed protocol.

Objective evaluation

On physical examination, none of the participants showed changes in HR or pulmonary auscultation. The following parameters were assessed at the start and end of the protocol: thoracic cirtometry, respiratory muscle strength, peak expiratory flow, SBP, DBP, SpO_2, Borg fatigue, and SDS. All these variables showed no statistically significant difference ($p > 0.05$).

Comparisons between TC2M execution and imagination

The main results showed that:
(1) the comparison between the number of executed [6±1.25 (4–8)] and imagined [7.8±2.74 (4–11)] laps was not statistically different [t(9)= -2.37; p=0.41; d=1.21], indicating similarity and suggesting that the participants actually imagined the proposed task (isochronic principle);

(2) the vividness shown by the participants on the KVIQ-10 Scale reported after the MI of the 2MWT was considered high [3.9±0.8 (3–5)];

(3) there was an increase in HR after MI of the 2MWT when compared with the moments before (69±7.9) and after (80±11.1), with a statistically significant difference

$[F(2.49)=45.0; p<0.001; \eta^2_p=0.89;$ power=100%; Figure 1]. Figure 2 shows the HR behavior of the participants before, during, and after the MI of the 2MWT; and

(4) there was also an increase in the RF after the MI of the 2MWT when compared with the moments before (16.1±2.0) and after (20.1±2.44), with a significant difference [Friedman $\chi^2(3)=1.22; p<0.001; \eta^2_p=0.51;$ power=100%; Figure 3].
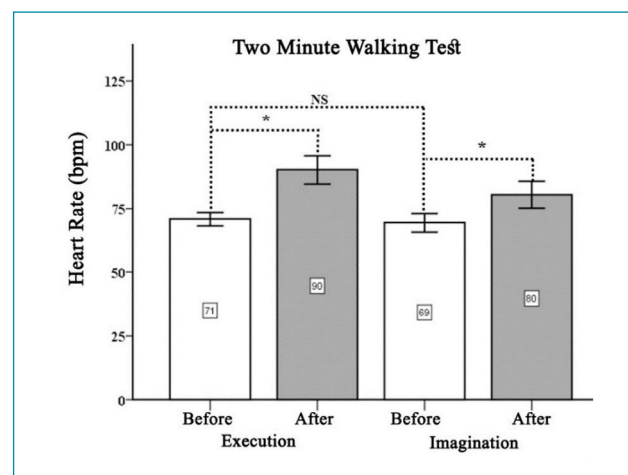
Figure 1. The participants (n=20) showed an increase in heart rate in beats per minute (bpm) after the execution and imagination of the 2-minute walk test, with a statistically significant difference (*p<0.001). Note that when comparing the heart rate between the moments before the execution and the moments before the imagination of the 2-minute walk test (2MWT), there was no statistical difference, indicating that the participants started from a similar baseline.
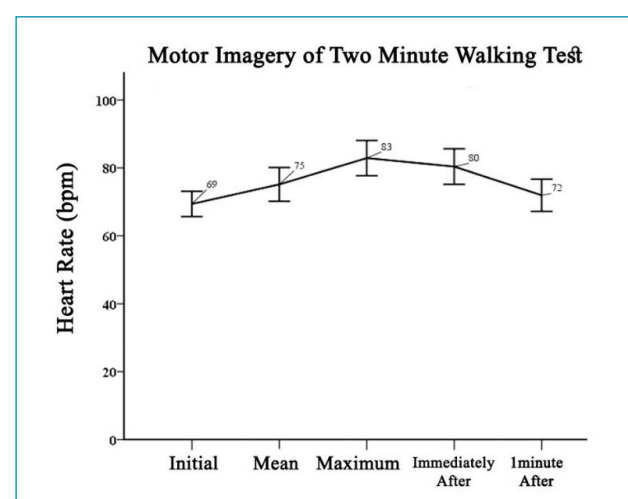
Figure 2. The line graph shows the heart rate behavior in beats per minute of the participants (n=20) before, during, and after the imagination of the 2-minute walk test. The following data are presented as mean±standard deviation: initial heart rate (69.4±7.56), mean heart rate (75.1±10.08), maximum heart rate (82.9±10.56), heart rate immediately after motor imagery of the 2-minute walk test (80.4±10.65), and heart rate after one min (71.9±9.64).
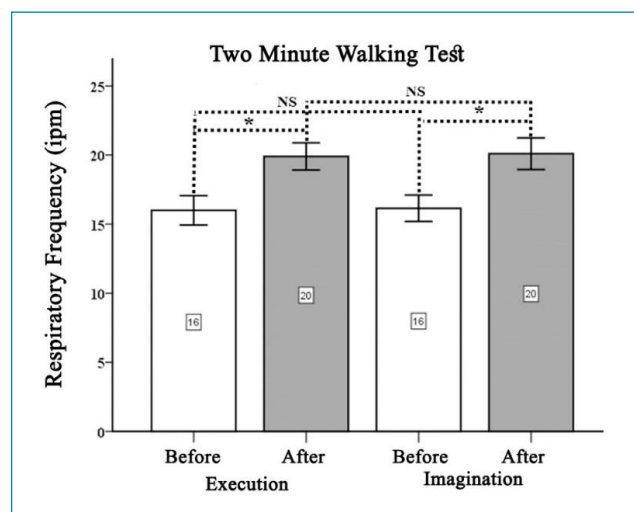
Figure 3. The participants (n=20) showed an increase in respiratory frequency in incursions per minute (ipm) after the execution and imagination of the 2-minute walk test, with a statistically significant difference (*p<0.001). Note that when comparing respiratory frequency between the moments before the execution and the moments before the imagination, as well as after the execution and after the imagination of the 2-minute walk test (2MWT), there was no statistical difference, indicating similarities.

DISCUSSION

The object of this study was to investigate the acute effect of kinesthetic MI of the 2MWT on the hemodynamic and cardiopulmonary variables of patients with HF. The main results observed showed that

(1) there was no difference in the number of laps performed and imagined, indicating that the participants actually imagined the test and;

(2) the MI of the 2MWT immediately increased the HR and RF of the participants.

In the context of MI, there are different aspects (temporal and biomechanical) that may have similarities, such as the number of repetitions executed and imagined during a fixed time[4,5], as well as the time that an individual requires to walk and imagine that he/she is walking a fixed distance[6]. In this study, it was observed that the number of laps executed and imagined in the 2MWT (biomechanical aspect) did not show statistical difference, indicating that the participants actually imagined the proposed tasks due to the similarities observed. The kinesthetic MI strategy has shown greater modulation in HR and RF, when compared with the visual MI strategy[19], justifying its use in this study. Besides that, the high levels of vividness in KVIQ-10 (>3) have shown greater modulation using kinesthetic MI when compared with low levels of vividness

(<2) and visual MI[5]. In this study, high levels of vividness of the movement were observed after the kinesthetic MI of the 2MWT (mean of 3.9), which may partially explain the effects of autonomic modulation observed.

Usually, when an individual plans to start a physical activity (e.g., walking), the areas of preparation and programming of movement are accessed (cerebellum, basal ganglia, reticular formation, ventrolateral bulb, and parieto-frontal area). At this time, the increase in sympathetic influx (cholinergic fibers) and the reciprocal inhibition of parasympathetic activity facilitate the anticipatory cardiopulmonary response, increasing HR and RF[11,13]. Similarly, when a healthy individual imagines this same physical activity, areas related to the preparation and programming of movement are also accessed, activating the cardiopulmonary anticipatory mechanisms[10,20] and partially explaining the observed effects. These modulations probably occur due to the change in neuronal activity, mainly in the reticular formation and in the ventrolateral bulb, located in the brain stem (which receives hypothalamic projections), responsible for modulating cardiopulmonary rhythmicity[11,13].

In this context, MI that is performed consciously is able to induce unconscious neurophysiological changes, when accessing the brain autonomic region responsible for controlling vital signs to keep the system in balance[8,19]. The cardiopulmonary anticipation mechanism can explain the elevations in HR and RF observed in healthy individuals[8,10], since the brain is able to anticipate the metabolic demands necessary to supply the demand for the exercise milliseconds before its execution[21]. However, until then, these anticipatory cardiopulmonary responses during MI were known only in healthy individuals and/or athletes[8-10,22,23]. In this study, it was observed that, even though patients have HF in class II, these anticipatory mechanisms do not seem to be altered by the pathophysiology of the disease, indicating that this group may benefit from kinesthetic MI as an adjunctive therapeutic strategy.

In this study, significant increases in HR and RF were observed immediately after the kinesthetic MI of the 2MWT, corroborating the findings of different studies that observed similar results in healthy individuals when performing the kinesthetic MI of anaerobic exercises in upper[19] and lower limbs[8] and aerobics[9,23-25] as the gait MI[9,23]. The MI of fast walking and running at different speeds has shown an increase in SBP. These effects seem to be related to the intensity of the mental effort generated by the participant[9]. The 2MWT consists of an exercise of low physical effort in its execution and mental in its imagination, explaining, in part, the non-modulation of SBP and DBP. Therefore, it seems that MI with a low level of mental effort may be relevant in cardiopulmonary physiotherapy because it does not present a risk of decompensation.

There were no changes in SpO_2 after MI of the 2MWT. Similarly, there are also no changes in oxygen consumption during gait MI[8],

indicating that MI does not cause changes in O_2 supply or metabolic expenditure. Recent evidence suggests that kinesthetic MI of breathing movements can control the levels of metabolic expenditure[26]. In addition, there was no acute change in respiratory biomechanics, indicating that MI did not interfere with chest mobility, resistance to expiratory flow, and respiratory muscle strength, as well as in the Borg fatigue and SDS, indicating that there was no patient decompensation after the MI of the 2MWT.

The results of this study point to the possibility of using kinesthetic MI safely, as a strategy in support of the classic cardiorespiratory physiotherapy programs of patients with HF in functional class I or II. However, the interpretation of these results requires caution for class III or IV, as the effects of MI on these patients are not yet known. Thus, further studies are needed to answer these and other hypotheses that may or may not change the clinical condition of these patients in the long term.

The study presents some limitations:

(1) the small sample size and
(2) the non-quantification of the participants' brain activity (e.g., electroencephalogram) or autonomic activity (e.g., electrocardiogram or echocardiogram) during the MI of the 2MWT.

However, these limitations do not neutralize the innovation of the work due to the correlation between MI and cardiopulmonary variability, even though sophisticated instruments were not used in this study. Despite the limitations described, the study has considerable scientific value, being a pioneer in MI research associated with autonomic functions in patients with HF.

CONCLUSIONS

The kinesthetic MI of the 2MWT showed an immediate increase in the HR and RF of patients with HF in functional class II, similar to the effects on healthy individuals described in the literature. This indicates that the anticipatory cardiopulmonary response of these patients was modulated immediately by the MI in a safe way, as there were no changes in the perceived effort scales. However, further studies are needed to investigate the effects of MI associated with cardiovascular physiotherapy.

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AUTHORS' CONTRIBUTIONS

NSS: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ACGM:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **KMA:** Data curation, Writing – original draft. **LBO:** Conceptualization, Formal Analysis, Writing – review & editing. **RFSA:** Conceptualization, Formal Analysis, Writing – review & editing. **MAAL:** Writing – review & editing. **MAON:** Writing – review & editing. **NSMN:** Writing – original draft. **VHVB:** Formal Analysis, Writing – review & editing. **JGS:** Writing – review & editing. **ABSF:** Conceptualization, Formal Analysis, Writing – review & editing.

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ORIGINAL ARTICLE

Prevalence of Burnout Syndrome and associated factors in medical students under different educational models

Thiago Santos Corrêa Prata[1] (iD), Dâmaris Alejandra Paula Calcides[2] (iD),
Erika Lima Vasconcelos[3] (iD), Adriana Andrade Carvalho[4] (iD),
Enaldo Vieira de Melo[5] (iD), Edméa Fontes de Oliva-Costa[5]* (iD)

SUMMARY

OBJECTIVE: The objective of this study was to estimate the current prevalence of burnout syndrome among medical students at the Federal University of Sergipe and identify its associated factors.

METHODS: This cross-sectional study was conducted with medical students randomly selected between April and June 2019. This study compared two medical schools from the same university with different teaching models: the Federal University of Sergipe, Aracaju campus, with a traditional teaching model, and the Federal University of Sergipe Lagarto campus, with a problem-based learning teaching model. An online questionnaire on the sociodemographic characteristics, personal aspects, and educational process of the participants, in addition to the Malash Burnout Inventory-Student Survey questionnaire for screening burnout syndrome, was distributed to the participants. The descriptive analysis of the data, calculation of the prevalence ratios, and multivariate analysis by logistic regression were performed.

RESULTS: This study included 213 students with an average age of 23±3.77, and 50.2% of the students were male. Among the sample, 21.6% of the students met the three-dimensional criterion for burnout syndrome and 51.6% met the two-dimensional criterion. Burnout levels were higher in the students who rarely received the emotional support they needed in the program (OR 3.98), those who thought about dropping out of the undergraduate (OR 2.88), and those who considered their academic performance to be regular or weak (OR 12.1). The traditional teaching model was not a factor associated with burnout syndrome.

CONCLUSIONS: The results suggest that a high prevalence of burnout syndrome is associated with psychosocial factors and the educational processes of medical students.

KEYWORDS: Burnout, psychological. Students, medical. Mental health. Education, medical.

[1]Universidade Federal de Sergipe, Grupo de Estudos e Pesquisas em Psiquiatria, Saúde Mental e Educação para as Profissões da Saúde, Departamento de Medicina – Aracaju (SE), Brazil.

[2]Universidade Federal de Sergipe, Grupo de Estudos e Pesquisas em Psiquiatria, Saúde Mental e Educação para as Profissões da Saúde, Hospital Universitário – Aracaju (SE), Brazil.

[3]Universidade Federal de Sergipe, Departamento de Medicina – Lagarto (SE), Brazil.

[4]Universidade Federal de Sergipe, Departamento de Farmácia – Lagarto (SE), Brazil.

[5]Universidade Federal de Sergipe, Departamento de Medicina – Aracaju (SE), Brazil.

*Corresponding author: edmeaolivacosta@gmail.com

INTRODUCTION

Burnout syndrome (BS) is defined as an inappropriate response to emotional stress and an excessive need to deal with chronic interpersonal stressors in the workplace[1,2]. Medical training is a significant source of stressors, such as the excessive course load, the large amount of program content, the requirement for excellent performance, and the need to deal with pain and death, which can contribute to mental health aggravations in medical students[1,3,4].

Freudenberger[5] scientifically reported on BS for the first time in 1974. He characterized BS by observing that professionals who cared for other people developed exhaustion, isolation, and even secondary aggressiveness in response to their excessive use of energy, force, and resources and that members of the workforce could become inoperative[5]. Maslach organized BS into three dimensions, namely, emotional exhaustion, cynicism, and low professional efficacy, from a sociopsychological perspective in workers and students[1,2].

The effects of inadequate prevention and delayed detection of BS can be observed at all stages of the medical career. An increase in suicidal ideation, substance abuse, and medical errors, in addition to a decrease in professionalism and the development of difficult relationships with patients are associated with BS[6]. Similarly, the consequences of BS during medical training can be recognized, such as a negative impact on academic life and general well-being; in addition, BS is an independent predictor of worse quality of life[7].

Exposure to stressors during undergraduate school can affect the performance, mental health, and future professional life of students. Therefore, alternative methods need to be developed, which allow early detection and intervention of BS.

This study aims to estimate the current prevalence of BS in medical students and identify its associated factors at two medical schools from the same institution, the Federal University of Sergipe (UFS), employing different educational models to stimulate the planning of preventive measures.

METHODS

Study site

We conducted this study simultaneously in two medical schools of the same public university in the state of Sergipe, Brazil. The Federal University of Sergipe Aracaju campus (UFS-AJU) is 59 years old and is located in the state capital; it adopts a traditional model of teaching. It divides the curriculum into six years: the first two years focus on knowledge of basic biological sciences, the following two years are dedicated to understanding the medical sciences, and the mandatory medical internships are completed in the last two years.

The Federal University of Sergipe Lagarto campus (UFS-LAG) is nine years old and is located in the interior of the state of Sergipe; it adopts an active teaching method, namely, problem-based learning (PBL). PBL is an interdisciplinary model that involves building knowledge based on real or simulated problems. Thus, students are active in the learning process.

Study population

Any students enrolled in medical school courses in either school were eligible to participate. This study sample was not randomized, and the medical students were selected consecutively to reduce sample bias.

We used G*Power software version 3.1.9.4 (2019) to estimate the sample size, using an alpha of 0.05 and a power of 0.8, whereas the expected ratio of UFS-AJU to UFS-LAG students was assumed to be 2 (0.25/0.125), and the expected sample size was 163 students from UFS-AJU and 81 students from UFS-LAG. However, 133 students at UFS-AJU and 80 at UFS-LAG volunteered to participate.

Study design

This was an analytical cross-sectional observational study, with data collected between April and June 2019.

Data collection

The data were collected using a form sent by email and social media from all students enrolled at both schools.

Instruments

Using an electronic form, we distributed two self-administered questionnaires. The first was a structured questionnaire with 28 precoded, close-ended questions about socioeconomic and demographic characteristics, personal aspects, and the educational process that were designed by the authors and that had been tested and improved in earlier studies[1,4,8,9].

The second questionnaire was the Maslach Burnout Inventory Student Survey (MBI-SS), adapted and validated in English and Portuguese[10,11]. This questionnaire comprises 15 items on the three dimensions of BS: emotional exhaustion (five items), cynicism (four items), and professional efficacy (six items). The following Likert scale was used to measure the frequency of each item: 0 (never), 1 (once a year or less), 2 (once a month or less), 3 (sometimes a month), 4 (once a week), 5 (a few times a week), and 6 (every day).

Maroco and Tecedeiro established the following thresholds for each dimension in the Portuguese translation of the MBI-SS: emotional exhaustion (low <10, moderate 10–14, and high >14), cynicism (low <2, moderate 2–6, and high >6), and professional efficacy (low <23, moderate 23–27, and

high >27). High emotional exhaustion and cynicism scores, in addition to low levels of professional efficacy, were used as the three-dimensional criterion to determine BS. The two-dimensional criterion was defined by high exhaustion and cynicism[12].

Data analysis

We created a database of the questionnaire records using the trial version of IBM SPSS. The statistical analysis comprised of three stages as follows:

1. The calculation of descriptive statistics to characterize the population profile.
2. Simple analysis, elaboration of tables, calculation of the prevalence ratios and their confidence intervals (95%), stratified analysis, and calculation of the adjusted prevalence ratios.
3. The analysis of multiple variables by logistic regression. We included variables that showed an association with the outcome in the model (p≤0.25). The final model contained only the independent variables that maintained an association with the outcome after adjustment (p≤0.05) based on the likelihood ratio test.

ETHICAL CONSIDERATIONS

The Human Research Ethics Committee of UFS approved the study under CAAE 92970618.3.0000.5546. Each participant had the right to refuse to participate in this study or withdraw their authorization, and the participants were guaranteed the confidentiality of the data provided.

RESULTS

A total of 213 students participated in this study, 133 of whom were from UFS-AJU (62.4%) and 80 of whom were from UFS-LAG (37.6%); the students had an average age of 23±3.77, with a minimum age of 17 years and a maximum age of 37 years. A total of 50.2% of the students were male and 93.4% were single. Table 1 summarizes the main variables based on the descriptive analysis of our sample by school of origin.

Most students (60.6%) were from outside the city where their schools were located, with 35.7% from other states and 24.9% from inland cities (excluding the capital), while 39.4% were from the capital. Furthermore, 84% of the students had only studied and had not worked, 56.3% lived with family members, 74.6% did not receive academic assistance, 51.2% practiced a certain religion, and 74.2% had no medical relatives.

Virtually, all students (96.2%) were satisfied with their careers in medicine. However, 51.2% of the students considered themselves to have regular or weak academic performance and only 45.5% considered the medical degree to be consistent with expectations. Concerning the educational process, 38.0% of the students were satisfied with the teaching and learning strategies of the program, while 41.8% had considered dropping out of the undergraduate.

In terms of emotional support provided during the program, 46.9% of the students indicated that they received support occasionally or rarely. Most of the students slept <8 h/day (97.6%). Previously diagnosed mental health conditions were reported by 21.6% of the students, and the use of psychiatric medicines prescribed by a doctor was reported by 27.2% of the students. Most students indicated that they had not consumed legal (55.4%) or illegal (69.0%) psychoactive substances.

In terms of experiences of serious illness within the family, 59.6% of the students reported such experiences. In conflict situations, 46.5% indicated that they engaged in dialogue. A little over half (55.4%) were physically active. Regarding the use of mobile phones and social networks, 51.2% felt uncomfortable when they did not use them for a while. A maximum duration of social media usage of 3 h/day was reported by 60.1% of the students.

The overall prevalence of BS was 21.6%, based on the three-dimensional criterion, with prevalences of 25.6% at UFS-AJU and 15% at UFS-LAG. Based on the two-dimensional criterion, the prevalence was 51.6%. Table 2 characterizes the sample studied according to the presence or absence of BS. After assessing each dimension, we found a high level of emotional exhaustion, with a prevalence of 71.4%; a high level of cynicism, with a prevalence of 57.3%; and low professional effectiveness, with a prevalence of 25.8% (Table 3).

In the last stage of the data analysis with logistic regression, the factors most strongly associated with BS were rarely receiving the emotional support needed during the program (OR 3.98; p=0.001), thinking about dropping out of the undergraduate (OR 2.88; p=0.01) and considering one's academic performance to be regular or weak (OR 12.1; p<0.0001). The different teaching models (i.e., traditional and PBL) in each school did not prove to be an associated factor with BS.

DISCUSSION

The prevalence of BS was 21.6% based on the three-dimensional criterion. At the UFS-AJU, the frequency has increased over the past few years. Previous studies in 2018 with interns and in 2009 with students of all levels showed that the prevalence of BS was 10.3%[1,4]. In our study, BS was present in 25.6% of the students. This incidence is higher than the national average (13.1%) but lower than the overall estimate (44.2%)[13,14].

Table 1. Descriptive analysis of socioeconomic, psychosocial, and educational variables among medical students attending medical schools with different educational models at a public university, Aracaju, Brazil, 2019.

	UFS-AJU (n=133)	UFS-LAG (n=80)
Prevalence of Burnout Syndrome (%)	34 (25.6)	12 (15)
Mean age (years)	22.9±3.5	23.2±4.2
Gender		
Male	69	38
Civil status		
Single	126	73
Married	7	6
Separated/divorced	0	1
Program stage		
Basic cycle (1st and 2nd year)	28	28
Clinical cycle (3rd and 4th year)	74	28
Internship (5th and 6th year)	31	24
Family income (in number of minimum wages)		
1–10	87	65
>10–20	34	10
>20	12	5
Satisfaction with medical school		
Satisfied	66	39
Partially satisfied	57	37
Dissatisfied	10	4
Perception of academic performance		
Regular or weak	73	36
Level of agreement that the teaching and learning strategies of the program are satisfactory		
Agree	37	44
Undecided	56	28
Disagree	40	8
Failed a course subject		
No	118	73
Has considered dropping out of the undergraduate		
Yes	53	36
Emotional support during the program		
Always or occasionally	62	51
Rarely	71	29
Diagnosis with mental health problems		
Yes	33	13

UFS-AJU: Universidade Federal de Sergipe – Aracaju; UFS-LAG: Universidade Federal de Sergipe – Lagarto.

An analysis of foreign studies observed a prevalence of BS of 38.2% among the undergraduates from Saudi Arabia[15], 26.7% among students from the United Kingdom[16], and 77% from New Zealanders[17]. In the United States, a study using the two-dimensional criterion found a prevalence of 35.2% among medical students at several universities across the country, which was lower than that found in this study (51.6%)[6]. Geographic location may be implicated in the prevalence of BS, with Oceania and part of the Middle East having higher levels of burnout than Central and South America and Europe[14].

Previous studies at the same institution indicated that medical students had a high level of mental illness. This population had high levels of depressive symptoms and common mental disorders, which were strongly associated with factors related to the teaching-learning sphere[8,9].

The evaluations of each subscale indicated high rates of emotional exhaustion and cynicism but low rates of low professional efficacy (Table 3), consistent with the literature[1,4,14]. Some authors have hypothesized that high scores in a specific dimension can precipitate an imbalance among other

Table 2. Distribution of medical students from two medical schools at a public medical university (n=213) by socioeconomic, psychosocial, and educational characteristics and prevalence of burnout syndrome, Aracaju, Brazil, 2019.

	With BS (n=46)	Without BS (n=167)	p
Gender			
Female	25	81	0.126
Male	21	86	
Civil status			
Single	44	155	
Married	1	12	0.126
Separated/divorced	1	0	
Family income (in the number of minimum wages)			
1–10	36	116	
>10–20	8	36	0.485
>20	2	15	
Program stage			
Basic cycle (1st and 2nd year)	3	53	
Clinical cycle (3rd and 4th year)	30	72	0.001
Internship (5th and 6th year)	13	42	
Educational institution			
UFS-AJU	34	99	0.048
UFS-LAG	12	68	
Perception of academic performance			
Good	4	100	<0.0001
Regular or weak	42	67	
Emotional support during the program			
Always or occasionally	11	102	<0.0001
Rarely	35	65	
Has considered dropping out of the undergraduate			
Yes	33	56	<0.0001
No	13	111	

UFS-AJU: Universidade Federal de Sergipe - Aracaju; UFS-LAG: Universidade Federal de Sergipe - Lagarto; BS: Burnout Syndrome.

Table 3. Prevalence of burnout syndrome and levels of each dimension* among medical students from two medical schools at a Brazilian public university, Aracaju, Brazil, 2019.

	n=213	%
Burnout syndrome, three-dimensional	46	21.6
Burnout syndrome, two-dimensional (emotional exhaustion and cynicism)	110	51.6
Emotional exhaustion		
Low (<10)	24	11.3
Moderate (10–14)	37	17.4
High (>14)	152	71.4
Cynicism		
Low (<2)	22	10.3
Moderate (2–6)	69	32.4
High (>6)	122	57.3
Professional efficacy		
High (>27)	119	55.9
Moderate (23–27)	39	18.3
Low (<23)	55	25.8

*The scores of the levels of each dimension are based on Maroco and Tecedeiro[12].

dimensional scores[1]. Imbalance in a single dimension can cause disadvantages to medical training. For example, high cynicism during a medical program can lead to serious problems in the doctor–patient relationship, such as difficulty in communicating bad news[18].

The main point of comparison in this study was between two medical schools from the same Brazilian public university with different methodologies. PBL, a method that encourages active knowledge seeking, has been identified as a potential protective factor against BS development, especially in schools with good planning and good curriculum management[3,19]. However, the use of either the traditional teaching method (practiced at UFS-AJU) or the PBL method (practiced at UFS-LAG) did not appear to be a factor associated with BS in this study.

The presence of BS was statistically associated with rarely receiving emotional support in this study. There are several important conditions that promote coping with stressors during undergraduate school, such as the existence of a supportive culture in educational institutions through the encouragement of support among colleagues, family networks, extracurricular activities, and counseling[20]. However, even when such support

is available, students avoid seeking professional help to mediate emotional or mental health problems because of the personal or cultural stigma perceived by the student and negative personal experiences[21]. Frajerman[22] suggested that mental health care for medical students must be comprehensive and that prevention must be carried out at the primary, secondary, and tertiary levels through institutional, group, and individual interventions[22].

The UFS-LAG has a structured psychosocial support network with social workers and psychologists, as well as support, if necessary, from a psychiatrist and pedagogue, that is readily available to students. Workshops on integrative and complementary health practices are also available to the entire academic community. These measures may be related to the lower levels of BS present in this population.

Interns at UFS-AJU had access to a Balint group (BG) for approximately 10 weeks during the mental health internship until its suspension in May 2019 by management; participation in the BG was associated with a reduction in the prevalence of BS and the mitigation of vulnerability factors among medical interns at this school[4]. Students at UFS-AJU only had access to the psychologist through the General Student Assistance Service of the University on another campus. When they needed psychiatric care, the student had to compete for openings in the general psychiatry outpatient clinic of the University Hospital of UFS or look for services outside the university since there is no exclusive psycho-pedagogical, psychological, and psychiatric support service for students on this campus.

A reliance on tests to assess students' performance, as at UFS-AJU, may be related to a greater chance of the development of BS among students who consider their academic performance to be regular or weak. These students may see their poor performance on tests as poor progress in the program, which can generate the desire to leave the undergraduate. As demonstrated in previous studies, the use of tests for performance evaluation is an important source of stress among medical students[23,24].

The percentage of students reporting a previously diagnosed mental disorder was the same as the percentage of student reporting BS (21.6%). This may be an overlap of diagnoses and may constitute a limitation of the study. Some mental disorders, such as depressive disorder or anxiety disorder, exhibit symptoms that fall within the first dimension of the BS scale (exhaustion). The difference is that psychological distress in SB is directly related to the professional environment.

However, we believe that we have fulfilled our aim in this cross-sectional study. In this type of study, we cannot test causality because exposure and effect occur simultaneously. Nonetheless, we highlight the importance of planning preventative measures.

CONCLUSIONS

The prevalence of BS was high in this study. Factors related to the psychosocial and educational spheres of medical students are associated with BS, but the teaching model adopted is not.

The medical schools surveyed and others with similar profiles should reflect on the role they play in the promotion and prevention of psychological distress. Further longitudinal studies could strengthen our findings.

AUTHORS' CONTRIBUTIONS

TP: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **EM:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. EOC: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **AC:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **DC:** Data curation, Formal Analysis, Writing – review & editing. **EV:** Data curation, Formal Analysis, Writing – review & editing.

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Effect of the Mediterranean diet in patients with chronic spontaneous urticaria

Havva Hilal Ayvaz[1]* 🆔, Aliye Kuyumcu[2] 🆔

SUMMARY

OBJECTIVE: Patients with chronic spontaneous urticaria often want to be informed about dietary modifications. There have been many studies evaluating dietary approaches in chronic spontaneous urticaria. In this study, we aimed to investigate the relationship between adherence to the Mediterranean diet and chronic spontaneous urticaria.

METHODS: In this cross-sectional case–control observational study, 100 patients (70 males and 30 females, mean age: 38.6±13.0 years) with chronic spontaneous urticaria and age- and sex-matched 100 healthy controls 70 males and 30 females, mean age: 38.7±13.8 years) were enrolled. A validated 14-item questionnaire evaluating the Mediterranean diet score was used for the assessment of adherence to the Mediterranean diet. The severity and the control of chronic spontaneous urticaria were assessed by Urticaria Activity Score over 7 days and Urticaria Control Test, respectively.

RESULTS: The mean Mediterranean diet score in the patient group was 5.40±1.88, whereas in healthy controls it was 6.30±1.39 (p<0.001). The Urticaria Activity Score over 7 days score of the patients was negatively correlated with the Mediterranean diet score, whereas the Urticaria Control Test score was positively correlated.

CONCLUSION: We reported that adherence to the Mediterranean diet may be an independent factor that decreases the risk of chronic spontaneous urticaria. It may also reduce the severity of chronic spontaneous urticaria symptoms.

KEYWORDS: Chronic Spontaneous Urticaria. Mediterranean Diet. Clinic activity.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a common skin disorder which is characterized by recurrent itchy wheals with or without angioedema[1]. In the majority of cases with CSU, the trigger cannot be identified and the patients try to suppress symptoms with many drugs including antihistamines or steroids for a long time. CSU has also a major impact on the quality of life of patients who have an insatiable desire for knowledge about their disease[2]. Thus, patients with CSU often ask clinicians about the required dietary modification.

The Mediterranean diet is a healthy eating pattern and is also found to be associated with reduced risk for cardiovascular diseases, stroke, metabolic syndrome, and carcinomas[3-5]. Furthermore, it was also reported that a decrease in the risk of chronic inflammatory diseases is associated with this diet[5].

There have been many studies about dietary approaches in CSU, including the diet without fish products, pseudoallergen-free diet, and low histamine diet[6-8].

To the best of our knowledge, there has been no study about the relationship between CSU and Mediterranean diet adherence. The aim of this study was to evaluate the relationship between CSU and the Mediterranean diet score (MDS).

METHODS

This cross-sectional case-control observational study was reviewed by the Ethics Committee of Suleyman Demirel University Hospital and approved by the report of the decision number 212 on August 10, 2020. This study was conducted according to the Declaration of Helsinki and all subjects provided informed consent.

Study population

Patients diagnosed with CSU (having symptoms longer than 6 weeks and underlying triggering factors could not be defined), aged over 18 years and under 65 years, who presented to the dermatology outpatient clinic of Suleyman Demirel University Hospital between September 2020 and December 2020, and sex- and age-matched healthy controls were considered for this study.

Participants with a history of cardiovascular or cerebrovascular events, active infection, and any uncontrolled systemic or skin diseases except CSU (for the patient group) and regular drug intake for any reason were excluded. Furthermore, CSU patients under the treatment of any systemic steroid such as omalizumab or immunosuppressive treatment such as cyclosporine were excluded.

Outcome measurements

Urticaria Activity Score over 7 days (UAS7) defines two symptoms: the quantity of wheals and intensity of itching, each on a 0–3 scale every day. The UAS7 is the sum of the two daily ratings from seven consecutive days, yielding a total score of 0–42, which means that UAS7 measures the severity of CSU symptoms in the previous week[9].

Urticaria Control Test (UCT) is a basic 4-item assessment tool to determine disease control in patients with CSU. It has mainly two parts, evaluating the frequency of symptoms and the suppression level of these symptoms by drugs. Low points indicate high disease activity and low disease control. The minimum and maximum UCT scores are 0 and 16, respectively. Less than 12 points indicate poorly controlled disease, whereas ≥12 points indicate well-controlled disease[10].

Questionnaire of the Mediterranean diet score

In the questionnaire of Mediterranean diet adherence, there are 14 questions based on assigning a score from 0 to 1 according to the daily intake of the eight components (Table 1)[11].

Table 1. Validated 14-item questionnaire of Mediterranean diet adherence.

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? (1 serving: 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving: 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥2

The interviews were conducted by the same physician via a face-to-face method. Through this questionnaire, the consumption of vegetables, fruits, legumes, nuts, whole grains, fermented dairy products, fish and monounsaturated fats, average alcohol, and red meat of an individual was evaluated[12]. The minimum and maximum diet scores are 0 and 14, and according to the Mediterranean diet the individuals with higher points were considered to be fed more consistently[12].

Statistical analysis

Data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean±SD, and categorical variables were reported as percentages and counts. The Student's t-test was used for comparisons of normally distributed variables, and the Mann–Whitney U test was used for non-normally distributed variables if two groups existed. One-way analysis of variance was used to compare normally distributed variables among three groups. Tukey's test was used for post-hoc analysis. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Pearson's correlation coefficients were used to assess the strength of relationships between continuous variables, and Spearman's correlation analysis was performed for noncontinuous and categorical variables. Univariate and multivariate logistic regression analysis consisted of the MDS and the variables (depression, high-density lipoprotein [HDL], low-density lipoprotein [LDL], creatinine, and fibromyalgia). In all the analyses, the p<0.05 was considered to be statistically significant. The number of patients required for this study in each group was 100 patients for sampling with 90% power and 0.05 type I error as at least 97 (R 3.0.1. open source program). The primary effect variable was determined as one point of MDS.

RESULTS

A total of 100 patients (30 males and 70 females) with CSU and sex- and age-matched healthy controls (30 males and 70 females) were enrolled in this study. Descriptive features of the participants are given in Table 2. The mean age in the patient group was 38.6±13.0 years (with an age range 18–65) and in the control group it was 38.7±13.8 years (p=0.983). Furthermore, there were no significant differences between the two groups concerning BMI, waist circumference, smoking, and use of alcohol (Table 2). Since depression and/or fibromyalgia syndrome was higher in the patient group, there were significant differences between the groups (p<0.018 and p=0.030, respectively). The mean levels of laboratory parameters of the participants were shown in Table 1.

Table 2. Baseline characteristics and laboratory parameters of the study groups.

	Patient group (n=100)	Control group (n=100)	p-value
Age, years	38.6±13.0	38.7±13.8	0.983
Female, n (%)	70 (70)	69 (69)	0.878
BMI, kg/m²	24.8±3.82	24.2±4.0	0.306
Waist circumference	83±3.8	85±2.6	0.357
Mediterranean diet score	5.40±1.88	6.30±1.39	<0.001
Smoking, n (%)	34 (34)	43 (43)	0.191
Use of alcohol, n (%)	12 (12)	12 (12)	1.000
Comorbidities			
Depression, n (%)	15 (15)	5 (5)	0.018
Asthma, allergies, rhinitis, n (%)	6 (6)	2 (2)	0.149
Diabetes mellitus, n (%)	5 (5)	8 (8)	0.390
Hypothyroidism, n (%)	14 (14)	7 (7)	0.106
Rheumatologic disease, n (%)	5 (5)	1 (1)	0.097
Fibromyalgia, n (%)	14 (14)	5 (5)	0.030
Hypertension, n (%)	6 (6)	5 (5)	0.756
Laboratory parameters			
Glucose, mg/dL	97.4±12.3	98.8±15.6	0.945
Creatinine, mg/dL	0.76±0.10	0.73±0.14	0.049
Total cholesterol, mg/dL	196.0±27.0	196.1±25.3	0.975
LDL-C, mg/dL	137.6±29.2	125.6±27.5	0.003
HDL-C, mg/dL	42.52±9.46	48.15±9.23	0.002
Triglyceride, mg/dL	142.1±38.5	146.1±52.8	0.536

Data are given as mean±SD, n (%) or median (interquartile range or lower-upper limit). BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. *p-value is significant at the 0.05 level.

Concerning LDL and HDL levels, there were significant differences between the two groups (p=0.003 and p=0.002) and the patient group had higher levels of LDL and HDL.

The mean UCT score of the patients with CSU was 8.66±3.60, the mean UAS7 score was 23.73±11.34, and the mean MDS was 5.40±1.88. The MDS of healthy controls was 6.30±1.39, which was significantly different from the patient group (p<0.001).

In particular, the UAS7 score was negatively correlated with the MDS, whereas the UCT score was positively correlated with the MDS (Figure 1).

Furthermore, univariate and multivariate logistic regression analyses were conducted to identify variables that are predictive of CSU in these 100 patients (Table 3). The variables included MDS, the presence of depression and fibromyalgia syndrome, creatinine, and LDL and HDL cholesterol levels. In univariate analysis, all parameters except creatinine levels were found to be significantly associated with CSU. Moreover, in multivariate analysis, the MDS, HDL levels, and depression were found to be significantly associated with CSU.
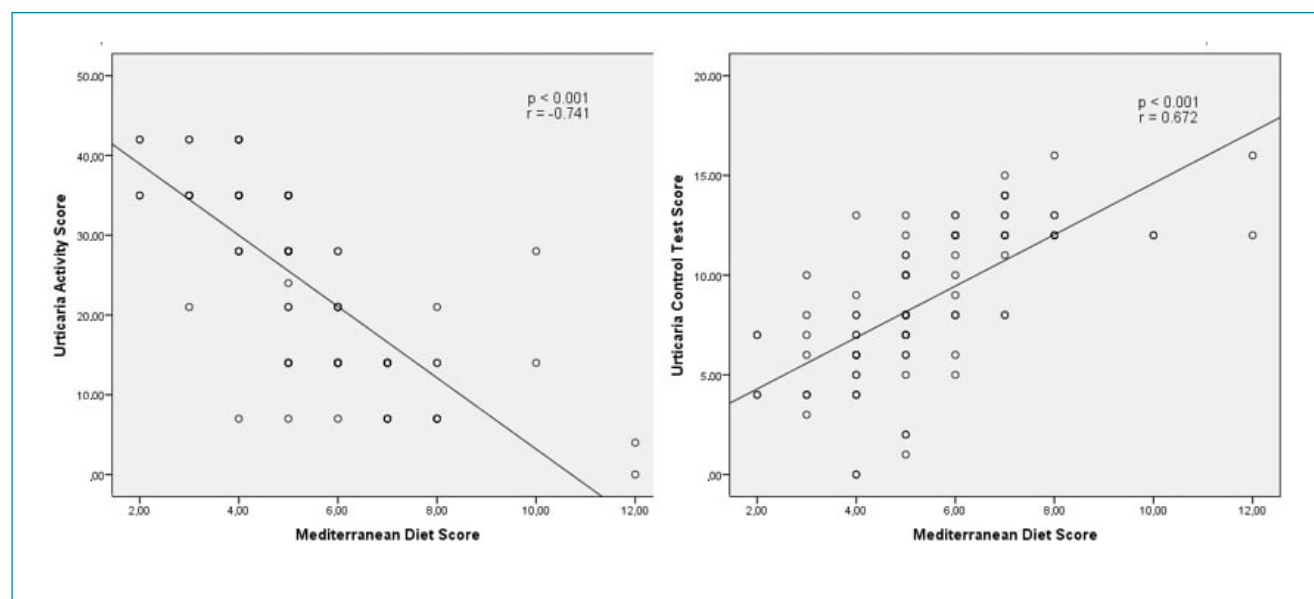
Figure 1. Correlation schemes of Mediterranean diet score with both Urticaria Activity Score over 7 days and Urticaria Control Test.

Table 3. Multivariate logistic regression analysis to predict CSU.

	Univariable OR (95%CI)	p-value	Multivariable OR (95% CI)	p-value
Mediterranean diet score	1.409 (1.167–1.701)	<0.001	1.433 (1.173–1.752)	<0.001
Depression	0.298 (0.104–0.855)	0.024	0.320 (0.280–0.361)	0.047
Fibromyalgia	0.323 (0.112–0.935)	0.037	0.341 (0.140–0.563)	0.81
Creatinine	0.098 (0.009–1.007)	0.051		
LDL-C	0.985 (0.975–0.995)	0.004	0.997 (0.984–1.009)	0.163
HDL-C	1.070 (1.034–1.107)	<0.001	1.049 (1.002–1.098)	0.043

CSU: chronic spontaneous urticarial; CI: confidence interval; OR: odds ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. *p-value is significant at the 0.05 level.

DISCUSSION

The relationship between CSU symptoms and diets has been investigated several times and the results are controversial. Some studies using diet restrictions showed that diet restrictions are unnecessary and ineffective[13,14], whereas other studies suggest that diet restrictions may result in complete or significant remission of symptoms in patients with CSU[15-17]. It was argued that these results may be related to the psychological relief of the patients after food restrictions and the importance of the oral challenge in CSU[13,14]. Although there was no particular restriction of diet exactly, our results showed that adherence to the Mediterranean Diet was negatively correlated with the severity of the symptoms of the patients with CSU.

In a study by Son et al.[18]. the effect of a histamine-free diet was evaluated in 22 patients with CSU, and a significant decrease in the severity of the disease and also in the plasma histamine level was found to be associated with this diet. Furthermore, Wagner[16] and Guida[19] reported similar results that a histamine-free diet may reduce the severity of symptoms in CSU. In fact, the recommendations of a histamine-free diet and the Mediterranean diet are almost the opposite. In a histamine-free diet, histamine-rich foods, such as some fishes, chicken, spinach, pork, mayonnaise, yogurt, cheese, ketchup, wine, beer, cabbage or radish, soybean paste, red pepper, are restricted, whereas in the Mediterranean diet consumption of red wine, seafood, all vegetables, and fruits are suggested[18].

Besides, many studies evaluate the effects of a pseudo-allergen-free diet on disease activity in CSU[15,17]. According to the results of these studies, a pseudoallergen-free diet is effective and beneficial for patients with CSU. A wide number of nutrients may act as pseudoallergens such as natural compounds (including all fruits, vegetables except mushrooms, tomatoes, and olives), all preservatives including foods (dyes, preservatives, and flavorings), vasoactive compounds (acetylsalicylic acid, histamine, and nitric oxide), and fats except butter and plant oils[5,17]. In fact, regarding the similarity of the pseudoallergen-free diet and the Mediterranean diet, both of them suggest preservative-free foods, butter, and plant oils. In the Mediterranean diet fruits are prominent, whereas they are restricted in the pseudoallergen-free diet.

Adherence to the Mediterranean diet has not been evaluated in patients with CSU in the literature until 2021. It was reported that the risk of cardiovascular diseases, stroke, chronic inflammatory diseases, and even carcinomas can be reduced with the Mediterranean diet[3-5]. In addition, it was shown that the anti-inflammatory and antioxidant effects of the Mediterranean diet have the potential to reduce systemic inflammation and oxidative stress which play a role in the pathophysiology of CSU disease[1,20]. In this preliminary study, we reported that adherence to the Mediterranean diet may be an independent factor that may lower the occurrence of CSU. It may also reduce the severity of CSU symptoms in patients. These results may be obtained due to the following features of the Mediterranean diet: in this diet, it is frequent that the distance between the source of food and the consumer is short, and local food is more preferred in the Mediterranean countries than the global food[21]. Local food is often fresh and involves no preservatives or less amount of the artificial ingredients. Similarly, there are often less pesticide residues in the local food and the Mediterranean in-house cooking methods are usually nutrient-preserving, allowing the preservation of the phytochemicals[22].

In addition, our study results are similar to those of many studies in which the prevalence of depression and fibromyalgia is higher in patients with CSU than healthy controls[23,24]. Adherence to the Mediterranean diet can reduce the frequency of these diseases; however, further controlled trials are required to support this observation.

This study has some limitations. We assessed only dietary habits and adherence to the Mediterranean diet of the participants, but not the physical activity or the psychological stress in their life. Therefore, the results and correlations of this study should be verified by future studies with broader and more detailed methods.

CONCLUSIONS

Although this diet seems to work in Turkish CSU patients, the relationship between compliance with the Mediterranean diet and disease severity may not be significant in CSU patients in other countries due to genetic changes or nutritional habits. One should perform further randomized controlled trials with larger samples in order to confirm this observation regarding the relationship between the Mediterranean diet and CSU disease. However, it is advised that the adoption of a healthy lifestyle and diet should be combined with the holistic management of patients with CSU.

AUTHORS' CONTRIBUTIONS

AHH: Conceptualization, Data Curation, Formal Analysis, Software, Writing – Original Draft. **KA:** Conceptualization, Data Curation, Formal Analysis, Software, Writing – Review & Editing.

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Time trends of physical inactivity in Brazilian adults from 2009 to 2017

Michael Pereira da Silva[1]* iD, Fabio Fontana[2] iD, Jhonathan Gritten Campos[3] iD,
Oldemar Mazzardo[4] iD, Dartel Ferrari Lima[4] iD, Ana Carolina Paludo[5] iD,
Wagner de Campos[3] iD

SUMMARY

OBJECTIVE: The aim was to evaluate the changes in the prevalence of physical inactivity in the Brazilian adults from 2009–2017.

METHODS: This study used a time-series research design based on the cross-sectional data of 462,498 Brazilian adults from 2009–2017. Participants were classified as physically inactive if they indicated not participating in physical activity in the last three months. The Prais–Winsten regression analyzed physical inactivity trends over time.

RESULTS: The overall prevalence of physical inactivity was stable (p>0.05). Physical inactivity increased for women in four state capitals (annual growth rate: Goiânia 1.62%, Campo Grande 3.28%, Porto Velho 0.93%, and Vitória 2.09%) and decreased in one (annual growth rate: Rio Branco 4.50%). Physical inactivity decreased for men in four state capitals (annual growth rate: Campo Grande 4.72%, Natal 2.73%, São Luís 4.94%, and Rio Branco 2.95%).

CONCLUSION: The physical inactivity among the Brazilian adults was stable between 2009 and 2017. Physical inactivity increased in women from Goiânia, Campo Grande, Porto Velho, and Vitória and decreased in women from Rio Branco and in men from Campo Grande, Natal, São Luís, and Rio Branco.

KEYWORDS: Sedentary behavior. Population surveillance. Epidemiology.

INTRODUCTION

Physical inactivity is the fourth leading cause of deaths worldwide[1], accounting for 6–10% of all deaths[2]. Considering that 27.5% of the world population performs an insufficient amount of physical activity (PA)[3], physical inactivity is a major modern time threat to public health. For substantial health benefits, adults should engage in at least 150 min of moderate-intensity PA or 75 min of vigorous-intensity PA weekly[4,5].

Surveillance of PA informs public health authorities and assists in evaluating research efforts and policies aimed at increasing population levels of PA[3]. Some countries have implemented PA surveillance systems, including the United States, Canada, Germany, France, and others[6]. In Brazil, the Ministry of Health has implemented a health surveillance system called VIGITEL[7]. This system provides annual information on PA behavior for 26 states and the Federal District of Brazil. VIGITEL describes the prevalence of physical inactivity based on adults reporting a lack of engagement in PA during leisure time, at work, at home, or commuting to work or school[7].

Previous investigations have examined the time trends of PA patterns based on VIGITEL data[8-12]. However, the lack of estimates of physical inactivity trends[8,9], the selection of a subsample of adults with health insurance[12], and the use of a

time-series statistical analysis which failed to account for serial autocorrelations[10,11] may limit the ability of previous studies to evaluate physical inactivity trends in the Brazilian adults. Additionally, the data on regional time trends of physical inactivity are scarce in Brazil. Therefore, this study aimed to evaluate the overall and state-capital-specific changes in the prevalence of physical inactivity in the Brazilian adults from 2009–2017.

METHODS

Study design

This study used a time-series design based on the cross-sectional data collected by VIGITEL from 2009–2017 in all 26 state capitals and the Federal District of Brazil. The detailed methodological procedures can be found elsewhere[7]. The VIGITEL project was approved by the National Commission on Ethics in Research Involving Human Participants (Protocol nº. 355,590). All participants provided informed consent form at the beginning of the telephone interviews.

Sample

The VIGITEL collected the data based on probabilistic samples of the Brazilian adults (≥18 years old) living in households with at least one fixed telephone line across all state capitals and the Federal District of Brazil and used the rake method to calculate post-stratification sample weights for each city[13]. From 2009–2017, VIGITEL conducted 462,498 interviews of adults of both sexes (Table 1).

Physical inactivity

The physical inactivity indicator refers to people who reported neither participating in PA during their free time in the last three months, partaking in intense physical exertion at work, actively commuting to work or school by walking or biking for at least 10 min, nor performing intense household cleaning[7,11]. The VIGITEL questionnaire has adequate validity (area under the receiver operating characteristic curve: AUC=0.75) and reliability (kappa=0.70)[14].

Data analysis

The Prais–Winsten regression models analyzed the time trends of physical inactivity. This procedure allows the correction of serial autocorrelations when analyzing values organized over time[15,16]. The prevalence rates were calculated using sample weights, log transformed, and used as dependent variables, while each year of observation was used as an independent variable. We assumed

Table 1. Total interviews conducted in state capitals and Federal District of Brazil from 2009–2017.

	2009 (n=54,367)	2010 (n=54,339)	2011 (n=52,144)	2012 (n=45,448)	2013 (n=52,929)	2014 (n=40,853)	2015 (n=54,174)	2016 (n=53,210)	2017 (n=53,034)	Total (n=462,498)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex										
Men	21,347 (39.26)	20,764 (38.21)	20,641 (39.60)	17,389 (38.26)	20,276 (38.31)	15,521 (37.99)	20,368 (31.60)	20,258 (38.07)	19,504 (37.78)	176,068 (38.23)
Women	33,020 (60.74)	33,575 (61.79)	31,503 (60.41)	28,059 (61.74%)	32,653 (61.69)	25,332 (62.01)	33,806 (62.40)	32,952 (61.93)	33,530 (63.22)	284,430 (61.77)
Age (years)										
18–24	7,760 (14.27)	7,364 (13.55)	6,971 (12.87)	5,353 (11.78)	4,316 (11.02)	4,316 (10.56)	5,050 (9.32)	5,163 (9.70)	4,510 (8.50)	52,321 (11.31)
25–34	10,664 (15.59)	10,573 (19.46)	10,147 (18.74)	8,020 (17.65)	8,253 (19.61)	6,307 (15.44)	7,163 (13.22)	6,945 (13.05)	6,000 (11.31)	74,072 (16.02)
35–44	11,369 (20.91)	10,902 (20.06)	10,436 (19.27)	8,580 (18.88)	9,069 (17.13)	7,054 (17.27)	8,463 (15.62)	7,925 (14.89)	7,416 (13.98)	81,214 (17.56)
45–54	10,238 (18.83)	10,271 (18.90)	10,359 (19.13)	8,723 (19.19)	10,004 (18.90)	7,656 (18.74)	9,750 (18.00)	9,374 (17.62)	8,937 16.85)	85,312 (18.45)
55–64	7,450 (13.70)	7,889 (14.52)	8,157 (15.07)	7,192 (15.82)	9,369 (17.70)	7,103 (17.39)	10,399 (19.20)	10,154 (19.08)	10,444 (19.69)	78,157 (16.90)
65 or above	6,886 (12.67)	7,340 (13.51)	8,074 (14.91)	7,580 (16.68)	10,400 (19.65)	8,417 (20.60)	13,349 (24.64)	13,649 (25.65)	15,727 (29.65)	91,422 (19.77)

Source: VIGITEL.

significant changes in the prevalence of physical inactivity when the regression coefficients differed from zero (p<0.05). We calculated annual growth rates and 95% confidence intervals (95%CI) using the following equations[16]:

Annual growth rate = $-1+10^b$
95%CI = $-1+10(b \pm t \times SE)$

Stata MP 14.1 (Stata Corp LLC, College Station, TX, USA) statistical package performed all the analyses.

RESULTS

Overall changes in physical inactivity

The prevalence of physical inactivity remained stable from 2009–2017 (Figure 1). In 2017, 13.7% of the sample reported being physically inactive.

Midwest and northeast regions

The prevalence of physical inactivity decreased for men living in the cities of Campo Grande (-4.72%, 95%CI -8.38– -0.46), Natal (-2.73%, 95%CI -5.16– -0.46), and São Luís (-4.94%, 95%CI -7.32– -2.50). The prevalence of physical inactivity increased for women living in Campo Grande (3.28%, 95%CI 1.39–5.20) and Goiânia (1.62%, 95%CI 0.23–3.28) (Table 2).

North, southeast, and south regions

The prevalence of physical inactivity decreased for the overall sample of adults living in the cities of Macapá (-3.39%, 95%CI -6.46– -0.23) and Rio Branco (-4.06%, 95%CI -5.59– -2.50) and increased in Curitiba (2.09%; 95%CI 0.69–3.28). The prevalence of physical inactivity decreased for men (-2.95%, 95%CI -5.81–0.23) and women (-4.50%, 95%CI -7.32– -1.60) from Rio Branco and for women from Macapá (-2.28%, 95%CI -4.50– -0.23) from 2009 to 2017. The prevalence of physical inactivity increased for women in Porto Velho (0.93%, 95%CI 0.23–1.89) and Vitória (2.09%; 95%CI 0.69–3.51) (Table 3).

Prevalence of physical inactivity in Brazilian adults from 2009 to 2017, VIGITEL, Brazil										
	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient	AGR
Overall	15.9	15.3	14.9	14.9	16.3	15.4	16.0	13.7	13.7	-,005	-
Men	16.3	15.7	15.1	15.2	16.8	16.2	16.0	12.2	13.9	-,009	-
Women	15.6	14.9	14.7	14.6	15.7	14.7	16.0	14.9	13.9	-,001	-
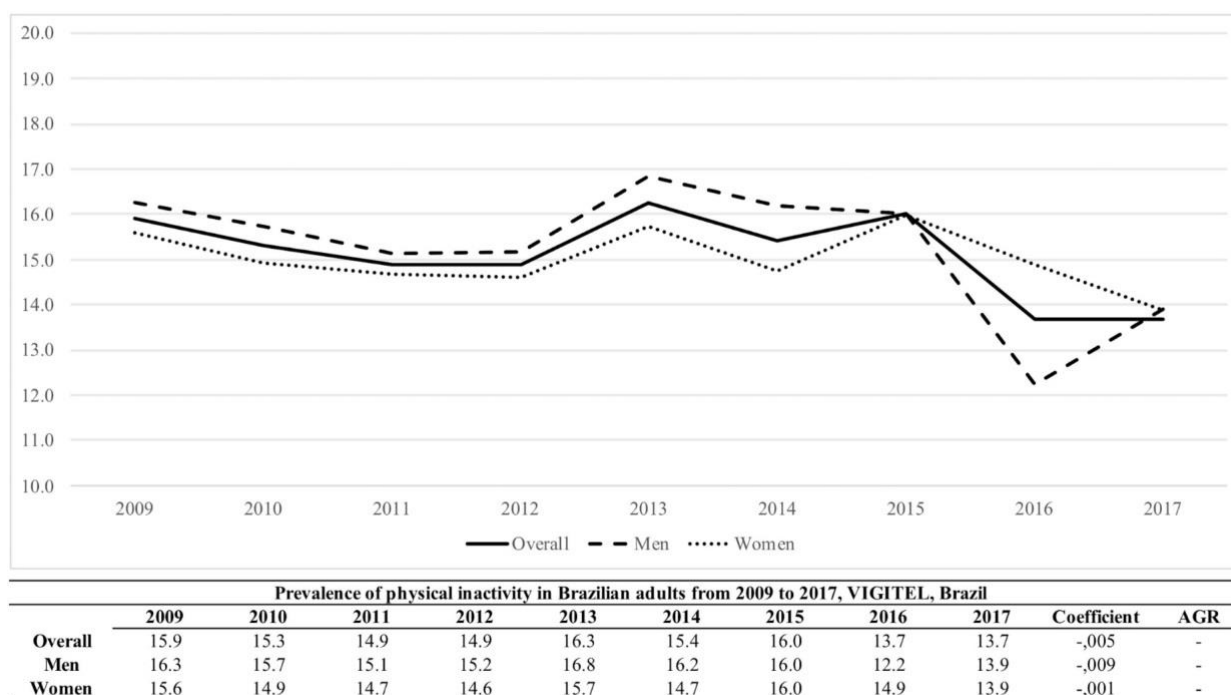
Figure 1. The prevalence of physical inactivity from 2009–2017 in Brazil (Source: VIGITEL, Brazil).

Table 2. Prevalence, regression coefficients, and annual growth rate for physical inactivity in the Midwest and Northeast regions of Brazil.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient	p	AGR (%)
Midwest												
Campo Grande												
Overall	12.30	13.90	15.70	14.00	13.90	13.00	13.80	13.30	12.70	-0.002	0.62	–
Men	14.00	16.70	18.70	15.20	14.10	14.40	14.00	12.90	9.70	-0.021	0.03	-4.72
Women	10.70	11.30	13.10	12.80	13.70	11.80	13.70	13.80	15.50	0.014	0.004	3.28
Cuiabá												
Overall	15.40	14.70	14.60	13.70	16.80	13.10	12.60	13.00	15.90	-0.005	0.27	–
Men	13.50	15.40	14.70	12.90	17.50	11.70	12.40	12.80	16.50	-0.004	0.22	–
Women	17.20	14.00	14.50	14.40	16.10	14.40	12.80	13.10	15.40	-0.006	0.18	–
Federal District												
Overall	13.20	15.80	12.20	11.90	13.10	14.00	13.90	10.30	10.70	-0.012	0.09	–
Men	7.30	22.70	9.80	11.50	12.30	13.50	12.60	9.00	8.90	-0.015	0.22	–
Women	18.40	9.70	14.30	12.30	13.90	14.50	15.10	11.40	12.40	-0.002	0.79	–
Goiânia												
Overall	13.80	12.20	12.90	12.10	14.60	13.90	17.90	11.40	13.40	0.004	0.49	–
Men	15.20	13.60	13.10	11.40	15.90	14.50	21.50	10.60	12.90	0.000	0.99	–
Women	12.60	11.00	12.80	12.80	13.40	13.40	14.60	12.10	13.80	0.007	0.04	1.62
Northeast												
Aracaju												
Overall	19.00	17.60	18.10	15.60	19.10	18.60	15.50	18.10	18.00	-0.001	0.62	–
Men	19.70	20.20	19.70	15.80	18.40	18.90	14.90	18.80	19.90	-0.004	0.43	–
Women	18.50	15.50	16.70	15.40	19.70	18.40	16.10	17.50	16.40	0.006	0.22	–
Fortaleza												
Overall	14.60	15.20	14.60	16.50	19.20	17.80	17.20	15.60	16.20	0.006	0.37	–
Men	15.30	16.40	16.30	16.60	20.10	15.10	16.70	13.00	15.60	0.003	0.72	–
Women	13.90	14.30	13.30	16.40	18.50	20.00	17.60	17.70	16.80	0.013	0.12	–
João Pessoa												
Overall	17.20	18.70	17.80	16.10	21.10	19.30	20.30	17.80	17.50	0.003	0.54	–
Men	17.70	19.50	20.80	15.80	22.40	20.20	17.90	17.70	15.70	-0.005	0.31	–
Women	16.70	18.00	15.20	16.20	20.10	18.60	22.30	18.00	19.00	0.010	0.07	–
Maceio												
Overall	20.30	17.80	16.70	18.20	19.90	16.80	19.40	17.00	18.40	-0.001	0.62	–
Men	22.80	16.70	18.20	18.40	21.40	16.60	21.10	15.80	18.20	-0.004	0.27	–
Women	18.20	18.80	15.30	17.90	18.60	17.00	18.00	18.00	18.70	0.001	0.54	–
Natal												
Overall	17.50	17.70	16.20	18.20	18.10	15.50	19.50	16.60	17.70	0.000	0.84	–
Men	16.40	22.20	19.50	18.10	20.20	13.40	20.00	15.80	16.20	-0.012	0.03	-2.73
Women	18.50	13.90	13.50	18.30	16.20	17.20	19.10	17.20	19.00	0.011	0.06	–
Recife												
Overall	18.60	17.00	18.20	18.50	19.30	18.20	19.20	16.80	17.70	-0.001	0.74	–
Men	15.30	15.50	18.10	21.50	17.70	17.80	18.70	13.80	17.20	0.003	0.97	–
Women	21.20	18.10	18.20	16.00	20.60	18.60	19.50	19.20	18.00	0.000	0.96	–

Continue...

Table 2. Continuation.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient	p	AGR (%)
Salvador												
Overall	14.40	13.70	14.60	15.00	14.30	13.80	17.10	12.10	14.10	-0.002	0.62	–
Men	12.90	12.40	13.20	15.50	15.50	13.80	16.90	9.90	15.10	0.001	0.88	–
Women	15.70	14.80	15.70	14.60	13.30	13.70	17.10	13.90	13.20	-0.005	0.26	–
São Luís												
Overall	18.00	16.60	15.20	13.90	19.00	13.80	18.20	15.60	13.60	-0.004	0.34	–
Men	18.40	18.20	15.90	12.90	16.70	12.60	16.40	12.10	10.80	**-0.022**	**0.002**	**-4.94**
Women	17.70	15.30	14.60	14.70	20.90	14.70	19.70	18.60	15.90	0.008	0.14	–
Teresina												
Overall	16.70	18.40	16.90	16.50	21.70	19.80	17.30	16.30	17.40	0.000	0.95	–
Men	15.80	19.40	18.70	14.70	24.00	19.70	15.50	14.60	17.00	-0.005	0.54	–
Women	17.50	17.60	15.50	17.90	19.80	19.90	18.70	17.70	17.60	0.002	0.60	–

AGR: annual growth rate. Bold values indicate significant changes in the prevalence of physical inactivity (p<0.05).

Table 3. Prevalence, regression coefficients, and annual growth rate for physical inactivity in the North, Southeast, and South regions of Brazil.

	Prevalence (%)											
	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient	p	AGR (%)
North												
Belém												
Overall	14.10	15.70	13.30	15.60	16.70	17.00	14.90	14.20	14.50	0.001	0.86	–
Men	12.20	12.20	12.40	14.10	13.80	15.20	15.10	9.90	10.90	-0.004	0.65	–
Women	15.70	18.80	14.00	16.90	19.20	18.50	14.80	17.80	17.50	0.003	0.56	–
Boa Vista												
Overall	15.00	16.50	11.30	14.30	16.30	15.30	14.30	12.30	14.20	-0.004	0.53	–
Men	15.30	14.40	11.70	16.00	16.80	15.40	15.00	12.30	14.00	-0.002	0.72	–
Women	14.80	18.60	10.90	12.60	15.80	15.30	13.50	12.30	14.40	-0.005	0.48	–
Macapá												
Overall	18.30	13.50	17.90	15.20	18.40	16.20	12.80	13.80	11.90	**-0.015**	**0.04**	**-3.39**
Men	18.10	9.50	18.30	15.90	17.80	14.50	9.90	12.50	9.30	-0.020	0.13	–
Women	18.60	17.30	17.60	14.50	19.00	17.70	15.60	15.00	14.40	**-0.010**	**0.04**	**-2.28**
Manaus												
Overall	15.50	10.70	16.20	13.80	16.00	15.50	17.10	13.50	12.30	0.002	0.75	–
Men	14.50	8.90	12.70	10.90	15.40	15.70	18.10	12.70	12.00	0.011	0.32	–
Women	16.50	12.30	19.40	16.60	16.50	15.40	16.20	14.30	12.50	-0.007	0.34	–
Palmas												
Overall	13.50	11.90	15.80	12.20	17.50	13.40	12.80	12.60	11.70	-0.005	0.43	–
Men	13.80	8.90	11.40	14.70	19.80	15.90	13.00	10.40	11.60	0.045	0.07	–
Women	13.30	13.60	20.20	9.90	15.30	11.10	12.60	14.60	11.80	-0.008	0.23	–

Table 3. Continuation.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	Coefficient	p	AGR (%)
Prevalence (%)												
Porto Velho												
Overall	12.50	13.30	12.40	12.80	16.20	11.60	15.00	12.40	13.00	0.001	0.65	–
Men	12.60	13.60	11.00	13.30	17.80	10.30	15.40	11.30	12.70	-0.001	0.85	–
Women	12.40	13.00	13.70	12.30	14.50	13.10	14.60	13.50	13.20	0.004	0.04	0.93
Rio Branco												
Overall	16.20	22.10	17.50	16.40	17.70	14.60	17.40	13.10	14.40	-0.018	<0.001	-4.06
Men	15.50	18.30	18.40	17.10	18.20	15.10	15.10	12.60	14.80	-0.013	0.03	-2.95
Women	16.90	25.60	16.70	15.80	17.30	14.20	19.40	13.50	14.10	-0.020	0.001	-4.50
Southeast												
Vitória												
Overall	14.80	13.20	12.90	14.20	14.30	14.40	15.70	12.30	14.90	0.002	0.57	–
Men	16.10	14.00	11.90	12.30	14.40	14.10	16.20	9.50	12.90	-0.009	0.28	–
Women	13.70	12.50	13.80	15.80	14.20	14.70	15.40	14.60	16.50	0.009	0.007	2.09
Belo Horizonte												
Overall	14.90	11.90	14.40	14.60	15.30	13.10	15.60	13.20	13.50	0.001	0.78	
Men	17.50	13.30	15.90	15.40	14.90	16.60	17.50	14.50	14.10	-0.001	0.83	
Women	12.70	10.70	13.20	14.00	15.70	10.20	14.00	12.20	13.00	0.002	0.71	
Rio de Janeiro												
Overall	16.10	14.80	12.50	16.60	15.90	16.50	14.40	13.80	14.50	-0.002	0.66	–
Men	18.50	13.00	13.30	15.90	17.40	17.30	15.20	11.40	13.40	-0.011	0.32	–
Women	14.10	16.40	11.90	17.20	14.60	15.80	13.80	15.80	15.40	0.003	0.36	–
São Paulo												
Overall	16.60	13.00	13.30	14.10	16.30	15.40	16.10	13.00	12.40	-0.007	0.37	–
Men	17.60	15.50	13.50	15.80	17.90	18.50	15.70	11.50	14.30	-0.009	0.35	–
Women	15.60	10.90	13.10	12.70	15.00	12.80	16.50	14.30	10.80	0.003	0.64	–
South												
Curitiba												
Overall	12.30	12.20	11.20	13.30	13.50	13.00	13.10	14.00	14.00	0.009	0.006	2.09
Men	14.80	13.70	9.90	13.40	13.10	14.20	13.20	14.50	16.40	0.009	0.24	–
Women	10.20	10.80	12.40	13.10	13.90	11.90	13.10	13.70	12.00	0.010	0.12	–
Florianópolis												
Overall	11.50	12.20	10.80	11.40	13.40	13.10	12.40	11.20	13.90	0.006	0.17	–
Men	11.30	13.30	11.40	9.50	13.00	12.90	10.60	10.00	14.00	-0.001	0.24	–
Women	11.70	11.30	10.30	13.20	13.80	13.40	14.10	12.20	13.80	0.011	0.06	–
Porto Alegre												
Overall	13.30	13.10	13.60	14.50	14.00	14.50	17.60	15.20	12.70	0.005	0.40	–
Men	12.60	13.10	12.30	16.80	13.60	13.40	18.30	15.90	12.00	0.009	0.21	–
Women	13.90	13.10	14.70	12.70	14.40	15.40	17.10	14.70	13.20	0.004	0.43	–

AGR: annual growth rate. Bold values indicate significant changes in the prevalence of physical inactivity (p<0.05).

DISCUSSION

Physical inactivity is a significant public health problem and an important factor for worldwide mortality[2]. Thus, monitoring of physical inactivity can inform public policies aimed at increasing the population levels of PA. This study assessed the time trends of physical inactivity in Brazil indicating that the prevalence of physical inactivity has remained stable from 2009–2017. In addition, stratifications indicated different time trends of physical inactivity by sex and state capital. More specifically, we observed an increase in inactivity for women in four state capitals and a decrease for men in four major state capitals.

This study indicated that the prevalence of physical inactivity for the overall sample remained stable from 2009–2017. Our results are similar to the findings of previous investigations. Guthold et al.[3] found a stable prevalence of physical inactivity worldwide and for Latin and Caribbean countries from 2001–2016 despite differences in the definition of physical inactivity. While Guthold et al.[3] defined physical inactivity as an insufficient level of PA to meet the current recommendations advocated by the WHO, we defined physical inactivity as a lack of PA engagement in four domains: leisure, transportation, work, and home[7,11]. Our findings also corroborate the results of previous studies using the VIGITEL data[10-12]. Even after accounting for the dependence of a measure of physical inactivity assessed at multiple time points using adequate time-series data analyses, the stability of prevalence of physical inactivity in the overall sample was similar to previous VIGITEL studies[10-12]. Increasing the participation of fairly sedentary individuals in PA is a challenge in Brazil.

The adherence to WHO PA recommendations has increased in Brazil since 2006[8]. Considering the results of this study and previous VIGITEL studies[10-12] indicating a stable prevalence of physical inactivity in the past decade, the growth in the adherence to PA recommendations is likely a result of changes in PA engagement of adults who are classified as insufficiently active. Even small increments in the PA habits of those reporting extremely low levels of PA are expected to contribute significantly in order to reduce the risk of early deaths[17,18]. To effectively reduce public health problems associated with physical inactivity, Brazil should focus on increasing the PA levels of the portion of the population who are fairly sedentary.

A closer inspection of our data revealed differences in the time trends by state capital and sex. While 18 Brazilian state capitals had a stable prevalence of physical inactivity for the overall sample, one state capital showed decreased the prevalence of physical inactivity for the overall sample, four state capitals showed decreased the prevalence of physical inactivity for men, and four other state capitals showed increased physical inactivity prevalence for women. To better understand these time trends, it is necessary to reflect on the goals Brazil has outlined for the reduction of chronic noncommunicable diseases including investing on policies to promote PA at the population level[19]. From this perspective, the National Policy for Health Promotion[19] was established in 2006, ratifying the commitment of Brazilian federal government to expanding public health actions and promoting new PA programs. Furthermore, the Brazilian Ministry of Health funded 748 PA programs in the first year of inception of the National Policy for Health Promotion[20]. Several other large-scale PA public programs were created by the Brazilian Unified Health System in this past decade[21]. These actions mainly reach populations of low socioeconomic status and intend to reduce economic disparities to PA access[19,21,22].

A recent study demonstrates that only 20% of the Brazilian adult population is aware of public PA programs, and 1.9% have ever engaged in one of these programs[22]. However, regional differences in the access PA public programs might help explaining the differences in time trends for each state capital and sex. In our study, the five state capitals decreasing physical inactivity are in regions with more participation in public PA programs such as the North, Northeast, and Midwest regions of Brazil[22]. Therefore, further studies should examine the impact of these programs on the time trends of physical inactivity in Brazilian state capitals.

The results for five Brazilian capitals were alarming (Curitiba, Goiânia, Campo Grande, Porto Velho, and Vitória). Physical inactivity increased in these cities, especially for women. Physical inactivity plays an important role in the alarming rates of obesity observed today, and the increase in this behavior can contribute to the maintenance of these rates in women. Obese women have the higher risk of cardiovascular diseases, diabetes, endometrial and breast cancer, subfertility, and worse obstetric and perinatal outcomes[23-25]. Increasing PA in women might help them manage their weight, especially in women at risk of obesity, and offer additional benefits to women's health.

Worldwide, the prevalence of physical inactivity is 8% higher in women than in men[3,26]. Brazilian women are more aware of PA public programs, but they engage in these programs to the same extent as men[22]. Identification and removal of barriers for participation of Brazilian women in PA may bridge the gap between awareness and engagement in these programs. Our results suggest reinforcing the need to design targeted policies that facilitate the engagement of Brazilian women in PA programs. Unsafe neighborhoods, lack of social support, and countless responsibilities are common barriers for the engagement of women in PA. Creating safe places for PA and offering support such as child care may encourage women to be more active[27].

STRENGTHS AND LIMITATIONS

This is the first study to show the time trends of the prevalence of physical inactivity for each Brazilian state capital. The VIGITEL estimate of physical inactivity is the strength of this study. It reflects the self-reported measures of nearly absolute lack of engagement in PA in several domains. It is clear that it limits the comparability with other major international studies, but it also offers valuable information regarding people who are fairly physically inactive.

The VIGITEL study limited the interviews to fixed telephone lines. The fixed telephone line is generally associated with sectors of the population with higher schooling and income. Although this procedure could lead to selection bias, we addressed this issue by using sample weights to guarantee the representativeness of the sample[28]. Moreover, a previous study using the VIGITEL survey suggested that excluding cellphone users did not impact the estimates of physical inactivity[13]. The self-reported measures of physical inactivity could be affected by recall and social desirability bias. However, these measures are common in nationwide surveys, and the VIGITEL questionnaire has adequate validity and reliability[14].

Physical inactivity has remained stable from 2009–2017 for the overall sample, but there were observed differences by region and sex. The overall prevalence of PA decreased in the cities of Macapá and Rio Branco and increased in Curitiba.

For men, the prevalence of physical inactivity decreased in Campo Grande, Natal, São Luís, and Rio Branco. For women, the prevalence of physical inactivity increased in Goiânia, Campo Grande, Porto Velho, and Vitória and decreased in Rio Branco.

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AUTHORS' CONTRIBUTIONS

MPS: Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **FF:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **GC:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **OM:** Writing – Original Draft, Writing – Review & Editing. **DFL:** Writing – Original Draft, Writing – Review & Editing. **ACP:** Writing – Original Draft, Writing – Review & Editing. **WC:** Writing – Review & Editing.

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Liver transplantation: survival and indexes of donor–recipient matching

Fábio Silveira[1]* , Fabio Porto Silveira[1] , Alexandre Coutinho Teixeira de Freitas[2,3] ,
Júlio Cezar Uili Coelho[2,3] , Eduardo José Brommelstroet Ramos[3] ,
Matheus Martin Macri[4] , Nertan Tefilli[5] , Luis Cesar Bredt[6]

SUMMARY

OBJECTIVE: The aim of this study was to determine the prospective capacity and impact of donor risk index, preallocation survival outcomes following liver transplant, donor model for end-stage liver disease, and balance of risk on patients' 30-day survival after liver transplantation.

METHODS: We prospectively analyzed patient survival in a multicentric observational cohort of adult liver transplantation through the year of 2019 at the state of Paraná, Brazil. The receiver operating characteristic curve, the area under the curve, and the best cutoff point (i.e., the Youden's index) were estimated to analyze the prognostic value of each index.

RESULTS: In total, 252 liver transplants were included with an average model for end-stage liver disease score of 21.17 and a 30-day survival of 79.76%. The donor risk index was the only prognostic variable with no relation to patients' 30-day mortality model for end-stage liver disease and donor model for end-stage liver disease have no prognostic value on receiver operating characteristic curve, but preallocation survival outcomes following liver transplant, survival outcomes following liver transplant, and balance of risk presented good relationship with this observation. The cutoff value was estimated in 11–12 points for balance of risk and 9–12 for preallocation survival outcomes following liver transplant and survival outcomes following liver transplant. The 30-day survival for the group of transplants with scores up to 12 points (n=172) in all the three indexes was 87.79%, and for those transplants with scores higher than 12 it was 36.36%.

CONCLUSIONS: The 30-day survival is 79.76%, and balance of risk, survival outcomes following liver transplant, and preallocation survival outcomes following liver transplant are the good prognostic indexes. The cutoff value of 12 points has clinical usefulness to predict the post-liver transplantation results.

KEYWORDS: Liver transplantation. Risk assessment. Survival analysis.

INTRODUCTION

Since liver transplantation was already well established as the most appropriate treatment for end-stage liver diseases, it involves a myriad of factors related to the donor, recipient, anesthetic-surgical procedure, and intensive care management which influence the occurrence of complications, survival, and costs[1,2].

Many indexes have been validated to analyze survival, e.g., donor risk index (DRI)[3], balance of risk (BAR)[4], survival outcomes following liver transplant (PSOFT/SOFT)[5], and donor model for end-stage liver disease (DMELD)[6].

Recently, Parana's State Transplant System has outgained national prominence for the increase in the number of brain death notifications, effective donors, and number of transplants, reaching the mark of 43.8 effective donors per million of population in 2019[7]. Thus, the State Transplant Agency is concerned not only with transplantation number, but also with receptor's survival[8]. No other prospective and multicentric study was published in Brazil evaluating state results.

To analyze this issue, it demanded a joint action evolving all hospitals registered for liver transplantation at the state and coordinated by the State Transplant Agency[9]. Each hospital had one representative composing the state technical board who was responsible to prospectively collect the data. This study aims to:

(A) determine patients' 30-day survival after liver transplantation during the year of 2019;

(B) examine the capacity of MELD, DMELD, DRI, PSOFT, SOFT, and BAR as the survival prognostic indexes in our local reality; and

(C) evaluate the impact of the selected prognostic indexes on patient survival.

METHODS

This is a prospectively collected multicentric observational cohort of all liver transplantation donors and recipients through the year 2019 at the state of Paraná, Brazil. The inclusion criteria were adult recipients (>12 years of age) who received deceased donor organs. The exclusion criteria were living donor organs, impossibility to finish the organ implant surgery, and multiple organ transplantation.

We analyzed patients' 30-day cumulative survival and the survival according to the following risk indexes calculated from the information collected from the donors and recipients as previously published: MELD, DMELD, DRI, PSOFT, SOFT, and BAR.

A logistic regression analysis to model the probability of the dichotomic event (dead/not dead) in a linear combination of one or more independent variables was used to study the associated factors. Quantitative variables were assessed by the analysis of variance (ANOVA) for parametric data and the Kruskal–Wallis test for nonparametric data.

Aiming to investigate the best observed representation of prognostic scores, which could be more appropriate in allocation decisions for our cohort, a receiver operating characteristic (ROC) curve with the calculation of the area under the curve (AUROC) was performed to all the indexes. The best cutoff point was estimated by calculating the highest Youden's index.

The level of significance adopted in all the analyses was 5%. The data collection and analysis were performed using EpiInfo™ Epidemiological software (version 7.2.2.16, Center for Disease Control and Prevention)[10].

As this study used only the aggregated data that are entirely anonymous, the approval of the Research Ethics Committee (CEP) was not necessary, according to the Resolution No. 510/2016 of the National Health Council (CNS) in Brazil.

RESULTS

The group under analysis consisted of 252 liver transplantations: 252 donors and 240 recipients (12 re-transplantations). Of the recipients, there were 179 (71.03%) males and 73 (28.97%) females. The mean age was 54.25±11.78 years, hepatopathy etiology was alcoholic in 33.3% (n=75), hepatitis B and C in 17.34% (n=39), and hepatocarcinoma in 12% (n=27). The average MELD score was 21.17±8.06, and considering the exception points it was 23.78±7.77 (Table 1).

Table 1. Baseline characteristics of donors and recipients.

Recipients (n)	240
Male gender % (n)	71.03 (179)
Age	54.25±11.78
White race % (n)	66.22 (149)
Body mass index (n)	27.05±5.35
Disease (alcohol-related) % (n)	33.3 (75)
MELD score	21.17±8.06
MELD score (adjusted)	23.78±7.77
MELD exception points % (n)	16.39 (39)
Re-transplantation	4.76 (12)
Portal vein thrombosis	6.34 (16)
Donors (n)	252
Age	41.47±15.82
Black race % (n)	6.34 (16)
Height (centimeters)	170±10.49
Cause of death-cerebrovascular	46.42 (117)
Donation site-regional	91.67 (231)
Cold ischemia time (min)	346±116.84

MELD: model for end stage liver disease.

Organ donation occurred within the state of Paraná in 91.67% of cases (n=231), donor's mean age was 41.47±15.82 years, black race was observed in 6.34% (n=16), and cerebrovascular etiology was the main cause of death in 46.42% (n=117), as shown in Table 1.

The cohort characteristics stratified according to the 30-day surgical mortality are shown in Table 2. DRI was the only prognostic variable without the statistical significance related to patients' 30-day surgical mortality.

The DMELD score ³1600 was observed in 3.98% (n=10) of transplants. The 30-day mortality in this group was 60%. The surgical mortality was lower (18.26%) on patients with the DMELD score <1600 (p=0.0044).

The sensitivity, specificity, Youden's index, and AUROC were calculated for the indexes that showed differences between groups. MELD and DMELD showed AUC<0.7 (0.68 and 0.66, respectively). Therefore, these indexes were not associated with the 30-day mortality and were not used.

The ROC curve and AUC referred to BAR (0.7297), PSOFT (0.7717), and SOFT (0.7875) are shown on Figure 1.

The calculated Youden's index point was located within 11–12 score band for BAR (0.2484), 9–12 score band for PSOFT (0.3564), and 9–12 for SOFT (0.3453).

The 30-day survival for the group of transplants with scores up to 12 (n=172) in all these three indexes was 87.79%, and for transplants with all the three indexes with scores higher than 12 it was 36.36% (p=0.000). Considering simply one index, these results were 84.51 and 53.85% for BAR (p=0.000), 87.23 and 57.81% for SOFT (p=0.000), and 86.67 and 45.24% for PSOFT (p=0.000), respectively.

DISCUSSION

The 30-day survival curve analysis showed the impact of several factors from the donor-recipient binomial. Currently, the MELD score is the criteria adopted for organ allocation[11]. It is a question of ethical debate whether the procedure should be indicated to patients with poorer prognosis[12,13].

The use of MELD improved organ allocation[14]; however, it does not have the same accuracy to predict the post-transplant mortality[15]. Thus, the post-transplantation MELD stratified survival analysis based on the international data would not be the representative of our reality. In our local cohort, the MELD score also did not show good sensibility and sensitivity to predict survival. Stratifying risk with more validated criteria in a local context is important to improve survival.

In our study, we observed the 30-day survival of 79.76%. Improvement in transplant survival has led to an increased demand for organs. One of the solutions is the use of expanded criteria donors. Nowadays, it has become an essential part of the therapeutic strategy[16]. The donor risk assessment has already been validated on the literature. DRI is based on a study of 20,023 patients, and it considers several risk factors of donors[5]. In our series, neither split liver transplantation nor donor after cardiac death was observed. This eliminates the two main factors that influence the prognostic value of DRI[17]. Probably, this is the reason why there was no DRI difference related to mortality and survival. Another explanation is that expanded criteria organs are uniformly used in the state. This is corroborated by the findings of another local study with a cohort from a period immediately prior to the present study[17], although our mean DRI is lower than the reported on other Brazilian regions[18], a value observed in our third quartile.

Table 2. Risk indexes according to the 30-day mortality.

	Cohort (n=252) %	30-day mortality		p-value
		Yes (n=51) 20.24	No (n=201) 79.76	
MELD	21.17±8.06	24.92±9.09	20.21±7.51	0.0013*
MELDa	23.78±7.77	27±11.01	22.96±6.48	0.0157*
DRI	1.44±0.35	1.48±0.38	1.43±0.34	0.5341
DMELD	849.08±397.30	1015.94±470.23	806.74±365.95	0.0057*
BAR	8.21±4.31	10.60±5.28	7.61±3.81	0.0001*
PSOFT	8.87±6.93	13.80±9.87	7.62±5.31	0.0001*
SOFT	9.14±7.12	14.07±9.67	7.89±5.70	0.0000*

MELD: model for end stage liver disease; MELDa: MELD-adjusted; DRI: donor risk index; DMELD: donor model for end stage liver disease; BAR: balance of risk; PSOFT: Preallocation survival outcomes following liver transplant; SOFT: survival outcomes following liver transplant. *p<0.05.
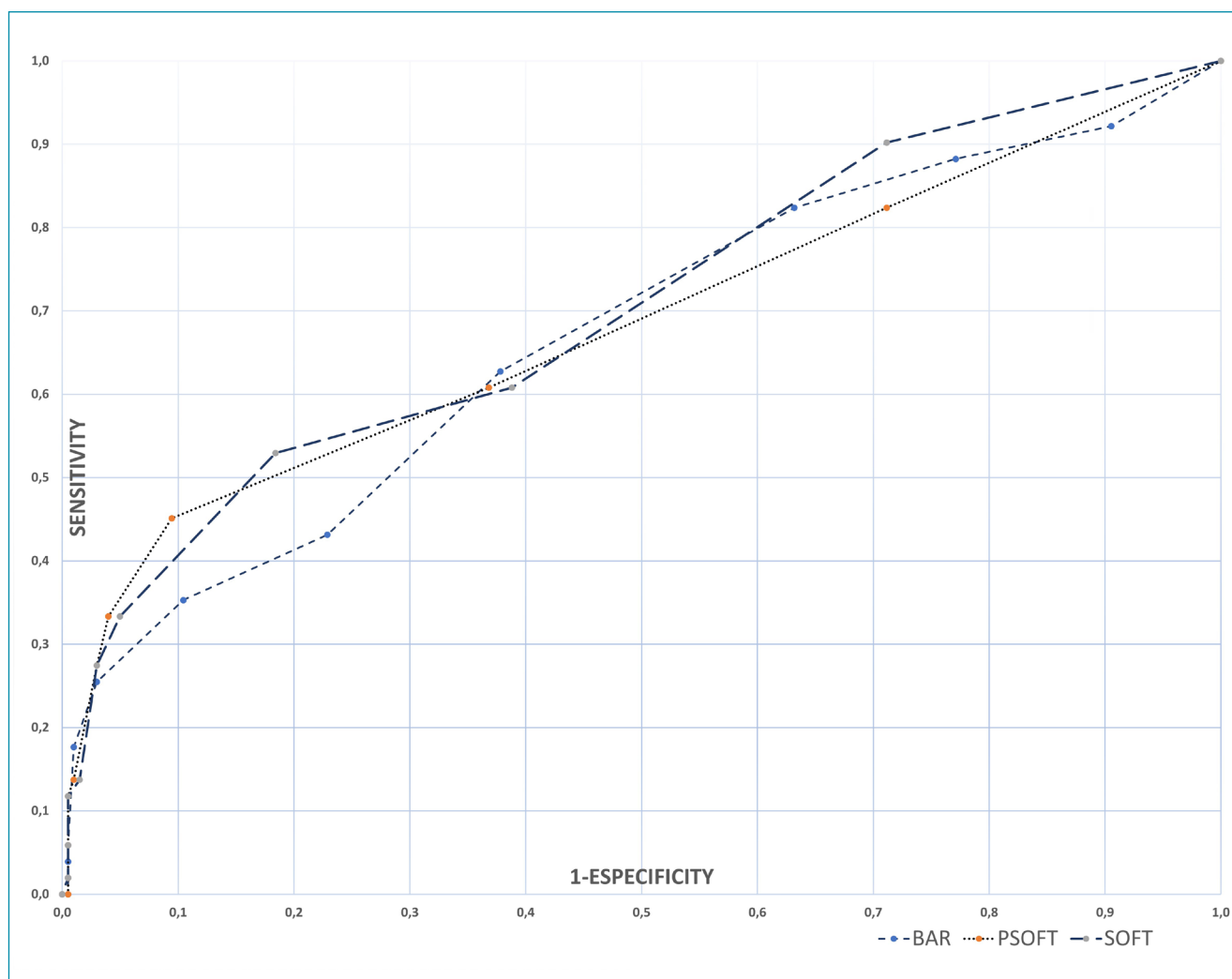
Figure 1. Receiver operating characteristic curve for balance of risk, preallocation and survival outcomes following liver transplant prognostic indexes.

Donor's age is an important risk factor for DRI. It influences two other components of the index[5], namely, etiology of brain death and cold ischemia time. Hence, another index was proposed to aid the allocation decision process[19]. DMELD is an index obtained by the multiplication of donor age and recipient's MELD score. Groups with DMELD >1600 (i.e., 9.2% of the sample from the seminal study) had less than 1-year survival rate[8]. In our cohort, the group with DMELD ≥1600 presented much higher surgical mortality (60%). Nevertheless, DMELD, as occurred to MELD, did not show good sensitivity and sensibility to predict survival (i.e., AUC=0.66), corroborating the findings of another Brazilian cohort[20].

Risk models that predict the post-transplant mortality aggregating donor and recipient characteristics, such as SOFT[7] and BAR[6] scores, are shown to be good prognostic models.

These scores, despite considering cold ischemia time, can be calculated at the time of an organ offer.

In our study, BAR score performed well, predicting the surgical mortality after liver transplant. The BAR score was formulated based on 37,255 patients of USA and Switzerland[6]. In another Brazilian cohort, BAR score demonstrated suboptimal performance[18]. In the original study, deterioration in survival was observed after 18 points as a cutoff value[6]. In the Brazilian context, the cutoff value was estimated at 11 points[18], in agreement with our findings, where the cutoff value was located in the range of 11–12.

We did not identify previous studies evaluating PSOFT and SOFT scores in the Brazilian population. Both presented better prognostic value than BAR used in our study. The cutoff value for both PSOFT and SOFT scores was in the stratification range of 9–12. Based on 21,673 North American patients[7],

PSOFT and SOFT scores include the anatomical characteristics (i.e., portal vein thrombosis and previous abdominal surgery) not included in BAR score. As with BAR score, the original PSOFT and SOFT study showed higher cutoff value for worse prognosis (36 points) than our findings.

Why is that? We can assume that in more developed countries more critical patients had better survival. It could be related to donor maintenance, organ harvesting solutions, dedicated anesthesiology, and ICU teams, medical supplies, etc. Although the 30-day mortality is acceptable for a developing country, our study shows that this rate may be improved.

When we aggregated the maximum cutoff values of the best performance scores in our analysis (i.e., BAR, SOFT, and PSOFT), we observed a survival rate of only 36.6%. This is a very relevant data, although it is a clinical and ethical challenge to deny a liver transplant based on risk analysis.

CONCLUSIONS

(A) The 30-day liver transplantation survival of 79.76% observed in our state is acceptable and comparable with other Brazilian services.
(B) BAR, SOFT, and PSOFT are the validated post-transplant survival prognostic scores in our state.
(C) The cutoff value of 12 points is able to identify enhanced risk situations.

AUTHORS' CONTRIBUTION

FS: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **FPS:** Data curation, Formal Analysis. **ACTF:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **JCUC:** Writing – review & editing. **EJBR:** Data curation. **MMM:** Data curation. **NT:** Data curation. **LCB:** Data curation.

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Association of laboratorial parameters and prognostic factors in uterine corpus cancer

Kaio Raffael Valotta Bezerra[1] ![ORCID], Agrimaldo Martins-Filho[1] ![ORCID], Marta Carolina Marques Sousa[1] ![ORCID], Eddie Fernando Candido Murta[1] ![ORCID], Rosekeila Simões Nomelini[1]* ![ORCID]

SUMMARY

OBJECTIVE: The aims were to compare the red blood cells, platelet count, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, red cell distribution width, and fasting glucose in peripheral blood of patients with benign and malignant uterine neoplasms and to relate these laboratory parameters with prognostic factors and overall survival in cancer.

METHODS: The results of the laboratory parameters were analyzed using the Mann-Whitney U test. Receiver operating characteristic curves were used to find the cutoff values. Overall survival was estimated using the Kaplan-Meyer method.

RESULTS: Higher values of neutrophil-lymphocyte ratio and fasting glucose were found in cancer patients. Higher platelet-lymphocyte ratio values were associated with other subtypes when compared with endometrioid subtype; higher values of red cell distribution width were found in stage II/IV when compared with stage I; lower hemoglobin values were related to stage II/IV and nonendometrioid histological type. Platelet–lymphocyte ratio <145.56 was associated with longer overall survival.

CONCLUSION: Hemoglobin and platelet–lymphocyte ratio values are prognostic factors in uterine corpus cancer.

KEYWORDS: Uterine neoplasms. Blood platelets. Lymphocytes. Prognosis. Survival.

INTRODUCTION

Cancer progression is influenced by the inflammatory response of the host, with inflammation being an indicator of prognosis, and several prognostic and diagnostic biomarkers have been identified[1]. Laboratory quantification of markers of the systemic inflammatory response, such as hypoalbuminemia, hyperfibrinogenemia, C-reactive protein, absolute leukocyte count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), were introduced as prognostic factors in patients with various types of cancer[2,3].

A study involving two of these inflammatory markers, NLR and PLR, revealed favorable results for these markers, proposing that they can be used as predictors of malignancy for solid tumors originating from various tissues. They could be used as a tool of screening for these tumors, as they are considered low-cost tests and readily available. However, there is a need for more research to assess the value of this finding in establishing scores and indicate the potential predictive value of NLR and PLR markers in gynecological cancers[4].

Endometrial cancer is classified into two subtypes on the basis of histological characteristics, hormone receptor expression, and grade, namely, type I or endometrioid and type II or nonendometrioid tumors[5]. This classification has helped to define the treatment, but the prognostic value remains limited because

endometrial cancer comprises a range of neoplasia with distinct genetic polymorphism and molecular features[6-9]. Therefore, the identification of biomarkers that can assist in the selection of patients for surgical treatment and an ideal adjuvant treatment is vital to improve the outcome. The aim of this study was to verify and compare the red blood cells, platelet count, NLR, PLR, red cell distribution width (RDW), and fasting glucose in peripheral blood of patients between benign and malignant uterine neoplasms before surgical treatment and to relate these laboratorial parameters with prognostic factors and overall survival (OS) in patients with primary uterine corpus cancer.

METHODS

A retrospective study was carried out at the Department of Gynecology and Obstetrics. The study sample consisted of 216 women, divided into two groups, namely, uterine corpus cancer (n=92) and leiomyomas (n=124). Patients who were referred to surgical treatment for these neoplasms were assessed. The following parameters were evaluated: age, parity, histological type, staging, red blood cells, neutrophil, lymphocyte and platelet count, RDW, NLR, PLR, fasting glucose, and OS.

The data were analyzed using GraphPad Prism software 6 and MedCalc 19.0.4. The results of laboratory parameters were compared between benign and malignant groups using the Mann-Whitney U test. For parameters that showed statistical significance, a "receiver operating characteristic" (ROC) curve was used to obtain the area under the curve (AUC) and to determine the best cutoff values between uterine corpus cancer and leiomyomas. In uterine corpus cancer, ROC curves were also used to determine the cutoff value between prognostic factors and laboratory parameters. The OS of the groups was estimated by the Kaplan–Meyer method followed by the log-rank test. The level of significance was <0.05.

This study was approved by the Research Ethics Committee of Federal University of Triângulo Mineiro (protocol number 89084018.9.0000.5154).

RESULTS

We evaluated 92 patients with uterine corpus cancer and 124 patients with leiomyomas. In the malignant group, the median age was 64 years (45–88), the median parity was two births (0–12), and 60 (65.2%) of the patients had the endometrioid histological type and 32 (34.8%) were of other subtypes. In relation to the control group (leiomyomas), the median age was 43 years (35–76), and the median parity was two births (0–8).

In the comparison between uterine corpus cancer and leiomyomas, higher values of NLR and fasting glucose were found in cancer patients (p<0.0001 and p=0.0002, respectively) (Figure 1A). There was no statistical significance in the evaluation of the other parameters (i.e., RDW, neutrophil, lymphocyte, and platelet count).

Regarding the ROC curve to verify the cutoff values of NLR in leiomyomas and uterine corpus cancer, the value of 2.852 was found (AUC=0.725 and p<0.001) (Figure 1B).

Evaluating the association of laboratory parameters with prognostic factors in uterine corpus cancer, higher PLR values were associated with other subtypes when compared with endometrioid subtype (p=0.0407), higher RDW values were found in stages II to IV when compared with stage I (p=0.0292), and lower hemoglobin values were related to stages II to IV when compared with stage I and other subtypes (nonendometrioid) and also when compared with endometrioid subtype (p=0.0024 and p=0.006, respectively) (Figure 2).

The ROC curves showed a cutoff value of 145.56 for PLR in relation to the histological type (AUC=0.635 and p=0.037), 11.8 in relation to hemoglobin and histological type (AUC=0.677 and p=0.003), and 12 in relation to hemoglobin and staging (AUC=0.686 and p=0.001) (Figure 3A–C).

Subsequently, survival curves were performed to verify whether there is a relationship between PLR and hemoglobin values and to verify OS of patients with uterine corpus cancer. This relationship was not found with hemoglobin levels. On the other hand, the OS of patients with PLR<145.56 was longer than that in patients with PLR>145.56 (p=0.0005) (Figure 3D).
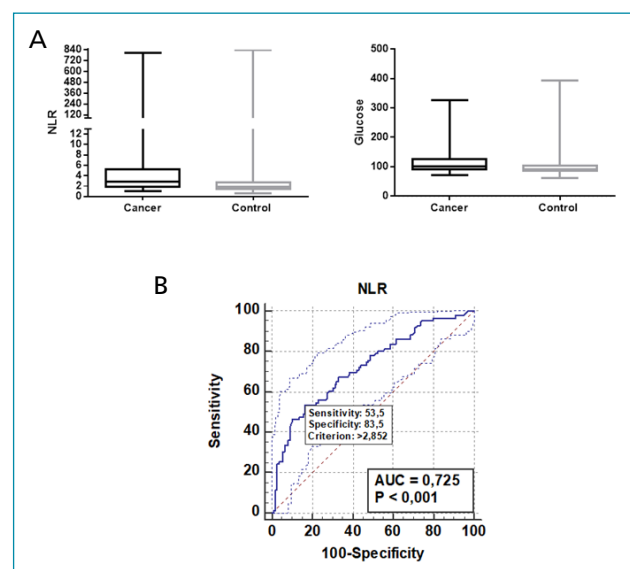
Figure 1. **(A)** Neutrophil–lymphocyte ratio and fasting glucose (g/dL) in uterine corpus cancer and leiomyomas. **(B)** Receiver operating characteristic curve; Neutrophil–lymphocyte ratio in leiomyomas and uterine corpus cancer.
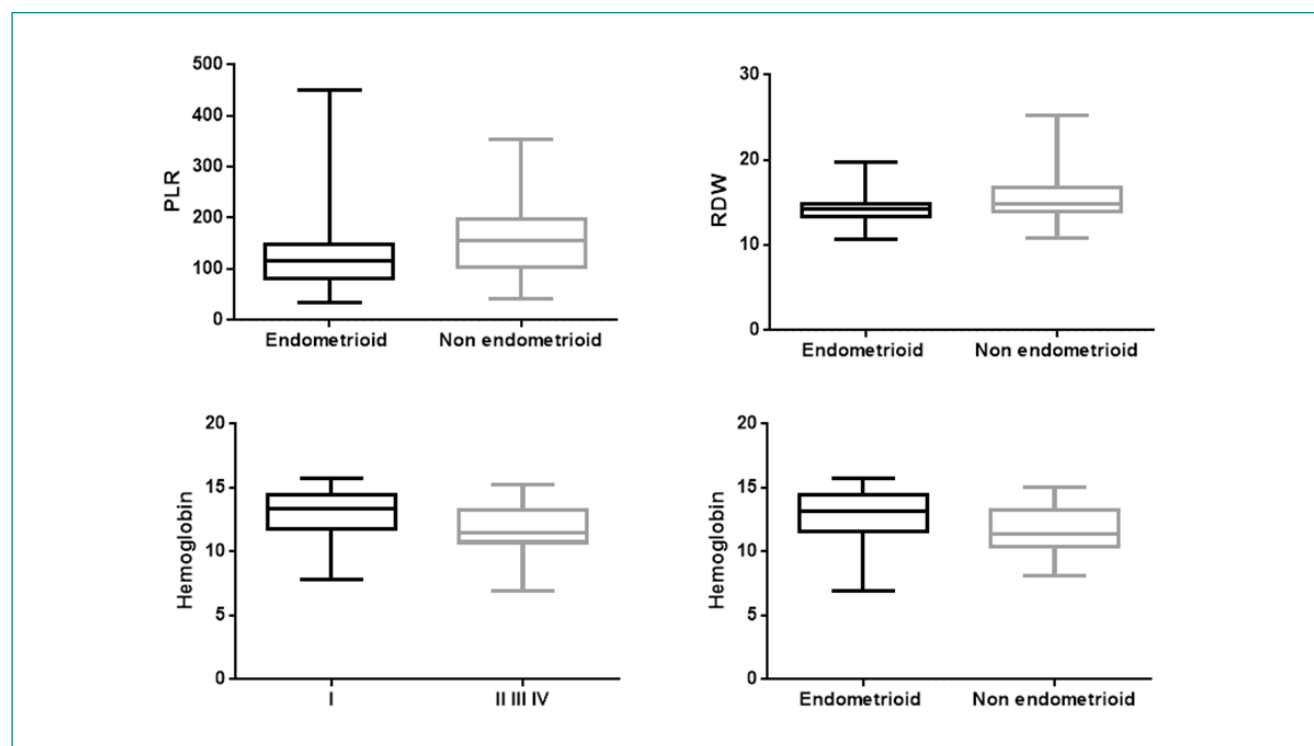
Figure 2. Laboratory parameters and prognostic factors in uterine corpus cancer.
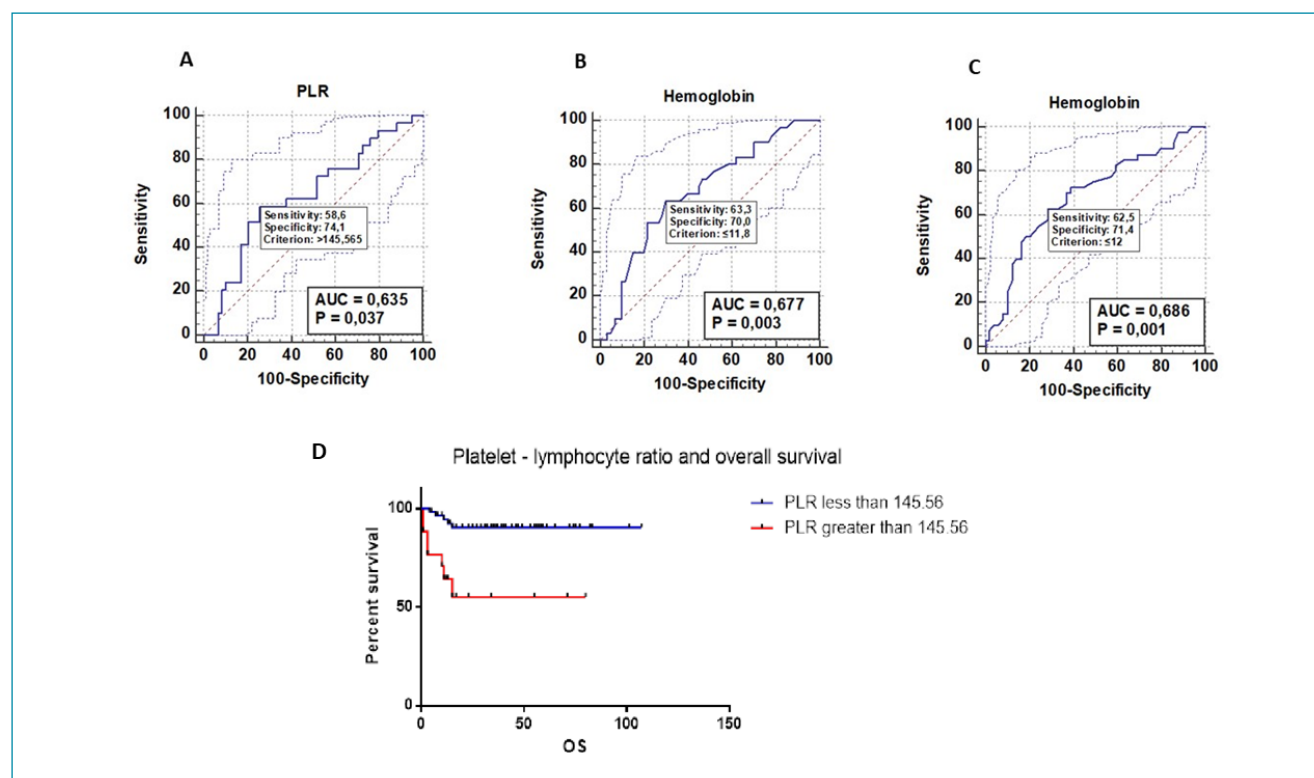
Figure 3. Receiver operating characteristic and survival curves: (A) Receiver operating characteristic curve, platelet–lymphocyte ratio and histological type (endometrioid *versus* other subtypes). (B) Receiver operating characteristic curve, hemoglobin and histological type (endometrioid *versus* other subtypes). (C) Receiver operating characteristic curve, hemoglobin and staging (I *versus* II–IV). (D) Overall survival and platelet-lymphocyte ratio.

DISCUSSION

Studies have demonstrated the relationship between inflammatory response markers and prognosis in endometrial cancer[10-13]. A study demonstrated that platelet volume and platelet distribution width might have a predictive value in the discrimination of benign and malign endometrium diseases[11]. In the comparison between uterine corpus cancer and leiomyomas, the cancer patients had higher values of NLR. Regarding the ROC curve to verify the cutoff values of NLR in leiomyomas and uterine corpus cancer, the value of 2.852 was found.

A study involving 763 patients with endometrial carcinoma showed a cutoff value of 3 for NLR; the sensitivity and specificity were found to be 68 and 69%, respectively, to predict lymph node metastasis[14]. Another study that applied cutoff values of 2.4 for NLR and 240 for PLR had independent prognostic significance[15]. A meta-analysis of 23 studies, including 6,869 patients, showed that PLR is related to a worse prognosis in ovarian tumors but not in endometrial tumors[12]. A higher pretreatment NLR was demonstrated as a predictor of lymph node metastasis in endometrial cancer[16]. A study found that patients with high baseline NLR (≥4.1) had more baseline distant metastases than patients with low baseline NLR (<4.1), and patients with high baseline PLR (≥0.3) had more distant metastases than patients with low baseline PLR (<0.3)[17]. The clinicopathological data and five year follow-up data were obtained for a retrospective series of 605 surgically treated endometrial cancer patients. By applying cutoff values of ≥2.4 (NLR) and ≥240 (PLR), NLR and PLR had independent prognostic significance[18]. Patients with elevated PLR had a high risk of decreased OS and unfavorable disease-free survival[13]. Another study demonstrated that the median OS in patients with a PLR of <300 was 37.4 months (95%CI 26.1–48.7), and it was 14.5 months (95%CI 11.7–17.2) in those with a PLR of >300. PLR, but not NLR, retained its significance as a prognostic marker on the multivariate Cox's regression analysis, along with staging (p<0.001) and residual disease (p=0.015)[10]. By evaluating the association of laboratory parameters with prognostic factors in uterine cancer, our study demonstrated that higher PLR values were associated with a nonendometrioid subtype when compared with endometrioid subtype (which has a better prognosis). A study demonstrated that the combination of NLR, PLR, and monocyte-lymphocyte ratio is a superior prognostic factor of endometrial cancer[19]. A meta-analysis demonstrated that elevated NLR and PLR values during pretreatment are biomarkers of poor prognosis in patients with endometrial cancer[20]. No significant association between NLR and prognostic factors was found. On the other hand, ROC curves showed a cutoff value of 145.56 for PLR in relation to the histological type. Moreover, OS of patients with a PLR<145.56 was longer than that in patients with a PLR>145.56.

Metabolic syndrome can be related to a high risk for mortality from cancer, including endometrial cancer, and leads to an unfavorable prognosis for patients with endometrial adenocarcinoma[21,22]. Our study did not assess all parameters of the metabolic syndrome, but it found that in the comparison between uterine corpus cancer and leiomyomas, cancer patients had higher values of fasting glucose when compared with the control group.

A study demonstrated that the frequency of preoperative anemia was 27.7%. Patients whose disease progressed to more advanced stages and those who presented with an unfavorable differentiation grade, myometrial invasion ≥50%, lymphovascular invasion, or tumor recurrence had significantly lower preoperative hemoglobin levels when compared with patients who did not present with anemia in the preoperative period. This study indicated that patients with preoperative anemia had significantly lower recurrence-free survival rates after five years and significantly lower OS rates when compared with patients without preoperative anemia, demonstrating that the preoperative hemoglobin rate is a prognostic factor with an important clinical significance[23]. By evaluating the association of laboratory parameters with prognostic factors in uterine cancer, lower hemoglobin values were related to stages II to IV when compared with stage I and nonendometrioid histological type and also when compared with endometrioid subtype. The ROC curves showed a cutoff value of 11.8 in relation to hemoglobin and histological type and 12 in relation to hemoglobin and staging. Thus, anemia was related to factors with a worse prognosis (histological type and staging). No relation was found with OS.

RDW is another blood count parameter that can be used in the management of endometrial diseases. In one study, the group with endometrial cancer had significantly higher levels of RDW compared with the benign group[24]. Other study demonstrated that combination of RDW, mean platelet volume, and CA125 can improve the differential diagnosis of endometrial cancer and endometrial hyperplasia[25]. In our study, the higher PLR values were associated with a nonendometrioid subtype when compared with endometrioid subtype. Higher values of RDW were found in stages II–IV when compared with stage I, and lower hemoglobin values were related to stages II–IV when compared with stage I and nonendometrioid histological type and also when compared with endometrioid subtype.

The identification of new cancer biomarkers in peripheral blood samples is promising due to the ease of sampling, and analysis methods are readily available. However, few blood-based biomarkers are validated and clinically used. Currently, surgical treatment decisions for endometrial cancer are based on a preoperative histopathological assessment of the tumor

biopsy in combination with the preoperative ultrasound image available. However, these preoperative data are often inconsistent with the postoperative data[26], indicating the need for the emergence of alternatives that increase the accuracy of the prognosis and diagnosis of this disease without adversely affecting the patients.

The limitations of this study are the heterogeneity of the histological subtypes studied and the lack of evaluation of the influence of molecular profile on the prognosis of uterine body cancer. On the other hand, our study reinforces the importance of investigating new prognostic markers in this cancer, which are easy to collect and inexpensive. New studies associating molecular profiles, gene polymorphisms, and laboratory parameters in uterine body cancer may lead to a better elucidation of prognostic factors in uterine body cancer.

Several prognostic biomarkers could be used in the management of uterine cancer. The group of malignant uterine tumors observed an increase in NLR and blood glucose levels, as well as an increase in RDW and PLR. In this group, the increase in PLR was observed in nonendometrioid tumors when compared with endometrioid subtype (which has a better prognosis). In nonendometrial tumors, a decrease in hemoglobin rates was also observed. In this study, it was observed that the increase in the OS rate of patients with malignant tumors was directly related to the decrease in PLR, indicating that this parameter is strongly linked to OS.

The identification of new cancer biomarkers in peripheral blood samples is promising due to the ease of sampling and low cost, and these methods of analysis are readily available. However, few blood biomarkers are validated in clinical use. The adoption of these practices in clinical conduct can better guide the oncologist in performing less aggressive surgeries and adjuvant treatments in patients whose laboratory parameters suggest prognostic factors that are more favorable.

CONCLUSIONS

The values of NLR and fasting glucose were higher in uterine cancer than in leiomyomas. In uterine corpus cancer, PLR was higher in nonendometrioid tumors, RDW was higher in II–IV stages, and hemoglobin was lower in II–IV stages and nonendometrioid tumors. RPL<145.56 was associated with longer OS.

AUTHORS' CONTRIBUTIONS

KRVB: Data curation, Methodology, Writing – original draft. **AMF:** Investigation, Methodology, Writing – original draft. **MCMS:** Data curation, Methodology, Writing – original draft. **EFCM:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **RSN:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – review & editing.

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Role of monocyte to high-density lipoprotein cholesterol ratio in predicting left atrial enlargement in hypertensive patients

Aziz Inan Celik[1] (iD), Muhammet Bugra Karaaslan[2]* (iD)

SUMMARY

OBJECTIVE: Left atrium enlargement is common in hypertension due to left atrium inflammation. Monocyte to high-density lipoprotein cholesterol ratio, an inflammation marker that has become very popular in recent years, is associated with many cardiovascular diseases. The aim of this study is to investigate the monocyte to high-density lipoprotein cholesterol ratio level to predict the Left atrium enlargement in hypertensive patients.

METHODS: A total of 216 participants (i.e., 115 hypertensive and 101 control group) were enrolled. Left atrial volumes and left atrial volume indexes were calculated using transthoracic echocardiography. The monocyte to high-density lipoprotein cholesterol ratio was calculated as the ratio of monocyte to high-density lipoprotein cholesterol levels.

RESULTS: The left atrial volumes, left atrial volume indexes, and monocyte to high-density lipoprotein cholesterol levels were significantly higher in the hypertensive group than in the control group (43.3±12.4 *versus* 31.4±7.9, p<0.001; 22.9±5.8 *versus* 17.1±3.7, p<0.001; 11.4 [4.2–25.0] *versus* 8.4 [3.5–18.0], p<0.001, respectively). On the multivariate logistic regression analysis, monocyte to high-density lipoprotein cholesterol ratio (OR 1.38; 95%CI 1.20–1.57; p<0.001), (OR 1.28; 95%CI 1.16–1.42; p<0.001), age, and sex (female) were the independent predictors for hypertension.

CONCLUSIONS: The increased monocyte to high-density lipoprotein cholesterol ratio level was associated with hypertension and increased left atrial volume indexes. The results of this study supported the presence of inflammation, measured with a readily available and inexpensive marker, in hypertensive patients and revealed the association with left atrial enlargement.

KEYWORDS: Hypertension. Inflammation. Left atrium. Monocytes. High-density lipoprotein.

INTRODUCTION

Hypertension (HT) is a significant and common risk factor for cardiovascular diseases worldwide[1]. Endothelial dysfunction and an increase in oxidative stress due to increased cardiac output and peripheral vascular resistance cause damage to cardiac and vascular tissues[2,3]. This increased oxidative stress and endothelial dysfunction stimulate inflammatory cells to secrete many cytokines[4]. Left atrium (LA) remodeling and enlargement are seen in patients with HT due to both an increase in LA pressure and inflammation[5]. The LA enlargement is associated with atrial fibrillation, stroke, cardiovascular events, and mortality[6].

Monocytes are the primary cells of the inflammatory response[7]. Monocytes play an essential role in the first stage of inflammation by binding to adhesion molecules expressed on the damaged endothelium[8]. High-density lipoprotein cholesterol (HDL-C) is involved in transferring excess cholesterol from peripheral regions to the liver. The biological activity of HDL includes antioxidant, anti-inflammatory, antithrombotic, and anti-atherosclerotic effects, and these conditions demonstrate positive effects on cardiovascular outcomes[9]. In recent years, the monocyte to HDL-C ratio (MHR) is a new and widely used inflammation and oxidative stress marker and is calculated as the monocyte count ratio to HDL-C ratio level[10].

In this study, we aimed to investigate the value of MHR to predict the LA enlargement in hypertensive patients.

METHODS

Study population

A total of 216 participants, of whom 115 were hypertensive and 101 were controls, were included in this prospective study. HT is defined as office systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, and patients receiving hypertensive treatment were included in the study. Blood pressure was measured according to the 2018 ESC/ESH clinical practice guidelines for the management of arterial hypertension[11]. The measurements, such as sex, age, body surface area (BSA, the Du Bois formulation, m²), body mass index (BMI, kg/m²), HT, diabetes mellitus (DM), smoking status, medications, lipid panels, MHR, and transthoracic echocardiography (TTE), included in this study were recorded. Patients with ≤18 years old and history of coronary artery disease, atrial fibrillation, malignancies, acute or chronic inflammatory or autoimmune disease, acute or chronic infectious disease, heart failure with reduced ejection fraction, moderate/severe valve stenosis or insufficiency, chronic liver failure (alanine transaminase [ALT] and aspartate transaminase [AST] levels higher than threefold of normal levels), and chronic kidney disease (Cockcroft–Gault, glomerular filtration rate [GFR] <60 mL/min/1.73 m²) were excluded. The study protocol was reviewed and approved by the Local Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Echocardiographic evaluation

The transthoracic echocardiographic examinations were performed using the Vivid S5® cardiovascular ultrasound system (6T-RS, 5.0 MHz probe TEE GE Medical System, Norway). Left atrial volume (LAV) was calculated using the biplane area-length method by the measurements obtained from the standard views following the recommendations of the American Society of Echocardiography. In brief, LAV was calculated using the formula: $(0.85 \times A1 \times A2)/(L)$, where A1 was the maximum planimeter LA area in an apical four-chambered (A4C) view anteroposterior diameter in parasternal long axis, A2 was the maximum planimeter LA area in an apical two-chambered (A2C) view, and L was the length measured from back wall to line across mitral valve hinge points (cm). Left atrial volume index (LAVI) was calculated by dividing the LAV by the body surface area.

Blood sample analyses

Peripheral venous blood samples were obtained from the patients on their admission. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring complete blood count (CBC) parameters, and CBC samples were collected in ethylenediaminetetraacetic acid (EDTA)-anticoagulated Monovette® tubes (Sarstedt). Monocyte count was calculated from the CBC analysis. The biochemical parameters, such as total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, were also measured. The MHR was calculated as the ratio of monocytes to HDL-C levels.

Statistical analysis

Descriptive statistics were given as mean±standard deviation and median with minimum–maximum values for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The normal distribution of numerical variables was analyzed by using the Kolmogorov–Smirnov test due to the sample size being greater than 50 and was checked by Q–Q plots and histograms. In comparing the two independent groups, the Independent Samples t-test was used where the numerical variables had a normal distribution. For variables without normal distribution, the Mann-Whitney U test was applied. To compare the differences between categorical variables, the Pearson's χ^2 and Fisher's exact tests were used in 2×2 tables. The Spearman's and Pearson's correlation coefficients were calculated to analyze the relationships between MHR and LAV with demographic and clinical variables. The univariate normality and multivariate multicollinearity with correlation coefficients and the variance inflation factor between the variables were used to deal with the collinearity problems before univariate and multivariate linear regression analyses. Univariate and multivariate logistic regression analyses were used for the determination of independent risk factors for HT. For statistical analysis and figures, Microsoft Office Excel and the "jamovi" project (2020), the jamovi software (version 1.2.24; retrieved from https://www.jamovi.org), and the JASP software (version 0.13.1; retrieved from https://jasp-stats.org) were used. The significance level (p-value) was set at 0.05 in all the statistical analyses.

RESULTS

There were a total of 216 patients in the study group. HT was present in 115 patients (53.2%). The mean age of the patients with HT was significantly higher (53.1 *versus* 44.8 years)

(p<0.001). There were considerably more nonsmokers in the hypertensive group (p=0.048). The median BMI was 31.2 kg/m² in the HT group, and it was significantly higher than that in the control group (p<0.001). The mean LAV was significantly higher in patients with HT (43.3 *versus* 31.4 mL) (p<0.001). The mean LAVI was 22.9 and 17.1 mL/m² in patients with and without HT, respectively. This difference was statistically significant (p<0.001).

The MHR was significantly higher in hypertensive patients than in those without HT (p<0.001). The median value was

11.4 in the HT group, while it was 8.4 in the control group. There were no significant differences in sex distribution, DM, alcohol use, and laboratory values except for MHR between the groups. The demographic and clinical features of the study are summarized in Table 1.

The correlation analysis revealed significant associations between MHR and other variables (Table 2). Age and BSA were positively correlated with MHR (r=0.143; p=0.036 and r=0.198; p=0.004, respectively). In the study group, MHR showed direct correlations to LAV and LAVI (r=0.248; p<0.001

Table 1. Demographic and clinical features of the study group.

	Overall (n=216)	Hypertension group (n=115)	Control group (n=101)	p-value
Age (year)[a]	49.2±9.2	53.1±7.7	44.8±8.7	<0.001*
Sex[b]				
Female	140 (64.8)	79 (68.7)	61 (60.4)	0.258***
Male	76 (35.2)	36 (31.3)	40 (39.6)	
Diabetes mellitusb	13 (6.0)	9 (7.8)	4 (4.0)	0.365***
Smoking[b]				
Nonsmoker	136 (63.0)	80 (69.6)	56 (55.4)	0.048***
Ex-smoker	35 (16.2)	18 (15.7)	17 (16.8)	
Active smoker	45 (20.8)	17 (14.8)	28 (27.7)	
Alcohol consumption[b]	1 (0.5)	0 (0.0)	1 (1.0)	0.468***
BMI (kg/m²)[c]	29.4 (16.5–46.2)	31.2 (19.4–46.2)	28.3 (16.5–45.5)	<0.001**
BSA (m²)[a]	1.9±0.2	1.9±0.2	1.8±0.2	0.030*
LAV (mL)[a]	37.8±12.1	43.3±12.4	31.4±7.9	<0.001*
LAVI (mL/m²)[a]	20.2±5.7	22.9±5.8	17.1±3.7	<0.001*
Cholesterol (mg/dL)[c]	175.5 (112.0–310.0)	177.0 (123.0–310.0)	170.0 (112.0–290.0)	0.117**
LDL (mg/dL)[c]	121.0 (76.0–231.0)	123.0 (84.0–231.0)	118.0 (76.0–206.0)	0.118**
Triglyceride (mg/dL)[a]	178.3±48.3	177.9±55.1	178.8±39.5	0.891*
HDL (mg/dL)[c]	37.0 (24.0–74.0)	37.0 (24.0–74.0)	38.0 (28.0–74.0)	0.776**
MHR[c]	10.0 (3.5–25.0)	11.4 (4.2–25.0)	8.4 (3.5–18.0)	<0.001**
Use of at least one drug[b]	57 (26.4)	57 (49.6)	–	N/A
Antihypertensive drugs[b]				
ACE inhibitor	22 (10.2)	22 (19.1)	–	N/A
ARB	26 (12.0)	26 (22.6)	–	N/A
CCB	29 (13.4)	29 (25.2)	–	N/A
Diuretics	29 (13.4)	29 (25.2)	–	N/A
Beta blocker	6 (2.8)	6 (5.2)	–	N/A

BMI: body mass index; BSA: body surface area; LAV: left atrial volume; LAVI: left atrial volume index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; MHR: monocyte-to-HDL-C ratio; ACE: angiotensin-converting enzyme; ARB: angiotensin-II receptor blocker; CCB: calcium-channel blocker. [a]Mean±standard deviation; [b]n (%); [c]Median [range].*Independent Samples t-test; **Mann-Whitney U test; ***Pearson's χ² and Fisher's exact test.

and r=0.177; p=0,009, respectively). Among the laboratory values, total cholesterol, triglyceride, and HDL were also significantly associated with MHR (p<0.05 for all), while the correlation between MHR and HDL did not reach the statistical significance (p=0.665) (Table 2).

In Table 3, univariate and multivariate regression analyses for HT are detailed. Univariate and multivariate regression analyses were employed to identify the independent risk factors of HT. Age (OR 1.13; 95%CI 1.09–1.18; p<0.001), active smoking (OR 0.42; 95%CI 0.21–0.85; p=0.015), BMI (OR 1.12; 95%CI 1.06–1.18; p<0.001), LAVI (OR 1.31; 95%CI 1.21–1.42; p<0.001), and MHR (OR 1.27; 95%CI 1.15–1.40;

p<0.001) were the significant independent risk factors. In the multivariate analysis, sex was found to be an independent risk factor beside age (OR 1.10; 95%CI 1.04–1.16; p<0.001), LAVI (OR 1.28; 95%CI 1.16–1.42; p<0.001), and MHR (OR 1.38; 95%CI 1.20–1.57, p<0.001). Female sex increased the risk for HT incidence by 2.88-fold, with 95%CI 1.10–7.54 (p=0.031).

To determine the cutoff value, the receiver operating characteristic curve (ROC curve) analysis using the sensitivity, specificity, and Youden's index based on the diagnosis of HT revealed that the optimal cutoff value for MHR was 9.2 (i.e., sensitivity of 77.39% and specificity of 63.37%; area under the curve AUC 0.711; 95%CI 0.646–0.770; p<0.001).

Table 2. Correlation analysis of monocyte to high-density lipoprotein cholesterol ratio with demographic features and laboratory findings.

	MHR	
	Rho	p-value
Age	0.143	0.036*
BMI (kg/m²)	0.121	0.077**
BSA (m²)	0.198	0.004**
LAV (mL)	0.248	<0.001**
LAVI (mL/m²)	0.177	0.009**
Total cholesterol (mg/dL)	-0.143	0.036**
LDL-C (mg/dL)	-0.034	0.618**
Triglyceride (mg/dL)	0.154	0.024*
HDL-C (mg/dL)	-0.474	<0.001**

MHR: monocyte to HDL-C ratio; Rho: Spearman's rank correlation coefficient; BMI: body mass index; BSA: body surface area; LAV: left atrial volume; LAVI: left atrial volume index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. *Pearson's r; **Spearman's rho.

Table 3. Univariate and multivariate regression analysis for the development of hypertension.

	Model for univariate logistic regression analysis		Model for multivariate logistic regression analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	1.13 (1.09–1.18)	<0.001	1.10 (1.04–1.16)	<0.001
Sex (female *versus* male)	1.44 (0.82–2.52)	0.203	2.88 (1.10–7.54)	0.031
Smoking				
Ex-smoker	0.74 (0.35–1.56)	0.431	1.27 (0.38–4.16)	0.698
Smoker	0.42 (0.21–0.85)	0.015	0.41 (0.13–1.23)	0.111
BMI	1.12 (1.06–1.18)	<0.001	1.06 (0.98–1.15)	0.119
LAVI	1.31 (1.21–1.42)	<0.001	1.28 (1.16–1.42)	<0.001
MHR	1.27 (1.15–1.40)	<0.001	1.38 (1.20–1.57)	<0.001

OR: odds ratio; CI: confidence interval; BMI: body mass index; LAVI: left atrial volume index; MHR: monocyte-to-HDL-C ratio.

DISCUSSION

In this study, the LA volume changes (i.e., LAV and LAVI) in HT patients were measured. The relationship of MHR, a biomarker showing especially inflammation in recent years, with both HT and LA volume changes was examined. At the end point, LAV, LAVI, and MHR levels were significantly higher in HT patients than in the control group. A significant correlation was found between the MHR level and LA volumes.

In patients with HT, LA length, surface area, and volume significantly increased compared with those in the control group patients. In the population-based studies, 27% of individuals with HT found an enlargement in LAVI[12]. The LA passive emptying decreases as a result of left ventricular (LV) diastolic dysfunction observed in patients with HT, and LA (i.e., LAV and LAVI) pressures and volumes increase[13]. Endothelial dysfunction and increased oxidative stress due to increased cardiac flow and peripheral vascular resistance damage the cardiac and vascular tissues by enhancing inflammation[14]. LA remodeling and enlargement are seen in patients with HT due to both increases in LA pressure and triggering of inflammation[5].

Inflammation has an essential role in the progression of atherosclerosis and cardiovascular diseases. Monocytes are critical in the occurrence of inflammation. Monocytes are activated by binding to adhesion molecules expressed on the damaged endothelium and play an essential role in the first step of atherosclerosis progression[15]. Activated monocytes migrate to the subendothelial region and develop into macrophages. Macrophages become foam cells by phagocytosing the oxidized LDL-C molecules, and these foam cells secrete pro-inflammatory and pro-oxidant cytokines[16].

Contrary to the effects of monocytes described earlier, HDL-C decreases monocyte activation and adhesion, regulates endothelial adhesion molecules' release, reverses the effects of oxidized LDL-C, and causes vasodilation by NO release[17]. This anti-inflammatory effect of HDL-C reduces the risk of cardiovascular events[18]. The increased levels of pro-inflammatory monocytes and low anti-inflammatory HDL-C are indirect indicators of inflammation. In recent years, many studies have found that the MHR is a marker of inflammation and prognosis in many cardiovascular events. Akboga et al. revealed that high SYNTAX score and MHR were interrelated in patients with stable angina pectoris[19]. A study conducted by Cetin et al. found that the Gensini and SYNTAX scores and MHR levels were positively correlated with the severity of coronary artery disease and had an independent correlation with future cardiovascular events such as acute coronary syndrome[20].

In this study, LAV, LAVI, and MHR were significantly higher in hypertensive patients than in the control group. Also, a significant positive correlation between MHR and LAV and LAVI was found. In reviewing the current literature, this is the first study that examined the relationship between MHR and LA volumes in hypertensive patients. It is known that the enlargement in LA volumes causes many cardiovascular end points (i.e., atrial fibrillation, stroke, etc.) in HT. This study showed that the increased MHR levels revealed the inflammation in HT patients, and also, this marker is overwhelmingly associated with LA volume changes.

This study has several limitations. First, the 2D-TTE was used, while the measurements could be performed more precisely using the real-time 3D-TTE or cardiac MRI. Second, the study was single centered, and a relatively lower number of patients were included. Third, the specific inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor–α (TNF-α), interleukin-6 (IL-6), and neutrophil to lymphocyte ratio, were not measured.

CONCLUSIONS

Our study demonstrated that MHR was significantly correlated with LAV and LAVI in hypertensive patients. The MHR is a low-cost and straightforward biochemical marker that shows inflammation in LA remodeling. Further prospective studies are needed to evaluate the association between MHR and LAV.

AUTHORS' CONTRIBUTIONS

AIC: Conceptualization, Data curation, Methodology, Writing – review & editing. **MBK:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Reliability of pressure pain threshold on myofascial trigger points in the trapezius muscle of women with chronic neck pain

Alessandra Kelly de Oliveira[1] , Almir Vieira Dibai-Filho[2] , Gabriela Soleira[1] ,
Ana Carolina Fracarolli Machado[1] , Rinaldo Roberto de Jesus Guirro[1]*

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the intra- and inter-rater reliability of pressure pain threshold measurement on myofascial trigger points in the trapezius muscle in women with chronic neck pain.

METHODS: This reliability study involved 30 volunteers with neck pain for more than 90 days. The assessment procedures were performed by blinded researchers. Two examiners, who were previously trained in the use of algometry, independently performed two assessments of the pressure pain threshold at two time intervals, one week apart.

RESULTS: The study sample consisted of 30 young adult women. Excellent intra- and inter-rater reliability were found for the pressure pain threshold on myofascial trigger points, with intraclass correlation coefficient values ranging between 0.752 and 0.874, standard error of measurement ranging between 0.18 and 0.22 kg/cm^2, and minimum detectable change ranging between 0.45 and 0.62 kg/cm^2.

CONCLUSION: The present study showed that the assessment of pressure pain threshold through algometry presents satisfactory intraclass correlation coefficient values, considering different time and examiners, contributing to the spread of the use of this tool as a quantitative method of pain evaluation in myofascial trigger points.

KEYWORDS: Neck pain. Reproducibility of results. Chronic pain.

INTRODUCTION

Cervicalgia is a prevalent musculoskeletal disorder, affecting about 30% of the world population[1], with emphasis on the involvement of the myofascial component of the trapezius muscle[2]. In Brazil, Genebra et al.[3] observed a prevalence of neck pain in approximately 20% of individuals in a sample composed of adults aged 20 years and above.

A common clinical sign in the trapezius muscle of patients with neck pain is the presence of myofascial trigger points[2]. They produce local and referred pain and may be active or latent[4]. In general, the most accepted method of diagnosis of myofascial trigger points in research and clinical practice are the criteria centered on palpation described by Simons et al.[5]

However, other instruments have been used to complement the assessment of these patients, mainly because of the complexity inherent in measuring pain[6]. Among other assessment methods, algometry has characteristics that allow the pressure pain threshold to be accurately measured in a given region such as muscle belly and tendons[7].

Some studies have been conducted to evaluate the reliability of the pressure pain threshold in different populations. Using the intraclass correlation coefficient (ICC), in a population of

[1]Universidade de São Paulo, Ribeirão Preto Medical School, Department of Health Science – Ribeirão Preto (SP), Brazil.
[2]Universidade Federal do Maranhão, Department of Physical Education – São Luís (MA), Brazil.
*Corresponding author: rguirro@fmrp.usp.br

healthy young adults, Waller et al.[8] identified adequate reliability in assessing the pressure pain threshold on the wrist, leg, and cervical and lumbar spine. In patients with neck pain, algometry has consistent reliability on the upper trapezius muscle and the anterior tibial belly[9]. Specifically for myofascial pain, Park et al.[10] identified excellent reliability for the pressure pain threshold on the upper trapezius, infraspinatus, extensor carpi radialis, and extensor indicis proprius muscles. However, these authors used Cronbach's alpha to measure reliability, an incoherent statistical method compared with ICC.

In view of the above and considering the scientific gap still present in the use of algometry in myofascial pain, the objective of this study is to evaluate the intra- and inter-examiner reliability of measuring the pressure pain threshold on myofascial trigger points in the upper trapezius muscle in women with chronic neck pain.

METHODS

Ethical aspects

The research was carried out in a laboratory of the university, and the study procedures were approved by the Research Ethics Committee of the institution (number blinded). Once selected, the volunteers were instructed about all the procedures involved, clarified about the research project and its objectives and characteristics, and asked to sign the free and informed consent form.

Research design

This reliability study involved two examiners, previously trained and familiarized with the use of the algometer, who performed the pressure pain threshold measurements at two time intervals, one week apart[11], making it possible to determine the intra- and inter-rater reliability.

Sample

The sample calculation was performed considering a confidence coefficient of 0.95 and the amplitude of the confidence interval for the ICC of 0.30. In addition, the calculation was performed to detect moderate reliability (ICC=0.75), according to the study conducted by Fleiss[12]. Therefore, a sample size of 24 volunteers was estimated. Concerning possible sample losses, 30 volunteers were recruited in the present study. The processing of the sample calculation was performed based on the study conducted by Bonett[13].

Thirty volunteers with neck pain for more than 90 days aged between 18 and 45 years were recruited. To identify the neck pain, the following diagnostic criteria were used: score on

the Neck Disability Index (NDI) ≥5 points and score on the Numerical Pain Scale (NPS) ≥3 at rest. In addition, all volunteers had an active myofascial trigger point, centrally located in the descending trapezius muscle, diagnosed according to the criteria established by Simons et al.[5], and the diagnosis was done by a physiotherapist with eight years of experience in myofascial pain.

The exclusion criteria were: a history of cervical trauma, degenerative diseases of the spine, systemic diseases, medical diagnosis of fibromyalgia and depression, and use of painkillers, anti-inflammatories, or muscle relaxants in the previous week.

Evaluation procedures

The assessment procedures were carried out by blinded researchers, according to the following description: a researcher with the previous knowledge of measuring the painful experience applied the assessment instruments for neck pain and diagnosed the myofascial trigger points at an initial moment. Then, two other examiners independently performed two assessments of the pressure pain threshold at two time intervals, one week apart, thus making it possible to measure intra- and inter-examiner reliability.

Initially, the data such as personal data, mass, height, body mass index, past illnesses, use of medications were collected, and then inspection and palpation of the evaluated region were performed.

The NPS was used to assess pain intensity. It is a scale validated for the Portuguese language, simple, and easy to measure, consisting of a sequence of numbers from 0–10, in which 0 represents "no pain" and 10 stands for "the worst pain one could ever imagine."[14] In this regard, the volunteers graduated their pain based on these parameters. Pain intensity was assessed at rest.

NDI was used to assess neck disability through the presence of pain. It consists of an instrument adapted and validated for the Brazilian population[15], and it is composed of 10 items, generating a score ranging from 0–50, the higher the score, the greater the disability.

An algometer (PTR-300 model, Instrutherm, São Paulo, SP, Brazil) was used to measure the pressure pain threshold. For this, the volunteers were placed in a chair, with the torso erect, back supported, feet resting on the ground, and hands resting on the thighs. The algometer with a rubber disk measuring 1 cm^2 at the edge was positioned and the examiner exerted a gradual compression with a constant speed of approximately 0.5 kg/cm^2/s, controlled by the sound feedback of a digital metronome[7], perpendicularly to the fibers of the upper trapezius muscle, bilaterally, exactly over the myofascial trigger points. These points were pressed until the pain was reported, and the value displayed on

the equipment's display was recorded in kg/cm². The pressure pain threshold measurement was performed three times for each muscle to obtain the mean value, with the order of collection (right or left myofascial trigger point) defined by drawing.

Statistical analysis

For the analysis of reliability, the $ICC_{2,3}$ was used to determine the intra- and inter-rater reliability of measuring the pressure pain threshold, with its respective 95%CI, standard error of measurement (SEM), and minimum detectable change (MDC)[16].

The interpretation of the ICC value was based on the study by Fleiss: low, values below 0.40; moderate, between 0.40–0.75; substantial, between 0.75–0.90; excellent, values greater than 0.90[12].

All statistical processing was performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (Chicago, IL, USA).

RESULTS

The study sample consisted of 30 women, 29 right-handed, at a mean age of 23.30 years (standard deviation [SD] 2.79), mean body mass index of 22.17 kg/m² (SD 3.78), mean pain intensity at rest of 3.80 (SD 1.15), mean disability of 12.03 (SD 4.49), and mean chronic pain of 39.70 months (SD 31.34).

Table 1 shows the mean values of the pressure pain threshold according to each examiner. Tables 2 and 3 show excellent intra- and inter-rater reliability, respectively, with ICC values varying between 0.752–0.874, SEM ranging between 0.18 and 0.22 kg/cm², and MDC varying between 0.45 and 0.62 kg/cm².

DISCUSSION

The results of the present study demonstrated adequate values of reliability in measuring the pressure pain threshold on the trigger point of the upper trapezius muscle of women with chronic neck pain using the algometry technique. These results presented are similar to those suggested by Koo et al.[17] who demonstrated that the evaluation of the pressure pain threshold using a manual algometer showed excellent reliability (ICC=0.914) in healthy subjects. Persson et al.[18] reported ICC between 0.70–0.90 for the evaluation of the descending trapezius muscle of 27 healthy women.

Pain assessment involves possible limitations resulting from the subjectivity inherent in the painful condition and the human capacity for physiological adaptation to painful stimuli, which are already reported in the literature[19,20]. Thus, the use of

Table 1. Mean and standard deviation of the pressure pain threshold according to the measurements of two evaluators (n=30).

PPT (kg/cm²)	Examiner 1		Examiner 2	
	Test	Retest	Test	Retest
Right upper trapezius	1.75 (0.56)	1.71 (0.54)	1.60 (0.47)	1.53 (0.42)
Left upper trapezius	1.76 (0.53)	1.71 (0.50)	1.55 (0.46)	1.44 (0.42)

PPT: the pressure pain threshold.

Table 2. Intra-rater reliability of measuring pressure pain threshold in participants with neck pain (n=30).

PPT	ICC	95%CI	SEM (kg/cm²)	SEM (%)	MDC (kg/cm²)	MDC (%)
Right upper trapezius	0.752	0.480–0.882	0.22	14.22	0.62	39.41
Left upper trapezius	0.781	0.609–0.877	0.21	13.80	0.57	38.26

PPT: the pressure pain threshold; ICC: intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement; MDC: minimum detectable change.

Table 3. Inter-rater reliability of measuring pressure pain threshold (PPT) in participants with neck pain (n=30).

PPT	ICC	95%CI	SEM (kg/cm²)	SEM (%)	MDC (kg/cm²)	MDC (%)
Right upper trapezius	0.858	0.778–0.914	0.18	11.17	0.50	30.95
Left upper trapezius	0.874	0.803–0.923	0.16	10.37	0.45	28.74

PPT: the pressure pain threshold; ICC: intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement; MDC: minimum detectable change.

algometry as a tool for measuring pain threshold has supported the development of studies that evaluate the properties of this method in painful conditions; given the above, we discussed the results found in this study.

Mutlu and Ozdincler[21] concluded that algometry can be used to assess the pressure pain threshold in patients with knee osteoarthritis; after finding adequate ICC values, these authors emphasized the importance of having this tool available to rehabilitation professionals in assessing the patients' pain. Walton et al.[9] assessed pressure pain threshold using algometry in women with and without acute neck pain and found values of excellent reliability for the intra-examiner (ICC=0.96) and substantial for inter-examiner (ICC=0.81), and although the values found in our study are slightly lower (0.752–0.874), they are considered substantial.

Walton et al.[22] evaluated the reliability of algometry in individuals of both sexes with neck pain without a specific cause. The ICC values were similar to the present study (ICC is equal to 0.89 for inter-examiner and 0.83 for intra-examiner) and, despite those values corresponded to good levels of reliability, the authors pointed out a limitation that may influence the result factors linked to the level of concentration/distraction of the volunteer at the time of the assessment since it is a test that depends directly on the volunteer's perception of their pain. In the present study, the evaluators received instructions to guide the volunteers on the importance of both being concentrated at the time of the evaluation; however, we agree that such factors mentioned by the authors above may interfere with the final result of the evaluation.

CONCLUSION

In the present study, the pressure pain threshold assessment using algometry shows satisfactory ICC values, considering different times and examiners, contributing to the spread of the use of this tool as a quantitative method of pain assessment on myofascial trigger points of women with chronic neck pain.

AUTHORS' CONTRIBUTIONS

AKO: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **AVDF:** Conceptualization, Data curation, Methodology, Writing – review & editing. **GS:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **ACFM:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **RRJG:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing.

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The effect of Mirabegron and Duloxetine combination in mixed-type urinary incontinence treatment

Ahmet Ariman[1]* , Erkan Merder[1] , Mehmet Gökhan Çulha[1]

SUMMARY

OBJECTIVE: Stress-type and urgency-type urinary incontinence are seen together in mixed-type urinary incontinence. Treatment is usually chosen according to the predominant type of incontinence. The aim of this study is to evaluate the effect of mirabegron and duloxetine combination in the treatment of mixed-type urinary incontinence.

METHODS: The data of 88 mixed-type urinary incontinence patients who applied to the urology outpatient clinic between January 2018 and December 2019 were retrospectively analyzed. We applied mirabegron and duloxetine treatment to the patients. The International Consultation of Incontinence Questionnaire-Short Form, Overactive bladder symptom score questionnaire and daily pad count were statistically evaluated before and after the treatment.

RESULTS: Statistically significant improvements were observed using the questionnaire forms and decreased daily pad usage after the eight-week treatment ($p<0.001$). Based on the clinical global effect scale, 62.50% of patients had a partial or complete response to treatment and also the use of daily pads were decreased from 3.7–0.89 on an average.

CONCLUSION: Combination use of mirabegron and duloxetine in the treatment of mixed-type urinary incontinence improved symptom scores and decreased pad usage.

KEYWORDS: Urinary incontinence. Mirabegron. Duloxetine hydrochloride.

INTRODUCTION

Urinary incontinence (UI) is defined as the complaint of involuntary loss of urine[1] and is one of the four most important problems of elderly patients according to the World Health Organization[2,3]. It is more common in women. Epidemiological studies have reported its prevalence between 25–45%[4]. Although it is not a life-threatening situation, UI negatively affects patients, their families, and their environment physically, psychologically, and economically.

UI is categorized as stress urinary incontinence (SUI, incontinence due to physical exertion, coughing, and laughing), urgency urinary incontinence (UUI, involuntary UI with a sense of urgency), and mixed-type urinary incontinence (MUI, both sense of urgency and incontinence with physical exertion). SUI is more common in young and middle age women and is seen in 10–12% of women in this age group[5]. The prevalence of UUI and MUI is between 8–30% and is more common in people aged 65 and above[2].

The type of UI can be diagnosed by the patient's history and bladder diary. Physical examination, urine analysis and culture, and residual urine volume measurement are among the basic tests.

Measures such as weight loss in obese patients, restriction of excessive fluid intake, and restriction of beverages such as

tea, coffee, and alcohol may be useful in the treatment of UI[6,7]. However, often medical or surgical treatment may be required.

Duloxetine is the only drug that increases urethral striated sphincter activity used in the treatment of SUI according to the systematic review result. It reduces the frequency of incontinence by 50% during the treatment process and provides a significant improvement in quality of life[8].

Patients receiving antimuscarinic therapy for pure UUI usually have a positive response to this treatment. Mirabegron, a selective β3-adrenoreceptor agonist, is an alternative in patients who discontinue antimuscarinics due to lack of response or side effects. Phase 3, multicenter, randomized controlled trials have shown that mirabegron is more effective in the reduction of incontinence episodes and improvement of health-related quality of life compared to placebo[9,10].

In our study group, we aimed to evaluate the effect of the duloxetine and mirabegron combination in MUI patients.

METHODS

The data of MUI patients who applied to the urology outpatient clinic between January 2018 and December 2019 were retrospectively analyzed after the approval of Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee. Among the 108 MUI patients evaluated, 88 patients were included in the study after applying the exclusion criteria. Our patients were evaluated with urine analysis, urine culture, ultrasonography (to determine post void residual urine volume), and clinical examination (abdominal, pelvic, and perineal) before treatment. Stress incontinence was demonstrated with the provocative stress (coughing) test in both supine and standing positions. UI was detected by questioning and predominant symptoms determined by the patient's history. If necessary, urodynamic evaluation was also performed on these patients. They were questioned about their quality of life and their desire for treatment. Of these, 50 patients had predominant urge-type MUI and 38 patients had stress-type MUI. Patients with only SUI or UUI were not included in this study. In total, 20 patients with urinary infections, urinary tract stones, urinary malignancy, chronic obstructive pulmonary disease and patients who had undergone previous surgical treatment for UI, patients with grade 3–4 cystocele, prolapse, and patients with over 150 cc. residual urine volume were excluded from the study and urodynamic evaluation was performed.

Pretreatment demographic data, body mass index (BMI), daily pad count, International Consultation of Incontinence Questionnaire-Short Form (ICIQ-SF), overactive bladder symptom score (OABSS) questionnaire, and bladder diaries

were recorded. Mirabegron 50 mg (once a day) and duloxetine 40 mg (twice a day) combination treatment was administered to MUI patients. After eight weeks of treatment, the patients were re-evaluated using the same forms and criteria. Pre and post treatment values were compared statistically. The clinical benefit of the patients was evaluated using the clinical global impact scale (CGI).

Power analysis was not done because study is unique. At least 75 patients were included for pilot studies.

Statistical analysis

SPSS 21.0 program (IBM, NY, USA) was used in statistical analysis. The distribution of variables was measured using the Kolmogorov-Smirnov test. The comparison of the questionnaire scores and the number of pads was evaluated by dependent sample t-test. A significant p-value was accepted as <0.05.

RESULTS

In our study group, 88 patients were between 42 and 70 years, with the mean age of 58.87±6.54 years. BMI was between 19.85 and 35.42 with a mean value 28.95±5.32. Table 1 shows patients data such as the number of birth and smoking history.

A total of 50 patients with dominant urge-type MUI did not completely respond to three month average antimuscarinic treatment. This was identified by questioning the symptoms of the patients (including three-day bladder diary). Another 38 patients with dominant stress-type MUI did not prefer surgical treatment, and they did not sufficiently benefit from three-month duloxetine treatment only. Before combination therapy, 18 of 50 patients (36%) in the UUI group and 25 of 38 patients (65%) in the SUI group performed pelvic floor muscle exercises (PFME) for two months, which did not provide enough benefit (Table 2).

After eight weeks of mirabegron 50 mg (once a day) and duloxetine 40 mg (twice a day) combination treatment, ICIQ-SF score decreased from 14.71±3.54–7.83±6.41 (p<0.001) and OABSS from 11.00±2.26–7.02±2.17 (p<0.001), and the number of pads per day decreased from 3.7±2.8–0.89±1.02 (p<0.001). Pre and post treatment values are shown in Table 3.

According to CGI, 55 out of 88 (62.50%) patients had a partial or complete response from the treatment. In our study group, 80 patients adapted to the treatment and completed the eight-week process. In eight patients, side effects (three patients had dizziness and nausea, three patients had hypertension attacks, and two patients had jaw spasm) were observed and were returned to normal when the drug was discontinued.

Table 1. Demographics of patients.

	All	UUI	SUI
	88	50	38
Age (Mean)	42–70 (58.87±6.54)	54–70 (63.61±5.6)	42–65 (50.85±5.8)
Gender (F/M)	88/0		
Smoking (+/–)	40/48	19/31	21/17
BMI (Mean)	19.85–35.42 (28.95±5.32)	19.85–31.35 (24.83±4.72)	23.94–35.42 (27.21±4.84)
Primiparity	82	44	38
Multiparity	74	39	35

UUI: urgency-type urinary incontinence; SUI: stress-type urinary incontinence; BMI: body mass index.

Table 2. Conservative treatments before combined drug therapy.

	UUI	SUI
PFME 88/43	50/18	38/25
Bladder training	50/50	38/38

PFME: pelvic floor muscle exercise; UUI: urgency-type urinary incontinence; SUI: stress-type urinary incontinence.

Table 3. Before and after treatment values of mixed-type urinary incontinence patients.

	Before treatment	After treatment
ICIQ-SF	14.71±3.54	7.83±6.41
OABSS	11.00±2.26	7.02±2.17
Daily pads	3.7±2.8	0.89±1.02
p<0.001		

ICIQ-SF: international consultation of incontinence questionnaire-short form; OABSS: overactive bladder symptom score.

DISCUSSION

Treatment is planned after the basic evaluations of UI diagnosis and after excluding other concurrent underlying urinary system diseases. Conservative treatment methods such as PFMEs can be tried first for SUI[11,12]. A systematic review of 21 trials involving 1281 women (665 PFMT, 616 controls) showed that women in the PFMT groups were eight times more likely than controls to report that they were cured and 17 times more likely to report cure or improvement in UI[13]. Consequently, the International Consultation on Incontinence (ICI) recommends that PFMT should be considered as a first-line treatment in women with UI[14]. PFMT was applied to 43 patients in our study group as a first-line treatment, but they could not get a complete result. Surgery is also a treatment option with a high success rate for SUI. However, pharmacological therapy is the next option for SUI treatment.

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is the only pharmacotherapy option used in many countries for SUI treatment. Although it reduces incontinence episode frequency by approximately 50%, it is unclear whether the benefits are sustainable, and side effects such as nausea are common. Also, three patients in our group complained of nausea. Therefore, the persistence with duloxetine was affected due to side effects. In a study group of 588 women, patients were classified into SUI-predominant MUI, UUI-predominant MUI, or balanced MUI in a randomized controlled trial versus placebo. Duloxetine was effective in improving incontinence and incontinence-quality-of-life (I-QOL) in all subgroups[15]. However, the effect of topical estrogen use in elderly female patients is still controversial[11,16,17]. There is also some evidence to suggest that administration of local estrogens in conjunction with antimuscarinics could have a synergistic effect in the management of postmenopausal women with overactive bladder[18].

Studies suggest that bladder training and PFME are the main treatment option for UUI in young women[6,11]. Antimuscarinic drugs are another option[11]. Suitable antimuscarinic drugs for

UUI are oxybutynin, tolterodine, fesoterodine, solifenacin, darifenacin, propiverine, and trospium chloride. These are more effective than placebo, safe, and well-tolerated treatments that improve health-related quality of life[19]. Traditionally, side effects such as dry mouth, constipation, cognitive impairment, and sleep disturbance have limited the usefulness of antimuscarinic agents.

The rate of continuous use of antimuscarinic drugs is very low. The rate of patients who continue to use these drugs at the end of one year is only 12–39%[20]. Side effects and treatment unresponsiveness have been reported as the main causes of withdrawal[21]. In a randomized controlled study conducted with a group of 854 women with MUI, it was observed that tolterodine was effective for the treatment of overactive bladder, but was not effective enough for SUI symptoms[22]. Similar results have been found for solifenacin[23].

A selective β3-adrenoreceptor agonist mirabegron might offer an alternative option for women not responding or facing serious side effects to antimuscarinics. The safety and tolerability of mirabegron were established over 12 months, with sustained efficacy observed over this treatment period[24]. Furthermore, in Canadian retrospective claims database study involving 19,485 patients, persistence at 12 months was 39% for mirabegron versus 14–35% for antimuscarinics. Patients taking mirabegron demonstrated, statistically significant, greater adherence than those taking antimuscarinics[25].

In this study, we used the combination of duloxetine and mirabegron in patients with MUI. We evaluated the ICOQ-SF, OABSS forms, and daily pad counts, and we found statistically significant improvements after eight weeks of treatment (p<0.001). Despite the side effects (e.g., hypertension, nausea, and dizziness) seen in 0.9% of the patients, they were able to continue the treatments during eight weeks. We did not find enough publications in the literature regarding the usefulness of the combination of mirabegron and duloxetine in the treatment of MUI.

The study has some limitations. First, there is no control group. Patients were evaluated according to their symptoms before and after treatment. The short follow-up period of the patients is another limitation. Evaluation of MUI can only be relied on the story of patients is among the limitations of the study.

CONCLUSION

In our study, we have shown statistically that using mirabegron and duloxetine combination in patients with MUI improves symptom scores and decreases daily pad usage. Since our study sample size was small, larger randomized controlled study groups are needed to better evaluate the effectiveness.

AUTHORS' CONTRIBUTIONS

AA: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **MGÇ:** Data curation. **EM:** Formal Analysis, Writing – review & editing.

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The levels of inflammatory biomarkers in hemodialysis and peritoneal dialysis patients

Mehmet Yildirim[1]* ⓘ, Seyyid Bilal Acikgoz[2] ⓘ, Ahmed Bilal Genc[3] ⓘ,
Selçuk Yaylaci[3] ⓘ, Hamad Dheir[4] ⓘ, Savaş Sipahi[4] ⓘ

SUMMARY

OBJECTIVE: In this study, we aimed to determine fibroblast growth factor 23, soluble alpha klotho, osteocalcin, indoxyl sulphate, sclerostin, Procollagen 1 N Terminal Propeptide, and beta-CrossLaps levels in hemodialysis and peritoneal dialysis patients, and to compare the levels of these markers among hemodialysis and peritoneal dialysis patients, as well as healthy individuals.

METHODS: The study included 30 hemodialysis and 23 peritoneal dialysis patients who were followed-up for at least six months at the Sakarya University Hospital, besides 30 healthy volunteers.

RESULTS: The participants were divided into three groups with similar characteristics in terms of age, gender and body mass index. Fibroblast growth factor 23, soluble alpha klotho, indoxyl sulphate, beta-CrossLaps, and Procollagen 1 N Terminal Propeptide levels were significantly higher in patients of both the hemodialysis and peritoneal dialysis groups than in the healthy volunteers' group. There was no difference in levels of these molecules between hemodialysis and peritoneal dialysis groups.

CONCLUSIONS: Fibroblast growth factor 23, sclerostin, indoxyl sulphate, beta-CrossLaps, and Paclitaxel-induced neuropathic pain levels were higher in patients of both groups as inflammatory markers. In our study, we found higher soluble alpha klotho levels in patients of both groups than in the healthy volunteers' group, suggesting that blood soluble alpha klotho levels may not correlate with renal klotho levels.

KEYWORDS: Kidney disease, chronic. End-stage renal disease. Inflammatory markers.

INTRODUCTION

Chronic kidney disease (CKD) has become an important health problem worldwide causing progressive illness, bone-mineral disorders, cardiovascular morbidities, and early deaths. In the course of CKD, bone-mineral disorders may occur due to the high level of blood phosphorus. Hyperphosphatemia causes secondary hyperparathyroidism, decreasing blood calcium and calcitriol levels. This clinical condition is defined as renal osteodystrophy (ROD). It may cause cardiovascular diseases, pathological bone fracture and, finally, increased risk of mortality[1].

Although the process pathophysiology has not been well understood yet, vascular calcification has been an initiator of vascular inflammation[2]. Therefore, the biomarkers, which show vascular inflammation in the course of CKD, could provide clinicians with early diagnosis and treatment of the CKD complications. In this piece of article, we will focus on inflammation pathways and potential inflammatory biomarkers.

As mentioned, secondary hyperparathyroidism starts the process of ROD. Loss of nephrons may cause phosphate retention in circulation and bones respond to it with increased

[1]Hacettepe University Faculty of Medicine, Intensive Care Unit, Internal Medicine Department – Ankara, Turkey.
[2]Samsun Ondokuz Mayıs University Faculty of Medicine, Internal Medicine-Rheumotology Department – Samsun, Turkey.
[3]Sakarya University School of Medicine, Internal Medicine Department – Sakarya-Turkey.
[4]Sakarya University School of Medicine, Nephrology Department – Sakarya, Turkey.
*Corresponding author: dryildirimmehmet@hotmail.com, drseyyid@gmail.com

fibroblast growth factor-23 (FGF-23) production. Excreted phosphorus levels increase in urine and FGF-23 binds both the FGF-23 receptors and the klotho. Additionally, FGF-23 inhibits cytochrome 27B1 (CYP-27B1) enzyme, which converts 25 hydroxyvitamin D to 1-25 dihydroxyvitamin D and increases renal calcium reabsorption using the transient receptor potential vanilloid 5 (TRPV-5) channel that needs klotho for activation. Studies have shown that FGF-23 concentration increases in patients with stage-2 and upper CKD, and may reach 1,000 times of normal range[3,4]. A previous study, in a large cohort, has reported that increased FGF-23 levels are independently associated with mortality among patients who are beginning hemodialysis treatment, suggesting further investigation to reveal whether FGF-23 might be a new biomarker[5].

Klotho is a protein secreted from multiple tissues, especially kidneys. Klotho has antiapoptotic, antioxidant, angiogenetic and antifibrinogenetic effects. In addition, klotho suppresses phosphate reabsorption and activates phosphate excretion and appears to protect kidneys in patients with CKD. In these individuals, soluble alpha klotho levels decrease due to impaired renal functions. Studies have shown that klotho may be a predictor of early disease and klotho deficiency may be an indicator of disease progression and complication, such as bone disorders and vascular inflammation[6].

Indoxyl sulphate is the uremic toxin produced by tryptophan metabolism and secreted from proximal tubules. In patients with CKD, secretion of indoxyl sulphate decreases. It has been proven that high levels of indoxyl sulphate are associated with endothelial oxidative stress, atherosclerosis and vascular inflammation[7].

Osteocalcin is an osteoblast-specific protein secreted from bones that regulates phosphorus and vitamin D metabolism and sexual functions. On one hand, it is expected that in the course of CKD, osteocalcin levels increase as a result of bone resorption. On the other hand, a study has reported a negative relationship between osteocalcin levels and mortality in patients with coronary artery disease[8].

Sclerostin is a glycopeptide secreted from osteocytes. Sclerostin inhibits Wnt pathway, which plays an anabolic role in bone metabolism. There is a negative correlation between blood sclerostin and parathyroid hormone (PTH) levels in hemodialysis patients[9]. A recent study has reported that higher sclerostin levels may prolong life expectancy in hemodialysis patients[10].

Procollagen 1 N Terminal Propeptide (PINP) is a bone formation marker produced during collagen synthesis. Osteoclasts, acids and neutral proteases reveal fragments containing C-terminal telopeptide in the process of bone destruction. Aspartic acid is added to these telopeptides and then beta-CrossLaps are formed. Beta-CrossLaps are released into the circulation, and when they are detected in the blood, it may result in the bone resorption and mature type 1 collagen degradation. Beta-CrossLaps levels may increase up to five times in patients undergoing hemodialysis compared with healthy volunteers[11].

Vascular inflammation and bone disorders are life-threatening complications of CKD and have been associated with severe complications in patients with CKD. These complications should be treated in the early phases of disease to improve prognosis. Therefore, markers that show this process to the clinicians in the early phases of these complications are strongly needed. FGF-23, klotho, indoxyl sulphate, osteocalcin, sclerostin, PINP and beta-CrossLaps are the markers that have recently been focused on. However, there has been no consensus on the routine used for these molecules yet, because their normal and risky levels have not been evaluated clearly yet and there are very limited data about the levels of these molecules in patients who undergo peritoneal dialysis.

The primary aim of this study was to compare the levels of these markers in dialysis patients and healthy population. Secondly, we aimed to identify the relationship between type of renal replacement therapy (RRT) in hemodialysis and peritoneal dialysis and the level of these markers.

METHODS

Patient selection

We have conducted a prospective cohort study including patients with CKD, who received hemodialysis and peritoneal dialysis treatments, and healthy volunteers. A total of 30 hemodialysis and 23 peritoneal dialysis patients, besides 30 healthy volunteers were included. Both groups of patients consisted of patients with CKD that had been receiving dialysis treatment for at least six months. The age range of patients was 18-80 years. Exclusion criteria were: temporary renal dysfunction, active infectious/inflammatory episodes or acute ischaemic vascular disease histories during the previous three months, additional diseases causing chronic inflammation, chronic liver disease and positive hepatitis serology. Additionally, patients who did not provide written consent were excluded from the study. Healthy volunteers in the age range of 18-80 years, who did not have chronic diseases and infectious diseases during the last three months were included in the study. All volunteers provided written consent.

Data collection

Demographic data (e.g. gender, age, start date of dialysis treatment, comorbidities, systolic and diastolic blood pressure and body mass index) and laboratory data (creatinine, C-Reactive Protein – CRP, albumin – A, calcium – Ca, phosphorus – P, Parathyroid hormone – PTH, total cholesterol, low-density lipoprotein – LDL, haemoglobin – Hb) of both groups of patients

were analyzed. In order to determine the levels of inflammatory biomarkers (FGF-23, soluble alpha klotho, indoxyl sulphate, osteocalcin, sclerostin, PINP, beta-CrossLaps), the blood samples of hemodialysis patients were collected before the second hemodialysis during a mid-week session, and the blood samples of peritoneal dialysis patients were collected before morning changes. These blood samples were stored at -80°C. Human FGF-23, sclerostin, osteocalcin, indoxyl sulfate, Procollagen 1 N Terminal Propeptide, soluble alpha klotho and Beta-CrossLaps ELISA kits were used to determine the molecular levels (supplied by Hangzhou Eastbiopharm Co., Ltd. – PRC, China). Due to the manufacturer instructions, 40 U/L of blood sample were collected from each volunteer and tested with micro-ELISA method. Results were identified with Triturus (Grifols) ELISA instrument with a 450-nm wavelength.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for all statistical analyses. Data were shown, such as frequency (percentage), number and mean±standard deviation. Kolmogorov-Smirnov test was used for assessing the normality of the distribution of the numerical variables. Student's-t and ANOVA tests were used to compare the differences among the groups regarding normally distributed numerical variables. Mann-Whitney U and Kruskal Wallis tests were applied to compare the differences among the groups regarding non-normally distributed variables. χ^2 test was used to assess categorical variables. Spearman's correlation analysis determined the relationship among non-normally distributed variables. Level of significance was accepted as $p<0.05$.

RESULTS

Demographic data and baseline characteristics of each group are shown in Table 1. There was no statistically significant difference for age, gender and body mass index among the three groups ($p=0.743$; $p=0.421$; $p=0.381$, respectively). In hemodialysis group, patients underwent dialysis treatment for 75.13±43.18 months; and in peritoneal dialysis group, 42.13±29.46 months ($p<0.05$). Eight (26.7%) patients of hemodialysis group and 6 (26.1%) patients of peritoneal dialysis group had a diabetes history, which did not show any significant difference. In both

Table 1. Demographic data, baseline characteristics and laboratory findings.

	Hemodialysis	Peritoneal dialysis	Healthy volunteers	p-value
	(n=30)	(n=23)	(n=30)	
Age, years	52.50±16.03	52.35±14.15	50.07±15.51	0.743*
Gender, F/M (%)	20 (66.7)/10 (3.3)	13 (56.5)/10 (43.5)	15 (50)/15 (50)	0.421†
Dialysis period (months)	75.13±43.18	42.13±29.46	-	0.003‡
Diabetes n (%)	8 (26.7)	6 (26.1)	-	0.962†
Systolic blood pressure (mmHg)	140.59±27.04	129.45±27.57	117.47±17.65	0.002*
Diastolic blood pressure (mmHg)	89.56±23.01	85.77±19.88	76.50±15.52	0.040*
BMI	24.23±4.32	25.38±5.08	25.86±4.38	0.381*
Creatinine (mg/dL)	9.94±2.30	8.51±3.00	0.86±0.22	<0.001*
CRP (mg/L)	12.67±12.55	28.61±44.68	5.37±5.57	0.004§
Albumin (mg/dL)	4.03±0.30	3.19±0.57	4.10±0.23	<0.001§
Ca (mg/dL)	8.56±0.69	9.16±0.94	9.40±0.28	<0.001*
P (mg/dL)	5.44±1.16	5.34±1.59	2.99±0.59	<0.001*
CaxP	46.48±9.78	48.42±13.37	28.30±6.10	<0.001*
PTH (pg/mL)	804.19±741.25	461.81±332.20	60.48±16.46	<0.001§
Total cholesterol (mg/dL)	163.97±35.81	204.78±62.84	219.08±41.12	<0.001§
LDL (mg/dL)	97.63±30.95	124.30±43.79	156.04±34.42	<0.001§
Haemoglobin (g/dL)	11.08±1.47	10.33±1.40	13.65±1.57	<0.001*

F: feminine; M: masculine; BMI: body mass index; CRP: C-Reactive Protein; Ca: – Calcium; P: phosphorus; CaxP: Calcium phosphate product; PTH: parathyroid hormone; LDL: low density lipoprotein.
*One-Way ANOVA Test; †Ki-Kare Test; ‡Mann Whitney U Test; §Kruskal Wallis Test

groups of patients, systolic (p=0.002) and diastolic blood pressure (p=0.04) were higher than in the healthy volunteers' group. The mean CRP levels of hemodialysis and peritoneal dialysis patients were higher than in healthy volunteers (12.67±12.55; 28.61±44.68; 5.37±5.57 mg/L, respectively, p=0.004). The mean albumin levels of healthy volunteers (4.10±0.23 mg/dL) were higher than in hemodialysis (4.03±0.30 mg/dL) and peritoneal dialysis patients (3.19±0.57 mg/dL; p<0.001). The mean calcium, phosphorus and PTH levels of hemodialysis and peritoneal dialysis patients were higher than in healthy volunteers (p<0.001; p<0.001; p<0.001). The mean of total cholesterol and LDL levels were higher in patients of both groups than in the healthy volunteers' group (p<0.001; p<0.001).

The mean blood levels of FGF-23, soluble alpha klotho, osteocalcin, indoxyl sulphate, sclerostin, PINP and beta-CrossLaps are listed in Table 2. The mean blood levels of FGF-23, soluble alpha klotho, indoxyl sulphate, sclerostin and PINP were significantly higher in hemodialysis and peritoneal dialysis groups than in the healthy volunteers' group (p<0.001), while there was no significant difference among these groups in terms of mean blood levels of osteocalcin (p=0.134). We found a positive correlation between soluble alpha klotho levels and systolic blood pressure in hemodialysis group (p=0.039; r=0.399). In the peritoneal dialysis group, there was an inverse correlation between soluble alpha klotho and CRP levels (p=0.008; r=-0.539).

DISCUSSION

FGF-23, soluble alpha klotho, indoxyl sulphate, sclerostin, PINP and beta-CrossLaps levels were significantly higher in both groups of patients than in the healthy volunteers' group, which is consistent with previous studies[12].

Studies showed a strong correlation between serum creatinine and FGF-23 concentration[4,13]. In our study, FGF-23 levels in hemodialysis patients were higher and they were also determined in a wide range. Lima et al. compared FGF-23 levels and bone histomorphometry parameters of dialysis patients and revealed that circulating FGF-23 concentrations may indicate alterations in ongoing bone formation[14]. Therefore, our study supports previous researches that found FGF-23 levels in a wide range[13,14]. It appears that a large meta-analysis is needed to determine the range of FGF-23 levels for CKD.

In the course of CKD, decrease of renal klotho expression causes increase of FGF-23 concentration. Firstly, Shimamura et al. reported that low levels of soluble alpha klotho could be a new marker in CKD[15]. However; some recent studies have shown that soluble alpha klotho levels may not reflect tissue klotho expression[16]. Seiler et al. followed up 312 patients with CKD for 2.2 years and found out that the level of soluble alpha klotho was not associated with severity of renal dysfunction and complications[17]. Interestingly, in the current study, soluble alpha klotho levels have been significantly higher in both groups of patients than in the healthy volunteers' group. Therefore, we can speculate that soluble alpha klotho levels in patients on dialysis treatment may not be a reliable marker or may not reflect the expression of renal klotho directly.

In 2011, a study indicated a negative correlation between glomerular filtration rate and indoxyl sulphate levels[18]. Furthermore, a meta-analysis confirmed the positive relationship between indoxyl sulphate and mortality[19]. As expected, in our study, the indoxyl sulphate levels were significantly higher in both groups of patients, and there was no statistically significant difference between hemodialysis and peritoneal dialysis groups.

Beta-CrossLaps and PINP have been used as bone loop markers in volunteers that do not have CKD. It has not been clear yet whether beta-CrossLaps and PINP can be used as bone turnover markers[20]. Nevertheless, few previous studies reported that beta-CrossLaps levels were significantly higher in patients undergoing hemodialysis[21,22]. Although there are limited studies

Table 2. Blood levels of markers.

	Hemodialysis (n=30)	Peritoneal dialysis (n=23)	Healthy volunteers (n=30)	p-value
FGF-23 (pg/mL)	772.33±369.74	657.13±339.30	325.40±232.44	<0.001*
Soluble alpha klotho (ng/mL)	12.06±3.72	11.65±4.42	6.79±3.02	<0.001†
Indoxyl sulphate (mcg/mL)	51.09±13.18	47.83±14.96	21.52±5.55	<0.001*
Osteocalcin (ng/mL)	61.38±31.12	52.90±19.52	46.89±28.47	0.134*
Sclerostin (ng/mL)	1.073±0.590	0.825±0.445	0.452±0.219	<0.001*
PINP (ng/mL)	1113.03±511.10	946.96±528.03	431.37±254.16	<0.001*
Beta-CrossLaps (ng/L)	1486.90±821.48	1163.35±627.86	680.83±508.52	<0.001*

*Kruskal-Wallis Test; †One-way ANOVA Test

focusing on the levels of these markers among peritoneal dialysis patients, a recent study has found out increased levels of beta-CrossLaps in peritoneal dialysis patients. However, hemodialysis patients have not been included in this previous study[23]. Our study has demonstrated that in dialysis patients beta-CrossLaps levels have been significantly higher than in healthy volunteers and there have been no statistically significant differences between hemodialysis and peritoneal dialysis patients.

In 2015, Liu and He reported that patients who received dialysis had significantly higher PINP levels than those who did not receive dialysis[24]. In the current study, PINP, which is a marker of bone formation, and the precursor molecule of beta-CrossLaps have been considered higher in both groups of patients than in the healthy volunteers' group.

A previous study from Austria has detected two times higher sclerostin levels in dialysis patients than in healthy volunteers[25]. In line with, the present study has shown that sclerostin levels were significantly higher in both groups of patients than in the healthy volunteers' group and there was no statistically significant difference between hemodialysis and peritoneal dialysis patients. However, another study has shown an inverse correlation between sclerostin and glomerular filtration rate in patients with CKD and those who did not receive dialysis treatment[12]. Further studies comparing sclerostin levels of pre-dialysis and dialysis patients are needed to enlighten these findings.

In the current study, we have not found differences in the osteocalcin levels between patients and healthy volunteers. It has been a remarkable finding, because there was no similar finding in the previous researches. Two studies (n=61 and n=98) have reported an inverse correlation between glomerular filtration rate and osteocalcin levels[26,27]. Also, it can be related to the fact that there have been fewer patients in our study than in the literature. Researches in larger cohorts are needed to confirm our findings.

There have been some limitations in the current study. Firstly, the longer treatment duration of the hemodialysis group might have caused higher levels of inflammatory biomarkers in this group. Secondly, there has been no data on patients' long period follow-up that could suggest the relationship between levels of markers and severe clinical complications of CKD.

Finally, we could not determine the effects of patients' medications on biomarker levels.

CONCLUSIONS

In the present study, FGF-23, indoxyl sulphate, sclerostin, beta-CrossLaps and PINP levels have been significantly higher in both hemodialysis and peritoneal dialysis group than in the healthy volunteers' group. There has been no significant difference of these markers between hemodialysis and peritoneal dialysis patients. Soluble alpha klotho levels in dialysis patients have been higher than in healthy volunteers, speculating that blood soluble alpha klotho levels may not directly reflect the renal klotho expression.

AUTHORS' CONTRIBUTIONS

MY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. **SBA:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation. **ABG:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review and editing. **SY:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review and editing. **HD:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review and editing. **SS:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review and editing.

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Cost-effectiveness analysis comparing intensity-modulated radiotherapy with conformational radiotherapy (3D-RT) for prostate cancer in the brazilian health system

Gustavo Arruda Viani[1]* , Caio Viani Arruda[2] , Rogerio Oliveira[2]

SUMMARY

OBJECTIVE: The intensity-modulated radiotherapy (IMRT) has been established as the standard external-beam radiation technique to treat prostate cancer in several countries. In Brazil, the public health system and the National Health Agency do not reimburse its utilization. This study compared the cost-effectiveness of IMRT and tridimensional radiotherapy (3D-RT) from a payer's perspective.

METHODS: We built a Markov model to delineate the health states after treatment with IMRT and 3D-RT. The treatment-related toxicity data were extracted from the literature. The sensitivity analyses were performed over potential parameters.

RESULTS: The incremental cost of IMRT was R$ 5,553.78. At a time horizon of 5 years, the quality-adjusted life expectancy after IMRT was higher than 3D-RT. The incremental cost-effectiveness ratio (ICER) of IMRT over 3D-RT was R$-296,74/quality-adjusted life year (QALY). Therefore, IMRT was the dominant strategy, which depended on the value of interventional procedures for severe toxicity and the difference between IMRT and 3D-RT reimbursement. The IMRT was still most likely to be cost-effective at a willingness-to-pay R$ 100,000/QALY, with a net monetary benefit (NMB) superior to 3D-RT after R$ 50,000.00, resulting in a difference of R$220.000,00 after 5 years.

CONCLUSIONS: IMRT generated more values than 3D-RT for external-beam treatment. Given its potential to reduce late toxicity with hypofractionation, these data reinforce its incorporation to treat prostate cancer in the Brazilian health system from a payer's perspective.

KEYWORDS: Prostate Cancer. Cost-effectiveness. Intensity-modulated radiotherapy.

INTRODUCTION

Radiotherapy plays a crucial role in the management of prostate cancer[1]. In the last decades, radiotherapy has passed through a significant technological advance with the development of intensity-modulated radiotherapy (IMRT)[2-4]. IMRT has the capacity of delivering the prescription dose to the target volume while sparing the normal tissues around the gland[2].

The retrospective cohorts and randomized clinical trials showed that IMRT produces similar biochemical control with reduced late toxicity and better quality of life[5-9]. In the RTOG 0126, patients who received IMRT with conventional fractionation had a reduction in any late toxicity compared with tridimensional radiotherapy (3D-RT)[9]. The only randomized trial comparing IMRT with 3D-RT using moderated hypofractionation for prostate cancer showed a significant benefit for late gastrointestinal (GI) toxicity grade 2 or higher and better quality of life[8].

Based on these outcomes, IMRT has been recommended as the standard technique for the patients with prostate cancer[10,11].

The American Society of Radiation Oncology (ASTRO) and National Comprehensive Cancer Network (NCCN) also suggest that the IMRT is considered to deliver radiation to the prostate[10,11]. However, in Brazil, the public health system (Sistema Unico de Saúde [SUS]) and health insurance do not reimburse the IMRT. The Brazilian Supplemental Health System (Agência Nacional de Saúde Supplementary [ANS]) does not have the IMRT registered[3]. Consequently, it is not reimbursed by health insurance companies.

The IMRT is more expensive and time-consuming, requiring much attention from the radiation oncologist and medical physicist in all steps involved in the process for the patient be and adequately treated at the machine[3]. However, even being more expensive, health systems from other countries, such as Canada and England, have incorporated the technique into their clinical practice due to its better cost-effectiveness[12].

In the Brazilian context, to the best of our knowledge, no study was published evaluating the cost-effectiveness of IMRT over 3D-RT. Therefore, this study aims to perform a cost-effective analysis with Markov chain comparing IMRT versus 3D-RT with a simulation using the data available in the medical literature on the perspective of health care system.

METHODS

A Markov model was designed to simulate the clinical outcomes of a 62-year-old man with localized prostate cancer. The Markov model allows us to hypothetically simulate the cohorts of patients with transitions between different health states using fixed increments of time[13]. In other words, this model considers a hypothetical patient with localized prostate cancer and simulates the possibility of the occurrence of events after treatment. Over the course, the patient may develop treatment-related toxicity, disease recurrence, or death from any causes; each of these events is correlated with a cost and a utility. The patient is followed up until death, and this process is repeated thousands of times to estimate an average cost and utility for each treatment. The two radiation techniques were compared using the Markov model, namely, IMRT to 70 Gy in 2.8 Gy per fraction and 3D-RT with the same total dose or dose per fraction. We assumed that patients started in a well state, i.e., with no evidence of disease or symptom like or similar to the radiation collateral effects. The analysis was conducted from the payer's perspective. The cycle length was calculated per month, and we used a lifetime time horizon of 5 years.

Toxicity and assumptions

All probabilities were extracted from the randomized clinical trials identified in the systematic search on the electronic databases[8,9]. Based on the outcomes of randomized clinical trials, we have assumed that biochemical failure and death was similar between IMRT and 3D-RT. Toxicities were defined as the probability of developing grade 2 or higher GI/genitourinary (GU) toxicity by the toxicity criteria of the Radiation Therapist Oncology Group (RTOG) or Common Toxicity Criteria (CTC). Patients could have any combination of these toxicities, assuming that the development of any toxicity was independent of the others. All toxicities from treatment were assumed to develop within 5 years from the treatment. Table 1 describes the rates of toxicities extracted from the randomized clinical trials.

Costs

The baseline costs of IMRT and 3D-CRT were extracted from the CBHPM payment schedule, as described in Table 1. Costs for the management of GI and GU toxicities were also extracted from the CBHPM 2016 schedule, as shown in Table 1. Routine follow-up visits, including periodic PSA control, were not included in the model once IMRT and 3D-RT were assumed to be identical[14].

Utility

The quality-adjusted life year (QALY) is considered the standard for the cost-effective analysis studies. It was used as the effectiveness measure. The QALY is defined as a combination of quality of life and length of life. In the QALY, each year of life is weighted by a factor that effectively reflects the quality of life[13]. This factor is determined by a health state utility. A utility is an econometric measure that a patient gives a value to his/her health status ranging from 0 (death) to 1 (perfect health). In this model, each health state, such as GI, is associated with a utility. A QALY is estimated by multiplying the length of life in such a health state by its utility. We used the utilities for health states reported by Sweart et al.[15], as detailed in Table 1.

Discounting and analysis

An annual discount of 5% on the costs and QALYs was given. All the analyses were performed by using TreeAge Pro software. The effect of adjusting the assumptions in the model was evaluated by using the sensitivity analysis. The difference between the cost of IMRT and 3D-RT, % grade 2 or higher GI toxicity, % grade 2 or higher GU toxicity, and price and number of medical procedures were ranged in the one-way sensitivity analysis. When a radiation modality was both more effective (higher QALYs) and less costly, it was considered dominating the other strategies. If a radiotherapy modality was not only more effective but also more costly,

the incremental cost-effectiveness ratio (ICER) was described. We also performed a net monetary benefit (NMB) to represent the value of an intervention in monetary terms in the case of the health system was the willingness to pay a threshold for a unit of QALY.

RESULTS

The Markov model was calibrated to replicate the rates of grade 2 or higher GI and GU toxicities in patients treated with IMRT and 3D-CRT, producing similar probabilities of complications to the extracted data from randomized trials, which was similar to

Table 1. Description of the parameters, values, and amounts considered in the Markov chain model including the costs, toxicity, and health transitions extracted from the literature for intensity-modulated radiotherapy and tridimensional radiotherapy.

Radiotherapy cost	Value	Unity	Reference
Medical visits	R$ 77.00	1	CBHPM, 2016[14]
Planning and simulation CT	R$ 339.14	1	CBHPM, 2016[14]
RT device to treat	R$ 564.64	1	CBHPM, 2016[14]
Computerized complex planning	R$ 1,457.48	1	CBHPM, 2016[14]
Total cost IMRT	R$ 22,440.21		CBHPM, 2016[14]
Total cost 3D-RT	R$ 16,906.48	1	CBHPM, 2016[14]
Fractionation Conventional hypofractionated	Number of fractions 39 25	Number of treatment 1	CBHPM, 2016[14]
Treatment complication costs	Frequency/year	Monetary value	Reference
Medical visits posttreatment	3	R$ 77.00	CBHPM, 2016[14]
Medical treatment for grade 2 or higher GI Follow-up visits Medical drugs (sulfasalazine)	3 12	R$ 77.00 R$ 90.00	CBHPM, 2016[14]
Interventional treatment for grade 2 or higher GI Interventional procedure (argon laser)	2	R$ 917.00	CBHPM, 2016[14]
Health states	Value	Standard deviation	Reference
Radiotherapy	0.73	0.2	Stewart et al. 2005[15]
Death	0	-	By definition
GI radiation side effects	0.71	0.09	Stewart et al. 2005[15]
GU radiation side effects	0.79	0.23	Stewart et al. 2005[15]
Both	0.70	0.24	Stewart et al. 2005[15]
Acute toxicity	Grade 2 or higher GI acute toxicity	Grade 2 or higher GU acute toxicity	Reference
Hypofractionation	24% 3D-RT 7% IMRT	27% 3D-RT 9% IMRT	Viani et al. 2016[8]
Conventional fractionation	18% 3D-RT 3.8% IMRT	13% 3D-RT 8.5% IMRT	Michalski et al. 2013[9]
Late toxicity	Grade 2 or higher GI acute toxicity	Grade 2 or higher GU acute toxicity	Reference
Hypofractionation	64% 3D-RT 21.7% IMRT	37% 3D-RT 12.3% IMRT	Viani et al. 2016[8]
Conventional fractionation	20.8% 3D-RT 14.8% IMRT	13.4% 3D-RT 7.4% IMRT	Michalski et al. 2013[9]

CT: computadorized tomography; RT: radiotherapy; IMRT: intensity-modulated radiotherapy; 3D-RT: tridimensional radiotherapy; GI: gastrointestinal; GU: genitourinary.

their targeted probabilities. Initially, the incremental cost of IMRT was R$ 5,533.73, i.e., 32% higher than 3D-RT. The cost-effectiveness analysis, considering the 5-year horizon, showed that the IMRT resulted in R$ 5,959.00, and the 3D-RT generated a value of R$ 1,2437.00, as demonstrated in Figure 1A.

The monetary value with IMRT was initially higher than the 3D-RT; however, after the period analysis, the 3D-RT generated a much higher expense than the IMRT, reaching its value and exceeding it, leaving a difference of R$ 6,478.00.

Regarding QALYs, IMRT presented a value of 41.08 and 3D-RT, 19.25; therefore, IMRT generated an increase in the QALYs of 21.8, and it means that IMRT provided a higher quality of life for the patient over 5 years who experienced fewer complications as a result of the radiotherapy
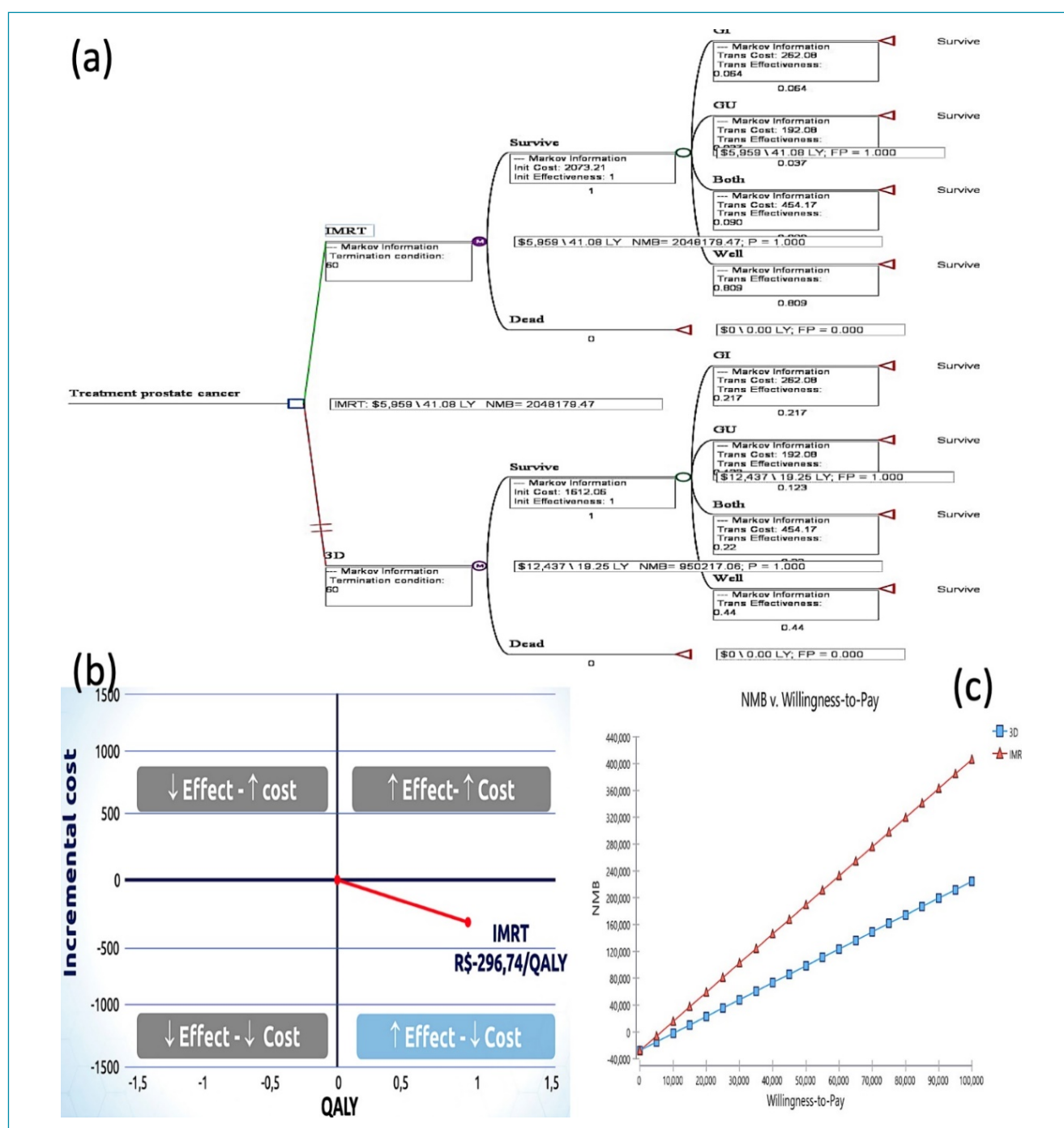
Figure 1. (a) Outcomes from the Markov chain model; (b) plan of cost-effectiveness showing intensity-modulated radiotherapy as dominant strategy; and (c) net monetary benefit comparing tridimensional radiotherapy with intensity-modulated radiotherapy.

procedure. Combining costs and QALYs, the IMRT had a value of R$ 145 per QALYs, while the 3D-RT obtained the value of R$ 646.00 QALYs. The ICER was R$ -296.74/QALY, as shown in Figure 1B.

In the sensitivity analysis, i.e., the difference in the reimbursement between IMRT and 3D-RT, the cost of the interventional procedure to treat severe toxicity influenced the IMRT as a dominant strategy. IMRT was also highly cost-effective similar to using a conventional hypofractionated schedule, as demonstrated in Table 2. The NMB is demonstrated in Figure 1C. After a horizon of 5 years, from the perspective of the health care payer, the IMRT generated R$ 220,000.00 more value than 3D-RT, mainly related to the reduction in severe late toxicities.

DISCUSSION

This study shows that IMRT is cost-effective compared with 3D-RT in the treatment of localized prostate cancer. Although IMRT has an initial incremental cost of R$ 5,533.73, it was associated with a lower risk of rectal and bladder toxicity, resulting in the absolute risks of severe complications very low to compensate for a significantly costlier treatment. IMRT was a strategy dominant with an ICER of R$ -296.74/QALY. Our data agree with other cost-effective analyses from other countries that pointed in the same direction[16-18].

Thus, our findings may have broad implications for the incorporation of IMRT as an option to treat localized prostate cancer in Brazil. In the sensitivity analysis, the outcomes were markedly consistent, reinforcing the argument that IMRT is cost-effective for the health payer in Brazil. The cost-effectiveness of IMRT was observed with hypo- or conventional fractionation. Besides, the cost-effectiveness had a strong relationship with the cost of rectal toxicity and with the difference between the costs of the radiation techniques. It means that from the perspective of the health payer, the IMRT at a monetary value of up to R$ 24,000.00 stays located at quadrant I on the plane of the cost-effective analysis, as shown in Figure 1B. Considering the values between R$ 17,000 and R$ 22,000, the IMRT was a dominant strategy. It is essential to consider that the number of medical visits during the follow-up and medical drugs was not significant in the sensitivity analysis. These points are relevant for health care payers to establish their strategy to maximize the benefits of incorporating IMRT as follows:

1. They should focus on the closer follow-up.
2. The early intervention for the GU/GI side effects may reduce the need for expensive treatment such as argon laser or surgery.
3. The integration of these actions could improve even more the cost-effectiveness of IMRT.

Considering the threshold of willingness to pay, the IMRT was cost-effective at R$ 50,000 and R$ 100.00/QALY generating a high NMB; this finding is also relevant from the payer's perspective. For example, if the health care payer is willing to invest R$ 100,000.00 in the IMRT as the incorporation of technology, after a horizon of 5 years, the IMRT produced an NMB of R$ 220,000.00 higher than 3D-RT, i.e., the health care payer left to spent this value with radiation complications, mainly, with toxicities.

Table 2. One-way sensitivity analysis comparing the incremental cost-effectiveness ratio of intensity-modulated radiotherapy with tridimensional radiotherapy.

Parameters	Model result		
	Range	Lower limit	Upper limit
Medical treatment			
Follow-up visits	3–12	IMRT*	IMRT*
Medical drugs (sulfasalazine)	12–24	IMRT*	IMRT*
Interventional procedure			
% of variation in the costs for the interventional procedure for GU or GI grade 2 toxicity	50–100%	IMRT†	IMRT*
Radiotherapy techniques			
% of radiotherapy difference between IMRT and 3D-RT	30–50%	IMRT*	IMRT†
Radiation fractionation	Conventional-hypofractionated	IMRT*	IMRT*

GU: genitourinary; GI: gastrointestinal; IMRT: intensity-modulated radiotherapy; 3D-RT: radiotherapy; *dominant strategy with incremental cost-effectiveness ratio<0/QALY; †incremental cost-effectiveness ratio<R$1000,00/QALY.

From the perspective of a public system, the IMRT value utilizing the CBHPM is very high compared with the current value paid for treating prostate cancer in the SUS. The Brazilian public health system does not recognize or specify the price by the radiation technique employed to treat the disease. Consequently, in Brazil, several radiation services are not stimulated to use the IMRT once the SUS pays only around R$ 5,000.00. It is relevant to note that the IMRT is more time-consuming, which requires better and rigorous quality control, and the patients spent more time in the machine per session. Therefore, a readjustment on the SUS reimbursement would be necessary to put the IMRT available for patients from the public health system.

Moreover, our data suggest that a wide margin of readjustment could be provided on the actual SUS reimbursement (R$ 5,000.00), maintaining its cost-effectiveness, mainly because of the high proportion of procedures to treat severe GI/GU toxicity concerning R$ 5,000.00. The need for surgical procedures or argon laser sessions to treat rectal bleeding, for instance, can significantly affect the cost-effectiveness of IMRT in this scenario favorably.

The incorporation of IMRT in the SUS and the Brazilian Supplemental Health System procedures is vital for prostate cancer treatment in Brazil. The novel radiation modalities, such as stereotactic body radiotherapy (SBRT), utilize the IMRT as a technical requirement to deliver ultra-hypofractionation with a dose higher than 6 Gy per fraction. Recently, a large randomized trial compared the UHFT-RT with the conventional radiotherapy showed a similar biochemical control and toxicity between the treatment delivering radiotherapy in 7 versus 39 fractions for the patients with intermediate- and high-risk prostate cancer[19]. SBRT is very precise and extremely comfortable and convenient to the patients, and without the IMRT, the Brazilian patients will not have access to this very effective and safe radiation modality.

The nature of our model-based analysis has some limitations. Our assumptions were based entirely on the solid outcomes for 5 years; therefore, they are more immature for an extended follow-up. However, it is reasonable to infer that the cost-effectiveness of the IMRT with hypofractionation can increase over time, mainly driven by rectal toxicity.

CONCLUSIONS

This study showed that IMRT is a cost-effective radiation modality versus the 3D-RT. Our analysis strongly suggests that IMRT should be preferred to treat the patients with prostate cancer independently of fractionation in a cost-conscious environment.

The cost-effectiveness was robust throughout the multiple sensitivity analyses. The value of reimbursement of grade 2 or higher GI/GU toxicities and the difference between IMRT and 3D-RT magnified these outcomes. Given the significant amount of men diagnosed with localized prostate cancer each year, our analysis strongly argues in favor of its incorporation by the public health system and the Brazilian Supplemental Health System (ANS).

AUTHORS' CONTRIBUTIONS

GAV: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CVA:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RO:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Epidemiological profile of dengue in Brazil between the years 2014 and 2019

Rafaella Menegazzo Oneda[1] (iD), Sandrini Regina Basso[1] (iD), Luísa Rodrigues Frasson[1] (iD),
Nicole Meller Mottecy[1] (iD), Leonardo Saraiva[2]* (iD), Cíntia Bassani[3,4] (iD)

SUMMARY

OBJECTIVE: The aim was to determine the epidemiological profile of dengue fever in Brazil between the years 2014 and 2019.
METHODS: This is an observational, descriptive, cross-sectional, and retrospective study, which was carried out through the analysis of secondary data collected from the National System of Notification Appeals (SINAN) and from SUS Computer Department (DATASUS).
RESULTS: The total number of reported cases was 5,867,255, and 2015 was the year with the highest cases (1,696,340). The cases were predominant in the Southeast and Midwest macro-regions, the female sex (55.6%), brown people (48%), and clinical and epidemiological criteria of confirmation (63.8%). Regarding the age group, it was observed that during the study period, the highest prevalence occurred in individuals between 20 and 39 years (38.3%). There was a change of serotype from DENV-1 to DENV-2, and dengue was the most prevalent classification (95.2%). Concerning hospitalization rates, there was a limited necessity of admissions (5.7%), as well as few deaths due to the notified disease (3,444).
CONCLUSIONS: There was a significant growth in the number of dengue fever cases in Brazil in 2019, which represents a public health problem.
KEYWORDS: Dengue. Aedes aegypti. Incidence. Health profile.

INTRODUCTION

Dengue is one of the main endemic diseases in Brazil. It is an arbovirus, transmitted via the bite of the *Aedes aegypti* mosquito, and can be divided into four different serotypes: DENV-1, DENV-2, DENV-3, and DENV-4[1]. The first report of dengue in Brazilian territory dates back to the end of the 19th century, but only in 1981 it was possible to isolate the serotypes of the virus, which has since spread throughout the country[2].

The classification scheme of dengue divides the disease into three different categories. The first, dengue without warning signs, has as initial and main symptom that includes the abrupt onset of a high fever (39–40°C) in association with severe headache, myalgia, arthralgia, and retro-orbital pain. Patients may

also manifest maculopapular rash, anorexia, diarrhea, nausea, and vomiting. The symptoms usually improve after the third day of their onset[3].

Some patients, after defervescence of fever, may progress to dengue with warning signs, the second category of the disease, presenting severe and continuous abdominal pain, persistent vomiting, pleural and/or pericardial effusion, ascites, postural hypotension, hepatomegaly, mucosal bleeding, lethargy, irritability, and progressive increase in hematocrit. These manifestations must always be investigated, since they can lead to the third and most dangerous category, severe dengue, promoting a range of outcomes including shock, hemorrhage, organs dysfunction and even death[3,4].

[1]Faculdade Meridional de Passo Fundo – Passo Fundo (RS), Brazil.
[2]Universidade de Passo Fundo – Passo Fundo(RS), Brazil.
[3]Faculdade Meridional de Passo Fundo – Passo Fundo (RS), Brazil.
[4]Hospital Servidor Público Estadual de São Paulo – São Paulo (SP), Brazil.
*Corresponding author: leo77saraiva@hotmail.com

The definitive diagnosis of dengue is performed in laboratory through the serology and viral antigen detection test. Since it is not possible to obtain the results of the tests immediately, the World Health Organization (WHO) recommends that the tourniquet test should be performed during the screening of all patients under the suspect of dengue and without the signs of bleeding[4,5].

The control of *A. aegypti* is the main form of disease prevention. From the above findings, it is clear that dengue is a problem that needs to be tackled in Brazil[6]. This study aimed to trace the epidemiological profile of the disease in the country between the years 2014 and 2019.

METHODS

This is an observational, descriptive, cross-sectional, and retrospective study. Data collection was performed using the information available at Notifiable Diseases Information System (SINAN) and at SUS Department of Informatics (DATASUS), in the period between January 1, 2014 and December 31, 2019. Through them, the relation between Brazilian macro-regions and the following variables were observed: the number of probable cases, serotypes, sex, race, age group, final diagnosis, disease progression, need for hospitalization, and the confirmation criteria of the disease.

Statistical analysis was performed using SPSS V20, Minitab 16, and Excel Office 2010 software. This study has a significance level of 0.05; therefore, all confidence intervals also met 95% of statistical confidence.

Since the data collection was performed online, and all the data are available at SINAN website and are of public domain, this research is, thereby, free of ethical risks.

RESULTS

In the period between 2014 and 2019, 5,868,413 suspected cases of dengue were identified in Brazil. The highest number of notifications occurred in 2015 (n=1,696,340), followed by 2019 (n=1,557,452), 2016 (n=1,514,873), 2014 (n=591,128), 2018 (n=265,372), and 2017 (n=243,248). Comparing the years of 2014 and 2019, the incidence of dengue increased from 291.5 to 741.12 cases per 100,000 inhabitants, as shown in Figure 1.

Among the analyzed macro-regions, the incidence per 100,000 inhabitants was higher in the Midwest (n=981,320), followed by the Southeast (n=3,378,636), Northeast (n=1,112,369), North (n=195,550), and the South (n=200,525) regions (Figure 2).

Regarding the sex of the evaluated population, the males represented 2,599,974 (44.4%) cases, while the females represented 3,258,284 (55.6%) cases. As for the age group, the

highest prevalence occurred in individuals between 20 and 39 years (38.3%).

Concerning the race, the brown skin prevailed in the North, Northeast, and Midwest (80.7, 78.5, and 57.8%, respectively) regions, while in the Southeast and the South regions the most affected populations were the whites.

This study also considered the need for hospitalization, which, overall, was low, but had most of its occurrences in the North (10.6%) and the Northeast (9.6%) regions. As for the disease progression, most patients got cured (n=4,275,802), and a total of 3,444 people died due to the disease during the study period.

In the matter of serotypes, DENV-1 prevailed (87.5%) between 2014 and 2017. However, in 2018 and 2019, DENV-2 was the most detected serotype in the country (63%). DENV-3, the least common of them, was responsible only for 7 cases in the North, 28 in the Northeast, 20 in the Southeast, 27 in the South, and 10 in the Midwest regions (Table 1).
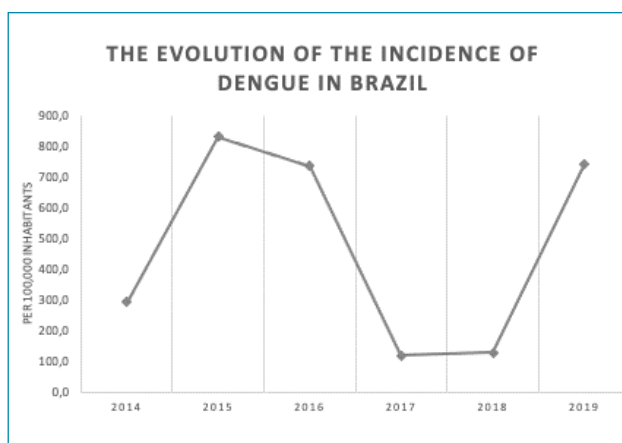
Figure 1. Evolution of the incidence of dengue in Brazil between the years 2014 and 2019.
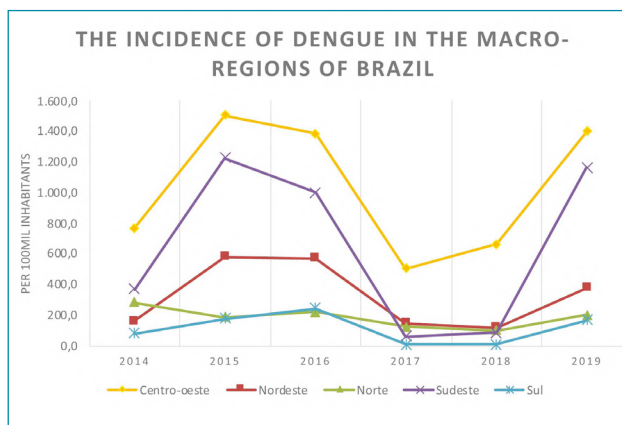
Figure 2. Incidence of dengue in the macro-regions of Brazil between the years 2014 and 2019.

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Table 1. Sociodemographic characteristics of patients with suspected dengue between 2014 and 2019 (n=5,868,413).

Variables n	2014	2015	2016	2017	2018	2019
Suspected cases of dengue						
Brazil	591,128	1,696,340	1,514,873	243,248	265,372	1,557,452
North	48,302	32,096	38,543	21,980	17,668	36,961
Northeast	90,489	328,713	325,046	84,830	66,496	216,795
Southeast	312,181	1,051,063	863,010	53,815	72,587	1,025,980
South	23,062	52,085	71,183	2,601	1,734	49,860
Midwest	117,094	232,383	217,078	80,022	106,887	227,856
Sex						
Males	268,619	756,125	656,191	110,483	118,782	689,780
Females	321,551	936,443	855,869	132,481	146,338	865,609
Age group (years)						
0–9	48,524	137,191	125,154	25,304	29,391	144,128
10–19	106,056	287,183	251,261	44,668	45,741	261,263
20–39	235,024	645,383	574,879	96,936	102,854	581,937
40–59	146,584	443,178	382,136	54,431	63,123	399,684
60–64	20,450	66,966	57,548	7,578	8,965	62,187
65–69	14,205	46,843	41,576	5,602	6,253	43,521
70–79	15,335	51,780	46,934	6,097	6,554	44,175
≥80	4,723	16,924	18,426	2,529	2,396	15,452
Race						
White	184,046	549,645	348,773	38,651	59,057	506,064
Black	20,788	52,884	48,749	6,900	8,537	64,786
Asian	3,955	9,162	9,475	1,807	2,491	11,343
Brown	165,529	392,875	427,466	116,667	114,445	573,710
Indigenous	1,410	3,181	3,641	685	830	4,630
Serotype						
DENV-1	2,340	5,191	3,785	283	456	4,198
DENV-2	30	71	133	204	687	7,972
DENV-3	12	23	42	9	3	10
DENV-4	611	358	106	51	12	398
DENV not informed	588,135	1,690,697	1,510,807	242,701	264,214	1,544,874
Death by dengue	496	1,004	724	205	221	795
Final classification						
Dengue without warning signs	447,403	1,297,439	1,054,127	164,396	193,367	1,244,823
Dengue with warning signs	8,620	21,934	9,658	2,864	4,536	20,263
Severe dengue	793	1,812	1,027	344	444	1,601
Confirmation criteria						
Ignored/Blank	85,880	295,623	398,344	72,585	63,464	228,148
Laboratory	229,507	533,746	326,670	43,313	61,758	421,562
Clinical-epidemiological	269,846	839,656	770,970	121,666	131,899	878,600
Under investigation	5,895	27,315	18,889	5,684	8,251	24,799
Need for hospitalization						
Ignored/blank	299,990	929,520	832,166	110,181	100,045	558,356
Yes	19,637	38,273	32,184	11,597	15,042	56,085
No	271,501	728,547	650,523	121,470	150,285	943,011

DENV 1, DENV 2, DENV 3, DENV 4: serotypes

DISCUSSION

According to the WHO, in the last decades, the incidence of dengue is increasing exponentially, especially in places near the tropics, such as the Americas and the Caribbean, and South-East Asia and Asia-Pacific regions[7]. It can be explained by factors such as the hot and humid climate, the low levels of basic sanitation, disordered urbanization, and the vector resistance to insecticides and larvicides[8,9].

In this context, this study showed that, in Brazil, between 2014 and 2019, 5,867,255 cases of dengue were reported, highlighting the years of 2015 (n=1,696,340), 2016 (n=1,514,873), and 2019 (n=1,557,452), in which there was a significant increase of occurrences. These data are aligned with the bulletin released by WHO, in 2020, in the Epidemiological Update of Dengue and Other Arboviruses, and, in Brazil, can be explained mainly by two events: the increase of rain in these years and the introduction of a new serotype of the disease, DENV-2, which barely circulated in the country before 2018, and, since then, has become the most prevalent serotype of dengue, as shown in this study[10,11].

Still with respect to the serotype, DENV-1 predominated in 2014, 2015, 2016, and 2017 (n=2,340, 5,191, 3,785, and 283, respectively). Despite that, the number of cases due to DENV-2, which, since 2018, became the most prevalent serotype, started to escalate already in 2017 (n=204).

Referring to the macro-regions of Brazil, two of them stood out: the Southeast region, which condensed the majority of dengue notifications (n=3,378,636), and the Midwest region, which registered the highest incidence per 100,000 inhabitants. The Southeast is the most populous region of the country, which may have contributed to this being the place with the most number of notifications[12].

Regarding the distribution of cases by sex, similar to what was evidenced by Martins et al.[13], this study also identified that the women were the most affected by the disease (55.6%). This cannot be explained by a single factor; however, Cardoso et al.[14] believed that, in addition to spending more time indoors, a favorable environment to *A. aegypti*, women tend to seek health care more commonly than men, and consequently they are diagnosed more.

Throughout the study period, in the North, Northeast, and Midwest regions, the brown people was the most afflicted race (80.7%, 78.5%, and 57.8%, respectively), a result confirmed by Oliveira et al.[15] but opposed to what was found by Santana e Duarte[16], who identified a predominance of the white race (32.4%) in the same regions. However, in the Southeast and the South regions, the white race was more affected[17].

The analysis of the age group revealed that individuals between 20 and 39 years (38.3%) were the ones who have fallen ill mostly. These results are different than those obtained by Bravo et al.[18] in the Philippines, where the most affected age group was between 5 and 14 years.

As laboratory tests are not always available, the clinical and epidemiological criterion was validated by the Ministry of Health and is usually adopted during endemics/epidemics/pandemics after the circulation of the virus is acknowledged in the area[19].

Regarding the final classification of the disease, dengue without warning signs was the most prevalent (n=4,401,555), while dengue with warning signs (n=67,875) and severe dengue (n=6,201) were less common. Overall, the need for hospitalization was low, but needed the most in the North (10.6%) and Northeast (9.6%) regions, which burdened the public health system and highlights a failure in *A. aegypti* eradication plan[20]. These data are remarkably different in India where, according to Ganeshkumar et al.[21], dengue is the main cause of hospitalization.

As a limitation of this study, we identified that the data were collected from a secondary source that is fueled by health professionals, who often do not fill out the forms correctly, therefore interfering in statistical analysis and results.

CONCLUSIONS

This epidemiological analysis showed that, in the period between 2014 and 2019, 5,867,255 cases of dengue were reported in Brazil, and 2015 was the year that registered the majority of notifications. The highest incidence per 100,000 inhabitants took place in the Midwest region, and most of the cases occurred in the Southeast region. There was a switch of serotype predominance which changed from DENV-1, in 2014 until 2017, to DENV-2 since then.

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AUTHORS' CONTRIBUTIONS

RMO: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **SRB:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **LRF:** Investigation, Writing – original draft, Writing – review & editing. **NMM:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **LS:** Writing – review & editing. **CB:** Conceptualization, Investigation, Writing – review & editing. All authors have contributed equally to this work.

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Decompressive hinge craniectomy with linear durotomies for ischemic stroke: a pilot study

Almir Ferreira Andrade[1] , Saul Almeida da Silva[1] , Ricardo Ferrareto Iglesio[1] ,
Vitor Salviato Nespoli[1] , Gustavo Noleto[1] , João Paulo Mota Telles[1] ,
Manoel Jacobsen Teixeira[1] , Eberval Gadelha Figueiredo[1]*

SUMMARY

OBJECTIVE: Decompressive craniectomy may be a life-saving measure in ischemic stroke patients, who still have several associated complications. The objective of this study is to evaluate a novel decompressive surgery technique for severe hemispheric ischemic stroke.
METHODS: For the hinge decompressive craniectomy (HDC), linear durotomies were performed. Vertical (one or two frontal and two parietal), and two horizontal (temporal), with approximately 5 cm long, linear durotomies were carried out. Duroplasty was performed using an autologous subgaleal tissue graft fixed with separate sutures to avoid CSF leak and direct contact of the cortex with the bone flap. The bone flap was fixed in three parietal locations. We compared 10 patients who underwent our modified HDC with 9 patients submitted to classical decompressive craniectomy (CDC). The primary outcome of this study was mortality.
RESULTS: Nineteen patients were included, with a mean age of 52.3 years (±8.2). Four (44%) patients from the HDC group had to be reoperated to remove the bone flap because of brain swelling worsening, but none of them died. The average time of HDC was 90 minutes. Overall 14-days mortality was 21.1% (n=4), and cumulative six-months mortality was 42.1% (n=8). Five (50%) patients submitted to CDC died, while 3 (33.3%) submitted to HDC died (χ^2=0.07, p=0.79). The mean length of stay was 46.7 days (±32.1) for HDC and 38.7 (±27.1) for CDC (p=0.60).
CONCLUSIONS: We present a modified technique of hinge craniectomy with linear vertical and horizontal durotomies, which seems to have reduced operative time and mortality compared to classical decompressive craniotomy, although the difference was not statistically significant.
KEYWORDS: Craniectomy. Stroke. Intracranial hypertension.

INTRODUCTION

Strokes that affect over 2/3 of a hemisphere, or malignant infarctions, are relatively rare, representing 1 to 10% of all supratentorial ischemic strokes (IS). However, they are associated with extremely high mortality rates, sometimes up to 80%[1]. Given the prevalence of IS, any therapeutic advances in this area would have a significant impact on our population.

The indications, timing, and technique of decompression for refractory intracranial hypertension (rIH) after IS are still controversial. Amorim et al. described the role of surgical decompression in the reestablishment of blood flow to the penumbra area and fluid distribution in the ischemic zone[2].

Although CDC is widely accepted for treating rIH, it is associated with significant morbidity, including the postoperative risk of seizures, hydrocephalus, infection, and progression of preexisting hematomas. Furthermore, it later requires a cranioplasty or a second surgical procedure to reimplant the bone graft.

New techniques have been developed, including different dural opening patterns and hinge-like craniectomies, and both the replacement of wide duroplasty with durotomies and the substitution of CDC with hinge-like techniques have proven effective[3-9]. However, these two emerging concepts have not yet converged in a single model to prevent early and late complications associated with unilateral decompressive craniectomy with dural expansion.

We have previously described a hinge craniectomy with superior fixation of the bone flap associated with vertical and horizontal linear durotomies and hermetic dural closure with autogenous galea. This technique demonstrated clear benefits in the treatment of patients with acute subdural hematomas secondary to traumatic brain injuries, reducing mortality and late complications of CDC[8]. The objective of the present study is to evaluate this technique applied to severe hemispheric IS, in terms of mortality and operative time.

METHODS

This study compared CDC and hinge decompressive craniectomy (HDC) for the treatment of patients with severe hemispheric stroke. From 2012 to 2014, 19 patients were selected at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP).

They were admitted to the Hospital with hemispheric IS, and the decision to perform craniectomy was multifactorial and discussed in interdisciplinary meetings. The most critical parameter to indicate craniectomy in these cases is the involvement of >2/3 of a hemisphere, which predisposes to significant intracranial hypertension, particularly after 2 or 3 days. The selection of the technique was based on the team's individualized judgment. Data were collected retrospectively.

HDC technique

For the HDC, linear "Burger type" durotomies were performed. Vertical (one or two frontal and two parietal), and two horizontal (temporal), with approximately 5cm long., linear durotomies were carried out. Duroplasty was performed using an autologous subgaleal tissue graft fixed with separate sutures (4.0 Prolene), to avoid CSF leak and direct contact of the cortex with the bone flap. We performed a 12x8 cm hinge craniotomy with bone flap fixation in three parietal locations to prevent inward displacement of the flap after deswelling.

CDC technique

The CDC consisted of a 12x8 cm craniectomy with a C-shaped duroplasty and placement of an autologous graft hermetically sutured. The bone flap was placed in the abdominal subcutaneous tissue.

Data

The primary outcome of this study was mortality. Covariates studied include age, gender, affected hemisphere, comorbidities, midline shift, hospital length of stay (LOS), and complications. Data were collected from medical records, pre and postoperative CT scans, and phone calls.

Data are presented as counts (valid %), if categorical, and mean (±standard deviation) or median (interquartile range, IQR), as appropriate. Chi-squared tests were used to compare categorical data between groups. Welch's t-tests were employed for continuous data, except for the comparison between pre and postoperative shifts within the same groups (paired t-tests). Analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Nineteen patients were included, with a mean age of 52.3 years (±8.2). All of them were initially treated according to the American Heart Association guidelines for ischemic stroke. The median time between ictus and surgical decompression was one day.

Nine were treated with HDC, and 10 underwent CDC (Table 1). Four (44.4%) patients from the HDC group had to be reoperated to remove the bone flap because of brain swelling worsening, but none of them died. The average time of HDC was 90 minutes.

Overall, 14-day mortality was 21.1% (n=4), and cumulative six-months mortality was 42.1% (n=8). Five (50%) patients submitted to CDC died, while 3 (33.3%) submitted to HDC died (χ^2=0.07, p=0.79). Mean LOS was 46.7 days (±32.1) for HDC and 38.7 (±27.1) for CDC (p=0.60).

Overall median preoperative midline deviation was 7 mm (IQR=7.5). The median preoperative shift for patients submitted to HDC was 6 mm (IQR=9) and 7 (IQR=3) for those submitted to CDC. Preoperative scan records were missing for one patient of the CDC group.

One patient presented with a midline shift >12 mm and did not survive. Nine others presented with shifts between 7–12 mm, of whom 5 (55.5%) died. Other eight presented with shifts between 0–6 mm, of whom 2 died (33.3%). Postoperatively, median shift was 6 mm (IQR=4) overall, 7 mm (IQR=4) for HDC, and 5 mm (IQR=3.75) for CDC. Comparing pre and postoperative midline shifts, CDC provided a significant improvement (p=0.02), while HDC did not (p=0.71) (Table 2 and Figure 2).

Table 1. Patient characteristics.

	HDC (n=9)	CDC (n=10)	Total (n=19)
Delta ictus-surgery	1 (0)	1 (0.75)	1 (0)
Age	54 (±7.7)	50.7 (±8.8)	52.3 (±8.2)
Female	4 (44.4%)	3 (30%)	7 (36.8%)
GCS	13 (4)	12 (3.75)	13 (4)
Anisocoria	1 (11.1%)	4 (40%)	5 (26.3%)
Midline shift	6 (9)	7 (3)	7 (7.5)

Data are presented as median (interquartile range), mean (±standard deviation), or count (valid %), as appropriate.
HDC: our modified hinge decompressive craniectomy; CDC: classical decompressive craniectomy; GCS: Glasgow coma scale.

Table 2. Midline shift.

Midline shift	HDC	CDC	Overall
Preoperative	6 (9)	7 (3)	7 (7.5)
Postoperative	7 (4)	5 (3.75)	6 (4)
0–6 mm	5 (55.5%)	3 (33.3%)	8 (44.4%)
7–12 mm	3 (33.3%)	6 (66.6%)	9 (50%)
>12 mm	1 (11.1%)		1 (5.6%)

Data are presented as median (interquartile range) or count (valid %).
HDC: our modified hinge decompressive craniectomy; CDC: classical decompressive craniectomy.
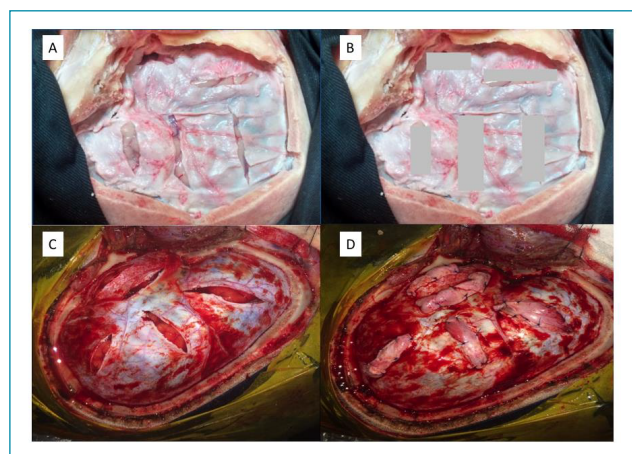
Figure 1. Hinge craniectomy with autologous duroplasty and linear durotomies. (A) Anatomical specimen used to picture the linear durotomies. Vertical durotomies were performed over the frontal and parietal lobes, and horizontal durotomies were performed over the temporal lobe. (B) Anatomical specimen used to picture the linear durotomies. Schematic representation of the duroplasties with autologous subgaleal graft to avoid bone/brian contact and to prevent cerebrospinal fluid leak. Patient with severe hemispheric stroke and clinically refractory intracranial hypertension submitted to our modified hinge craniectomy with vertical and horizontal durotomies (C) and autologous subgaleal graft (D) to prevent brain herniation and cerebrospinal fluid leak.

DISCUSSION

We present a modified HDC to treat intracranial hypertension due to IS. With this technique, surgeries lasted an average of 90 minutes, which is significantly faster than the CDC. Even though 4 (44.4%) patients who underwent HDC crossed over to the CDC group, mortality in the group initially treated with HDC was still lower than CDC (not statistically significant). Therefore, we hypothesize there is a subgroup of patients with malignant IS for whom the HDC is sufficient for decompression.

CDC presents multiple disadvantages, such as hydrostatic edema, vasoparesis, brain herniation through the bone defect, and potentially harmful axonal stretching[10,11]. Late complications of CDC are also well known, including sinking skin flap syndrome and metabolic and hydrodynamic dysfunctions, leading to neuropsychological alterations in patients without bone flap. For these reasons, studies have suggested a hinge-like fixation of the bone flap in the superior border of the craniotomy[6-8].

New approaches

New techniques include dural phenestrations[3], basal durotomy in the shape of an inverted "U" with concomitant duroplasty[4], lattice-pattern[5], and longitudinal durotomies[6]. These studies yielded positive results but have not addressed the problem of the bone opening, which unavoidably demands a second operation to perform cranioplasties.

Other authors have focused on solving the traditional skull defect. Goettler and Tucci developed the "Tucci Flap," maintaining the bone flap through anterior fixation to the skull[7]. Another hinge-like approach was published in a large series in 2007, with inferior temporal fixation of the bone flap. However, the authors did not modify the wide duroplasty technique[8].

Comparing techniques

Kenning et al. found no differences comparing CDC and their proposed hinge craniectomy in 50 patients (30 traumatic injuries, 10 IS, 10 hemorrhagic strokes)[12]. In 2012, studying 28 patients with IS, the same authors concluded that hinge craniectomy in middle cerebral artery (MCA) strokes resulted in higher intra-hospital mortality compared to CDC, although cosmetic and functional long-term results were superior. Furthermore, all surviving patients submitted to CDC required a second operation, while only 20% of those treated with hinge techniques did[13].

Hinge craniectomies were also proven to have low infection rates, providing safe and adequate intracranial pressure control in both trauma and stroke cases. It allows expansion of the flap to relieve brain swelling but contains parenchymal herniation[8].

Burger et al. proposed durotomies to substitute classical duroplasty[14]. In their study, intracranial pressure dropped 44% after removal of the bone flap, and an extra 26% after vertical durotomies. Ten days after surgery, there was no pressure rebound, even after sedation weaning and intracranial pressure became stable after 24–72 hrs (<20 mmHg). In our study, although midline shifts were reduced more significantly in the early postoperative period with CDC, mortality was not significantly different between groups. These findings suggest that secondary brain swelling observed after classical craniectomies might be due to oversized and unrestrained dural opening.

The DESTINY II trial randomized 112 patients with extensive IS to either CDC or intensive clinical treatment. The primary outcome was survival without severe disability in 6 months. Patients who underwent surgical decompression presented significantly lower mortality (33%) compared to clinical treatment (70%). Infections were more frequent in the surgical group, and brain herniation was more frequent in the clinical group[15,16].

In our institution, eligibility criteria for decompressive craniectomy after IS are age >18 or ≤60 years; significant brain swelling presenting within 48 hours after stroke; GCS at admission >3 and <15, with progressive consciousness impairment, NIHSS 7. We merged the existing concepts of linear durotomies and hinge-like fixation of the bone flap, with the original added feature of 3-4 frontoparietal and 1-2 temporal durotomies. To the best of our knowledge, no studies have yet proposed a similar approach.

It is noteworthy that 44% of patients submitted to HDC had to be reoperated to remove the bone flap due to progression of brain swelling, placing the flap in the abdominal subcutaneous tissue. Nonetheless, no herniation was observed through the durotomies, which were maintained. Mortality was not significantly different between the two groups. However, both groups present lower mortality rates compared to standard clinical treatment, which can be as high as 70%, as reported in previous studies[16].

CONCLUSIONS

We present a modified technique of hinge craniectomy with linear vertical and horizontal durotomies, which seems to have reduced operative time and mortality compared to classical decompressive craniotomy, although the difference was not statistically significant. Further studies are necessary to compare different techniques accurately.

ETHICAL STATEMENT

IRB approval was waived due to the retrospective nature of the study.

AUTHORS' CONTRIBUTIONS

AFA: Conceptualization, Data curation, Methodology, Investigation. **SAS**: Data curation, Methodology, Writing – original draft. **RFI**: Data curation, Methodology, Writing – original draft. **VSN**: Methodology, Writing – original draft. **GN**: Investigation, Methodology. **JPMT**: Data curation, Formal analysis, Software. **MJT**: Supervision, Writing – review & editing. **EGF**: Supervision, Writing – review & editing.

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Female students are the most psychologically affected by the COVID-19 outbreak: a case study in an academic community in Brazil

Ana Carolina Paludo[1]* , Michael Pereira Silva[2] , Jaqueline Puqueves de Souza[3] ,
Marcus Peikriszwili Tartaruga[1] , Deoclecio Gruppi[1] , Timothy Cavazzotto[1]

SUMMARY

OBJECTIVE: The study evaluates psychological responses to the COVID-19 outbreak in the students, professors, and staff due to the social distancing and transition of the classroom activities through online learning.

METHODS: 518 participants from a University community in Brazil answered an online survey with questions related to demographic data, psychological responses, and preventive measures. Absolute and relative frequencies described the sample, Chi-square and z-test tested associations between the variables, adopting $p<0.05$.

RESULTS: Female (71.20%), young age -18 to 35 years (82.60%), students (76.10%), living in a family with 1 to 3 members during quarantine (55.40%) were more prevalent respondents. Women, young age, and students had a significantly higher rate of negative feelings in all psychological questions. Curiously, negative feelings during social distances affect the participants, independent of living quarantine alone or with family/friends during the COVID-19 outbreak.

CONCLUSIONS: Our findings demonstrated that the COVID-19 outbreak affected the psychological responses in the Brazilian academic community, also, women, young age, and students appear to be a risk group to negative psychological responses. The long-term quarantine due to the COVID-19 pandemic may cause further worsening in the psychological responses, especially in those in the risk group.

KEYWORDS: COVID-19 pandemic. Disease Outbreak. Quarantine. Psychological stress. Students.

INTRODUCTION

Nowadays, a severe acute respiratory syndrome (SARS), known as Coronavirus disease 2019 (COVID-19) quarantined the majority of countries. SARS-COVID-19 was first identified in December 2019 in the city of Wuhan, located in central China, and had spread worldwide[1]. Because of its widespread transmission, recognized as a pandemic disease by World Health Organization (WHO), measures to limit viral transmission and minimize contact with people infected by COVID-19, such as social distancing, have been recommended worldwide and imposed in some countries.

Based on the negative effect of quarantine, as reported elsewhere[2,3] and its uncertain ending date, the scientific community has published valuable recommendations and strategies regarding the possible effect of quarantine and social isolation on mental health[4,5] and psychological impact[6]. Moreover, recent studies demonstrated psychological responses to the COVID-19 outbreak in Chinese[7], Italian[8,9] and students from South India[10], Bangladeshi[11] and so one[12].

The academic environment *per se* has already demonstrated to be stressful for professors and both graduate and undergraduate students, demonstrating a negative relationship with

wellbeing and mental health[13-15]. Consequently, considering the quarantine and social isolation condition plus a new challenge of online learning, the psychological responses could be exacerbated in the University community. The main aim of this study was to evaluate the psychological responses to the COVID-19 outbreak in students, professors, and staff from a Brazilian University.

METHODS

Participants

A total of 526 respondents participated in the survey, and 518 were part of the final sample. Inclusion criteria were: being a member of the University selected (student, professor, or staff), being home-quarantined, and 18 years older. The local ethics committee approved the study (protocol number 4,002,656). Informed consent was acquired online, in the first part of the survey.

Procedures

An online survey platform with a designated link was sent to the University community after one month of quarantine. We used social media and institutional email to reach a large number of university members. The survey was completed from 1st to May 30th, 2020. This study is a part of a more comprehensive research project intituled "COVID-19: Psychological and behavioral impacts of social isolation in the university community in a Midwest State of Paraná – Brazil".

Measures

Descript data from sociodemographic questions were obtained through open and close-ended questions regarding the participants' age, biological sex, position (student, professor, or staff), number of members living together during quarantine, and contact with someone diagnosed with COVID-19. Moreover, behavioral responses as food consumption, sedentary behavior, and physical activities also were asked.

Psychological responses were measured using some items from the SELF-Reporting Questionnaire (SRQ-20) described in Table 1. The SQR-20 is a reliable tool in Portuguese[16] that assess mental disorder such as depression and anxiety, include the questions Q1, Q2, Q3, Q4, Q7, and Q9. Also, questions regarding preventive measures were asked (Q5 and Q8). Participants should answer "frequently," "sometimes," or "never" for each question.

Statistical analysis

We used absolute and relative frequencies to describe demographic characteristics, psychological responses, and preventive measures. Chi-square and z-test tested the association between psychological responses and demographic characteristics. All the statistical analyses were performed using SPSS version 25.0, adopting $p<0.05$.

RESULTS

The majority of the respondents were female (71,2%), aged between 18 and 35 years (82,6%), students (76,1%), living in a family with 1 to 3 members during quarantine (55,4%). 37% left the city at the beginning of the quarantine, and only 10 (all students) had a family or friend diagnosed with COVID-19.

The behavioral and preventive responses overall are displayed in Figure 1. At least 5% of the sample were quarantined alone; 52% of the women were eating more than normal, and 9-11% of the participants increased alcohol consumption. Women reported 2h more in front of the TV and cell phone compared to men. The majority of respondents answered "sometimes" for the presence of

Table 1. Psychological and preventive questions.

Question number	Question
Q1	Do you feel nervous, tense, or worried more than usual?
Q2	Do you have trouble thinking clearly?
Q3	Do you find it difficult to enjoy your daily activities?
Q4	Do you find it difficult to make decisions?
Q5	Are you using preventive measures such as wearing masks, using hand sanitizer, and washing hands and clothes when you go outside?
Q6	Do you find it difficult to work home-office?
Q7	Have you lost interest in things?
Q8	How often are you going outside?
Q9	Do you feel tired more than usual?

psychological parameters in all questions. Questions about feeling nervous, tense, or worried (Q1) and feeling tired more than usual (Q9) had the highest frequencies of "frequently" amongst the psychological questions. For preventive measures, almost all respondents are using preventive measures such as wearing masks, using hand sanitizer, and washing hands "frequently" (Q5), and the majority are going outside "sometimes" (Q8).

Table 2 shows the association between psychological responses and preventive measures with sex, age, education, and quarantine living environment. Considering the biological sex, females demonstrated a significantly higher frequency of negative feelings for all psychological questions than men. Similar responses were shown by the youngest (18–35 years old) compared to the oldest (more than 35 years old), and graduate and undergraduate students compared to professors and staff. No significant association was found regarding living quarantine conditions for the number of family members and psychological responses.
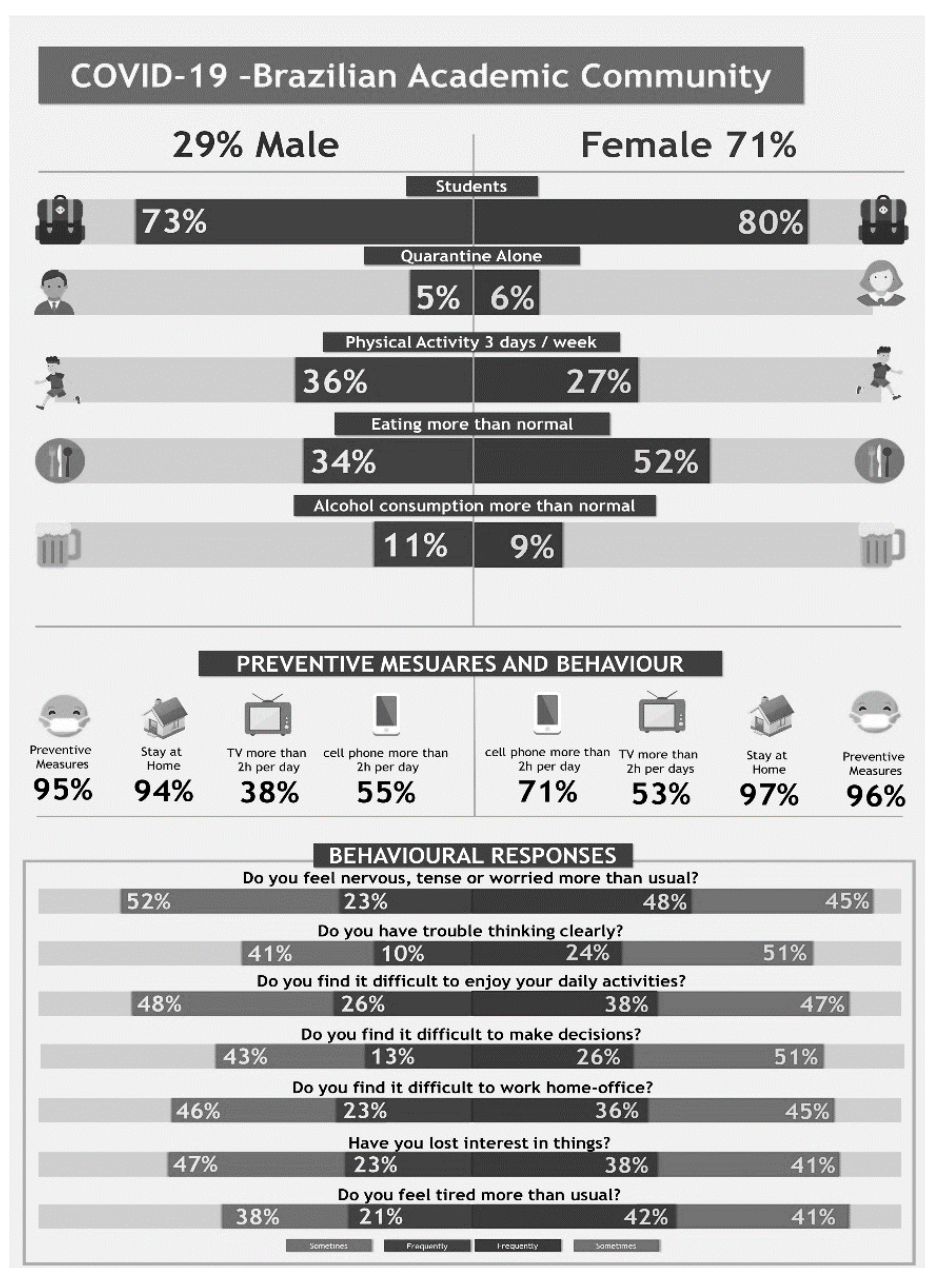

Figure 1. Infographic of the overall responses.

Table 2. Psychological and preventive measures separated by sex, age, education, and quarantine living condition (n=518).

		Sex			Age			Position			Quarantine			
		Female	Male	p	18-35	>35	p	Student	Prof/staff	p	Alone	1-3	>4	p
Q1	F	48.0*	22.8*	<0.001	43.2*	28.9*	0.011	42.6	34.7	0.123	37.9	40.1	42.1	0.895
	S	45.5	52.3		46.5	52.2		47.0	49.2		44.8	48.4	46.5	
	N	6.5*	24.8*		10.3*	18.9*		10.4	16.1		17.2	11.5	11.4	
Q2	F	24.1*	10.1*	<0.001	22.2*	10.0*	<0.001	23.6*	8.9*	<0.001	17.2	20.6	19.8	0.249
	S	50.9*	40.9*		50.5*	36.7*		48.7	46.0		51.7	43.9	53.5	
	N	24.9*	49.0*		27.3*	53.3*		27.7*	45.2*		31.0	35.5	26.7	
Q3	F	37.9*	25.5*	0.002	38.3*	15.6*	<0.001	37.8*	23.4*	0.011	34.5	35.9	32.2	0.683
	S	46.9	47.7		45.8	53.3		44.2*	56.5*		55.2	45.3	48.5	
	N	15.2*	26.8*		15.9*	31.1*		18.0	20.2		10.3	18.8	19.3	
Q4	F	26.3*	12.8*	<0.001	25.5*	7.8*	<0.001	27.2*	7.3*	<0.001	13.8	24.4	20.8	0.658
	S	50.7	43.0		50.5*	38.9*		48.5	48.4		51.7	46.7	50.5	
	N	23.0*	44.3*		24.1*	53.3*		24.4*	44.4*		34.5	28.9	28.7	
Q5	F	95.7	94.6	0.759	95.3	95.6	0.806	95.2	96.0	0.721	93.1	95.8	95.0	0.935
	S	4.1	4.7		4.2	4.4		4.3	4.0		6.9	3.8	4.5	
	N	0.3	0.7		0.5	0.0		0.5	0.0		0.0	0.3	0.5	
Q6	F	36.0*	22.8*	<0.001	33.6	25.6	0.318	35.3*	22.6*	0.028	34.5	32.4	31.7	0.129
	S	45.3	45.6		44.6	48.9		42.9*	53.2*		27.6	48.1	44.1	
	N	18.7*	31.5*		21.7	25.6		21.8	24.2		37.9	19.5	24.3	
Q7	F	38.2*	22.8*	0.002	38.8*	10.0*	<0.001	40.9*	11.3*	<0.001	34.5	34.8	32.2	0.979
	S	41.2	47.0		43.5	40.0		41.4	47.6		41.4	42.5	43.6	
	N	20.6*	30.2*		17.8*	50.0*		17.8*	41.1*		24.1	22.6	24.3	
Q8	F	2.7	6.0	0.165	3.3	5.6	0.071	4.1	2.4	0.063	6.9	3.1	4.0	0.670
	S	70.7	70.5		69.2	77.8		68.0	79.0		69.0	72.8	67.8	
	N	26.6	23.5		27.6	16.7		27.9	18.5		24.1	24.0	28.2	
Q9	F	42.5*	21.5*	<0.001	39.7*	21.1*	<0.001	39.1*	28.2*	0.012	48.3	39.0	31.2	0.137
	S	41.5	37.6		40.4	40.0		40.6	39.5		24.1	38.3	45.5	
	N	16.0*	40.9*		19.9*	38.9*		20.3*	32.3*		27.6	22.6	23.3	

p: Chi-square. *Significant differences by z-test for sub-groups; F: Frequently; S: Sometimes; N: Never.

DISCUSSION

The main aim of the present study was to evaluate the psychological responses due to COVID-19 outbreak in students, professor, and staff from a Brazilian University and the main findings were:

1) Female, young age (18–35 years old) and students were most sensible to present frequently negative psychological responses compared to their counterparts;
2) Independently of spend quarantine alone or with more than 4 people, the psychological responses are similar; and
3) Majority of the academic population are using preventive measures (wearing mask, washing hands…) and going outside "sometimes".

The results of the current study indicated that females, young age, and students were associated with "frequently" negative psychological responses. This finding has been presented in recent studies during the COVID-19 outbreak. Female and younger than 30 years appeared to be risk factors for negative psychological responses in Italy's population[8,9]. In China, data suggest that females and students suffered significant psychological impacts and a higher level of stress, anxiety, and depression[7]. Indeed, women tend to be more vulnerable to experiencing psychological distress as well as more change to developing post-traumatic symptoms, as evidenced in the literature[17]. Therefore, during the quarantine period, it seems that women suffer more distress than men, and this gender difference

can be explained for several reasons, from behavioral to physiological factors, as discussed by Song et al.[18].

Regarding young people, participants who are 18 to 35 years old showed a higher frequency of "frequently" negative psychological responses than those with more than 35 years old. A similar response was found in the Chinese population, where younger participants (<35 years) were more likely to develop anxiety and depressive symptoms during the COVID-19 outbreak than older participants (≥35 years) (AOR=1.65, 95%CI 1.49–2.02)[7]. As discussed elsewhere[8], the negative psychological responses and higher anxiety in younger people may be explained due to easy and great access to information through social media[19]. Literature demonstrated that in normal conditions, the communication load resulting from internet multitasking is significantly related to increasing perceived stress[20]; therefore, these amounts of information can trigger negative psychological responses.

Lastly, our results showed that graduates and undergraduates present "frequently" negative psychological responses compared to professors and staff. This finding corresponds with those students in Bangladesh (n=505 college and university) in which 69.3% of students reported mild to severe level of psychological impact due to the COVID-19 outbreak, and additionally, university students had higher psychological impacts than college students[11]. Among Indian pharmacy students, 18 % reported extremely severe depression, and about 27.5 % with severe anxiety, and about 12.5 % with severe stress[10]. This response can be explained by uncertainty of academic progression and postponement of examinations, leading to a stressor factor in students mind[21], especially in graduating final year students due to uncertainty about the pandemic effect may have increased their worry about graduating, finding a job, or enrolling in further study[22].

Taken together, females and students have demonstrated a considerable risk of adverse psychological responses in normal conditions. Recently, a longitudinal study with Chinese college students reported that female students suered from significantly higher levels of anxiety than their male counterparts on average[23]. In Brazil, a recent study with university students (n=1,827) also demonstrated that 32% of students presented a major depressive episode. The major depressive episode was more frequent among females, aged between 21 and 23 years, showing a risk of 60% to present depressive episode[24]. Therefore, the need for intervention in this specific group is necessary to promote a possible understanding of the situation.

Despite the present study be one of the first to evaluate the psychological effect of the COVID-19 outbreak in a Brazilian University community, it is not without limitations and caution regarding the generalization of our findings is recommended. We used an online convenience sampling strategy, which required participants' access to the internet. It limited the participation of those who do not have internet access. The sample does not represent all the University community, limiting the generalizability of our findings. Finally, this study does not use a specific tool to evaluate psychological distress or anxiety and depression; therefore, we cannot classify the severity of these domains during the quarantine period. However, the current data, together with recent studies, suggest that the recent quarantine due to COVID-19 outbreak affect the psychological responses in people, especially in female, young aged, and students.

CONCLUSIONS

During almost two months of quarantine and social isolation due to COVID-19, in Brazil, an academic community demonstrated to be affected by negative psychological responses. Female gender, young age, and student seem to be the group with the major psychological impact of the outbreak. The results present a general picture of the psychological impact of the COVID-19 outbreak on students, professors, and staff in Brazil. Attention is required from public health authorities and members of the academic community, to cope with this situation.

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AUTHORS' CONTRIBUTIONS

ACP: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **MPS:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **JP:** Conceptualization, Methodology, Visualization, Writing – review & editing. **DG:** Conceptualization, Writing – review & editing. **MPT:** Conceptualization, Writing – review & editing. **TC:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

ETHICAL ASPECTS

The project was reviewed and approved by the Research Ethics Committee of the UNICENTRO – University (protocol number 4.002.656).

DATA AVAILABILITY STATEMENT

Data associated with this publication is archived in the Git hub Integration Platform by link: https://github.com/timcavazzotto/Psycho_Response_Covid19_Unicentro.

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ORIGINAL ARTICLE

Anxiety and depression scores in patients subjected to aortic and iliac aneurysm repair procedures

Cynthia de Almeida Mendes[1] ⃝, Nelson Wolosker[1,2,3] ⃝, Alexandre Fioranelli[1,4] ⃝,
Ricardo Abreu Feijó de Mello[3] ⃝, Maria Fernanda Cassino Portugal[1]* ⃝,
Marcelo Fiorelli Alexandrino da Silva[1] ⃝, Roberto Augusto Caffaro[1] ⃝,
Lucas Lembrança Pinheiro[1] ⃝, Marcelo Passos Teivelis[1,3] ⃝

SUMMARY

OBJECTIVE: This study examines the changes in anxiety and depression scores of 84 patients subjected to aortic or iliac aneurysm correction with no previous psychiatric history.

METHODS: Patients were referred to the evaluation using the Beck Anxiety and Depression Inventories no more than 3 days before surgery (i.e., preoperative [Pre-Op]), 30 days after revascularization (i.e., Early postoperative [PO]), and at least 6 months after revascularization (i.e., Late PO).

RESULTS: Mean anxiety scores declined from baseline at both the Early (mean difference: 2.75, $p<0.001$) and Late PO (mean difference: 2.74, $p=0.001$). The depression levels showed no significant variation in either evaluation (Early PO; mean difference: −0.84, $p>0.05$, Late PO: 0.87, $p=0.05$). A more severe degree of anxiety at baseline was related to better anxiety results both in the Early PO ($p=0.041$) and Late PO ($p=0.008$). An endovascular technique was related to the improvement in depression symptoms in the Early PO ($p=0.01$) but the worsening of the symptoms in the Late PO ($p=0.033$).

CONCLUSIONS: Patients subjected to aortoiliac aneurysm corrections have a higher incidence of anxiety and depressive symptoms. Anxiety symptoms, but not the depressive ones, improved considerably following the successful treatment. The formal psychiatric evaluation may be beneficial for patients with less improvement in the symptom.

KEYWORDS: Anxiety. Depression. Aortic aneurysm. Iliac aneurysm.

INTRODUCTION

Anxiety and depression are common ailments of patients hospitalized for surgery, especially those of more complex nature[1]. Incidence may be heightened by previous mood disorders, underlying diseases, longer hospital stays, postoperative (PO) complications, and lack of familial support[2].

Regardless of the technique employed for aneurysm correction, the mortality and morbidity rates are not negligible, and these patients are often elderly with multiple comorbidities[3,4]. These aspects alone may generate certain anxiety, possibly leading to more severe mood alterations both preoperatively and postoperatively.

The preoperative (Pre-Op) levels of anxiety and depression were assessed in 150 patients subjected to the abdominal aortic aneurysm (AAA) repair[5]. Although several independent risk factors for Pre-Op anxiety were determined, authors did not evaluate PO anxiety or depression[5].

The development of depressive symptoms was compared between 109 surgical and nonsurgical patients with aortic diseases (i.e., aneurysms or occlusive disease)[1]. The rates of PO psychiatric morbidity were high (32%). Surgical patients were over four times more likely to develop the psychiatric disorders (odds ratio: 4.8, p=0.02)[1].

The studies evaluated the levels of anxiety and depression before and after surgery for several diseases. An improvement of psychiatric symptoms was noted after the implantation of left ventricular assist device in patients with advanced heart failure[6] as well as in patients treated for cerebral aneurysms[7].

Although earlier studies have established an increased prevalence of mood disorders among patients with AAA undergoing surgical correction[1,8], none have examined the variation on the degree of symptoms in the short- and long-term after surgery.

The aim of this study was to compare the changes in anxiety and depression symptoms and to assess the factors associated with these changes, in the Early- and long-term PO period after the surgical correction of AAA.

METHODS

Eighty-four patients subjected to the elective AAA correction were prospectively evaluated between June 2015 and November 2019. Patients had no history of anxiety or depression and underwent aneurysm repair either by conventional open surgery or endovascular repair surgery at the Hospital Israelita Albert Einstein – Vila Santa Catarina Unit or at the Santa Casa de Misericórdia Hospital, São Paulo, Brazil. This study was approved by the institutional review boards in both centers, and all patients provided written informed consent.

Table 1 shows the clinical and operative characteristics of the patients. Patients were evaluated on three occasions, namely, preoperatively (Pre-Op), no earlier than 3 days before surgery; 1 month after treatment (Early PO); and at least 6 months after treatment (Late PO). Patients were followed-up for 629 days.

The anxiety and depression scores were assessed by the validated Portuguese version of Beck Depression and Anxiety Inventories[9]. Symptoms were graded according to the Beck's scales in the four established levels, namely, minimum, mild, moderate, and severe[9].

STATISTICAL ANALYSIS

The quantitative characteristics were presented as means with standard deviations, whereas qualitative attributes were presented as absolute and relative frequencies.

Table 1. Clinical and surgical characteristics.

	No. of patients	Percentage (%)
Sex		
Male	57	69.50
Female	25	30.50
Age		
Range	57–84	
Average±standard deviation	69.83±6.47	
Median	70	
Hypertension	69	84.10
Diabetes	23	70.70
Active smoking	56	68.30
Previous myocardial infarction	14	17.1
Previous stroke	8	9.90
ASA classification		
I	1	1.30
II	36	46.80
III	40	51.90
Aneurysm diameter	6.39±1.35	
Type of aneurysm		
Infrarenal AAA/juxtarenal AAA	69	84.10
Thoracic aorta aneurysm	5	6.10
Iliac aneurysm	4	4.90
Thoracoabdominal aneurysm		4.90
Type of treatment		
Endovascular	47	57.30
Conventional	35	42.70
Reoperation	12	14.60
ICU length of stay (days)	3.76±5.20	
Overall length of stay (days)	7.41±8.63	
Length of follow-up (days)	629±403	
Mortality	11	13.40

ASA: American Society of Anesthesiologists; AAA: abdominal aortic aneurysm; ICU: intensive care unit.

The anxiety and depression scores were presented according to the Beck's scales[9] and summarized as means with standard deviations or absolute and relative frequencies. The incidence of symptoms was compared between treatment period and technique groups by the generalized estimating equations with marginal normal distribution and identity link function, assuming a first-order auto-regressive correlation matrix between assessment intervals[10]. For the models that presented statistical significance, the analysis was complemented by using the Bonferroni multiple analysis[11] to discern between which techniques or intervals the scoring differences occurred.

The Wilcoxon signed-rank test was used for comparing the Pre-Op anxiety and depression grading with the following evaluation intervals[12]. The differences were calculated between the anxiety and depression rating of each assessment time and the baseline, and these were tested against the qualitative characteristics of the patient by using the likelihood-ratio test[12], whereas the quantitative characteristics were assessed by using the ANOVA analysis[11].

All analyses were performed using the SPSS Statistics software for Windows version 22.0 (IBM Corp., Armonk, NY, USA). All tests were performed using the significance level of 5%.

RESULTS

Anxiety evaluation

Patient distribution according to anxiety degree in each assessment is shown in Figure 1.

Most patients presented minimal or mild anxiety levels in all three assessments. Table 2 shows the overtime variation in the anxiety levels per patient.

In the Early-PO assessment, a significant decrease in the levels of anxiety was observed when compared with the Pre-OP (p=0.004). In the long-term evaluation (Late PO), the anxiety levels remained significantly better than baseline (p=0.039).

The mean anxiety degrees overtime also demonstrated improvement after treatment both in the Early PO (i.e., mean difference of 2.75 and p<0.001) and Late PO (i.e., mean difference of 2.74, p=0.001) in relation to baseline (Pre-Op). There was no significant difference in anxiety levels when the Early- and Late-PO assessments were compared (i.e., mean difference: -0.01, p>0.999).

The only variable related to a significant change in anxiety levels was the baseline degree of anxiety (Pre-Op), in which a more severe degree at Pre-Op was related to better results both in the Early PO (p=0.041) and Late PO (p=0.008).

Depression evaluation

Patient distribution according to the degree of depression symptoms in all three assessments is demonstrated in Figure 1.

The majority of the patients presented with minimal or mild depression in all three assessments.

Overtime variation of depression levels per patient is demonstrated in Table 2.

The depression levels showed no significant variation in either the early or the long-term evaluations. This was maintained even when patients were separately evaluated with regard to the surgical technique.

Mean depression degrees overtime also demonstrated no change in symptom severity after treatment, both in the Early PO (i.e., mean difference: -0.84, p>0.05) and Late PO (i.e., mean difference: 0.87, p=0.05) in relation to the Pre-Op baseline. There was no significant difference in depression levels when the Early- and Late-PO assessments were compared (mean difference: -0.03, p>0.999).

The only variable related to a significant change in depression levels was the surgical technique, with the endovascular technique related to the improvement in depression symptoms in the short-term (Early PO; p=0.01) but the worsening of the symptoms in the long-term (Late PO; p=0.033).
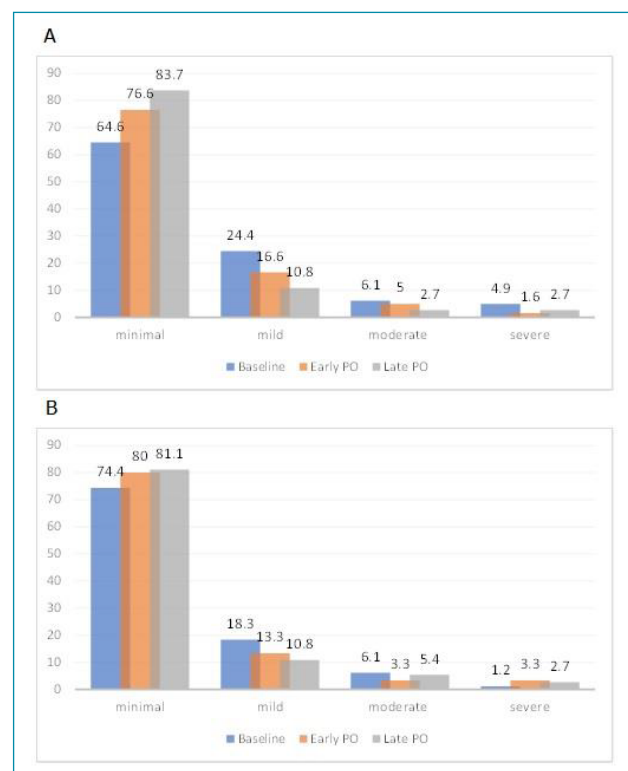
Figure 1. Patient distribution according to anxiety (A) and depression (B) degrees in each assessment.

Table 2. Overtime variation in patient distribution by severity level of anxiety and depression symptoms.

Variable	Pre-Op anxiety levels					p*
	Minimal	Mild	Moderate	Severe	Total	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Early-PO anxiety level						
Minimal	34 (56.7)	10 (16.7)	1 (1.7)	1 (1.7)	46 (76.7)	
Mild	3 (5.0)	5 (8.3)	2 (3.3)	0 (0.0)	10 (16.7)	
Moderate	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.7)	3 (5.0)	0.004
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)	
Total	37 (61.7)	15 (25.0)	5 (8.3)	3 (5.0)	60 (100)	
Late-PO anxiety level						
Minimal	24 (64.9)	4 (10.8)	1 (2.7)	2 (5.4)	31 (83.8)	
Mild	1 (2.7)	2 (5.4)	1 (2.7)	0 (0.0)	4 (10.8)	
Moderate	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)	0.039
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.7)	
Total	25 (67.6)	7 (18.9)	2 (5.4)	3 (8.1)	37 (100)	
Variable	Pre-Op depression levels					p*
	Minimal	Mild	Moderate	Severe	Total	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Early/Early-PO depression level						
Minimal	43 (71.7)	5 (8.3)	0	0	48 (80.0)	
Mild	2 (3.3)	4 (6.7)	2 (3.3)	0	8 (13.3)	
Moderate	0	1 (1.7)	1(1.7)	0	2 (3.3)	0.366
Severe	0	0	1 (1.7)	1 (1.7)	2 (3.3)	
Total	45 (75.0)	10 (16.7)	4 (6.7)	1 (1.7)	60 (100.0)	
Early/Late-PO depression level						
Minimal	29 (78.4)	0	1 (2.7)	0	30 (81.1)	
Mild	3 (8.1)	1 (2.7)	0	0	4 (10.8)	
Moderate	1 (2.7)	0	1 (2.7)	0	2 (5.4)	0.408
Severe	0	0	0	1 (2.7)	1 (2.7)	
Total	33 (89.2)	1 (2.7)	2 (5.4)	1 (2.7)	37 (100.0)	

*Wilcoxon signed-rank test; Pre-Op: preoperative; PO: postoperative.

DISCUSSION

All patients were selected for treatment by the same criteria and underwent the treatment following the same protocols. Patients' questions pertaining to their disease, treatment options, possible complications, mortality risk, and PO expected recovery are routinely discussed. Patients presenting with known mental illness were not included in this study. The sample was predominantly of male patients between 70 and 80 years of age, as expected[13].

Few studies have analyzed the development of anxiety and depressive symptoms in patients with aortic aneurysm[1,5]; however, to the best of our knowledge, none have evaluated the overtime evolution of symptoms in the same pool of patients.

Although anxiety and depression are highly prevalent mood disorders in the general population[14], reported prevalence rates of these disorders vary in accordance with the instruments used for diagnosis and the heterogeneity of studied populations[15]. The use of questionnaires allows better quality of the data collection in screening and the follow-up evaluation of patients[15].

Several studies have associated anxiety and depressive symptoms with cardiovascular disease[2,6,7,16,17]. Some cerebral structural

abnormalities have also been attributed to vascular disease, predisposing especially the elderly to what is referred to as "vascular depression"[18]. This population superposes with the higher incidence of arterial aneurysms[14]. Aneurysm risks of rupture and death are well established, and the mere knowledge of the disease may lead patients to concerning thoughts, possibly causing mood disorders[5].

Until this study, the correlation in variation of anxiety and depression levels and surgical correction of arterial of aneurysms was unknown.

A decline in the anxiety levels was found in both the Early PO (6.6%) and Late PO (5.4%), which may be secondary to the adequate correction of the disease. Patients with aortic aneurysms are often aware of the severity and potentially fatal nature of their condition[5]. When the treatment is successful, well-instructed patients understand that they may return to normal routine and that their risks have been lowered to average standards, although not entirely risk-free. This improvement in anxious symptoms provides significance especially because anxious patients have been shown to have higher rates of emergency department visits and hospitalization[17].

All included patients were given a Pre-Op informed consent form, which detailed risks and complications of the proposed procedure. Although this may represent an anxiety-raising factor, this anxiety seems to be resolved after treatment, regardless of the surgical technique employed.

Other studies demonstrated this same improvement in anxiety and depression scores following surgical treatment[6,7].

Few medical conditions represent a global-level epidemiological impact such as depression. This multifactorial and heterogeneous disorder is often associated with poor general clinical condition and may lead to negative consequences such as misdiagnosis of symptoms[19].

No statistically significant change from the baseline levels of depression was observed at either the Early PO (6.6%) or the Late PO (8.1%).

The only statistically significant difference regarding the overtime variation in depression symptoms concerned the surgical technique that was employed. Patients subjected to endovascular procedures presented better levels of depression in the Early PO than those subjected to conventional repair. The endovascular approach correlates with lower in-hospital morbidity and diminished hospital stay, which could explain why depression was lower in the short-term evaluation for these patients. In the long-term, however, patients subjected to the endovascular procedures showed the higher levels of depression. These findings correlate with those of an earlier study that attributed a worsening of quality-of-life scores in endovascularly treated patients[20]. A possible explanation for this score inversion is the fact that, although an initially more invasive technique, patients may consider the conventional open repair a more definite treatment alternative, whereas the endovascular procedures require virtually unending annual control.

It may be surmised that the continuance of depressive symptoms as opposed to an observed improvement in anxiety following aneurysm correction surgery is due to the different nature of symptoms; while anxiety is often associated with the patients' impression of future events, depressive symptoms correlate to immediate events[21].

Most patients underwent endovascular treatment, being therefore required to maintain a rigid control follow-up, which may cause mood changes at the time of reassessment.

Patients were not undergoing any psychological treatment at the moment of inclusion; however, at a 6-month follow-up, four patients were under psychological or psychiatric care. One of these had the highest Pre-Op anxiety and depression scores in the sample and maintained the highest scores at the 6-month follow-up, despite proper specialized care.

Our study is limited by the relatively small sample and the possibility of bias due to questionnaires being filled by the patients without supervision of a trained psychology professional. Additionally, none of the included patients underwent formal psychiatric evaluation before treatment.

The use of the Beck's scale may represent a screening tool for the identification of patients with severe anxious or depressive symptoms, and a formal psychiatric evaluation should be suggested for patients with persistent symptoms after treatment.

Proper screening and treatment of anxiety and depression are of great importance among patients with aortic aneurysm, both before and after treatment, incurring positive change in the patients' condition for self-care, control of risk factors, and follow-up adherence.

CONCLUSIONS

Patients present an improvement in the levels of anxiety both in the short- and long-term following aortic aneurysm correction, maintaining, however, unchanged levels of depression.

The psychiatric evaluations may be beneficial for the patients with surgical aneurysm, especially those with the increased and unimproved levels of anxiety or depression.

ETHICAL ASPECTS

The authors declare to have no relations, professional or otherwise, that could be construed as conflict of interest for the publication of this study. This study was duly approved by the Ethics Committee of the Hospital Israelita Albert Einstein under the protocol number (CAAE) 47459515.8.1001.0071 on February 12, 2016.

AUTHORS' CONTRIBUTIONS

CAM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **NW:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **AF:** Conceptualization, Formal analysis, Investigation, Methodology, Validation. **RAFM:** Data curation, Resources, Software. **MFCP:** Data curation, Formal analysis, Resources, Software, Project administration, Writing – original draft, Writing – review & editing. **MFAS:** Data curation, Formal analysis, Resources, Software, Project administration. **RAC:** Conceptualization, Formal analysis, Investigation, Methodology, Validation. **LLP:** Data curation, Formal analysis, Resources, Software, Project administration. **MPT:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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A propensity score-matched case-control study of laparoscopy and laparotomy for endometrial cancer

Licerio Miguel[1] , Julio Cesar Rosa e Silva[1] , Omero Benedito Poli Neto[1] ,
Daniel Guimarães Tiezzi[1] , Jurandyr Moreira de Andrade[1] ,
Francisco Jose Candido dos Reis[1]*

SUMMARY

OBJECTIVE: A surgery is essential for the management of early endometrial carcinoma. Due to the comorbidities associated with the disease, the complications of surgery are common. Laparoscopic surgery may reduce surgical complications but also have oncological risks. We aimed to compare recurrence and overall survival (OS) associated with laparoscopy and laparotomy for early endometrial cancer.

METHODS: We included women treated for presumed early endometrial carcinoma at the Clinics Hospital of Ribeirão Preto Medical School from January 1998 to December 2017. We designed a 1:2 propensity score-matched case-control and compared the patients' characteristics, short-term outcomes, recurrence, and OS.

RESULTS: A total of 252 women were included in this study, 168 underwent laparotomy, and 84 underwent laparoscopy. The two groups were well balanced according to most of the variables, and obesity was a characteristic of patients in both groups. Laparoscopy was associated with increased surgical time (194.7 min vesus 165.6 min; p<0.001) and reduced rate of surgical complications (6.5% versus 0; p=0.038). Laparoscopic surgery was not associated with the risk of tumor recurrence (HR: 0.41, 95%CI 0.14–1.19, p=0.100) or all-cause mortality (HR: 0.49, 95%CI 0.18–1.35, p=0.170).

CONCLUSION: Laparoscopy was safe in terms of oncological outcomes and was associated with a lower rate of surgical complications. Our data support the use of minimally invasive surgery as the preferential approach in the management of early endometrial carcinoma.

KEYWORDS: Endometrial carcinoma. Laparoscopy. Laparotomy. Survival.

INTRODUCTION

Uterine corpus cancer accounts for 7% of all female malignant tumors and 4% of estimated cancer deaths[1]. Among the uterine corpus tumors, endometrial carcinoma corresponds to 97%[2]. Endometrial carcinoma is associated with the well-defined risk factors such as obesity, nulliparity, or genetic risk[3]. Compared with other female tumors, endometrial carcinoma has a good prognosis. Its mortality-to-incidence ratio is 0.24, which is lower than breast cancer (0.32), ovarian cancer (0.63), or cervical cancer (0.55)[4]. However, endometrial carcinoma frequently coexists with obesity[5] that in association with comorbidities such as hypertension, diabetes, and pulmonary disease may lead to incomplete staging, increased surgical time, increased blood loss, and abdominal wall infection and dehiscence[6,7].

Over the past two decades, the use of laparoscopy and, more recently, robotic surgery for the treatment of endometrial

cancer has expanded substantially. The minimally invasive techniques reduce complications related to the surgery[8]. Several studies showed the advantages of the laparoscopic technique over conventional laparotomy. The main short-term advantages relate to pain reduction and better postoperative quality of life[9-11]. Some risks, such as urinary tract or intestinal injury and tumor dissemination, may also be associated with the minimally invasive techniques. Current evidence, from clinical trials and meta-analysis, points to the equivalence between conventional laparotomy and laparoscopic surgery in terms of the long-term outcomes[12,13].

The data from the clinical trials are the gold standard for evaluating interventions in oncology. However, the real-world clinical data are essential to characterize the advantages and risks of interventions in clinical practice. This study aimed to compare laparoscopy with laparotomy, concerning the overall survival (OS) and the disease-free survival (DFS) using a propensity score-matched case-control from a single institution.

METHODS

Study design

We designed a 1:2 propensity score-matched case-control of early endometrial carcinoma treated at Clinics Hospital of Ribeirão Preto Medical School from the year 1998 to 2017. The Institutional Board for Ethics in Research approved the study (CAAE: 81115817.5.0000.5440), and the informed consent was waived. The study was reported following the strengthening the reporting of observational studies in epidemiology (STROBE) checklist for the case-control studies.

Inclusion and exclusion criteria

Patients with a histological diagnosis of endometrial cancer without clinical or image evidence of cervical or extrauterine disease were eligible. The exclusion criteria were as follows: advanced disease at diagnosis, previous surgical treatment for endometrial cancer, surgery not performed for other reasons (e.g., impaired performance status), and prior chemotherapy or radiotherapy for the endometrial cancer treatment.

Surgical procedures

During this period, deciding whether to use laparoscopic surgery or traditional laparotomy followed the surgeon's preference. For laparoscopic surgeries, we used umbilical Veress needle entry in all cases, CO_2 for abdominal distention, and the Trendelenburg position. The bipolar electrical devices were used for vessel sealing. Vaginal approaches were used for colpotomy and section of cardinal/uterosacral ligaments.

Midline incisions were used as the preferred routes for laparotomies. In both types of surgeries, the decision on when to perform lymphadenectomy was based on preoperative image and biopsy (i.e., histology and grade) and intraoperative findings (i.e., the estimation of myometrial invasion). As a general rule, women with grade I/II superficial endometrioid tumors did not undergo lymphadenectomy.

Variables and statistics

The variables collected were as follows: type of surgery, age at diagnosis, body mass index (BMI), sonographic uterine volume, tumor histology, the International Federation of Gynecology and Obstetrics (FIGO) stage of tumor, tumor grade, preoperative CA-125 levels, adjuvant treatment (i.e., radiotherapy and chemotherapy), duration of anesthesia, duration of surgery, lymphadenectomy and number of nodes, intraoperative complications, surgical postoperative complications, clinical postoperative complications, thromboembolic events, blood transfusion needed, hospital postoperative stay, and 5-year DFS and 5-year OS.

The disease-free survival (DFS) is defined as the interval from the time of primary surgery to any documented disease recurrence. The OS is defined as the interval from primary surgery to death by any cause. For patients who were still alive at the time of analysis, DFS and OS were censored at the last follow-up date.

A total of 400 cases (i.e., 84 laparoscopic surgeries and 316 open surgeries) were eligible for the study. In this group, we had the randomly missing data for CA-125, BMI, and uterine volume. Therefore, the values were imputed[14] using the Amelia R package. After the imputation of the missing data, we calculated the propensity score using the variables, such as age, race, education, BMI, previous surgery, histology, stage, grade, uterine weight, CA-125, and preoperative comorbidities. Then, 84 laparoscopic cases were matched 1:2 to open surgery cases, resulting in 252 cases analyzed.

Summary statistics were used to compare the variables between laparoscopy and laparotomy groups. Qualitative variables are displayed using frequencies and percentages. The Kaplan-Meier product-limit estimator and the Cox proportional-hazards regression model were used for the survival analysis. The data manipulation and statistical analysis were performed with R version 4.0.2.

RESULTS

In our matched case-control study, 168 patients underwent conventional laparotomy and 84 underwent laparoscopic surgery. The characteristics of the included patients and outcomes are presented in Table 1. The two groups were well balanced

Table 1. Characteristics of patients and outcomes according to the type of surgery.

Variable	Laparoscopy	Laparotomy	p-value
Cases	n=84	n=168	
Age (years)	64.2 (11.6)	64.5 (10.1)	0.856
Body mass index (kg/m²)	33.7 (8.7)	32.9 (7.2)	0.492
Uterine volume (cm³)	105.8 (73.5)	109.3 (87.6)	0.759
Histologic type			
Endometrioid carcinoma	78 (92.9%)	155 (92.3%)	0.964
Carcinosarcoma	3 (3.6%)	7 (4.2%)	
Serous carcinoma	2 (2.4%)	3 (1.8%)	
Mixed cell carcinoma	1 (1.2%)	3 (1.8%)	
FIGO stage			
IA	39 (46.4%)	76 (45.2%)	0.917
IB	27 (32.1%)	57 (33.9%)	
II	9 (10.7%)	19 (11.3%)	
IIIA	5 (6%)	7 (4.2%)	
IIIB	2 (2.4%)	2 (1.2%)	
IIIC	2 (2.4%)	7 (4.2%)	
Grade			
I	42 (50%)	78 (46.4%)	0.864
II	32 (38.1%)	68 (40.5%)	
III	10 (11.9%)	22 (13.1%)	
CA-125 (U/mL)	44.7 (73.4)	32.0 (100.4)	0.304
Duration of anesthesia (min)	233.5 (58.5)	204.6 (60.1)	<0.001
Duration of surgery (min)	194.7 (55.7)	165.6 (58.2)	<0.001
Lymphadenectomy			
Pelvic	64 (76.2%)	111 (66.1%)	0.19
Pelvic and aortic	0 (0%)	2 (1.2%)	
None	20 (23.8%)	55 (32.7%)	
Number of nodes	7.0 (8.8)	8.0 (6.0)	0.809
Intraoperative complication	3 (3.6%)	7 (4.2%)	1
Surgical postoperative complication	0 (0%)	11 (6.5%)	0.038
Clinical postoperative complication	5 (6%)	7 (4.2%)	0.754
Thromboembolic event	1 (1.2%)	3 (1.8%)	1.000
Blood transfusion	1 (1.2%)	13 (7.7%)	0.065
Postoperative hospital stay (days)	2.0 (0.0)	2.0 (1.0)	0.336
Radiotherapy			
None	53 (63.1%)	100 (59.5%)	0.503
External	9 (10.7%)	13 (7.7%)	
Brachytherapy	3 (3.6%)	13 (7.7%)	
Combined	19 (22.6%)	42 (25%)	
Adjuvant chemotherapy	5 (6%)	11 (6.5%)	1.000

FIGO: International Federation of Gynecology and Obstetrics

according to most of the variables. Obesity was an important characteristic of both groups. Endometrioid histology (92.9 and 92.3%), stage 1 (78.5 and 79.1%), and low grade (88.1 and 86.9%) were predominant in laparoscopic and open surgery groups, respectively. Adjuvant radiotherapy was used for 36.9% of laparoscopic and 40.5% of open surgery cases. Adjuvant chemotherapy was used for 6% of laparoscopic and 6.5% of open surgery cases. Both groups presented similar results on the percentage of women submitted to lymphadenectomy, the number of nodes harvested, intraoperative complications, postoperative clinical complications, thromboembolic events, blood transfusion, and postoperative hospital stay. We observed increased anesthesia time (233.5 min versus 204.6 min; p<0.001) and surgery time (194.7 min versus

165.6 min; p<0.001) for laparoscopy. Laparoscopy was associated with a lower rate of surgical complications than laparotomy (6.5% versus 0; p=0.038).

Table 2 shows the hazard ratio for several prognostic variables associated with recurrence and all-cause mortality. Laparoscopic surgery was not associated with neither the risk of tumor recurrence (HR: 0.41, 95%CI 0.14–1.19; p=0.100) nor the all-cause mortality (HR: 0.49, 95%CI 0.18–1.35; p=0.170). We observed an increased risk of recurrence associated with serous histology, tumor stage, and tumor grade. The risk of the all-cause mortality increased with age at diagnosis, serous histology, and tumor stage.

The Kaplan-Meier curves showed no significant differences in DFS or OS or comparing the two groups (Figure 1).

Table 2. Cox regression model for recurrence and all-cause mortality.

Variable	Recurrence			All-cause mortality		
	HR	95%CI	p	HR	95%CI	p
Surgery type						
Laparotomy	Ref					
Laparoscopy	0.41	(0.14–1.19)	0.100	0.49	(0.18–1.35)	0.170
Age	1.02	(0.97–1.06)	0.477	1.06	(1.01–1.1)	0.015
Histology						
Endometrioid	Ref			Ref		
Serous	23.63	(1.38–405.52)	0.029	9.28	(1.54–56.07)	0.015
Carcinosarcoma	1.67	(0.3–9.22)	0.557	2.64	(0.42–16.4)	0.298
FIGO stage						
IA	Ref			Ref		
IB	2.72	(0.74–9.96)	0.132	3.53	(0.98–12.75)	0.054
II	6.1	(1.25–29.68)	0.025	3.66	(0.65–20.55)	0.140
IIIA	35.78	(5.12–249.94)	<0.001	5.59	(0.72–43.46)	0.099
IIIB	61.68	(6.55–580.91)	<0.001	61.01	(6.67–558.06)	<0.001
IIIC	75.7	(7.78–736.48)	<0.001	37.4	(4.48–312.5)	<0.001
Grade						
I	Ref			Ref		
II	4.59	(1.22–17.2)	0.024	0.99	(0.36–2.76)	0.990
III	13.85	(2.39–80.12)	0.003	1.29	(0.27–6.23)	0.755
Radiotherapy						
None	Ref			Ref		
External	1.41	(0.28–7.03)	0.679	0.2	(0.02–1.71)	0.141
Brachytherapy	0.18	(0.03–1.09)	0.062	0	(0–Inf)	0.997
Combined	0.4	(0.12–1.33)	0.134	0.77	(0.25–2.42)	0.655
Chemotherapy	0.06	(0–0.79)	0.033	0.5	(0.07–3.72)	0.496
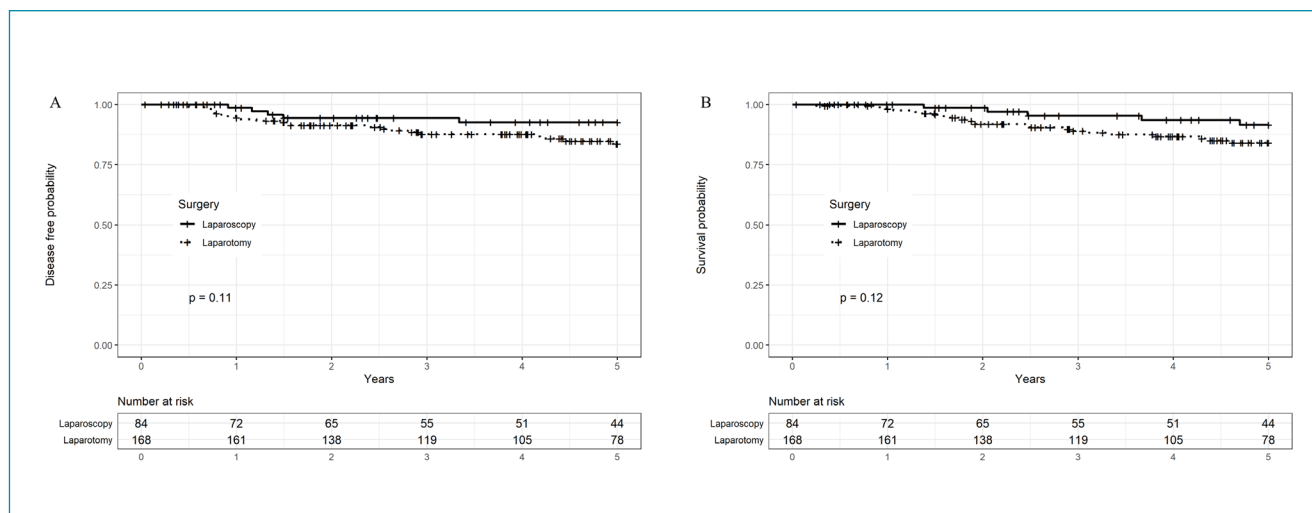
Figure 1. Kaplan-Meier curves of women with early endometrial cancer undergone laparoscopic surgery or conventional laparotomy. (A) 5-years disease-free survival. (B) 5-years overall survival.

DISCUSSION

Our results confirm that the laparoscopic surgery is safe in terms of oncological outcomes for early endometrial carcinoma. Although there was an increase of 30 min on the time of surgery and anesthesia, the risk of surgical complications was significantly reduced. The laparoscopic surgery was not associated with the 5-year risk of tumor relapse or all-cause mortality.

The main advantages of this study were as follows: a well-documented cohort, the comprehensive follow-up, and the concomitance over time of laparoscopy and laparotomy. The follow-up allowed the long-term observation of outcomes, and the concomitance of procedures was essential to minimize the bias due trends in survival associated with improvements in treatment quality[15]. Our study design also allowed comparing both the procedures' effectiveness in a real-world setting[16]. A limitation of our study was that laparoscopy or laparotomy was performed according to the surgeon's preference, and therefore the procedures were conducted by different surgeons who might have different skills and experience.

Compared with laparotomy, laparoscopy was associated with fewer complications. Our results are concordant with others in demonstrating a reduced risk of surgical complications in patients who underwent laparoscopic surgery, as well as the association of laparoscopy with a significantly longer operative time[17,18]. However, the clinical trials did not find differences in the surgical complications between laparotomy and laparoscopy[19]. A meta-analysis of the data from eight randomized controlled trials found similar intraoperative complication rates in both surgical approaches, less blood loss in laparoscopy, shorter operative time in laparotomy, and significant advantage of laparoscopy over laparotomy in terms of postoperative complications[20].

Similar to others[8], we found that the surgical technique was the most important variable associated with the complication rate.

There are few studies on the long-term outcomes of laparoscopic surgery published. We did not find evidence of any increment of risk of recurrence associated with laparoscopic surgery. This result is similar to a previous meta-analysis[21]. The GOG-LAP2 trial also confirmed the laparoscopic safety in terms of recurrence and survival[22] with a median of 5 years of follow-up. As early endometrial cancer has a high probability of cure with surgical treatment, the main causes of death among these patients are not endometrial cancer itself. The leading cause of death is the cardiovascular disease[23,24]. The laparoscopic surgery is associated with fewer surgically related complications and better postoperative quality of life[10,25], which may be associated with improved general health conditions posttreatment and has the potential to reduce the all-cause mortality.

CONCLUSIONS

In conclusion, our data add to the concept that the minimally invasive technology should be applied whenever possible in these cases.

AUTHORS' CONTRIBUTIONS

LM: Data curation, Formal analysis, Investigation, Writing – review & editing. **JCRS:** Validation, Writing – review & editing. **OBPN:** Data curation, Validation, Writing – review & editing. **DGT:** Data curation, Validation, Writing – review & editing. **JMA:** Validation, Writing – review & editing. **FJCR:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – original draft.

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Trends in teenage pregnancy in Brazil in the last 20 years (2000–2019)

Denise Leite Maia Monteiro[1]* [iD], Ida Peréa Monteiro[2] [iD],
Márcia Sacramento Cunha Machado[3] [iD], Zenilda Vieira Bruno[4] [iD],
Filomena Aste da Silveira[5] [iD], Marta Francis Benevides Rehme[6] [iD],
Albertina Duarte Takiuti[7] [iD], Nádia Cristina Pinheiro Rodrigues[8] [iD]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the frequency of teenage pregnancy in all Brazilian regions and states in the period of 2000–2019 among two age groups, namely, 10–14 and 15–19 years old, and correlate it with the human development index.

METHODS: A cross-sectional study was performed by using the data from the Live Birth Info System from the National Health System's database.

RESULTS: The percentage of live births from teenage mothers (age 10–19 years) in Brazil decreased by 37.2% (i.e., 23.4 in 2000 to 14.7% in 2019) in all regions. Amazonas and Maranhão were the only states to show increased fertility rates for teens in the age group of 10–14 years. The fertility index decreased from 80.9–48% in all states among mothers aged 15–19 years. Only the Southeast and South regions showed levels below the Brazilian average (i.e., 38.2 and 39%, respectively). The proportion of live birth showed an inversely proportional trend to the human development index score.

CONCLUSIONS: Brazil shows a decline in the percentage of live birth among adolescent mothers and the fertility rate. Live birth is inversely proportional to the human development index score. However, the teenage pregnancy numbers are still high, with great regional inequality in the country.

KEYWORDS: Pregnancy in adolescence. Prevalence. Epidemiology. Social conditions. Human development.

[1]Universidade do Estado do Rio de Janeiro, Centro Universitário Serra dos Órgãos – Teresópolis (RJ), Brazil.

[2]Centro Universitário São Lucas, Secretaria Municipal de Saúde – Porto Velho (RO), Brazil.

[3]Universidade Federal da Bahia, Bahia School of Medicine, Bahiana School of Medicine and Public Health – Salvador (BA), Brazil.

[4]Universidade Federal do Ceará, School of Medicine – Fortaleza (CE), Brazil.

[5]Universidade Federal do Rio de Janeiro, Centro Universitário de Valença – Valença (RJ), Brazil.

[6]Pontifícia Universidade Católica do Paraná, School of Medicine – Curitiba (PR), Brazil.

[7]Universidade de São Paulo, Faculty of Medicine – São Paulo (SP), Brazil.

[8]Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública Sérgio Arouca, Instituto de Medicina Social da Universidade do Estado do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.

*Corresponding author: denimonteiro2@yahoo.com.br

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INTRODUCTION

Adolescent pregnancy is a major public health problem globally. In developing countries, 21 million adolescents become pregnant between the ages of 15–19 every year, and approximately 12 million give birth. Furthermore, 777,000 births occur to girls under the age of 15[1]. Although the estimated overall adolescent-specific fertility rate has declined over the past 20 years[1], the actual number of births to adolescent girls has only shown a minor decline[2]. Regional differences in adolescent fertility rates exist, and pregnancy is more likely to occur in marginalized communities, often driven by poverty, poor education, and unemployment[1].

Early pregnancy has numerous health consequences for adolescents and their newborns. Complications during pregnancy and childbirth represent the leading cause of death among girls aged 15–19 years worldwide due to greater risks of eclampsia, puerperal endometritis, systemic infections, and prematurity. Furthermore, social and economic consequences, such as rejection, violence, and interruption of studies, compromise their future[1].

An epidemiological study conducted between 2000–2011 showed that Brazil experienced a decline in the percentage of live births (LBs) to adolescent mothers from 2001 onward. This decline tended to be inversely correlated to the human development index (HDI)[3].

This article aims to evaluate the frequency of adolescent pregnancy in Brazil from 2000–2019 in the five different regions, 27 states, and two age groups (i.e., 10–14 and 15–19 years) while correlating the data with each region's HDI.

METHODS

A cross-sectional study was conducted using the data from the Brazilian National Information System on Live Births (SINASC), maintained by the Brazilian Unified Health System's Information Technology Department (DATASUS). The aim was to gather the epidemiological data on births reported throughout Brazil[4]. The following variables were used: births according to the mother's place of residence, age, region, and year of birth[4].

The study population consisted of women who had LBs from 2000–2019, the last year with the available data at the time of the study, in the five official regions of Brazil. Information on the total number of LBs by region and for those in the age groups of 10–14 and 15–19 years was obtained to calculate the percentage of LBs to adolescent mothers. The age-specific fertility rate (ASFR) per 1,000 adolescents in the same age group, as well as in the same region and state, was calculated using the Brazilian Institute of Geography and Statistics (IBGE) population projection tables[5].

The association between the frequency of adolescent pregnancy and the HDI of each region was analyzed. This represents a summarized measure of the long-term progress as the HDI assesses income, education, and health. Each region's HDI was obtained by calculating the mean of the HDIs of the states pertaining to that region weighted by their respective populations[6].

The relative and absolute frequencies of LBs according to the mother's age group and year of birth were calculated. The percentage increase or decrease for the period was calculated as follows:

$$\frac{\%LB_{2019} - \%LB_{2000}}{\%LB_{2000}} \times 100$$

Choropleth maps were used to describe the results.

Because SINASC is a public-access database, the project did not require a Research Ethics Committee review. R-Project (version 5.4.0) and ArcGis (version 10.0.4) software were used.

RESULTS

In 2000, adolescent pregnancy accounted for 23.4% of all births, decreasing to 19.3% by 2010; then, it remained stable until 2013. Annual reductions were only observed from 2014 (18.9%) until 2019 (4.7%). For the 20-year study period, the frequency of LBs to adolescents decreased by 37.2%.

In absolute numbers, there were 750,537 LBs to adolescent mothers in 2000, of which 28,973 LBs were to mothers aged 10–14 years (ASFR 3.4/1,000 adolescents aged 10–14 years) and 721,564 LBs were to mothers aged 15–19 years (ASFR 80.9%). In 2019, a reduction was observed, with 419,252 (ASFR 2.5%) and 399,922 births (ASFR 48.0%), respectively. Stratifying the data by age, the percentage reduction in the age group of 10–14 (15–19 years) was 26.5% (40.7%) (Table 1).

The North Region had the highest rate of adolescent pregnancy, followed by the Northeast and Central-West regions. Only the Southeast and South regions had rates below the Brazilian average. Figure 1 shows the ASFR distribution by region both in the age groups of 10–14 and 15–19 years.

Assessing the 2017 HDI for each Brazilian region, the highest HDI was observed in the Southeast and South regions (0.80), followed by the Central-West (0.79), North (0.73), and Northeast (0.71) regions. The rates of LBs to adolescent mothers in the Southeast and South regions were the lowest, which shows an inversely proportional trend to the HDI (Figure 1).

Regarding the frequency of births in the age group of 10–14 years, the highest rates are also concentrated across states in

Table 1. Distribution of the annual age-specific fertility rate of 10–14-year-old and 15–19-year-old girls (2000–2019).

Year	10–14 years old	Estimated population aged 10–14 years	ASFR/1.000	15–19 years old	Estimated population aged 15–19 years	ASFR/1.000
2000	28,973	8,614,988	3.4	721,564	8,920,682	80.9
2001	27,931	8,556,415	3.3	696,955	8,931,314	78.0
2002	27,664	8,519,877	3.3	665,437	8,874,671	75.0
2003	27,239	8,500,653	3.2	645,806	8,500,653	76.0
2004	26,276	8,487,543	3.1	635,014	8,673,626	73.2
2005	26,752	8,473,701	3.2	634,385	8,595,641	73.8
2006	27,610	8,462,615	3.3	605,270	8,537,516	70.9
2007	27,963	8,455,516	3.3	582,409	8,501,358	68.5
2008	28,678	8,451,680	3.4	570,560	8,482,441	67.3
2009	27,807	8,449,676	3.3	546,959	8,469,621	64.6
2010	27,049	8,444,955	3.2	525,581	8,456,048	62.2
2011	27,785	8,453,733	3.3	533,103	8,445,364	63.1
2012	28,236	8,441,389	3.3	531,909	8,438,804	63.0
2013	27,989	8,407,297	3.3	532,002	8,435,542	63.1
2014	28,244	8,351,178	3.4	534,364	8,434,160	63.4
2015	26,700	8,276,054	3.2	520,864	8,430,077	61.8
2016	24,135	8,165,124	3.0	477,246	8,439,451	56.6
2017	22,146	8,052,464	2.8	458,777	8,427,714	54.4
2018	21,172	7,938,241	2.7	434,956	8,394,229	51.8
2019	19,330	7,823,491	2.5	399,922	8,338,727	48.0

Source: Brazilian Institute of Geography and Statistics (IBGE)-Research Division[5]. Coordination of Population and Social Indicators. The Sector of Studies and Analyses of Demographic Dynamics. Projection of the population of Brazil, and its federative units by sex and age for the period of 2000–2030. ASFR: age-specific fertility rate.

the North Region: Roraima (7.3%), Amazonas (6.1%), and Acre (5.6%). In the Northeast, the highest rates were in the states of Maranhão (4%) and Alagoas (3.9%). Rates lower than 2% were only in the Southeast and South regions and in the Federal District (the area of the national capital city, Brasília). Amazonas was the only state in the North Region to show an increase in births (10%), while in the Northeast Region, only Maranhão showed an increase of 1.9%. All other states experienced a reduction in births.

Similarly, births to adolescents aged 15–19 years are also more frequent in the North Region (75%), with a 110.6% rate in Roraima, followed by Amazonas and Acre, each with 84.6% and next comes the Northeast Region, with an ASFR of 54.5%, with the highest rates in the states of Maranhão (72%) and Alagoas (63.1%). The Central-West Region comes in third (50.1%), with the highest rates in the states of Mato Grosso (64.7%) and Mato Grosso do Sul (61.6%). No state showed an increase in the ASFR for this age group.

In the study period, the North Region presented a percentage reduction of 11.9% in the age group of 10–14 years and 32.9% in the age group of 15–19 years in terms of ASFR, while the Northeast Region presented a reduction of 16.4 and 35%, respectively. The Central-West, Southeast, and South regions presented reduction rates from 37.6–51.2% (Table 2).

DISCUSSION

This study's results complement the published data[3] by updating the trends of adolescent pregnancy in the period of 2000–2019. It becomes, therefore, the first study based on the national data available from the SINASC/DATASUS database for the year 2019.

In the study period, a slow decline was initially observed, followed by a period of stability, and then a more consistent reduction in the last five years. After a large increase in adolescent
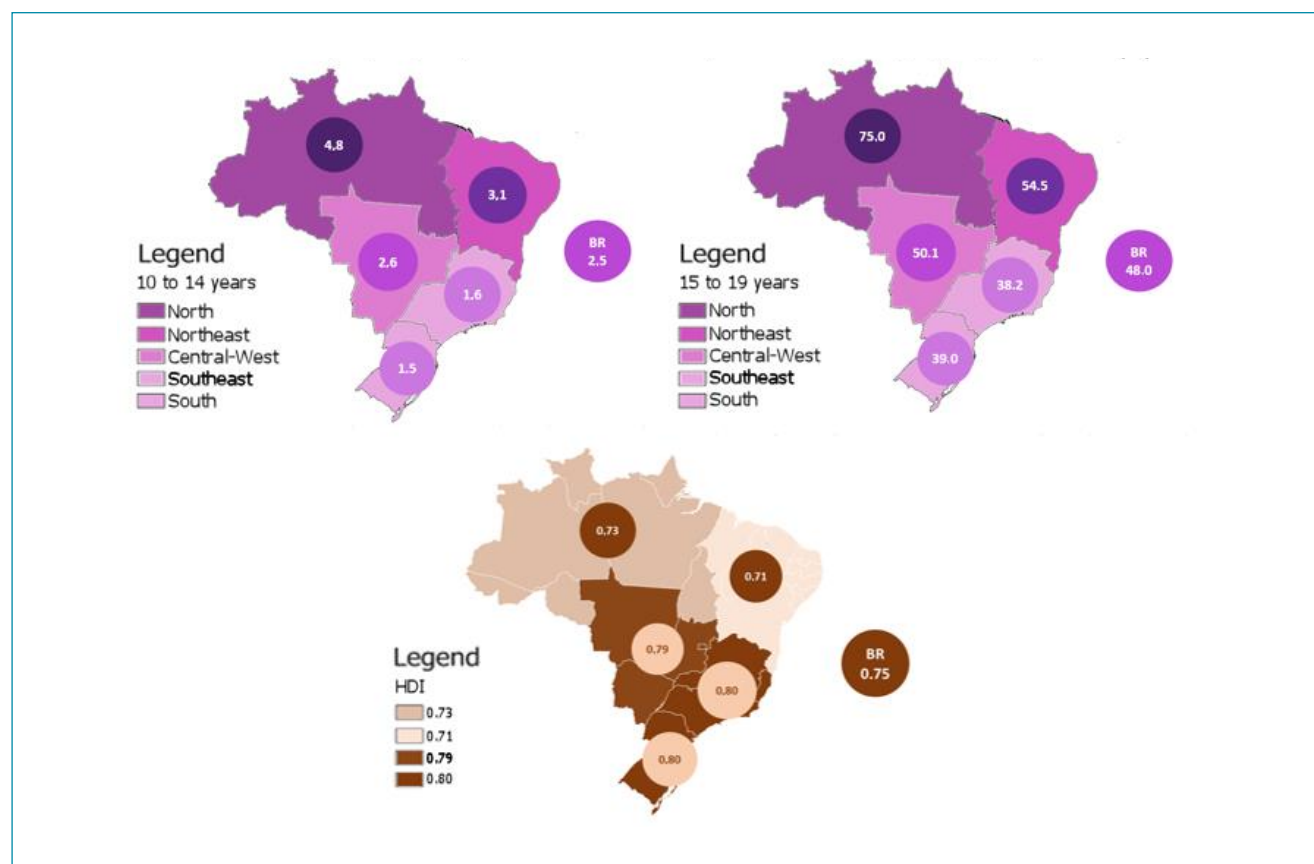
Figure 1. Distribution of age-specific fertility rate per 1,000 adolescents by region (2019) and mean human development index (HDI) by region (2017). Source: DATASUS/SINASC[4], PNUD Brasil, Ipea e FJP[6].

pregnancy rates in the 1990s, Brazil took 15 years to return to the 1994 level (i.e., 19.8% in both 1994 and 2009).

The pregnancy in adolescents aged 15–19 years, measured by the ASFR, showed a 40.7% reduction over the study period (from 80.9–48%). The international literature only reports the data for this age group, perhaps because pregnancy before the age of 15 years is uncommon in most developed countries.

This study also evaluated the age group of 10–14 years, finding a 26.5% decrease. These results show progress in the reduction of adolescent pregnancy in relation to the period of 2000–2011, when there was a 5% increase in the number of LBs to mothers aged 10–14 years, which was even more pronounced in the North (12.5%) and Northeast (13.4%) regions. Meanwhile, among 15–19-year-olds, there was a 19.1% reduction[3]. This study was the first to observe a reduction in adolescent pregnancy in the age group of 10–14 years, which could also be observed in the North (-11.9%) and Northeast (-16.4%) regions. The South Region stands out for the highest rate of reduction, from 13% in 2000–2011 to 51.2%.

Among mothers aged 15–19 years, the downward trend was observed in the period of 2000–2011 remained. In the North Region, there was a 15 (32.9%) decrease in 2000–2011 (2000–2019). Similar reductions happened in other regions: Northeast (17.6–35%), Southeast (22–46.5%), South (19.9–48.8%), and Central-West (27.9–46.7%)[3].

The worldwide adolescent fertility rate has decreased by 11.6% in the past 20 years. However, there are large regional differences, ranging from 7.1% in East Asia to 129.5% in Central Africa[1]. In Latin America and the Caribbean, the rate has fallen from 65.6% (2010–2015) to 60.7% (2015–2020), representing a 7.5% decrease. Chile reduced its rate from 53.5–26.5% between 2010–2017; Uruguay showed a 72% decline after 20 years, reaching 36% in 2018 (-50%). Costa Rica also shows a decline since 2013, going from 29.8 (2013)–21.5% (2018)[7].

The United States showed a 59.8% decline in adolescent ASFR between 2000–2018, but it still exhibits a rate of 18.5%, the highest among developed countries[8], primarily among Hispanic/Latino, Black, Native Indian, and socioeconomically disadvantaged youth of any race or ethnicity[9].

Table 2. Distribution of the age-specific fertility rate per 1,000 adolescents by federative units of Brazil (2000–2019).

	Adolescents of 10–14 years old			Adolescents of 15–19 years old			
Region	2000	2019	ASFR/1000 Evolution% 2000–2019	2000	2019	ASFR/1000 Evolution% 2000–2019	
Brazil	3.4	2.5	-26.5	80.9	48.0	-40.7	
North Region	5.4	4.8	-11.9	111.7	75.0	-32.9	
Roraima	10.8	7.3	-32.3	142.8	110.6	-22.6	
Amazonas	5.6	6.1	10.0	111.9	84.6	-24.4	
Acre	7.3	5.6	-23.2	134.1	84.6	-36.9	
Pará	4.9	4.6	-5.9	103.4	74.0	28.4	
Amapá	6.6	4.0	-39.8	129.6	68.4	-47.2	
Tocantins	6.2	3.4	-44.6	120.4	59.7	-50.4	
Rondônia	4.7	2.7	-43.5	118.8	55.0	-53.7	
Northeast Region	3.7	3.1	-16.4	83.8	54.5	-35.0	
Maranhão	3.9	4.0	1.9	87.1	72.0	-17.4	
Alagoas	4.8	3.9	-17.7	99.8	63.1	-36.8	
Sergipe	3.9	3.2	-15.9	89.2	50.0	-44.0	
Piauí	3.8	3.0	-22.1	93.0	57.4	-38.3	
Bahia	3.4	3.0	-12.0	77.4	51.0	-34.1	
Pernambuco	3.8	2.8	-26.7	90.0	53.2	-40.9	
Paraíba	3.2	2.8	-12.4	72.1	53.2	-26.2	
Rio Grande do Norte	4.3	2.7	-37.3	88.9	43.7	-50.8	
Ceará	3.5	2.7	-22.2	78.6	47.5	-39.6	
Southeast Region	2.5	1.6	-37.6	71.4	38.2	-6.5	
Rio de Janeiro	3.6	2.3	-35.8	79.7	45.4	-43.0	
Espírito Santo	2.9	1.9	-34.6	78.6	44.5	-43.3	
Minas Gerais	2.0	1.6	-21.0	65.0	38.1	-41.4	
São Paulo	2.4	1.3	-46.1	71.1	35.1	-50.6	
South Region	3.1	1.5	-51.2	76.1	39.0	-48.8	
Paraná	3.3	1.8	-45.9	82.3	42.2	-48.8	
Rio Grande do Sul	3.4	1.4	-58,7	72.1	36.2	-49.8	
Santa Catarina	2.4	1.3	-45.9	72.2	38.0	-47.4	
Central-West Region	4.2	2.6	-39.1	94.0	50.1	-46.7	
Mato Grosso	5.2	3.6	-30.7	104.8	64.7	-38.3	
Mato Grosso do Sul	5.5	3.5	-37.1	100.0	61.6	-38.4	
Goiás	3.7	2.1	-43.5	93.0	45.2	-51.3	
Federal District	2.8	1.5	-45.8	78.4	34.4	-56.1	

Source: DATASUS/SINASC[4]. ASFR: age-specific fertility rate.

According to the World Bank, there was also a significant reduction in European countries. In 2000, Germany had a 12.6% ASFR for the age group of 15–19 years, Portugal had 20.3%, and the United Kingdom had 28.3%. In 2018, these rates had decreased to 7.8, 8.0, and 12.6%, respectively.

Analyzing the pregnancy in the age group of 15–19 years in five African countries (i.e., Kenya, Tanzania, Uganda, Malawi, and Zambia) shows that social inequalities are evident, with higher rates in adolescents from rural areas, without adequate education, and from poorer families. Knowledge about contraceptive methods and access to schooling were important determinants[10]. In 2017, the fertility rates among 15–19-year-olds in these five countries were 96, 132, 140, 136, and 141%, respectively[11].

The World Bank report refers to the "opportunity cost" if additional investment in girls had been made, i.e., the costs associated with adolescent pregnancy and school dropout. Brazil missed out on earning the equivalent of US$3.5 billion due to teenage pregnancy, while productivity in India would also increase by US$7.7 billion due to the same[9].

An estimated 7.5 million girls are married worldwide before the age of 18[12]. Brazil ranks fourth in the world for child marriages, with 2.9 million cases. In many places, girls experience pressure to marry and have children early or choose to become pregnant because they have limited educational and employment prospects, contributing to increased rates of adolescent pregnancy and recurrence[1].

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has forced many young people to stay in their homes, which may, therefore, increase domestic and sexual violence as well as adolescent pregnancy[7].

Adolescents are at risk of repeat pregnancy, as 12–49% of adolescent mothers become pregnant again within one year after delivery[13]. Silva et al. found among 12,168 adolescents, a pregnancy recurrence prevalence of 29.1%[14]. An important factor for recurrence is the lack of effective contraception in the postpartum period, with long-acting reversible contraceptives (LARCs) being a good indication in such cases[13,15].

This study's main limitation is that the available data are on pregnancies that had LBs as an outcome and exclude those with unfavorable outcomes, such as stillbirth or miscarriage. Therefore, the data may be underestimated.

CONCLUSIONS

Brazil shows a decline in the percentage of LBs among adolescent mothers and the fertility rate. The rate of LBs is inversely proportional to the HDI. However, the teenage pregnancy numbers are still high, with great regional inequality in the country.

Brazil must invest more in specific public policies against unplanned adolescent pregnancy. Reducing school dropouts, providing comprehensive education on sexuality, developing life skills, promoting social changes, and prohibiting early marriages are examples of possible actions[12,16]. Furthermore, the guidance on contraceptive methods, their availability, and encouraging their correct and consistent use, especially of LARCs, are fundamental for responsible sexuality and family planning, which are important for the country to achieve the United Nations' Sustainable Development Goal (SDG) Target 3.1 of reducing maternal mortality to 30 per 100,000[17].

AUTHORS' CONTRIBUTIONS

DLMM: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **ADT:** Conceptualization, Writing – original draft. **NCPR:** Conceptualization, Data curation, Formal Analysis, Methodology. **MSCM:** Methodology, Data curation, Formal Analysis, Writing – original draft. **IPM:** Data curation, Formal Analysis, Writing – review & editing. ZVB: Data curation, Formal Analysis, Writing – original draft. **FAS:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MBR:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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Comparison of AIMS65 and Glasgow Blatchford scores in predicting mortality in patients with upper gastrointestinal bleeding

Rohat Ak[1]* , Nihat Müjdat Hökenek[2]

SUMMARY

OBJECTIVE: Several mortality prediction scores are available for patients with upper gastrointestinal bleeding who visited the emergency department; however, most of the available scores include endoscopic data. Endoscopy is difficult or impossible to access for many emergencies departments worldwide. The aim of this study was to evaluate and compare the performance of the albumin, INR, alteration in mental status, systolic blood pressure and age 65 score and the Glasgow-Blatchford score in predicting mortality in patients with upper gastrointestinal bleeding who visited the emergency department and for which endoscopic data were not required.

METHODS: The data of patients with acute upper gastrointestinal bleeding who visited the emergency department during the study period were retrospectively analyzed. The data were obtained from the hospital automation system using the international classification of disease codes *via* computer registration. The prediction accuracy of AIMS65 and Glasgow-Blatchford score was compared using the area under the receiver operating characteristic curve method.

RESULTS: There were 422 patients in total; the mean age of these patients was 68.5 while 62.6% were males. The mortality rate was 30 (7.1%). The AIMS65 score performed better with an AUC 0.706 [95%CI 0.660–0.749; $p<0.001$] compared with the Glasgow-Blatchford score (AUC 0.542; 95%CI 0.4693–0.576; $p=0.11$).

CONCLUSION: In this study, it was revealed that AIMS65, which is a score that can be easily calculated only with the data in the emergency department, outperformed Glasgow-Blatchford score in predicting mortality in patients with acute upper gastrointestinal bleeding who visited the emergency department.

KEYWORDS: Assessment, risk. Emergency care. Gastrointestinal endoscopy. Mortality. Upper gastrointestinal tract. Mortality.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a common cause of hospitalization and a disease with high mortality rates in the emergency department (ED). Despite the advances in intensive care technologies and the endoscopic treatment of UGIB, mortality remains a major problem. It has been reported that the overall rate of mortality due to the disease ranges from 3–15%. These rates increase even further for those in an unstable hemodynamic condition[1-3].

The guidelines from the American College of Gastroenterology recommend the use of early risk scores in the management of patients with acute UGIB[4]. The number of published risk scoring systems for these patients has increased rapidly in recent years[5-7]. Among these, the AIMS65 score, developed by Saltzman et al.[8], includes five variables, namely, albumin, international normalized ratio (INR), altered mental status, systolic blood pressure, and an age above 65 years. The values of the scores can range from 0–5 and are used to estimate in-hospital mortality[8]. The Glasgow-Blatchford score (GBS) includes eight variables, namely, blood urea nitrogen (BUN), hemoglobin level, systolic blood pressure, pulse, melena, syncope, liver disease, and heart failure. Any score higher than zero in this score is

interpreted as the risk of needing a transfusion, endoscopy, or surgical intervention[9].

This study aims to evaluate and compare the performances of the AIMS65 and GBS in predicting in-hospital mortality in patients with UGIB who visited the ED.

METHODS

This retrospective observational study was carried out in the ED of a tertiary care teaching hospital between January 1, 2019 – January 1, 2020. The electronic patient database of the hospital was scanned for the determined period of this study; patients above the age of 18, who were diagnosed with UGIB and hospitalized after visiting the ED according to the codes of the International Classification of Diseases (ICD) 10th revision, were included in this study. The definition of acute UGIB was based on the presence of at least one of the following three features: hematemesis, melena, or solid clinical evidence and laboratory support for acute blood loss from the upper gastrointestinal (UGI) tract[10]. Patients with missing records, patients transferred from other hospitals, patients with variceal bleeding, patients with records of less than 30 days, and patients with a diagnosis other than UGIB after hospitalization were excluded from this study. The institutional review board approved the analysis and issued a waiver of consent (Ethics Committee Ruling number: 2021/514/200/16).

The following data were collected for each patient: age, gender, information about their mental status, symptoms at admission (i.e., hematemesis, coffee-like substance vomiting, melena, syncope, lethargy, blood pressure, and pulse), comorbidities (i.e., ischemic heart disease, diabetes mellitus, congestive heart failure, and liver disease), medications, and laboratory results (i.e., albumin levels, INR, BUN, and hemoglobin). If the Glasgow Coma Scale score of the patients was <14 or their consciousness status included disorientation (i.e., lethargy, stupor, or coma), then their mental status was considered to have changed. AIMS65 and GBS scores were calculated for each patient as previously defined[8,9]. The data for each scoring system were entered into an Excel database (Microsoft Inc., Richmond, WA, USA) and analyzed by one of the researchers. After the data analysis, the other researcher presented quality improvement feedback. The primary outcome of this study was 30-day all-cause in-hospital mortality.

Statistical analysis

All calculations were performed using SPSS 15.0 for Windows and MedCalc. Descriptive criteria include the median and interquartile range values and are presented as a percentage distribution. The conformity of the data to the normal distribution was verified with the Kolmogorov–Smirnov test. Receiver-operating characteristic (ROC) curves for 30-day mortality were calculated for AIMS65 and GBS, and the predictive accuracy of each scoring system was measured by the area under the receiver-operating curve (AUC). The method established by DeLong et al. was used to compare the ROC curves of the risk scores[11]. This study was completed with a 95%CI and statistical significance was accepted as p<0.05.

RESULTS

Among the 558 patients admitted with the definition of acute UGIB during the study period, 136 individuals were excluded based on the exclusion criteria. The data from the total of 422 patients with acute UGIB were then recorded, retrospectively. In this study, 62.6% of the patients are men while the median age is 68.5 years. More than half of the patients (74.2%) had melena as an admission symptom (Table 1).

Mortality occurred in 30 (7.1%) of the 422 patients who were included in this study (Table 1). While death occurred in 2.7% of patients with an AIMS65 score value of 0, the mortality rate for values of 1, 2, 3, 4, and 5 is 6.2, 8.5, 46.2, 50.0, and 100%, respectively (Table 2). As a result of the ROC analysis, the AUC was determined to be 0.706 (95%CI 0.660–0.749) for the AIMS65 score. The sensitivity of predicting the probability of death in individuals with a value above 0 was 50.0% and the selectivity was 78.8%; it was found to be statistically significant (p=0.001). In the GBS, patients with values between 0–5 had a mortality rate of 9.1%, while the values between 6–12 and 13–23 had mortality rates of 5.3 and 9.7%, respectively. As a result of the ROC analysis, the AUC was found to be 0.542 (95%CI 0.4693–0.576), and the value of GBS in predicting mortality was not found to be statistically significant (p=0.11) (Figure 1).

DISCUSSION

UGIB is a common gastrointestinal emergency that can cause high morbidity and mortality at a rate of 3–10%[12,13]. There are more than 300,000 hospital admissions per year in the USA due to UGIB[14]. In the United Kingdom, the rate is 103–172/100,000 admissions per year, with a mortality rate of 8–14%[15]. It is important to determine the necessary level of care such as early endoscopy, early surgical/interventional radiological procedures, or intensive care for a medical emergency with such a high mortality rate. Many international guidelines suggest early risk stratification to determine the appropriate care of patients who are admitted to the ED with UGIB[16]. The results of this study demonstrate that the AIMS65 score is superior to the GBS in the context of 30-day in-hospital mortality in patients with UGIB.

Medical treatment in EDs must be managed rapidly. Some patients identified as being at high risk of death may be given priority for a transfusion and hospital admission after UGIB.

Many scoring systems have been developed that can be used for this purpose. However, most of the current scoring systems are not useful for EDs since they are based on endoscopic data. Moreover, many EDs worldwide do not have access to endoscopy.

Risk predicting models to be used in the ED should be easily calculated and reproducible. The AIMS65 score is a

Table 1. Characteristics of patients.

Baseline characteristics	Median (IQR) or n (%)
Age	68.5 (27)
Male, n (%)	264 (62.6)
Clinical parameters	
Heart rate (beats/min)	98 (15)
SBP (mmHg)	120 (20)
DBP (mmHg)	65 (12)
Laboratory results	
Hb (mg/dL)	8.8 (2.5)
Platelet count (dL)	212.5 (114)
BUN (mg/dL)	63 (55)
Cr (mg/dL)	0.8 (0.4)
Albumin (mg/dL)	29 (15)
INR	1.2 (0.3)
Presenting symptoms	
Hematemesis, n (%)	84 (19.9)
Melena, n (%)	313 (74.2)
Hematochezia, n (%)	58 (13.7)
Mental status change, n (%)	7 (1.7)
Syncope, n (%)	24 (5.7)
Comorbid illness	
Liver disease, n (%)	9 (2.1)
Congestive heart failure, n (%)	38 (9)
Renal disease, n (%)	24 (5.7)
Diabetes mellitus, n (%)	90 (21.3)
Hypertension, n (%)	170 (40.3)
Medications	
Clopidogrel, n (%)	26 (6.2)
Warfarin, n (%)	40 (9.5)
Nonsteroidal anti-inflammatory drugs, n (%)	83 (19.7)
Acetylsalicylic acid, n (%)	97 (23)
Length of hospital stay (d)	3
Mortality, n (%)	30 (7.1)

SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; ALB: albumin; BUN: blood urine nitrogen; Cr: creatinine; INR: international normalized ratio.

Table 2. Distribution of patients and 30-day mortality in each scoring systems.

	Number of patients (n=422)	30 day mortality (n=30)
AIMS65 score		
0	147 (34.8)	4 (2.7)
1	177 (41.9)	11 (6.2)
2	82 (19.4)	7 (8.5)
3	13 (3.1)	6 (46.2)
4	2 (0.5)	1 (50)
5	1 (0.2)	1 (100)
p-value		0.001
Glasgow-Blatchford score		
0–5	22 (5.2)	2 (9.1)
6–12	246 (58.3)	13 (5.3)
13–23	154 (36.5)	15 (9.7)
p-value		0.23

p-value: χ^2 test for 30-day mortality.
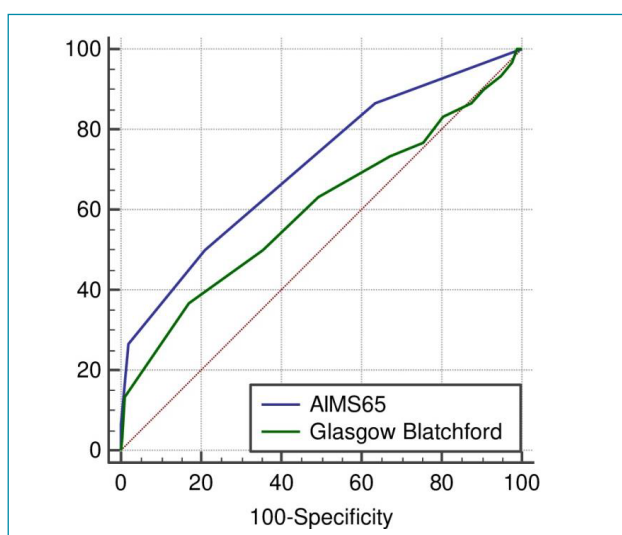
Figure 1. Receiver-operating characteristic curves comparing the prediction of 30-day in-hospital mortality in patients with acute upper gastrointestinal bleeding based on the AIMS65 and Glasgow-Blatchford scores.

prognostic scoring system with good performance, especially in the early diagnosis of patients with UGIB who have a high risk of in-hospital mortality[8]. The AIMS65 score is a five-variable prediction tool using physical examination findings, vital signs, routine laboratory values, and age; it provides risk prediction in EDs without emergency endoscopy. Similarly, GBS is based on simple clinical and laboratory parameters and does not require emergency endoscopy[9]. However, the GBS is not useful for routine clinical practice due to its limitations: some scoring items from the medical history of a patient may not readily be available in EDs.

In this study, AIMS65 performed well in predicting mortality with an AUC 0.706. GBS was found to be ineffective in predicting mortality (AUC 0.542). In a study by Stanley et al., the AIMS65 score was found to be superior to GBS (AUC 0.69) with an AUC 0.78[5]. A study conducted by Min Park et al., which had a sample size of 523 patients, reported that the AIMS65 (AUC 0.79) was superior to GBS (AUC 0.61)[17]. Additionally, in the study conducted by Yaka et al., with 254 patients, it was emphasized that the AIMS65 (AUC 0.849) was more successful than GBS (AUC 0.809) in predicting mortality[18].

We asserted that the disappointing performance of GBS in predicting mortality can be explained by the fact that this risk scoring system was originally developed to predict the requirement for intervention (i.e., transfusion, endoscopy, or surgery) and not for mortality prediction. There are some limitations to this study. First, this is a single-center study conducted on a relatively small population and requires confirmation in a larger, multi-center cohort. In addition, due to the retrospective nature of this study, the data were obtained from an electronic registry system; this limited the amount of data able to be implemented due to incomplete or outdated information.

CONCLUSIONS

In this study, it was found that the AIMS65 score, which can be easily calculated with only the data from the ED, outperformed GBS in predicting mortality in patients with acute UGIB admitted to the ED. However, more multi-center and prospective studies are required to demonstrate the wider applicability of this score.

AUTHORS' CONTRIBUTIONS

RA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft. **NMH:** Validation, Visualization, Writing –review & editing.

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Comment on "The relationship between thyroidectomy complications and body mass index"

Qiong-mei Han[1] ⓘ, Jie Ding[2]* ⓘ

Dear Editor,

We were lucky enough to read the study by Üstün et al.[1] in which they found that no relationship between a high BMI and thyroidectomy complications and surgery can also be performed safely in this patient group. Although the authors' findings found no effect on postoperative complications of the thyroid gland, I would like to make some of my own points.

To begin with, the study was a cohort study, so how long was follow-up observed for the subjects, 24 hours after surgery or 48 hours? Postoperative complications of different weight types may occur at different times.

In addition, although the authors describe in Table 1 that differences in gender and age groups between the two groups are not statistically significant, the small sample size may lead to a smaller degree of certainty in the conclusions of the study. The age difference between the two groups is 5 years, and although the difference in the gender ratio between the two groups is not statistically significant, the p-value is very close to 0.05. In summary, large samples of clinical studies are still needed to make conclusions more reliable.

AUTHORS 'CONTRIBUTION

QH: Conceptualization, Writing – review & editing. **JD:** Data curation, Formal analysis, Writing – original draft.

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[1]Yankuang New Journey General Hospital, Department of Endocrinology – Jining, China.
[2]Yankuang New Journey General Hospital, Department of Spinal Surgery – Jining China.
*Corresponding author: jiangzuomeilang886@163.com