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TIMBRO EDITORA

Does androgen deprivation therapy in patients with prostate cancer protect from COVID-19?

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Since the end of 2019, with the disease caused by the new coronavirus in China spreading throughout the world, the entire scientific community has been focused on the search for medications that can minimize severe forms of the disease. Simultaneous research is being developed on the effect of several drugs, such as chloroquine, hydroxychloroquine, antiviral drugs, corticosteroids, antibodies, plasma transfusions, and initial vaccine testing[1]. However, no studies have been able to find an effective medication for treatment that is better than the immune response of each organism.

Previous data have revealed a greater susceptibility of men to the coronavirus than women[2]. An Italian study directed its attention at testosterone after assessing patients at 68 hospitals in the region of Veneto, where the majority of severe cases in need of hospitalization (60%) and intensive care (78%) were men[3]. The authors demonstrated that men with cancer affected by the coronavirus had more severe forms of the disease. However, after analyzing patients with prostate cancer, they found that the rates of infection by COVID-19 were five times lower among those in androgen deprivation therapy (ADT) compared to those with prostate cancer not undergoing this type of therapy (OR 4.05; 95% CI 1.55 to 10.59)[3].

These findings led to the molecular evaluation of the gene transmembrane protease, serine 2 (TMPRSS2), which is involved in numerous physiological and pathological processes, including cancer and viral infection[4]. This gene is highly expressed in localized and metastatic prostate cancer and its transcription is regulated by androgen receptors (ARs)[5]. It has been demonstrated that ARs regulate the expression of TMPRSS2 in non-prostatic tissues as well, including the lung. *In vitro* and *in vivo* results have shown that the administration of androgens

induces the expression of TMPRSS2 in epithelial cells of the human lung, and the suppression of androgens reduces the transcription of TMPRSS2 in the murine lung[6]. Therefore, this regulation may explain the increased susceptibility of men to developing a severe infection by SARS-CoV-2 compared to women.

However, it is possible that the greater social distancing of patients undergoing ADT plays a role in the lower frequency of COVID-19 among such patients. The data need to be validated in large cohorts correcting for other variables, such as cardiometabolic comorbidities and obesity[3]. Therefore, it seems far too soon to declare that ADT for men in treatment for prostate cancer has a protective effect with regards to COVID-19.

Since the expression of the TMPRSS2 gene may be related to a lower infection rate by COVID-19 in men undergoing ADT, randomized, controlled clinical trials are needed to confirm or refute the hypothesis that androgen deprivation protects patients with prostate cancer from COVID-19.

Conflicts of interest

The authors have nothing to disclose

Author's Contribution

All authors have contributed equally to the work.

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The psychopathological scenario in asthma

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Dear Editor,

According to recently published data in Portugal, respiratory diseases are the 5th leading cause of hospitalization, the 1st leading cause of intra-hospital mortality, and the 3rd leading cause of mortality (preceded by cardiovascular and oncological diseases)[1].

Asthma is a respiratory disease characterized by chronic and heterogeneous airway inflammation, defined by a constellation of respiratory symptoms such as wheezing, dyspnea, chest tightness, and coughing. The symptoms are diverse in their frequency and intensity and are associated with a variable limitation of expiratory flow[2]. The prevalence of asthma is high, particularly in pediatric and young adult patients.

As a potentially disabling chronic disease with high expression at a young age, the importance of early intervention is highlighted to guarantee symptomatic control. This involves a complex process of adaptation and implies adherence to a therapeutic plan that includes pharmacological and non-pharmacological measures.

The diagnosis of a chronic disease leads to a set of changes in social, professional and personal roles, which increases the vulnerability to psychopathology. The psychological component influences the respiratory condition, namely: i) the onset of asthmatic crises; ii) the persistence/worsening of symptoms during the crises; and iii) resistance to pharmacotherapy. The presence of anxious and depressive symptoms can negatively influence the clinical outcome, contributing to: i) worse quality of life, ii) less adherence to drug therapy; iii) greater severity of symptoms; iv) greater functional deficit; v) increased frequency and therapeutic dosage; vi) greater use of health services; and vii) reduction of average life expectancy.

In reverse, asthma as a chronic and disabling disease can be a triggering factor for anxiety and/or depressive disorders.

There are some immunological pathways that explain the relationship between these disorders. Chronic elevation of cortisol in stressful situations leads to greater resistance to the anti-inflammatory effects of glucocorticoids[3]. There is a specific increase in the cytokines IL-1β and IL-6, which are related to neurodegeneration[4]. This is a risk factor for systemic and/or airway inflammation in asthma[5]. Another cytokine involved in inflammatory responses, such as alpha interferon (IFN-α), can contribute to glucocorticoid resistance by decreasing the function of glucocorticoid receptors. It leads to fatigue in individuals with depression[6].

Additionally, a depressive mood is related to an increase in the fraction of exhaled nitric oxide (FeNO)

in asthma[7]. On the other hand, excess glucocorticoids in asthma can also activate immune pathways, which increase the vulnerability to psychopathology[6].

The rate of adherence to treatment for patients with asthma is relatively low, occurring in just about 30% of cases[8]. Asthma treatment guidelines such as GINA or the latest revision of the Clinical Guidance Standard of the General Directorate of Health on monitoring and treatment for asthma control, recommend building a good doctor-patient relationship, which improves adherence and prognosis.

Thus, there is a close correlation between psychiatric comorbidity and worse clinical outcomes in asthma, and a better understanding of this association may have a significant clinical impact. There is a need for an integrated care response, with medical and psychiatric guidance combined in a multidisciplinary approach, with effective clinical communication of an individualized plan and a consequent potential reduction in hospital costs.

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The face mask as an established symbol against COVID-19

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The COVID-19 pandemic is often described as a state of war[1]. However, military conflicts take place in defined geographic areas, even when designated as a world war. On the other hand, SARS-COV-2 spread from the city of Wuhan to every continent in a few months. Similarly to warfare, almost every social activity was compromised, leading to economic and social stagnation in most affected areas. However, while war is permeated by the hope for a peace treaty that will clear the trenches, the viral pandemic will not have a sharp stop after an agreement; it will languish slowly and gradually, without a brisk end, leaving behind bereavement and exhaustion.

With over 32 million infected people and more than 990 thousand deaths, the campaign against COVID-19 needs a symbol of protection analogous to an armor. In this context, the universal use of face masks earns this connotation, by covering almost the entire area susceptible to the "bullet", i.e., the virus, and representing the commitment to defend our superior respiratory tract[2]. Face masks create a mechanical barrier to our constant manipulation of the oral and nasal mucosa, and the discomfort promoted by its conscious use acts as a permanent reminder of the transmission risk.

The unusual visuals produced by a face mask further impose social distancing, which is also paramount for safety in restarting economic and social activities. Masks provide protection when the possibility of contagion or transmission is high such as in the presence of respiratory symptoms, as cough or sneezes. Face masks also lower the risk in the presence of pre-symptomatic or asymptomatic carriers, especially when distancing is kept, and physical contact is minimized[3].

In the history of pandemics, perhaps the most conflicting tasks are those related to reopening, due to the lack of established parameters that would allow for unquestionable decisions. It is important to notice that most protocols for a safe reopening place too much emphasis on the potential role of inanimate objects or surfaces in spreading the disease[4]. Ultimately, hand washing and avoiding manipulation of the airway are more effective to contain viral spread than obsessively cleaning surfaces and objects.

Moreover, increasing awareness for strategies to decrease contagion within households is critical, as studies show a high rate of domiciliary SARS-COV-2 transmission. In any location, it is important to be cognizant about the risk of infection, which incites the need for protection[5], reminding that the small discomfort of wearing a face mask is not comparable to that of a ventilator in an intensive care unit.

Author's Contribution

All authors made substantial contributions to all aspects of the preparation of this manuscript.

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Telehealth actions in times of COVID-19: information with evidence

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SUMMARY

The coronavirus pandemic (COVID-19) brought up discussions about improvements in both primary healthcare and hospital care in Brasil. In addition, the use of information and communication technology tools has become more prominent in the transmission of health information to patients remotely. Through content dissemination actions for professionals and direct guidance to users, remote telehealth/telemedicine services offer qualified actions that can reduce unnecessary referrals and decrease the flow of patients in health units. Information and communication technologies are allies in the fight against COVID-19.

KEYWORDS: Telemedicine. Coronavirus Infections. Primary Health Care. Brasil.

PALAVRAS-CHAVE: Telemedicina. Infecções por Coronavirus. Atenção Primária à Saúde. Brasil.

Dear Editor,

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its rapid spread have caused important changes in health services worldwide. Although the focus of care is on the treatment of severe cases in hospitals, primary health care (PHC) services have also been impacted by the coronavirus disease 2019 (COVID-19) pandemic. In Brasil, due to the spread of COVID-19 throughout the territory, PHC has undergone important changes in the work process and in the way care is provided. Family health teams have had to reorganize their demands to provide essential evidence-based care, as well as secure information on protective measures against the new coronavirus[1]. In view of the current epidemiological scenario, in which social distance is recommended to avoid agglomerations and the spread of SARS-CoV-2, an old tool has gained substantial importance – telemedicine and telehealth.

The Brazilian Telehealth Networks, created in 2011 and currently implemented throughout Brasil through State Centers, is an important tool to promote training for PHC professionals and to enable enhancements

in healthcare assistance, ensuring agility in decision making. In this sense, unnecessary referrals to specialized services are reduced.

The activities promoted by the Telehealth Program were already part of the daily lives of the teams that make up the Family Health Strategy (ESF, acronyms in Portuguese) even before the pandemic. The program offers actions such as teleconsulting (among professionals), teleregulation, telemonitoring, web lectures, and the publication of Second Training Opinions (content published in the Virtual Health Library, based on good evidence related to PHC priority problems)[1-4].

In face of the new challenge introduced by the COVID-19 pandemic, the Brazilian Ministry of Health published an ordinance on an exceptional and temporary basis, which allows remote interaction actions (between professionals and patients) to carry out pre-clinical care, care support, medical visits, treatment monitoring, and diagnosis[5].

Recently, the teleconsultation procedure in primary care started to be included in the SUS procedure table (June 24, 2020, through Ordinance No. 526/2020)[6].

Additionally, the Brazilian Ministry of Health has implemented other free communication channels to provide information on COVID-19, such as a phone number (136) and a smartphone app (Coronavirus SUS)[7]. With the purpose of monitoring suspected and/or confirmed cases of COVID-19 in self-isolation, the states from Northeast Brasil have implemented an exclusive communication channel. Through it, SARS-CoV-2-infected people are monitored daily via remote assistance (text messages or phone calls) by healthcare professionals. These measures allow information at a distance, avoiding unnecessary agglomerations and queues at health units[8].

Since the World Health Organization's pandemic announcement in March 2020, the Telehealth Center of the State of Sergipe also has promoted remote education activities (web lectures, teleconsulting, and folders) to family health teams working in all 75 municipalities of Sergipe state[9]. From March to June 2020, 18 web lectures were held, with an average of 93 participants, ranging from 19 to 427 participants by web lecture, resulting in a total of 1,670 listeners. During this period, issues related to COVID-19 were the most discussed topic. Thus, the framework of Information Technology and Health Communication (ITHC) services have also been adapted to the current demand generated by the COVID-19 pandemic[1].

Since information technologies contribute to the qualification of health professionals, resulting in evidence-based care, more financial resources are needed to expand telehealth activities. It is necessary to have a financial source for the permanent qualification of teleconsultancy professionals, to expand the number of computers with internet access in primary care services, and improve ITHC devices[3]. These investments on telehealth should occur both during the pandemic and in the post-pandemic period.

The transmission of health information, with updated scientific evidence, through telehealth, promotes a reduction in the circulation of individuals in health services, guarantees services that can be provided at a distance to users with comorbidities, thus reducing the risks of dissemination and contamination by COVID-19[4,10].

Conflicts of interest

The authors have no conflict of interest to declare.

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Author's Contributions

Gois-Santos, V.T.; Santos, V.S.; Freire, D.A.; Libório, L. S.; Ferreira, E.C.G. worked on the conceptualization, discussion of the theme and writing; Santos, V.S revised and edited the text.

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Ultrasound in the first trimester of pregnancy

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

INTRODUCTION

Routine ultrasound is established as part of prenatal care and is more frequently used during the second trimester[1]. However, in recent years it has been increasingly used during the first trimester, a period that starts from the moment the feasibility of pregnancy is confirmed by verifying the presence of a gestational sac in the uterine cavity with an embryo showing cardiac activity until 13 weeks + 6 days of gestation.

OBJECTIVE

The purpose of this Guideline is to provide recommendations that may assist in the decision-making regarding the use of ultrasound in pregnant patients during the first trimester.

METHODS

The recommendations in this Guideline will be based on a systematic review of the literature guided by questions based on real-life scenarios. We selected four questions considered essential for the formulation of recommendations.

We will consider eligible mainly randomized clinical trials and systematic reviews of randomized clinical trials; however, controlled observational studies, "before and after" studies, and guidelines will also be considered acceptable when intervention studies with these designs are not available. The MEDLINE via PubMed and CENTRAL (Cochrane) databases will be searched using specific search strategies (Table 1).

TABLE 1. SEARCH STRATEGIES USED IN THE MEDLINE AND CENTRAL DATABASES

Database	Strategy
MEDLINE via PubMed	(Pregnancy Trimester, First OR First Trimester OR Phases, Early Placental OR Pregnancy Trimesters, First OR First Pregnancy Trimester OR Pregnancies, First Trimester) AND (Ultrasonography OR Echography OR Ultrasonic Diagnoses).
CENTRAL (Cochrane)	Pregnancy AND first trimester AND (Ultrasonography OR ultrasound)

The search period will comprise from the inception of the database until August 2019, without language restrictions. Three independent researchers (G.R.A., R.S.S., and W.M.B.) will analyze the publications retrieved based on their titles and abstracts. Cases of disagreement will be resolved by consensus. The risk of bias in clinical trials will be assessed using the tool proposed by the Cochrane Collaboration[2]. Systematic reviews will be assessed using the AMSTAR tool[3], and guidelines using the AGREE II instrument[4].

The evidence was evaluated according to the Oxford classification[5], which establishes the strength of evidence-based on the study design chosen.

Grades for recommendation and levels of evidence:

A: Experimental or observational studies of higher consistency.

B: Experimental or observational studies of lower consistency.

C: Uncontrolled studies/case reports.

D: Opinion deprived of critical evaluation, based on consensus, physiological studies, or animal models.

Conflict of interest

No conflict of interest was declared by the participants in the preparation of this guideline.

What is the goal of first-trimester ultrasound?

In recent years, first-trimester ultrasound has played a crucial role not only for assessing fetal viability and determining the gestational age but also as a screening tool for the identification of chromosomal abnormalities by measuring the thickness of the nuchal translucency (NT)[6] (A). In addition, several studies have demonstrated the capacity of the examination, in the first trimester, to identify more than 80% of the main congenital fetal malformations unrelated to chromosomopathies, with sensitivity between 12.5 and 83.7%[7,8] (A). It has also been described how some ultrasound markers used for combined testing (such as augmented NT, reverse flow in the ductus venosus, tricuspid regurgitation, absence of internal translucency) can be correlated with the presence of anatomic malformations.

First-trimester ultrasound is used to confirm the feasibility of the gestation, establish the gestational age with accuracy, determine the number of fetuses, and, in the presence of a multiple pregnancy, assess chorionicity and amnionicity. Ultrasound also provides the opportunity to detect severe fetal anomalies and, in health systems that track aneuploidy, it is possible to measure the thickness of the nuchal translucency (NT). It is recognized, however, that many severe malformations can develop later in pregnancy, or may not be detected in this period even with adequate equipment and by experienced professionals[9] (A).

When should first-trimester ultrasound be used?

There is no reason to use first-trimester ultrasound as a routine examination only to confirm pregnancy in the absence of any risk factors. However, when indicated, it must be used between 11 and 13 weeks + 6 days, since it would provide an opportunity to check the objectives presented above, selecting cases that should be referred for invasive examinations (e.g. chorionic villus or amniocentesis biopsy) to obtain diagnostic confirmation by karyotype. Before starting the examination, the physician should inform the pregnant woman and/or couple of the possible benefits and limitations of first-trimester ultrasound[9] (A).

What is the safety of Doppler ultrasonography in the 1st trimester?

For safety reasons, the use of Doppler is not indicated during a routine examination. Doppler ultrasound is associated with higher energy production and, consequently, greater potential biological effect, particularly when applied to a small region of interest[10,11] (A).

Doppler examinations should be used *in the first trimester only if clinically indicated*[9] (A). The main reason for defending the *use of Doppler with caution* at the beginning of pregnancy is not because we know that it causes damage, but because we do not know if it is safe and the first quarter is a particularly vulnerable period of fetal life.

What is the value of Doppler ultrasonography in the 1st trimester in predicting and identifying preeclampsia (PE)?

The efforts to effectively predict PE in the first trimester of pregnancy is motivated by the desire to identify women who are at high risk of developing PE to ensure that the necessary precautions can be taken early to improve placentation and, thus, prevent or at least reduce the frequency of its occurrence. In addition, the identification of a group "at-risk" will allow tailored pre-natal monitoring to anticipate and recognize the onset of clinical syndrome and manage it immediately.

The increase in perception of the pathophysiology of PE is reflected in the current screening strategies, which are based on the history, demographic data, biomarkers (including blood pressure), and uterine artery Doppler.

Considering that the *ultrasound screening* for PE should not be removed from the general concept of prenatal care, professionals who carry out this screening should have up-to-date knowledge about the proven risk factors for PE and seek to identify them during the screening.

A *global risk assessment for PE should cover four broad areas*[12] (A), including:
- Personal risk profile (including age, ethnicity, parity, smoking, obstetric and medical history, and method of conception);
- Metabolic risk profile [including body mass index (BMI) and history of diabetes];
- Cardiovascular risk profile (including existing cardiovascular conditions and measurement of the mean arterial pressure);
- Placental risk profile (including uterine artery Doppler and maternal serum biomarkers).

The use of ultrasound as a tool for screening/predicting PE is based on the fact that the faulty placentation results in an incomplete transformation of the spiral arteries. Villous and vascular histopathological lesions of the placenta are four to seven times more common in pregnancies with PE than in pregnancies without PE[13] (A) and are associated with greater resistance to blood flow in the uterine artery[14] (A). The measurement of impedance (or resistance) to the flow in the uterine arteries by Doppler assessment makes the incomplete transformation of spiral arteries quantifiable.

Combined screening [including maternal factors, mean maternal arterial pressure (MAP), uterine artery Doppler, and serum level of placental growth factor (PLGF- an angiogenic protein produced by the placenta, whose synthesis is decreased in women with a high risk of pre-eclampsia] at 11-13 weeks seems to be the most effective screening model for identifying women at risk of PE[15] (A).

When it is not possible to measure the PLGF and/or UTPI (uterine artery pulsatility index), the initial screening test should be a combination of maternal risk factors with maternal risk with MAP, and not only maternal risk factors[15] (A). The risk calculator is available for free at: https://fetalmedicine.org/research/assess/preeclampsia/First

Measurement of biochemical markers: for screening in the first trimester, the best biochemical marker is the PLGF. Plasma A protein associated with pregnancy (PAPP-A), with results commonly expressed in multiples of the median (MoMs), is useful if measurements of PLGF and UTPI are not available.

Recommendations
For ultrasound in the first trimester of pregnancy:
- There is no reason for using it as a routine examination only to confirm pregnancy, in the absence of any risk factors. (A)
- When indicated, it must be used between 11 weeks and 13 weeks + 6 days. (A)
- It is a screening tool to identify chromosomal anomalies.
- It identifies over 80% of the main fetal malformations unrelated to chromosomopathies, with sensitivity between 12.5 and 83.7%. (A)
- Some ultrasound markers used for combined testing can be correlated with the presence of anatomic malformations. (A)
- Many severe malformations can develop later in pregnancy or may not be detected during this period by US. (A)

For Doppler ultrasound in the first trimester of pregnancy:

For safety reasons, it is not indicated during a routine examination. (A)

Combined screening including maternal factors, mean maternal arterial pressure, uterine artery Doppler, and serum level of placental growth factor at 11-13 weeks seems to be the most effective screening model for identifying women at risk of PE. (A)

When it is not possible to measure the PLGF (best biochemical marker) and/or UTPI, the initial screening test for PE should be a combination of maternal risk factors with MAP and not only maternal risk factors. (A)

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Autoimmune encephalitis (AIE)

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QUESTION: In autoimmune encephalitis, is the treatment with immunoglobulins better than the conventionally used corticosteroids or plasmapheresis?[1]

Answer: The evidence available comparing corticosteroids with immunoglobulin in the treatment of patients with clinical symptoms of paraneoplastic encephalitis is limited and of poor quality, with few patients studied through case reports and observational cohorts. Therefore, there is no consistent evidence currently available that allows us to estimate the benefits and/or the risks from the use of immunoglobulin in comparison to the current use of corticosteroids in these patients.

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Centers of physical activities and health promotion during the COVID-19 pandemic

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INTRODUCTION

In December 2019, in Wuhan, Hubei province in China, severe cases of pneumonia of unknown cause were reported and spread rapidly across several countries worldwide, generating a global crisis[1-5]. Thus, in view of the increase in the number of cases throughout the world, on 11 March 2020, the World Health Organization (WHO) declared the new Coronavirus (COVID-19) outbreak a global pandemic. This led many countries to close their borders and impose long periods of restrictions (quarantine and lockdown) or partial restrictions (flexibilization of activities) to their inhabitants[6,7].

Scientific evidence suggests that COVID-19 is transmitted from person to person, this being the most likely route of virus spread, through direct transmission through respiratory droplets between people when infectious droplets produced by sneezing, coughing, speaking, or simply exhaling reach the mucous (mouth and nose) or conjunctiva (eyes) membranes of another person[8,9]. Another explanation for the transmission of the virus would be by indirect means, perhaps resulting from the contamination of objects and/or airborne transmissions of the virus in confined spaces and/or spread by infected

asymptomatic individuals[10-12]. It is noteworthy that the contagion occurs mainly by respiratory droplets and close contact; however, these modes of transmission do not explain all cases of COVID-19 contagion[13].

To combat the proliferation of this disease, most nations adopted a so-called "social distancing" of approximately 1.5-2 m to be maintained between individuals, as well as the closure of several businesses. As a result, local authorities ordered the closing of shops, restaurants, bars, theaters, concert halls, and indoor physical activities centers, such as gyms, CrossFit studios, and others, as well as outdoor physical activities venues, such as parks, avenues, squares, and others[14].

In this case, it is necessary to reflect on this scenario of the pandemic and closure of physical activity centers because when analyzing the clinical course and risk factors for COVID- 19 it is possible to identify it as incomplete, especially for people who are not part of any risk groups[15.16]. Epidemiological data on COVID-19 indicate that comorbidities such as hypertension, respiratory, cardiovascular, metabolic, and immune diseases, in addition to an advanced age are classified as important risk factors for the severity of COVID-19[17.18].

The current literature emphasizes that physical inactivity produces adverse effects on health, contributing to the emergence of risk factors associated with COVID-19[19-21]. Therefore, the need to maintain a good level of physical activity as a protective measure is highlighted. In addition, physical exercise is associated with an increase in immunity and may be useful in the prevention of infections and in complementary treatments for chronically ill patients[22.23].

It seems that the world has forgotten that it has faced other pandemics before and, with greater emphasis, needs now to fight another pandemic, of a different nature, represented by physical inactivity and sedentary habits[24-26]. According to the WHO[27], in Brasil alone, sedentary-lifestyle related diseases kill 300,000 individuals yearly, and, worldwide, there are approximately 3.2 million annual deaths due to this behavior that is detrimental to the health and quality of life of the population.

Considering the above, we present the following question: why is it that, in some countries, physical activity centers remain closed? WHO[27] encourages the maintenance of regular physical activity practice as a strategy for health promotion. Thus, our objective is to elucidate, through scientific evidence, the importance and possibilities of reopening indoor and outdoor physical activities centers to improve and maintain the health and the quality of life of the population.

Possibilities for Reopening Indoor and Outdoor Physical Activity Centers during the COVID-19 pandemic

The quarantine and social distancing were initially the best options to understand the clinical and epidemiological aspects of the disease, in addition to stopping the spread of the virus. However, prolonged isolation, coupled with the closure of indoor and outdoor physical activity centers, implies a radical change in lifestyle, generating negative consequences to the health and quality of life of the population, particularly those in risk groups[28].

In fact, the Brazilian Society of Exercise and Sports Medicine (SBMEE), in partnership with the Brazilian Society of Endocrinology and Metabolism (SBEM), Brazilian Society of Diabetes (SBD), and the Brazilian Association for the Study of Obesity and Metabolic Syndrome (ABESO), assessed that the outdoor exercises, in parks, avenues and other outdoor physical activities venues are allowed, provided that some measures are observed and the recommendations on health and sanitation of local authorities are observed, which may vary between states and even cities[29]. In addition, in point of view published by Brazilian researchers, it has been suggested that outdoor physical activities should be recognized as essential during the COVID-19 pandemic[30].

Blocken et al.[14] conducted a streamlined study investigating whether a person, when approaching another person at a distance of 1.5 m or more, could cause a transfer of droplets to this second person. Simulations were made by Computational Fluid Dynamics (CFD) in a wind tunnel, previously validated and calibrated with measurements for droplet movement and evaporation and airflow around a runner, with the movement of droplets produced by a person who breathes or walks beside another person walking or running nearby.

The study concluded that, in the absence of headwind, tailwind, and crosswind, when walking fast at 4.0 km/h, this distance is around 5 m, and when running at 14.4 km/h, it is around 10 m. Based on this information, countries like Spain and France, in the first week of May, allowed their citizens to leave home to practice outdoor physical exercises, respecting a schedule that separated groups at greatest risk from others[14].

According to Blocken et al.[14], indoor physical activity centers are places that provide equipment and

specific services for the regular practice of physical exercises. Their equipment and services can cover a wide range of physical activities such as: I. equipment for aerobic exercises with stationary exercise bikes, treadmills, rowing machines, and elliptical machines; II. isodynamic (machines) and alodynamic (free weights) equipment[31]; III. Group exercise services in which coaches or instructors teach classes of aerobics, cycling/spinning, step, yoga, Pilates, stretching, and other group activities in general, and IV; Additional facilities, such as racing tracks, various sports courts, boxing rings, swimming pools, and alternative spaces. The aforementioned authors highlight categories I, II, and III, noting that the people who perform these exercises remain stationary during the practice.

That are no questions regarding the role of regular physical activity in health promotion and in the quality of life of the population, as presented in the Sustainable Development Goals of the United Nations (UN)[32] - Figure 1. For many years, even in difficult times, such as this we are currently experiencing with the COVID-19 pandemic, physical activity has had and still has an important role in maintaining the quality of life of the population[20,33-35]. However, even with all these contributions to the health and quality of life, several countries are still keeping their indoor and outdoor physical activity centers closed, preventing the practice of regular physical activity by the population, making it more difficult for people to cope with the impact caused by the COVID-19 pandemic[36].

Nevertheless, in general, government authorities are allowing a gradual reopening of commercial activities, through the use of health and sanitation protocols, and the indoor and outdoor physical activity centers the last in line to be authorized to reopen. Given this scenario, to provide adequate conditions for the operation of the indoor physical activity centers, it would be necessary to create a safety certificate, issued by health departments and technical regulators, aiming to provide safety to practitioners during the COVID-19 pandemic, as well as TO allow that indoor physical activity centers can remain open safely during the hypothetical upcoming waves of COVID-19, as well as in future pandemics[14].

International sports organizations such as the Dutch Olympic Committee (NOC) and the Dutch Sports Federation (NSF), which are regulatory organizations for all sports activities, professional and recreational, in the Netherlands, issued a Protocol for responsible exercising[37]. The biosafety protocol contains a detailed list of protective measures and precautions for physical activities that do not involve physical contact between people[38].

The protocol is divided into four categories: I. Operators, II. Practitioners, III. Staff, and IV. Suppliers, highlighting that all measures for hygiene and respiratory etiquette established so far remain applicable, among them: the use of masks; maintaining a physical distance of 1.5 m at all times; when coughing or sneezing, covering the nose and mouth using the arm or

FIGURE 1. CONTRIBUTIONS OF PHYSICAL ACTIVITY TO SEVERAL OF THE SUSTAINABLE DEVELOPMENT GOALS OF THE UNITED NATIONS[32].

elbow fold, or, when a tissue paper is used, discarding it immediately in the trash; washing your hands with soap and water several times a day, or disinfect them with an aseptic solution of alcohol (alcohol gel 70%); not sharing personal items; staying home after having tested positive for the virus; staying home when presenting at least one of the typical symptoms; staying home when one of you family members and/or housemates tests positive for the virus; and staying home when one of your family members and/or housemates has a fever (temperature equal to or higher than 38ºC) or a feeling of tightness on the chest and/or shortness of breath[37,38].

By following this protocol, operators would control the maximum number of practitioners in the facilities of physical activity centers, provide masks, gloves, and goggles for the staff, provide alcohol gel 70% for the staff and practitioners. Likewise, the operators are responsible for overseeing the periodic cleaning of spaces with a greater flow of people and equipment, as well as the intensive cleaning of bathrooms, in addition to door handles and other surfaces, as well as measuring the temperature of staff members, collaborators, and practitioners at the entry, and also monitoring the actions of staff members and practitioners so guarantee they meet the biosecurity protocols. They also would be responsible for the demarcations between the pieces of equipment and spaces, in order to meet the distancing measures. It is also important to highlight that, in general, meeting the physical distance of 1.5 m is usually not a problem since many of the exercise machines already take up considerable space[37,38].

Indoor physical activity centers should inform the practitioners that, when using the drinking fountains, they should avoid direct contact with the surface, thus encouraging each practitioner to use their own bottle; a paper towel should be used at the end of the operation, with the possibility of disposal in a waste collector that does not require manual contact. Subsequently, hand hygiene must be completed using alcohol gel 70%. In the event that it is not possible to comply with these guidelines, it is recommended to deactivate the drinking fountains[37-39].

It is recommended that the staff and practitioners, in common areas (parking lots, internal access areas, cafeterias, and etc...), wear a mask, and alcohol gel 70% must be available on each table or countertop, respecting the minimum distance of 1.5m; these are also requirements that must be met by the operators[37-39].

For each indoor space, the maximum number of practitioners should be determined taking into account the peculiarities of each space, such as ventilation and proposed activities. It is recommended to have a compulsory reservation of time slots, respecting the maximum number of people allowed in a given time, avoiding public transportation, if possible, use sanitary facilities at home and not in the center, start training only after washing hands, observing the minimum distance of 1.5m, avoid greeting others with handshakes, kisses, and hugs, and leaving the center immediately after completing the physical activity[37,38].

Regarding the use of masks by practitioners of physical activity, operators, staff members, and other persons who attend the centers, it is worth mentioning that a distinction must be made between the different types of masks and their effectiveness. Scientific evidence[40-42] suggests that all types of masks have reduced exposure to aerosols and respiratory droplets, proving to be relatively stable over time regarding wear and not being affected by the duration and type of activity, remembering that there is a degree of variation of effectiveness according to the type of mask.

It is necessary to highlight that the use of masks has been the subject of debates across several countries worldwide, with various radical statements for and against their use and regarding their usefulness in various situations. However, there is an agreement when it comes to protection since all the different types of masks have some protective effect. Another important issue concerns the feeling of safety and freedom that the mask provides the population, allowing them to perform daily activities[40-49]. Regarding the use of masks and their effectiveness for practitioners of indoor physical activity, Van der Sande et al.[42] highlight the possibility of creating specific masks to meet the needs of different sports activities without compromising their protective effects against droplets and aerosols and being resistant to sweat without compromising the respiratory flow.

It is recommended that staff members are able to perform their activities from home, remaining home as much as possible, following recommended hygiene protocols, not sharing personal or professional utensils with other staff members, and keeping the environment and work tools clean and disinfected. For suppliers, a time must be established for deliveries, preferably before the opening and first disinfection of the facilities and equipment and/or after the closing of

the center. All individuals must wear gloves, announce where the goods are to be placed, and, if possible, completing prior disinfection of the goods[32].

Considering all these recommendations based on scientific evidence, another question that can be presented is: if indoor physical activity centers are closed, would not the sweat produced by practitioners have the potential for airborne and respiratory droplets transmission of the virus? In this case, we must highlight that the main mode of transmission is direct, i.e., from person to person, through direct contact or droplets spread by the coughing and/or sneezing of an infected individual or by contact with sweat on machines, free weights, benches, treadmills, and bicycles, in which case by performing the disinfection of sites and equipment periodically it is possible to avoid this mode of transmission[38].

Scientific evidence has shown that temperature and humidity have proven useful to avoid or spread the virus[50,51]. Wang et al.[51] highlighted in their study that high temperatures and high humidity reduce the transmission of COVID-19. In the case of indoor physical activity centers, it is recommended to keep spaces open and/or with temperatures above 22 degrees Celsius and humidity between 50% and 80%, measures that have had effective results in reducing contamination[50].

Another matter that deserves attention is the type of ventilation of indoor physical activity centers, highlighting that ventilation is the process by which "clean" air (usually outside air) is intentionally supplied to a space and stale air is removed, a process that can be carried out by natural or mechanical means[52].

Research carried out by Ai e Melikov[53] reviewed studies on the propagation area of exhaled droplets between occupants of closed spaces, focusing specifically on the dissemination of droplet nuclei from mouth/nose and nose/mouth for non-specific diseases. They emphasized the importance of internal airflow patterns and indicated that future research is necessary on three specific areas: the importance of internal airflow pattern direction, the dynamics of air transmission, and the application of Computational Fluid Dynamics (CFD) simulations.

In view of the COVID-19 pandemic, the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) acknowledged the potential for transmission of aerosols that transmit COVID-19 and stated that facilities of all types should follow, at least, the latest standards and guidelines published and good engineering practices[54]. The ASHRAE standard 62.1 specifies the ventilation rates for a better indoor air quality, which are acceptable for indoor physical activity centers like gyms[55].

Therefore, it is possible to see how important it is that every protocol, when deployed, is consistently deployed and the compliance of participants monitored regarding the sanitary measures contained therein since individual responsibilities are not more important than the common welfare.

CONCLUSIONS

As mentioned at the beginning of the article, when analyzing the clinical course and risk factors for COVID-19, we identified that several matters around the practice of physical activities during the current pandemic require a more in-depth approach. It is necessary to consider the positive effects of these activities in the general population, according to their degree of risk and comorbidities. One thing is for sure based on scientific evidence: the prophylactic and therapeutic effects of regular physical activity on the health and quality of life of the population.

Thus, we believe that, based on the evidence presented in this study, it would be possible to reopen indoor and outdoor physical activity centers safely, through certifications issued by technical and health organizations, while respecting the existing biosecurity measures. Aiming not to interrupt or completely change the lifestyle of individuals during the COVID-19 pandemic and allowing them to maintain an active lifestyle, which is very important for the health of the population in general. Particularly for individuals in risk groups, people must follow the determinations of the health authorities and practice physical activities at home guided by a physical education professional duly qualified and authorized.

Conflicts of interest

The researchers involved in the work declare there are no conflicts of interest.

Acknowledgments

Author's Contribution

All authors have contributed equally to the work.

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Renal changes in COVID-19 infection

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SUMMARY

The COVID-19 (SARS-CoV-2) infection started in China, Wuhan City, Hubei Province, in December 2019, and it was declared a pandemic in mid-March 2020, caused by a new coronavirus strain called SARS-CoV-2. The pathogenesis of kidney injury attributed to SARS-CoV-2 is not well defined yet. Observations show that the kidney damage caused by the new virus mutation is mainly tubular, with impairment of glomerular filtration and high levels of urea and creatinine. A study with seriously ill patients with COVID-19 showed that acute kidney injury was present in 29%. In the face of this evidence, based on recent studies, we can see the great renal contribution as an impact factor in the evolution of COVID-19, not just as a complicator of severity, but maybe part of the initial cascade of the process, requiring a deeper analysis using conventional biomarkers of kidney injury and more aggressive clinical intervention in patients at risk, in an attempt to reduce mortality.

KEYWORDS: Acute kidney injury. Infections. Coronavirus Infections/physiopathology. Betacoronavirus.

INTRODUCTION

The COVID-19 (SARS-CoV-2) infection started in China, Wuhan City, Hubei Province, in December 2019, and it was declared a pandemic in mid-March 2020, caused by a new coronavirus strain called SARS-CoV-2, with single-stranded RNA, positive sense and characterized by the initial appearance of a respiratory syndrome, ranging from a simple flu-like syndrome to severe respiratory insufficiency, with a high mortality rate in specific groups. It constitutes an entity with a strong impact on human health, with more than 2 million people affected, thus requiring efforts in understanding its diagnosis and therapy. Despite the greater respiratory, immune, and hematopoietic impairment, other organs seem to be involved, among them, the renal and cardiovascular system are not only part of the inflammatory storm, but also intrinsic targets of the virus. Heart failure and acute kidney injury are complications widely described in patients with more severe disease progression and requiring intensive care, in most reports.

DISCUSSION

The pathogenesis of kidney injury attributed to SARS-CoV-2 is not well defined yet, but it seems to be multifactorial, involving mechanisms related to systemic hypoxia, coagulation abnormalities, sepsis, with a high release of cytokines, or even cell destruction due to virosis[1]. The virus shows tropism by the angiotensin 2-converting enzyme receptor (ACE 2), connecting to it through protein S (Spike protein), present in its skeleton, which promotes its entry into the cell and its cytopathic action. Besides that, the virus has an inhibitory effect on the enzyme, interfering in cytoprotective actions. This receptor is expressed in the lungs, kidneys, heart, and intestine. In the kidneys, it is found mainly in the proximal tubules and podocytes and in an amount 100 times greater than in the lungs; however, without description in the glomerulus or mesangium. Unlike SARS-CoV, which occurred in 2002, when it was suggested that renal impairment would probably be related to multiple organ failure, in SARS-CoV-2, the viral capsid nucleus protein was examined in situ post-mortem in the kidney, and it was discovered that the SARS-CoV-2 antigens accumulated in the renal tubules, suggesting that SARS-CoV-2 directly infects the human kidney, inducing acute kidney injury (AKI) and contributing to viral spread in the body. At light microscopy, diffuse proximal tubular lesion, loss of brush border, non-isometric vacuolar degeneration, and even frank necrosis were observed. There was no description of vasculitis, interstitial inflammation, or hemorrhage[2]. The difference between the greater renal tropism of SARS-CoV-2 in relation to SARS-CoV can be explained by the increased affinity of SARS-CoV-2 with ACE2, allowing greater infection of the kidney, which can act as viral reservoir[3-5]. Previous studies have also shown that the SARS-CoV-2 infection can induce lymphopenia and, simultaneously, increase the number of inflammatory cytokines (cytokine storm)[6]. The AKI has been described in previous studies of SARS and MERS-CoV infections with occurrence in 5-15% of the cases, and mortality of 60-90% in that group. In COVID-19, an average incidence of 3-9% of AKI has been reported but maintaining a still high mortality rate and suggesting an important role of renal impairment and in the evolution of the disease, as well as alerting the need for early screening for renal changes[1]. Observations show that the kidney damage caused by the new virus mutation is mainly tubular, with impairment of glomerular filtration and high levels of urea and creatinine[7,8]. A study of 701 patients with COVID-19 from Tongji Hospital, affiliated with the University's Tongji School of Medicine Huazhong Science and Technology Institute, showed that 44% of patients had proteinuria and hematuria, 26.9% had hematuria alone, 14.1% had an increase in nitrogen slags, and 3.2% met Kidney Disease Improving Global Outcomes (KDIGO) criteria for acute kidney injury. The authors concluded that kidney damage was an independent risk factor for death and that the greater the proteinuria and hematuria, the greater the risk of death[5]. Another study with 58 seriously ill patients with COVID-19 showed that acute kidney injury was present in 29%[9]. In New York, 1,150 patients were observed for a period of 30 days (03/02/2020 to 04/01/2020) and showed that 257 (22%) had critical status, with 29% of these evolving to AKI and renal replacement therapy[10]. In Wuhan, an observational study with 147 patients with severe respiratory failure who evolved to AKI presented, by Cox's univariate analysis, risk of death 5.3 times greater than those without kidney injury[11].

CONCLUSION

In the face the evidence presented, based on recent studies, we can see the great renal contribution as an impact factor in the evolution of COVID-19, not just as a complicator of severity, but maybe as part of the initial cascade of the process, requiring a deeper investigation using conventional biomarkers of kidney injury and more aggressive clinical intervention in patients at risk, in an attempt to reduce mortality through the optimization of hemodynamics, research of drugs with evidence of nephroprotective action, immunomodulators, in addition to the guidelines already established for patient management.

Author's Contribution
All authors have contributed equally to the work

RESUMO

Infecção pelo COVID-19 (SARS-CoV-2) começou na China, cidade de Wuhan, província de Hubei, em dezembro de 2019, e foi declarada pandemia em meados de março de 2020, causada por uma nova cepa de coronavírus chamada SARS-CoV-2. A patogênese da lesão renal atribuída à SARS-CoV-2 ainda não está bem definida. Observações mostram que o dano renal causado pela nova mutação viral é principalmente tubular, com comprometimento da filtração glomerular e apresentação de altos níveis de uréia e creatinina. Estudo com pacientes gravemente enfermos com COVID-19 mostrou que a lesão renal aguda estava presente em 29%. Diante dessas evidências, com base em estudos recentes, podemos ver a grande contribuição renal como um fator de impacto na evolução do COVID-19, não apenas como um complicador da gravidade, mas talvez como parte da cascata inicial do processo, exigindo uma investigação de análise mais profunda usando biomarcadores convencionais de lesão renal e intervenção clínica mais agressiva em pacientes em risco, na tentativa de reduzir a mortalidade.

PALAVRAS-CHAVE: *Lesal renal aguda. Infecções. Infecções por coronavirus/fisiopatologia. Betacoronavirus.*

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The hidden prevalence of leprosy: a comparative study between two Brazilian cities

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SUMMARY

OBJECTIVE: *We compared the hidden prevalence of leprosy in two Brazilian cities with distinct differences regarding geographic region and socio-economic development profile, namely, Juazeiro, Bahia and Joinville, Santa Catarina.*

METHODS: *A retrospective epidemiological study based on secondary data obtained from leprosy case notifications in the cities of Juazeiro-BA and Joinville-SC, 2007-2017. To calculate hidden prevalence, we used the method proposed by Gil Suárez and Lombardi.*

RESULTS: *Joinville had 105 cases of leprosy that went undiagnosed (addition of 42.0% to the registered prevalence). For Juazeiro, it was estimated that 295 cases went undiagnosed (addition of 18.9%).*

CONCLUSION: *Joinville presents a higher hidden prevalence than Juazeiro.*

KEYWORDS: *Leprosy. Epidemiology. Cross-sectional studies. Prevalence.*

INTRODUCTION

Leprosy is an infectious, chronic, neglected disease, whose etiological agent is *Mycobacterium leprae*. It is an obligate intracellular parasite with an affinity for the skin and peripheral nerves, causing dermatological and neurological lesions and deformities, depending on the immunogenic potential of the bacillus and the human organism's response time[1].

Brasil holds the first place worldwide in detection coefficient and the second place in absolute number of new registered cases, after India. In 2016, there were 214,783 new cases of leprosy worldwide, which represents a detection rate of 2.9/100,000 population, according to the WHO. This year, Brasil reported 25,218 new cases, with a detection rate of

12.2/100,000 population. The country is thus classified as highly endemic[2,3]. Over the past decades, there has been an effort by the Brazilian government to diminish the disease's impact; however, in the Northeast, North, and Central-West Regions, epidemiological indicators demonstrate that the disease is far from being eliminated as a public health problem[3,4].

When analyzing the history of leprosy in Brasil, it is possible to observe that, although there has been an important reduction in the prevalence of the disease, the rate of detection has not effectively diminished. This reality is explained by the hidden endemic, the deficiency of public assistance programs, the precarious state of public health services, treatment abandonment, low level of public awareness, late diagnosis, the advent of sequelae and, consequently, the high burden of social prejudice which accompanies the disease[5]. It is believed that, to this day in Brasil, approximately one-third of notified patients with leprosy receive irregular treatment or abandon treatment, thus developing bacilli that are resistant to medication[6].

In the state of Bahia, in 2015, 2,548 new cases of leprosy were reported, with a detection coefficient of 16.76 new cases/100,000 population[7]. In the same year, in the state of Santa Catarina, 171 new cases were reported, with a detection coefficient of 2.51/100,000 population[8]. In 2015, 133 new cases were notified in the city of Juazeiro, Bahia, with a detection coefficient of 60.92/100,000 population, and 20 new cases were notified in Joinville, Santa Catarina (3.56/100,000 population). Thus, according to the parameters indicated by the Ministry of Health, Juazeiro has not yet reached the goal of eliminating leprosy as a public health problem; whereas in Joinville-SC, leprosy appears to be eliminated, that is, with a prevalence <1.0/10,000 [9].

The aim of this study is to compare the hidden prevalence of leprosy in the cities of Juazeiro, Bahia, and Joinville, Santa Catarina, 2007-2017.

METHODS

This is a retrospective epidemiological study based on secondary data obtained from leprosy case notifications in Brasil's Notifiable Diseases Information System (SINAN, acronym in Portuguese) and DATASUS, in the cities of Juazeiro, Bahia, and Joinville, Santa Catarina, from 2007 to 2017, to calculate the detection coefficient, percentage of cases with disability grades, and hidden prevalence.

The estimated hidden prevalence was calculated using the method proposed by Gil Suárez and Lombardi[10] and indicated by the PAHO and the WHO, which is based on the assumption that diagnoses of cases with physical disabilities indicate late detection and, thus, the presence of undiagnosed cases within a determined area. Accordingly, calculations are obtained using the following coefficients:

1. Annual percentage of cases with disability grades = cases with disability / cases evaluated.

2. Annual estimated hidden prevalence = new cases × percentage of cases with disabilities.

Forms used by healthcare professionals at the moment of patient diagnosis to evaluate the disability grade were filled out in accordance with the parameters stipulated by the Ministry of Health[9]. The following criteria were considered: grade 0, there is no neural involvement in the eyes, hands or feet; grade 1, there is a decrease or loss of sensation; and grade 2, presence of disabilities and deformities such as lagophthalmos, claws, bone resorption, drooping hands and feet, among others[9].

This study did not require approval from the ethics committee as it used open public domain data without the identification of individuals.

RESULTS

Between the years 2007 and 2017, in the city of Juazeiro, Bahia, 1,561 new cases of leprosy were notified, corresponding to an average detection coefficient of 65 cases/100,000 population. The detection coefficient in the general population decreased from 79.0/100,000, in 2007, to 51.9/100,000 in 2017. The proportion of individuals with physical disabilities was greater than 10% in all years of the time series, reaching 27.6% in 2008 (Figure 1).

The number of new cases of leprosy showed no large variations during the study period, with an arithmetic mean of 142 cases per year. During the study period, 208 (13.3%) patients were diagnosed with disability grade 1, and 81 (5.2%) were diagnosed with grade 2. Furthermore, 28 (1.8%) patients were not assessed for their disability grade at the time of diagnosis (Table 1).

When analyzing the percentage of cases of patients with disabilities in relation to the number of cases evaluated, the highest percentage of patients with some disability grade was observed in 2008, when 27% of the 159 new cases notified presented some degree of disability; on the other hand, in 2015, there was a

significant drop in the number of cases of patients diagnosed with disabilities which were registered in only 11.3% of the 133 new cases (Table 1).

Making use of the method proposed by Gil Suárez and Lombardi[10], it was estimated that approximately 295 cases of leprosy were not diagnosed and/or registered between the years of 2007 and 2017, in Juazeiro, Bahia. This number would represent an addition of 18.9% to the registered prevalence and would result in a real prevalence of 1,856 cases during the period. This result was obtained by the sum of the known prevalence (1,561 cases) and the hidden prevalence

FIGURE 1. DETECTION RATE IN GENERAL POPULATION (A) AND PERCENTAGE OF DISABLED PATIENTS - DEGREE 1 AND 2 (B) IN THE PERIOD FROM 2007 TO 2017 IN JUAZEIRO-BA AND JOINVILLE- SC.
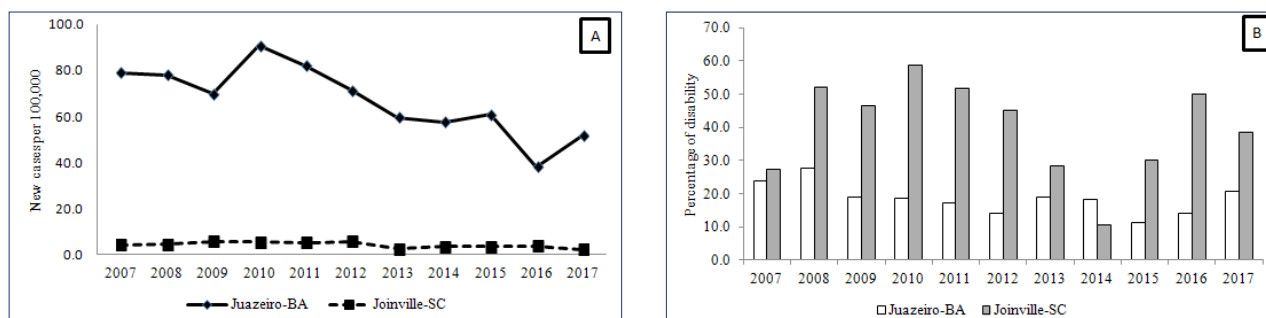
TABLE 1. NUMBER AND PERCENTAGE OF NEW CASES OF LEPROSY AND DEGREE OF DISABILITY FROM 2007 TO 2017 IN JUAZEIRO-BA AND JOINVILLE-SC.

(A) Juazeiro, Bahia					
Year of diagnosis	Degree zero	Degree 1	Degree 2	Not rated	Total
	n (%)	n (%)	n (%)	n (%)	
2007	117 (73.6)	34 (21.4)	3 (1.9)	5 (3.1)	159
2008	113 (71.1)	29 (18.2)	14 (8.8)	3 (1.9)	159
2009	115 (79.9)	20 (13.9)	7 (4.9)	2 (1.4)	144
2010	152 (80.4)	27 (14.3)	8 (4.2)	2 (1.1)	189
2011	142 (82.1)	23 (13.3)	7 (4.0)	1 (0.6)	173
2012	129 (84.9)	14 (9.2)	7 (4.6)	2 (1.3)	152
2013	98 (76.6)	12 (9.4)	11 (8.6)	7 (5.5)	128
2014	99 (79.2)	191 (5.2)	3 (2.4)	4 (3.2)	125
2015	116 (87.2)	7 (5.3)	8 (6.0)	2 (1.5)	133
2016	72 (85.7)	8 (9.5)	4 (4.8)	0 (0.0)	84
2017	91(79.1)	15 (13.0)	9 (7.8)	0 (0.0)	115
Total	1244 (79.7)	208 (13.3)	81(5.2)	28 (1.8)	1561
(B) Joinville, Santa Catarina					
Year of diagnosis	Degree zero	Degree 1	Degree 2	Not Rated	Total
	n (%)	n (%)	n (%)	n (%)	
2007	16 (72.7)	3 (13.6)	3 (13.6)	0 (0.0)	22
2008	11(47.8)	8 (34.8)	4 (17.4)	0 (0.0)	23
2009	16 (53.3)	11 (36.7)	3 (10.0)	0 (0.0)	30
2010	11(37.9)	17 (58.6)	0 (0.0)	1 (3.5)	29
2011	13 (48.1)	13 (48.1)	1 (3.7)	0 (0.0)	27
2012	17 (54.8)	8 (25.8)	6 (19.4)	0 (0.0)	31
2013	9 (64.3)	2 (14.3)	2 (14.3)	1 (7.1)	14
2014	17 (89.5)	0 (0.0)	2 (10.5)	0 (0.0)	19
2015	13 (65.0)	4 (20.0)	2 (10.0)	1 (5.0)	20
2016	10 (45.5)	4 (18.2)	7 (31.8)	1 (4.5)	22
2017	8 (61.5)	3 (23.1)	2 (15.4)	0 (0.0)	13
Total	141(56.4)	73 (29.2)	32 (12.8)	4 (1.6)	250

Source: SINAN leprosy database, 2007-2017.

FIGURE 2. PERCENTAGE OF HINDDEN LEPROSY IN JUAZEIRO, BAHIA, AND JOINVILLE, SANTA CATARINA, IN THE PERIOD FROM 2007-2017
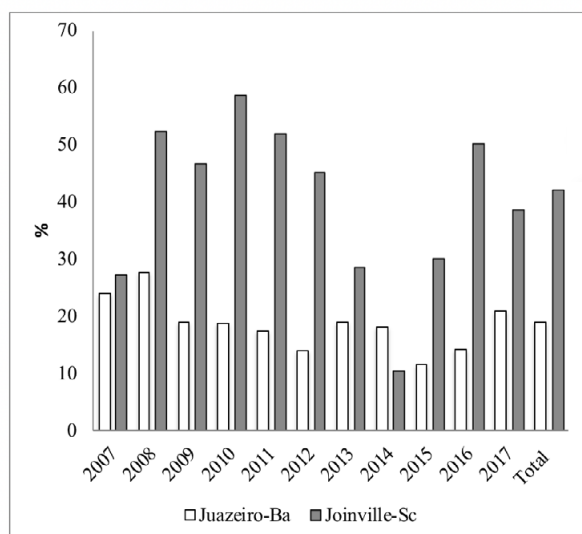
(295 cases). In this case, it is also possible to affirm that 15.9% of people affected with leprosy went undiagnosed and, therefore, untreated.

In Joinville-SC, 250 new cases of leprosy were registered with a detection coefficient of 4.28/100,000 population. Throughout the time series, the detection coefficient decreased from 4.4/ 100,000 in 2007 to 2.3/ 100,000 in 2017. The percentage of disabled people reached 58.6% of new diagnoses in 2010 (Figure 1). Additionally, during the study period, 105 (42.0%) patients were diagnosed with some disability grade, 73 (29.2%) patients with disability grade 1, and 32 (12.8%) with grade 2 (Table 1).

When calculating the hidden prevalence in Joinville by the method proposed by Gil Suárez and Lombardi[10], it was shown that 105 cases of leprosy went undiagnosed and/or unregistered between 2007 and 2017. This represents an addition of 42.0% to the registered prevalence and a real prevalence of 355 cases, making it possible to estimate that 29.6% of people affected with leprosy went undiagnosed and untreated during the period (Figure 2).

DISCUSSION

One of the problems which programs for controlling and combating leprosy face is that of determining the magnitude of the disease within their area in order to establish public policies capable of dealing with this serious problem. This study has shown evidence that the cities of Juazeiro, Bahia, and Joinville, Santa Catarina, although distinctly different in

terms of geographic location and economic and social situation, present detection coefficients which are, respectively, very high and average, as well as a high proportion of cases diagnosed with some disability grade, especially grade 1. The evaluation of physical disability grade is an essential procedure in the initial approach to patients receiving healthcare services for leprosy[11].

Considering that leprosy is an endemic disease in Brasil, the need for more efficient control strategies within national territory is clear. Examples of such strategies include increasing access to basic healthcare, qualifying professionals to recognize signs and symptoms of the pathology, and developing educational actions in healthcare that will make it possible to diagnose and treat more cases earlier[11]. The disease is usually associated with regions with low socio-economic indexes; however, the observation that Joinville presents a considerable detection rate and an elevated hidden prevalence is contrary to what would be expected, given that, according to municipal human development index (MHDI) data from 2012 to 2017, the city had a value of 0.809, which is considered very high by the United Nations (UN), and it held the 21st position in the ranking of Brazilian cities[12].

Juazeiro, on the other hand, presented an MHDI of 0.677, considered average, and it held the 2,503rd position in the ranking, during the same period[12]. Keeping in mind that the fundamental parameters of MHDI are per capita income, education, and life expectancy (characteristics of regions that are socio-economically well developed), Joinville could be considered a city with good health conditions[12]. A disease related to poverty would, thus, be expected to have lower rates of detection and hidden prevalence, in light of the high quality of life, more health information available to the public and, consequently, more access to services provided to the population[13].

Juazeiro is a reference center for the diagnosis of cases of leprosy, not only in the Vale do São Francisco Region, but also in the state of Bahia. It has, for a few decades, had a Regional Reference Center, where a leprosy specialist, dermatologist, physical therapist, and epidemiological surveillance team work together and are responsible for a significant part of diagnoses, as verified by the high detection coefficient and the high incidence observed in this article's data analysis and according to information from the local secretary of health[7,14]. As seen in the tables, the problem persists for a considerable percentage of patients who receive

a late diagnosis when they already present a disability grade, likely due to the absence of investment in health education by public institutions and to the rotation of the teams that have already been trained to manage this disease, which entails a delay in carrying out the diagnosis and early treatment. This problem ends up negatively influencing the context in which the disease is combated and eliminated, contributing to an increase in the incidence and rate of detection, given that untreated patients are important sources of transmission of the etiological agent[14].

In the state of Santa Catarina, Joinville is the city with the highest number of cases of leprosy. The municipality has a Municipal Sanitary Unit Leprosy Program, which provides care and treatment through the Unified Health System. The team that provides regional support is composed of medical doctors, nurses, psychologists, physical therapists, and social workers. In addition to this program that has been made available, the population also has access to healthcare in the form of diagnosis and treatment at Basic Healthcare Units, as well as home follow-up by community health agents, thus guaranteeing integral care. Notwithstanding the strategies developed in this municipality for combating the disease, gaps still exist, both on public healthcare services and due to the population's lack of knowledge regarding the disease[15].

In order to evaluate the health levels of a population, the absolute values of cases of a disease or injury should not be utilized, because they do not take the population size into consideration. For this reason, health indicators have been constructed in the form of ratios[15]. In this context, when analyzing the absolute values of the city of Joinville, a considerably lower number of cases was observed, with a prevalence rate of 0.12 per 10,000 population, which is considered low; in contrast, the average detection coefficient was

4.28 per 100,000 population, which classifies it as a medium endemic city[2,14]. Despite these coefficients, this city has a considerable hidden prevalence, as shown in the observed data. These values reflect problems on the operational level, showing that, notwithstanding efforts to eliminate the disease over the past decades, there have been irregularities in the work of the teams responsible for diagnosis and follow-up, both at the primary healthcare units and at the reference units[14]. In addition to this, many patients either do not know the signs and symptoms of this disease or they believe that it no longer exists, especially since this is a city with high socio-economic development. This, therefore, provides evidence of the need to continue investing in health policies in this region.

CONCLUSION

In relation to the panorama presented by these cities, we have observed a detection rate capable of impacting continuity of transmission in both areas, with a high hidden prevalence of the disease, especially in Joinville-SC. This means that it is necessary to undertake efforts not to relax disease control in these cities that have shown apparent decreases in the number of leprosy cases and to monitor closely areas where new cases with some disability grade are notified, given that these are, consequently, areas with a high hidden prevalence, in order to take steps, albeit at a late stage, toward the actual elimination of this disease as a public health problem.

Author's Contribution
All author's participated equaly in the concept development, study planning, data collection and analysis, discussion of the results, scientific drafting, as well as in the revision and approval of the final version of the work.

RESUMO

OBJETIVO: *Comparar a prevalência oculta de hanseníase entre duas cidades brasileiras com diferenças distintas quanto à região geográfica e perfil de desenvolvimento socioeconômico, como Juazeiro, Bahia e Joinville, Santa Catarina.*

MÉTODOS: *Estudo epidemiológico retrospectivo baseado em dados secundários obtidos nas notificações de casos de hanseníase nos municípios de Juazeiro-BA e Joinville-SC, 2007-2017. Para o cálculo da prevalência oculta foi utilizado o método proposto por Gil Suárez e Lombardi.*

RESULTADOS: *Joinville teve 105 casos de hanseníase que não foram diagnosticados no período (adição de 42,0% à prevalência registrada). Para Juazeiro, estimou-se que 295 casos não foram diagnosticados (adição de 18,9%).*

CONCLUSÃO: *Joinville apresentou maior prevalência oculta que Juazeiro.*

PALAVRAS-CHAVES: *Hanseníase. Epidemiologia. Estudos transversais. Prevalência.*

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Metachromatic leukodystrophy: pediatric presentation and the challenges of early diagnosis

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INTRODUCTION

Metachromatic leukodystrophy (MLD; OMIM 250100) is an autosomal recessive hereditary disease caused by a deficiency of the Arylsulfatase A (ARSA) enzyme and, more rarely, of Saposin B, which is responsible for the interaction with the sulfatide, allowing the ARSA to degrade it. Therefore, it is classified as a hereditary metabolic disorder that evolves with a reduction of sulfatide degradation. Initially, the disease was known as "diffuse cerebral sclerosis" and, in 1938, it was named "metachromatic leukodystrophy" and classified as a lipidosis in 1958 and 1959, based on the discovery of a high concentration of sulfatídes (3-O-Sulfogalactosylceramide) (Figure 1) demonstrated by Jatzkewitz and Austin[1,2].

ARSA deficiency causes metachromatic lipids to accumulate on the white matter of the central and peripheral nervous system, which is responsible for causing demyelination and may also affect organs

FIGURE 1. CHEMICAL STRUCTURE OF THE SULFATIDE (3-O-SULFOGALACTOSYLCERAMIDE).
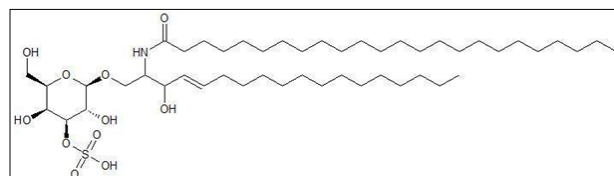
SOURCE: The authors, 2019.

such as the kidneys, gall bladder, spleen, and other visceral ones[1-3]. There are different variants (leading to different levels of residual enzymatic activity) and variations regarding the age of onset of the first symptoms and speed of disease progression, thus, it has been classified as: infantile (late infantile, 0 to 4 years), juvenile (4 to 15 years), and adult (over 15 years) (Annex 1)[3,4]. In addition, the diagnosis can be suspected when the patient begins to show signs of loss of intellectual,

cognitive, and/or motor abilities, and it is possible to confirm it based on the dosage of the ARSA enzyme and sulfatídes (Diagram 1)[3,5].

The infantile type (late infantile) usually manifests during the second year of life, with a gait disorder of sudden onset as well when the child begins to learn to walk[6]. Often, an orthopaedist is sought before the neurological manifestations appear. Strabismus, dysarthria, spasticity, and intellectual deterioration appear gradually. Coarse tremors or coarse abnormal movements (athetosis) of the extremities may appear. The deep tendon reflexes of the lower limbs are reduced or absent[7]. In addition, spasticity episodes may be triggered by any feeling of discomfort (including constipation or cholecystopathy) and may result in severe episodes of stiffness and shaking, crying, sweating, and fever of unknown origin. During the third and fourth years of life, there is a rapid progression of the disease with the onset of visual abnormalities, such as optic atrophy and progressive amblyopia[8,9].

The juvenile form, sometimes, can be divided into early and late[10]. The first is manifested between 4 to 6 years with abnormal gait and posture, emotional and behavioral disorders, ocular atrophy, and progressive spastic tetraparesis. The late juvenile type appears between the ages of 4 and 15 years, starting with more prominent behavioral abnormalities, poor school performance, and regression of language, followed by motor disorders and spastic tetraparesis that progresses more slowly[3,10]. Whereas in the adult type, two clinical presentations have been described: one was characterized mainly by signals from the central nervous system (pyramidal and cerebellar dystonia) and peripheral neuropathy, whereas the other clinical presentation begins with behavioral abnormalities, i.e., mood disorders, peculiar reactions in social interactions, progressive mental deterioration, and the presence of peripheral neuropathy may or may not be identified[11]. In these cases, an initial diagnosis of schizophrenia is established. Most of these patients

DIAGRAM 1. FLOWCHART FOR THE DIAGNOSIS OF METACHROMATIC LEUKODYSTROPHY.
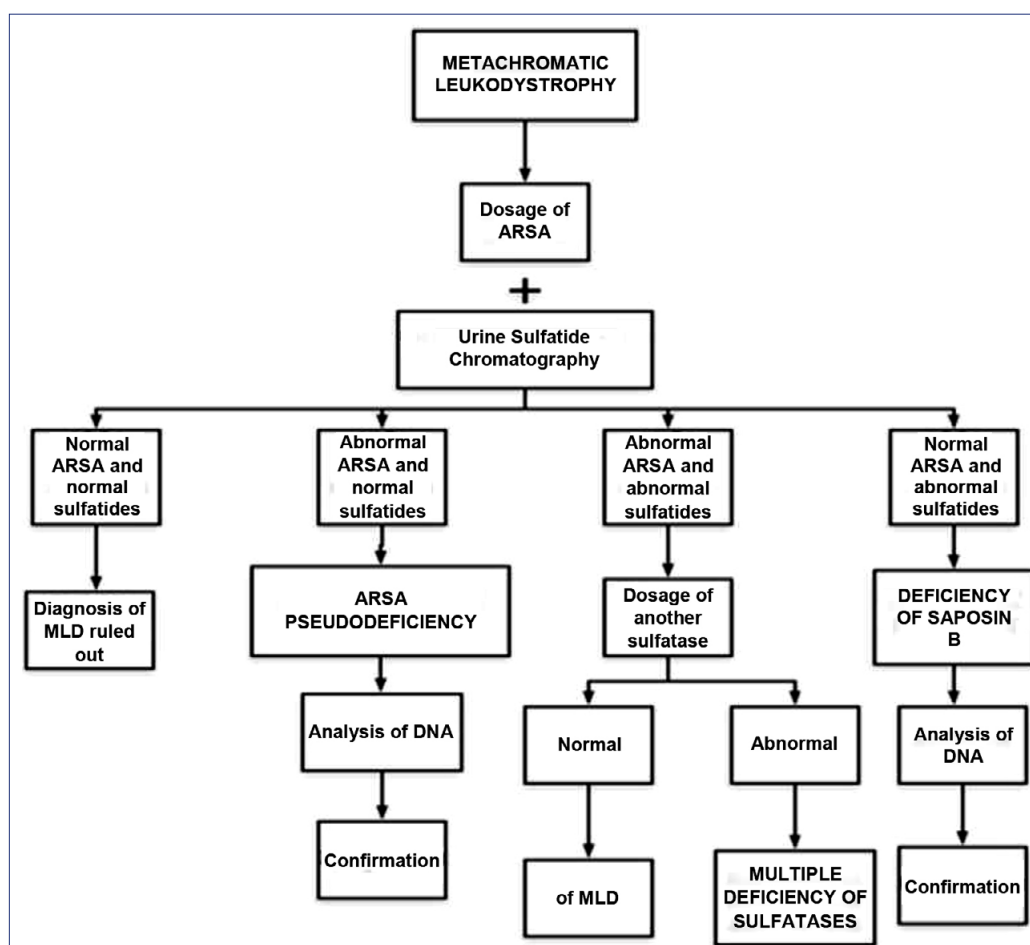
SOURCE: Adapted from Artigalas[3].

remain for several years without any other neurological symptom[11,12].

We report a case series of patients with infantile MLD whose diagnosis was late due to little knowledge about the signs and symptoms of this group of diseases by the medical community.

METHODS

Review of clinical, laboratory, and neuroradiologic data of the sample of patients affected by metachromatic leukodystrophy at a referral center for the treatment of rare diseases in the state of São Paulo.

RESULTS
Case 1

Male patient, 6 years old, son of non-consanguineous parents. Born by cesarean delivery, at full-term. Presented, at birth, APGAR 9 in the 1st minute and 10 in the 5th minute, weighed 2700g and head circumference of 35 cm (P50). At 2 years and 3 months, sought treatment with an orthopedist due to regression of gait associated with frequent falls and, at 3 years, started presenting regression of language and a complete inability to ambulate. Magnetic resonance imaging of the skull and an electroencephalogram (EEG) were requested, which presented the following abnormalities: abnormal white matter (diffuse alteration of myelinization with signs of axonal dysfunction and active myelin damage) and GEE compatible with diffuse encephalopathy. There was a suspicion of neurometabolic disease and, thereafter, exams were requested for the enzyme dosage of blood ARSA and the dosage of urine sulfatídes, which showed reduced activity of the ARSA enzyme and high concentrations of sulfatídes in urine, respectively. At 4 years and 4 months, the parents reported the onset of anorexia as a result of pneumonia, with the need for using gastrostomy in an attempt to improve the condition. Currently, the child weighs 11.3 kg and measures 93 cm, BMI of 13.06 kg/m² (P15), undergoes follow-up with a speech therapist and physiotherapist, and takes Carbamazepine, Oxcarbazepine, Simvastatin, Phenobarbital, N-acetylcysteine, Phosphoethanolamine,'1 Botulinum Toxin. Diagram 2.

Case 2

A female patient, 5 years old, daughter of consanguineous parents, was referred for neurologic evaluation due to a gait dysfunction. Pregnancy without intercurrences. G1P1A0C1. Born by cesarean delivery due to pelvic fetal presentation. Presented, at birth, APGAR 9 in the 1st minute and 10 in the 5th minute, weighed 3210g (P50), measured 47 cm, and 35 cm (P15) of head circumference. According to the curve of head circumference for the first 2 years of age, all markings were close to the P50 line. At 1 year and 9 months, upon presenting progressive difficulty in ambulation, a magnetic resonance imaging of the skull (Figure 2A) was completed, which showed no evidence of demyelination and presented all other parameters within normality. The mother reported that, at 2 years and 1 month, there was asthenia and regression of the ability to ambulate, even with assistance, and a gradual reduction of the volume of speech until it was completely lost. At 2 years and 3 months, there was asthenia of the cervical muscles and the onset of limb spasticity. Therapy with Sodium Valproate was prescribed, and the onset of frequent choking with liquids (water and medicines) was noticed. Thus, a diet of food pastes was started and, finally, a nasoenteral tube was used for 11 months. Frequent episodes of gastroesophageal reflux and aspiration pneumonia were reported in the following 3 months. At 3 years and 3 months, a Nissen surgery was carried out for the correction of reflux and gastrostomy. At 3 years and 9 months, a new magnetic resonance imaging of the skull (Figure 2B) was completed, which showed abnormal bilateral signal and symmetrical periventricular and subcortical white matter, supra- and infratentorial, conferring it a striped/tiger pattern appearance. Currently, the child weighs 17 kg, is 105 cm tall, has a BMI of 15.419 kg/m², and takes Baclofen, Ranitidine, Levetiracetam, Risperidone, N-acetylcysteine, Phenobarbital, Beclomethasone, Montelukast, Lactulose, Budesonide. Diagram 2

Case 3

Female patient, 3 years and 9 months old, child of non-consanguineous parents. Presented, at birth, APGAR 9 in the 1st minute and 10 in the 5th minute, weighed 3400g and measured 49 cm, which placed her at the percentile 50 of age and height based on age. She was born with hypoglycemia, with suspected early sepsis, and was hospitalized in the ICU for 7 days. She was exclusively breastfed on free demand during the first six months. The patient presented normal neurological, psychological, and motor development up to the age of 2 years. She evolved to the inability to ambulate at 2 years and 4 months. At 2 years and 7 months, magnetic resonance imaging was completed,

FIGURE 2. (A) MAGNETIC RESONANCE OF THE SKULL WITH NO SIGNS OF ABNORMALITIES. (B) MAGNETIC RESONANCE OF THE SKULL FROM THE SAME PATIENT SHOWING A STRIPED/TIGER PATTERN (RED ARROW).
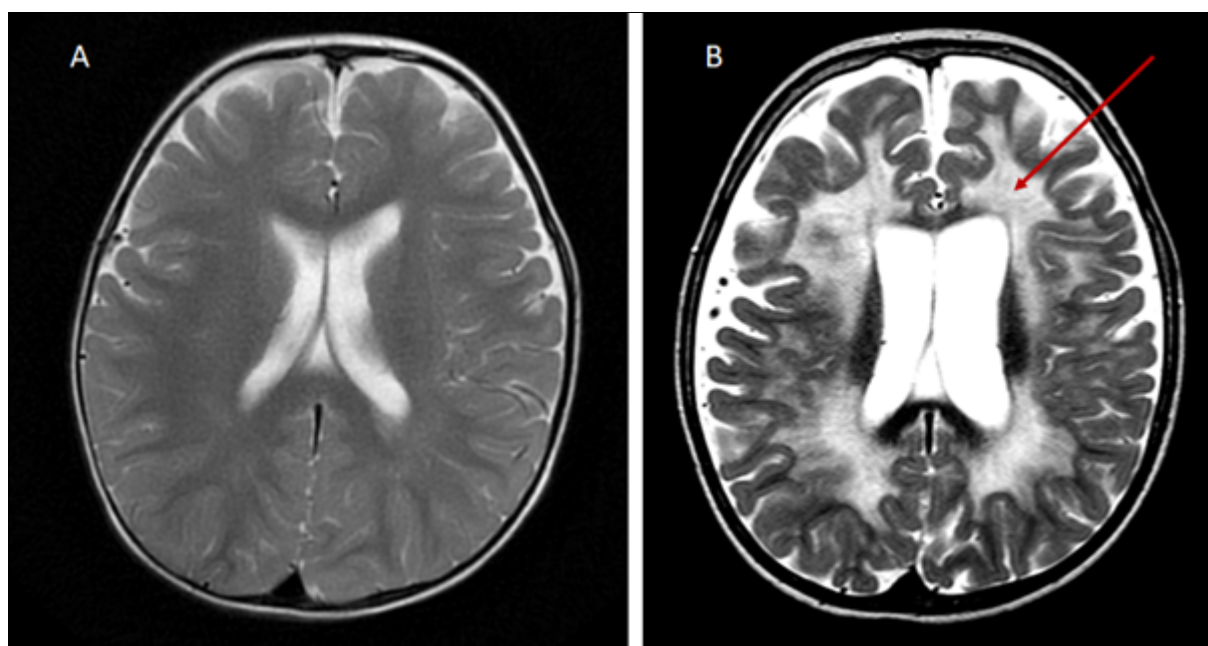
SOURCE: The authors, 2019.

which showed extensive abnormal areas in the white matter of the brain hemispheres, suggestive of cerebral metabolic disease. After imaging examination, CSF was collected, which showed demyelination. At 3 years, there was the onset of dysphagia for solid foods. Currently, the diet consists of food pastes. The mother reports that she underwent cesarean delivery, at 37 weeks, due to maternal diabetes and that there were no complications. The patient presents spasticity and,

DIAGRAM 2. COMPARISON BETWEEN THE PATIENTS REPORTED, BASED ON THE LEVEL OF CONSANGUINITY, ENZYME LEVEL OF BLOOD ARYLSULFATASE A, PATHOGENIC VARIANT, AGE OF INITIAL SYMPTOM, INITIAL SYMPTOM, AND AGE AT DIAGNOSIS.

Late Infantile Presentation			
Neuroradiological finding (skull MR)	Striped/Tiger Pattern (abnormal bilateral signal and symmetrical periventricular and subcortical white matter)		
Pathogenic variants found	C.465+1G>A	C.1178OG	c.769G>C
Age at initial symptom	Between 1 year and 9 months of age and 2 years and 3 months		
Age at the diagnosis	Between 2 years and 6 months of age and 3 years and 6 months		
Clinical evolution.	Usually initiated by the decline of motor function and/or language, which evolves with progressive neurological, psychological, and motor deficits until death.		

SOURCE: The authors, 2019.

therefore, has recently undergone surgery to correct the shortening of the Achilles tendons in both lower limbs, associated with the use of Botox and orthoses. Currently, the child weighs 12.98 kg, is 98 cm tall, is in the percentile 15 for height/age and below the percentile 5 for weight/age, has a BMI of 13.51 kg/m² and takes Simvastatin, Vitamin D, Vitamin B12, Baclofen, Clonazepam, N-Acetylcysteine, *Curcuma Longa* (Zingiberaceae). Diagram 2

DISCUSSION

MLD is characterized by metachromatic granules produced by the accumulation of sulfatídes[13]. In this condition, the ARSA enzyme, which is coded by the *ARSA* gene, is abnormally present[14]. Patients with this condition can be classified based on the age of onset of the disorder. Up to 4 years of age, MLD is called "late infantile", at ages 4-15 years is referred to as "juvenile", and after the age of 15 years of age, as "adult"[15]. The three patients reported are classified as the late infantile presentation. Initially, MLD presents with focal neurological deficits, behavior disorders, and several other nonspecific signs and symptoms that make its early diagnosis a challenge[16].

In the late infantile presentation, at least 75% of the cases present the onset of symptoms, on average, prior to 18 months of age, while our study found that the first symptoms appeared only at 24 months on

average[17]. According to Kehrer et al.[18], the initial clinical manifestations commonly described in the late infantile presentation are changes in muscle tonus, in particular in the lower limbs, which evolves to motor regression, present in 70% of the late infantile cases and in all 3 patients described in our study. In addition, the regression of speech and language is present in ⅔ of our patients, compared to 48% of those affected by the late infantile presentation in the study analyzed. Another important factor to be emphasized is the time between the first symptoms and the date of the diagnosis. According to this same author, the average time between these parameters was 12 months in patients with the late infantile presentation, which was also observed in the present study. However, a greater time interval stands out in the patient of the second report, i.e., 2 years and 3 months from the initial symptoms until the diagnosis, which may affect the prognosis.

In the study by Barboura et al.[19], two patients with the late infantile presentation showed MLD-characteristic lesions on the white matter of the periventricular region on magnetic resonance, similar to the findings of the study by Groeschel et al.[20], which also identified the same abnormality in their patients. We emphasize that, in addition to the demyelination affecting predominantly the periventricular region, it spares the subcortical area (U-fibers) of the white matter, as observed in the study by Barboura I and the present one. In addition, Groeschel et al.[20] mention that the MRI images in the late infantile presentation are normal until the onset of the first symptoms. The same can be seen in the case of patient number 2, who showed no signs of demyelination and other MLD patterns in the first magnetic resonance imaging completed.

In terms of laboratory exams, according to Van Rappard et al.[21], the examination of the Arylsulfatase A enzyme activity should not be the only parameter since this may be low in cases of pseudo-deficiency of MLD alleles, which is caused by low enzyme activity but the patient presents no symptoms. With the examination of urine sulfatídes it is possible to distinguish it from actual ARSA deficiency since, if the results are positive, MLD is confirmed. In the study presented, the first two patients had reduced activity of the Arylsulfatase enzyme and in the examination of the third patient, the activity is undetectable. The statement by Van Rappard et al.[21] corroborates the present study, supporting the understanding that complementary examinations are necessary to evaluate patients in all possible ways, which will contribute to an early diagnosis and improvement of their quality of life.

Even though there is still no curative treatment for this disease, new therapeutic possibilities are emerging, such as intrathecal enzyme replacement and hematopoietic stem-cell transplantation (HSCT) associated with gene therapy.

HSCT aims to treat the manifestations of MLD in the central nervous system; however, there are obstacles that still prevent it from being timely offered to patients because it preferably should be performed in a pre-symptomatic or oligosymptomatic phase with an allogeneic donor. Other obstacles consist in the identification of a HLA-compatible donor to minimize the risks of the procedure, such as graft-versus-host disease, and who should not be a carrier of pathogenic variants of MLD[2]. Although there has been a significant improvement in allogeneic transplantation, the therapy is still controversial since data from results are limited and difficult to generalize to the public affected due to the use of different eligibility criteria and transplantation protocols and different responses to its deployment with different presentations of MLD. In addition, transplantation cannot be offered to individuals with significant neurological involvement[17,22].

Recently, advances have allowed combining HSCT with gene therapy. Gene therapy is the delivery of genetic material, using viral vectors, to the cells or tissues of an individual for therapeutic purposes. It is possible to modify stem cells and autologous hematopoietic progenitor cells using a lentivirus that expresses a functional ARSA enzyme, this is currently being tested in clinical trials with promising results. Studies have shown a reconstitution of ARSA activity in hematopoietic cells and in the cerebrospinal fluid. There is evidence of prevention of disease onset or interruption of its progression with the restoration of normal levels regarding motor function and the conduction of impulses in the peripheral nerves[17,22].

Enzyme replacement therapy (ERT) is an alternative that benefits from the enzyme provision via the intrathecal route in patients with the late infantile presentation; it requires a trained neurosurgery team for the procedure to be performed and this method is not capable of enabling the patient to produce the enzyme[23].

Unfortunately; none of the patients described could participate in the clinical studies previously described due to the late diagnosis when they already presented advanced and irreversible sequelae from the disease.

CONCLUSION

In short, Metachromatic Leukodystrophy is a rare, devastating, and progressive hereditary disease. Given the possibility of emerging treatments specific to this illness, it is vital to obtain an early diagnosis. Even in the absence of specific therapies, the correct diagnosis allows the family genetic counseling and better therapeutic follow-up of patients to manage the complications from the disease.

Author's Contribution

All authors participated in the study design with substantial contributions to the concept and design, data acquisition, analysis, and interpretation, and drafting of the paper, with final approval of the version to be published, thus conforming to the uniform requirements of the International Committee of Medical Journal Editors.

ANNEX 1. MLD PRESENTATIONS: CLINICAL MANIFESTATIONS, DIFFERENTIAL DIAGNOSES, AND LABORATORY TESTS.

Findings	Late Infantile Presentation	Juvenile Presentation	Adult Presentation
Age of onset	Between 0 and 4 years	Between 4 and 15 years	From 15 years onward
Main clinical manifestations	-Developmental delay (gait, speech, etc.) -Frequent falls -Hypotonia -Decreased or absent tendon reflexes -Optic atrophy and nystagmus -Epileptic seizures	-Behavioral changes -Learning difficulties -Ataxia and frequent falls -Extrapyramidal involvement -Epileptic seizures	-Behavioral changes (depression, anxiety, etc.) -Progressive dementia -Ataxia -Epileptic seizures
Survival	From 6 months to 8 years	From 10 to 20 years	From 10 to 30 years
Main differential diagnoses	-Krabbe Disease -Mitochondrial Encephalopathy -Canavan Disease -Alexander Disease -Neuroaxonal Dystrophy	-X-Linked Adrenoleukodystrophy -Mitochondrial Encephalopathy -Neuroaxonal Dystrophy -Juvenile Krabbe Disease -Juvenile Gangliosidoses (GM1 and GM2)	-Psychosis -Neuropathies with a motor predominance -Adult Krabbe Disease -Neuropathy, ataxia, and retinitis pigmentosa (NARP) -Adrenomyeloneuropathy
Image of the CNS (MRI or CT)	-Abnormalities in the periventricular and centrum semiovale white matter -U-Fibers are spared -Beginning of the posterior pole in the anterior direction	-Abnormalities in the centrum semiovale white matter -Beginning of the anterior pole in the posterior direction	-Abnormalities in the centrum semiovale white matter -Beginning of the anterior pole in the posterior direction

SOURCE: Adapted from Artigalas[3]

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Cerebellar infarction after sneezing

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SUMMARY

Vertebral Artery Dissection (VAD) is a rare condition that can be caused by a wide amplitude of neck movement, which injures the vessel wall and can cause ischemia in the cerebellum. We present a 37-year-old man with herniated lumbar disc and allergic rhinosinusitis, which caused sneezing spells. After one of these bouts with a ricochet of the head, he presented C3 misalignment with local pain. Twenty-one days later, affected by a new crisis, he presented left temporal headache, nystagmus, and vertigo. After 3 days, Magnetic Resonance Imaging (MRI) identified 2 regions of cerebellar ischemia and filling failure of the right vertebral artery. After 2 days, Computed Angio-tomography (CT Angiography) was performed and showed right VAD with a local thrombus, without aneurysmal signs. Transcranial Doppler did not indicate an increase in blood flow from this artery. The suggested treatment involved administration of anticoagulant Apixabana 5mg, 12/12h, for 3 months, until the condition was reevaluated with new Angio CT and MRI. It was recommended that the patient was released from work for 1 month and forbidden from doing intense physical exercises for 3 months; however, due to setbacks, these deadlines were extended until a new appointment, 4 months after the first visit. The new tests showed no changes, indicating that the condition was stable. This case aims to indicate the possible investigations of the diagnosis and therapeutic options of the rare association between VAD with cerebellar infarction in a well-documented case.

KEYWORDS: *Vertebral artery dissection. Cerebral Infarction. Stroke.*

INTRODUCTION

Vertebral Artery Dissection (VAD) is a rare condition, with an incidence of 0.97 to 1.5 cases per 100,000 inhabitants per year, affecting mostly young people and adults of both sexes[1-3]. Dissection generally occurs in the C2 and C3 segments of the vertebral artery and can be caused by a wide neck movement, with distention of the vessel wall[2,4]. Thus, there is an endothelial lesion prone to dissecting blood intrusion into the wall, with probable thrombus formation, stenosis, or aneurysm. The association between these factors is capable of causing ischemia in the cerebellum, an organ irrigated by the vertebral artery, generating symptoms such as nystagmus, occipital headache, cervical pain, and vertigo[5]. Next, a case of VAD will be presented after a sneezing crisis, which caused cerebellar infarction.

Case report

This case was duly submitted to and approved by the Research Ethics Committee, and the patient's consent was obtained.

A 37-year-old male physician sought a neurological appointment due to complaints of mild left temporal headache and some episodes of vertigo with 1 week of evolution. He had a history of a herniated disc in the lumbar region and allergic rhinosinusitis. He denied smoking and alcohol use, as well as daily medication use. He has a family history of vascular abnormalities: the mother had a Cavernous Sinus aneurysm and the father had an atherosclerotic infarction (not due to vascular fragility).

The patient had frequent sneezing spells in salvo motivated by allergic rhinosinusitis, which were responsible for the bouncing movement of the head. About one month before the appointment, during one of these crises, the patient had a misalignment of the C3 vertebrae that caused local pain, which was minimized by the administration of muscle relaxant and anti-inflammatory medication. The condition was detected 2 weeks later, and there was complete recovery after physiotherapy. Three days before the neurologic appointment, the patient was again affected by sneezing associated with severe headache restricted to the left temporal frontal region. The patient reported having held back some of the sneezing, which indicates that the ricochet was intensified, acting as the cause of the distension of the vessel wall and, because he is a medical professional, there was a well-defined temporality and causal factor. To control the crisis, he used analgesics (Paracetamol) and antihistamines (Dexchlorpheniramine maleate). Right after one of these crises, nystagmus was observed without compromising horizontal balance, for 40 minutes, until it was resolved spontaneously. However, the patient remained with mild left temporal headache and limited episodes of vertigo that motivated the search for a professional three days later. During the neurologic appointment, the physical examination was completely normal, with no vestibular or oculomotor changes, absence of movement, and strength deficits. There were also no relevant changes from other devices.

Investigation

The patient underwent Magnetic Resonance Imaging (MRI) (Fig. 2) on the day of the appointment, which showed two regions of ischemia in the posterior region of the right cerebellar hemisphere and filling failure of the affected right Vertebral Artery. This same region, on a Computed Tomography (CT) (Fig. 1), was hypodense, which is consistent with cytotoxic edema in acute ischemias. Then, two days later, a Computed Angiotomography (AngioTC) (Fig. 1) was performed, which found a right VAD with a local thrombus, without signs of aneurysm. A Transcranial Doppler was also performed, showing no signs of increased blood flow from the same artery.

FIGURE 1. CT AND ANGIOCT ACUTE VASCULAR INSULT AND RIGHT VERTEBRAL MURAL THROMBUS

A: Axial angioCT: the right vertebral artery (yellow arrow) shows a mural thrombus restricted to the upper cervical segment with segmental stenosis below 40% (ECST);

B: Axial CT (red arrow): hypodense area in the right cerebellar hemisphere, compatible with acute/subacute ischemic vascular insult.

FIGURE 2. MRI DEMONSTRATING ACUTE VASCULAR INSULT.
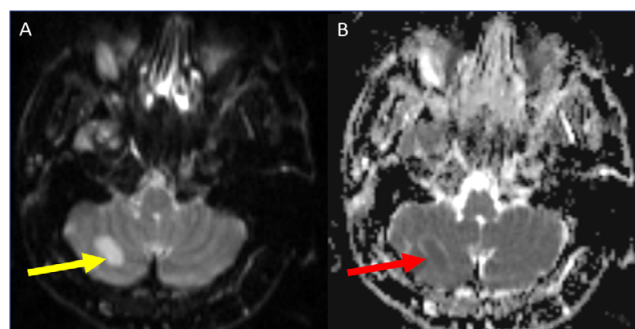
MRI in DWI axial sequence showing a hypersignal area (yellow arrow) with corresponding low signal on the ADC map (red arrow), in figure B. Together with the clinical data, an area with diffusion restriction due to acute/subacute ischemic vascular insult.

Treatment

In the same day of the appointment, a therapy plan was created involving anticoagulant Apixabana 5mg, 12/12h, for 3 months, until the condition was reevaluated with a new Angio CT and MRI. Furthermore, he should be removed from work for a month and was forbidden from practicing intense physical exercises for 3 months.

Results and follow-up

Due to delays in the results of the AngioCT and in scheduling a new medical appointment, the patient was advised to stay on the medication until the new appointment with the doctor, which happened 4 months later. On this occasion, after evaluating the new AngioCT and MR, which showed no changes, and given the stability of the case, medication was suspended.

In addition, the patient tried to follow the recommendation to resume the practice of physical activities 3 months after the first consultation, but when he tried to exercise, he had mild neck pain. Thus, he preferred to suspend activities until the return visit, a month later, during which a correlation between a new VAD was discarded, which cleared the patient to practice exercise provided no high impact was involved.

After 4 months of treatment, the patient was clinically free from the condition and was instructed only to maintain weight control. Since then, he reported having two new mild attacks of rhinosinusitis, but these did not cause cerebellar symptoms as before. Thereby, the patient was cured and has been neurologically stable for 9 months of follow-up up until now.

DISCUSSION

The reported case shows a Cerebellar Infarction secondary to VAD. Probably, the thrombus that caused the ischemia was formed after an injury to the intimal layer of the artery, caused by ricocheting of the head during an intense sneezing attack[4]. This theory is supported by evidence that proves that the stretching and exaggerated retraction of the neck may be responsible for the damage of vessels in this region[4-6].

A literature review on the topic indicated that some of the most common signs and symptoms in VAD are nystagmus, cerebellar ataxia, vertigo, tinnitus, nausea and vomiting, neck pain, paresis, headache, and, more rarely, dysphagia and dysarthria[1,2,6-10]. In this specific case, the initial condition had nonspecific symptoms such as pain in the neck; however, it evolved with neurological impairment, such as nystagmus, vertigo, and left temporal headache.

The diagnosis of VAD associated with cerebellar infarction requires good anamnesis and follow-up with imaging exams[6]. Although arteriography is considered the "gold standard" for diagnosing VAD, since it is an invasive method, it is generally replaced by MRI and CT, which allow the analysis of the main cervical and intracranial arteries[7].

In the case reported, although the physical examination was normal, due to the report of nystagmus, headache, and vertigo, the diagnostic hypothesis of a tumor was raised and an MRI was requested. The exam revealed a region compatible with ischemic vascular insult, so AngioCT and Transcranial Doppler were indicated for better evaluation. Such tests identified thrombus and alteration in the flow of the vertebral artery, confirming that it was a case of stroke due to VAD, and not a neoplasm as previously thought.

Therapeutic intervention in cases of VAD consists mainly of administrating anticoagulants and antiplatelet agents and should be started as quickly as possible[1,11,12]. Evidence on the topic suggests that there is no significant difference between the results of using these two drugs, but many prefer to use antiplatelet drugs because they have a lower risk of bleeding than anticoagulants[11,12]. When these drugs are not effective, alternative interventions such as reperfusion, intervention in embolism, or surgery can be performed.

For our patient, specifically, anticoagulants were chosen because it is a more conservative approach. The patient reacted well to the adopted therapy and had no complications, so there was no need to try another approach. It is worth mentioning that there was no need for surgery, considering that the area of the vertebral artery that underwent dissection was extracranial, and had no tendency to increase.

The control exams, AngioCT and MRI, 4 months after the event, showed that the penumbra area in the cerebellum was well supplied by the collateral branches, and there was complete resolution of the previous condition (Fig. 3).

FIGURE 3. MRI AND CT CONTROL IMAGES
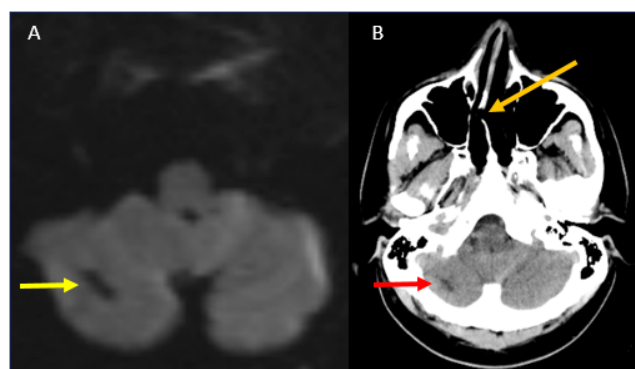
A: MRI in DWI axial sequence showing a low signal area (yellow arrow); there is no diffusion restriction in this image;

B: CT showing hypodense area with a density similar to CSF (red arrow), indicating previous vascular insult. Orange arrow indicating deviated septum, a potential cause of chronic rhinosinusitis.

CONCLUSION

This report presented a rare and well-documented association between sneezing and cerebellar infarction caused by VAD, highlighting its characteristic manifestations and the measures to be taken in order to assist doctors in quickly identifying and treating this unusual condition, avoiding possible complications and irreversible aftereffects.

Author's Contribution

GBC, MAR e CACSJ: Participated in the study conceptualization, report organization, literature review, and final revision.

ALMN, ACQ, ALSM e DGPLR: Transcribed the report, organized the text, participated in the literature review, and text drafting.

RESUMO

A Dissecção da Artéria Vertebral (DAV) é quadro raro que pode ser causado por movimentação de grande amplitude do pescoço, que lesiona a parede desse vaso, podendo provocar isquemia no cerebelo. Apresentamos um homem de 37 anos, com hérnia de disco e rinossinusite alérgica que lhe causava crises de espirros em salva (CE). Após uma dessas crises com ricocheteamento da cabeça, apresentou desalinhamento de C3 com dor local. Vinte e um dias depois, acometido por nova crise, apresentou cefaleia temporal esquerda, nistagmo e vertigem. Decorridos 3 dias, o paciente foi submetido a Ressonância Magnética (RM), que identificou 2 regiões de isquemia cerebelar e enchimento comprometido da artéria vertebral direita. Após 2 dias, foram feitos Angiotomografia Computadorizada (Angio TC), que constatou DAV direita com trombo local, sem sinais aneurismáticos, e Doppler Transcraniano, que não indicou aumento do fluxo sanguíneo dessa artéria. O tratamento sugerido envolvia administração de anticoagulante Apixabana 5mg, 12/12h, por 3 meses, até que o quadro fosse reavaliado com novas Angio TC e RM. Foi recomendado que o paciente ficasse afastado do trabalho por 1 mês e de exercícios físicos intensos por 3 meses, porém devido a contratempos, esses prazos foram prorrogados até nova consulta, 4 meses após a primeira. Os novos exames não apresentaram alterações, indicando que o quadro estava estável. Esse caso tem como objetivo indicar as possíveis investigações do diagnóstico e opções terapêuticas da rara associação entre DAV com infarto cerebelar em caso bem documentado.

PALAVRAS-CHAVE: *Dissecação da artéria vertebral. Infarto Cerebral. Acidente vascular cerebral.*

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Mortality of motorcyclists due to traffic injuries in Brasil: a population-based study in Brazilian capitals

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SUMMARY

OBJECTIVE: *To analyze the mortality trend of young men who were victims of traffic injuries involving motorcycles in all Brazilian capitals from 2001 to 2015.*

METHODS: *A time-series study on all deaths of men aged 20-39 years old due to traffic injuries involving motorcycles in all 27 Brazilian capitals. We used the joinpoint regression model for temporal analysis and calculated the Annual Percent Change (APC) and Average Annual Percent Change (AAPC) to verify the mortality trends.*

RESULTS: *A total of 12,058 deaths of young men were recorded in the Brazilian capitals during the period studied. The highest mortality rates were observed in Boa Vista/Roraima (34.0/100,000 population) and Palmas/Tocantins (29.80/100,000). Twelve of the 27 capitals showed an increasing trend in mortality, with the highest percentage increase being observed in Salvador (APC: 29.0%) and São Paulo (APC: 13.1%). None of the capitals showed a decline in the trend of mortality.*

CONCLUSIONS: *Overall, the mortality of young men from traffic injuries involving motorcycles shows an increasing trend in 12 of the 27 capitals, which represents a public health problem that requires the implementation of more effective public policies.*

KEYWORDS: *Accidents, traffic. Mortality. Epidemiology. Public Health. Motorcycles.*

INTRODUCTION

Mortality due to traffic injuries has become a public health problem worldwide[1]. In 2016, traffic caused about 1.35 million deaths, representing the eighth global cause of mortality[1,2]. Of these deaths, 50% were of individuals considered more vulnerable (pedestrians, cyclists, and motorcyclists), and young men constituted the risk group[1,2].

In 2016, Brasil registered 37,345 deaths resulting in a mortality rate of 18.1/100,000 population[3], and it was one of the five countries with the highest traffic-related mortality, alongside India, China, USA, and Russia[1]. An estimated 4.6 billion dollars are spent annually on traffic-related deaths and injuries in Brasil[4].

Because of the high number of deaths due to traffic injuries, the World Health Organization (WHO) attributed the period of 2011-2020 as the "Decade of Action for Road Safety" with the goal of halving mortality from traffic injuries in the world[5]. Brasil has implemented the National Injury Reduction Plan, which involves strategic actions to improve road safety and reduce the occurrence of traffic injuries and deaths[6]. Since Brasil is a country of continental dimensions with marked socioeconomic disparities, studies are needed to assess the behavior of the trend of mortality from traffic injuries, especially with population groups at increased risk of death. In addition, investigations into how mortality rates behave can support public strategies and policies aimed at road safety[7].

This study investigated the mortality trend of young men who were victims of traffic injuries involving motorcycles in all Brazilian capitals from 2001 to 2015.

METHODS

This was a time-series study including all deaths of young men aged 20 to 39 years old due to traffic injuries involving motorcycles that occurred in the 27 state capitals of Brasil from 2001 to 2015.

Data on the population were obtained from the Brazilian Institute of Geography and Statistics (IBGE). Data on the deaths were obtained from the Mortality Information System (SIM, in Portuguese) (http://www2.datasus.gov.br). All deaths of young men with the International Classification of Diseases (ICD-10) codes V20–V29 were included. The mortality rate was calculated by dividing the number of deaths of men aged 20-39 years old by the population of men aged 20-39 years old per 100,000 population. Data were obtained by year for each of the state capitals of the country.

The temporal trend analysis was calculated using the joinpoint regression model (Joinpoint Regression Program 4.5.0.1, National Cancer Institute, USA) with Monte Carlo permutations and error autocorrelation based on date. This method allows identifying trends and change points and determining the Annual Percentage Changes (APC) and overall period (Average Annual Percent Change – AAPC). Trends were categorized as stable, increasing, or decreasing[8]. We considered a 95% confidence interval (95% CI) and 5% significance for all analyses.

The study did not require approval from an ethics committee as the databases are in the public domain without individual identifiers.

RESULTS

A total of 12,058 deaths of men aged 20 to 39 years old due to traffic injuries involving motorcycles were recorded in the Brazilian capitals from 2001 to 2015. This corresponds to 17% (12,058/71,090) of deaths across the country in the period. The mortality rate in the capitals went from 5.52/100,000 (n=394 deaths) in 2001 to 12.32/100,000 in 2015 (n=107 deaths) (AAPC 6.8%; 95% CI 4.8 to 8.9; P <0.01) (Figure 1). In 2001, 12 capitals had mortality rates higher than the national (6.84/100,000). In 2015, eight capitals had a higher mortality rate than the national rate (18.33/100,000). When considering the entire period (2001-2015), eight capitals stood out with rates higher than the national rate (14.80/100.00), two from the Northern region (Boa Vista/Roraima and Palmas/Tocantins), two from the

FIGURE 1. TIME TREND OF THE MORTALITY RATE OF MEN 20-39 YEARS OLD DUE TO TRAFFIC INJURIES INVOLVING MOTORCYCLES, PER BRAZILIAN CAPITALS FROM 2001-2015.
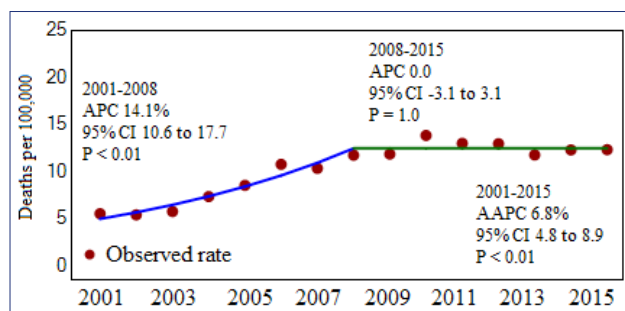
Northeast (Teresina/Piauí and Aracaju/Sergipe), three in the Central-West (Goiânia/Goiás, Cuiabá/Mato Grosso and Campo Grande/Mato Grosso do Sul), and one in the South (Florianópolis/Santa Catarina). The highest mortality rates were observed in Boa Vista/Roraima (34.00/100,000 population) and Palmas/Tocantins (29.80/100,000) (Figure 2).

Twelve of the 27 Brazilian capitals showed an increasing trend, three in the North, five in the

Northeast, two in the Southeast and two in the Central West. The largest increase in mortality rate was detected in Salvador/Bahia (AAPC: 29.0%; p <0.001), with a mortality rate varying from 0.4/100,000 in 2001 to 9.4/100,000 in 2015, followed by São Paulo/São Paulo (AAPC: 13.1%; p <0.001), with a rate going from 4.4 to 11.1/100,000 from 2001 to 2015. None of the capitals had a decreasing trend (Table 1). The absence of death records in different years of the time series

FIGURE 2. MORTALITY RATES IN YOUNG MEN 20-39 YEARS OLD DUE TO TRAFFIC INJURIES INVOLVING MOTORCYCLES, PER BRAZILIAN CAPITALS FROM 2001-2015.
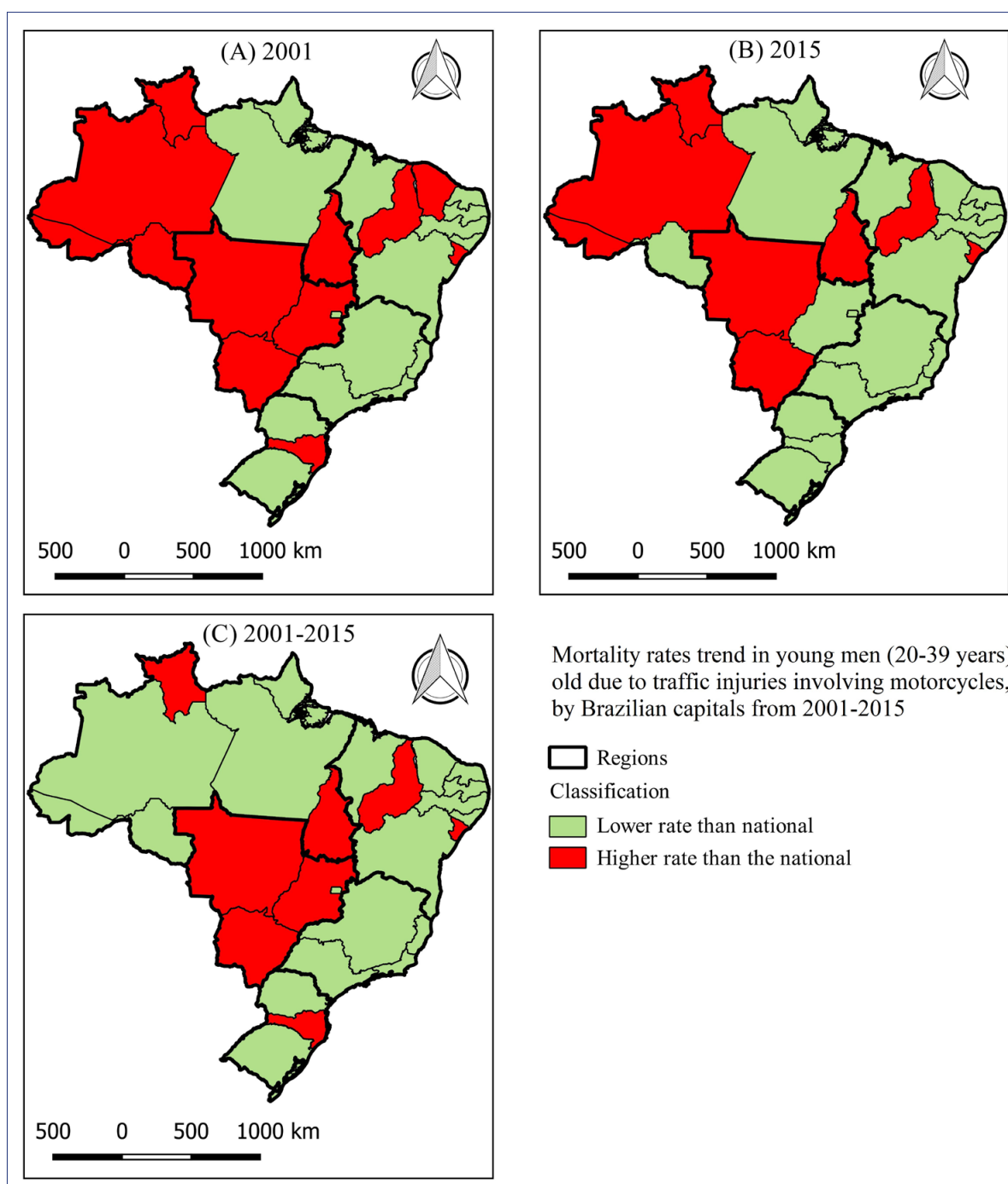
in Rio Branco/Acre (2003, 2006, and 2008–2011) and Macapá/Amapá (2011) made the application of segmented regression unfeasible. Rio Branco/Acre and Macapá/Amapá registered 74 and 68 deaths in the period, respectively (Table 1).

DISCUSSION

Brasil has experienced a change in its morbidity and mortality profile in recent decades, with a considerable increase in deaths from chronic diseases and external causes (interpersonal violence and traffic injuries)[9-11]. In this study, we investigated the deaths of a population group at a higher risk of death (young men aged 20-39 years) due to traffic injuries involving motorcycles to identify the behavior in a 15-year time series in Brazilian capitals. Our findings call attention to the increasing trend in mortality, even in the period after the introduction of an emergency plan to reduce traffic-related deaths.

In view of this finding, some explanations are offered. Factors such as tax incentives for the installation of industrial motorcycle manufacturing centers, combined with the increased purchasing power of the Brazilian population and easier access to credit, resulted in an expansion in the number of motorcycles, not only in absolute numbers, but also in comparison with other vehicles[9,12]. In 1990, for example, the

TABLE 1. TREND OF MORTALITY RATES IN YOUNG MEN AGED 20-39 YEARS OLD DUE TO TRAFFIC INJURIES INVOLVING MOTORCYCLES, PER BRAZILIAN CAPITALS FROM 2001 TO 2015.

Capital	Period	APC (95% CI)	AAPC (95% CI)	Trend
Porto Velho/Rondônia	2001–2015	10.5 [a] (5.2; 16.0)	10.5 [a] (5.2; 16.0)	Increasing
Rio Branco/Acre	_[b]	_[b]	_[b]	_[b]
Manaus/Amazonas	2001–2015	6.0 [a] (2.7; 9.5)	6.0 [a] (2.7; 9.5)	Increasing
Boa Vista/Roraima	2001–2003 2003–2007 2007–2015	-65.9 (-89.3; 8.9) 47.0 (-17.7; 162.5) -0.9 (-12.7; 12.5)	-4.8 (-22.3; 16.7)	Stable
Belém/Pará	2001–2015	11.2 [a] (5.3; 17.6)	11.2 [a] (5.3; 17.6)	Increasing
Macapá/Amapá	_[b]	_[b]	_[b]	_[b]
Palmas/Tocantins	2001–2015	-2.0 (-4.5; 0.7)	-2.0 (-4.5; 0.7)	Stable
São Luís/Maranhão	2001–2015	6.2 [a] (3.0; 9.6)	6.2 [a] (3.0; 9.6)	Increasing
Teresina/Piauí	2001–2015	11.5 [a] (8.5; 14.6)	11.5 [a] (8.5; 14.6)	Increasing
Fortaleza/Ceará	2001–2015	-0.3 (-3.4; 2.9)	-0.3 (-3.4; 2.9)	Stable
Natal/Rio Grande do Norte	2001–2015	4.1 (-1.8; 10.4)	4.1 (-1.8; 10.4)	Stable
João Pessoa/Paraíba	2001–2015	10.0 [a] (4.1; 16.2)	10.0 [a] (4.1; 16.2)	Increasing
Recife/Pernambuco	2001–2015	9.3 [a] (4.9; 13.9)	9.3 [a] (4.9; 13.9)	Increasing
Maceió/Alagoas	2001–2015	0.7 (-4.6; 6.4)	0.7 (-4.6; 6.4)	Stable
Aracaju/Sergipe	2001–2015	6.9 [a] (3.8; 10.1)	6.9 [a] (3.8; 10.1)	Stable
Salvador/Bahia	2001–2015	29.0 [a] (16.2; 43.2)	29.0[a] (16.2; 43.2)	Increasing
Belo Horizonte/Minas Gerais	2001–2015	6.9 [a] (2.3; 11;7)	6.9 [a] (2.3; 11.7)	Increasing
Vitória/Espíríto Santos	2001–2015	0.3 (-6.2; 7.4)	0.3 (-6.2; 7.4)	Stable
Rio de Janeiro/Rio de Janeiro	2001–2009 2009–2012 2012–2015	16.3 [a] (8.9; 24.1) -33.0 (-63.2; 21.9) 29.8 (-3.8; 75.2)	5.8 (-6.5; 19.6)	Stable
São Paulo/São Paulo	2001–2015	13.1 [a] (5.7; 21.0)	13.1 [a] (5.7; 21.0)	Increasing
Curitiba/Paraná	2001–2006 2006–2015	39.0 [a] (6.4; 81.7) -5.1 (-14.9; 5.9)	8.8 (-2.0; 20.7)	Stable
Florianópolis/Santa Catarina	2001–2015	1.6 (-3.2; 6.5)	1.6 (-3.2; 6.5)	Stable
Porto Alegre/Rio Grande do Sul	2001–2015	2.9 (-0.3; 6.2)	2.9 (-0.3; 6.2)	Stable
Campo Grande/Mato Grosso do Sul	2001–2008 2008–2015	28.4 [a] (14.6; 43.8) -4.6 (-14.8; 6.8)	10.7 [a] (3.1; 18.7)	Increasing
Cuiabá/Mato Grosso	2001–2015	4.5 (-0.4; 9.6)	4.5 (-0.4; 9.6)	Stable
Goiânia/Goiás	2001–2004 2004–2015	20.4 (-2.7; 49.0) -1.7 (-4.5; 1.2)	2.7 (-1.8; 7.4)	Stable
Brasília/Distrito Federal	2001–2007 2017–2015	30.8 [a] (12.3; 52.2) -4.3 (-13.2; 5.6)	9.4 [a] (1.5; 18.0)	Increasing

Legend: [a] Statistical significance (P <0.05); [b] Inconsistent data made the temporal analysis unfeasible; APC: Annual Percent Change; AAPC: Average Annual Percent Change.

Brazilian fleet of motorcycles was 1.5 million and in 2014 this number reached 22 million units circulating in the country[13]. Also, the main consumers of these vehicles are young men, with lower purchasing power and low educational level[14,15].

In the North and Northeast regions, the expansion in the number of motorcycles was even more intense. In the North region, the motorcycle fleet increased from 224,150 in 2001 to 1,757,003 in 2015, accounting for an increase of around 684%[16]. In the Northeast region, the motorcycle fleet varied from 766,886 in 2001 to 5,825,032 in 2015, which represents an increase of nearly 660%[16]. In this study, the three capitals with the highest rates were observed in the North (Boa Vista/Roraima and Palmas/Tocantins) and Northeast (Teresina/Piauí) areas. In Teresina/Piauí, 84% of victims of traffic injuries assisted by the Emergency Ambulance Service in 2009 were involved in motorcycle injuries and 76% of these individuals were men[17].

Other factors can play an important role when associated with the significant increase in motorcycles, such as: precarious conditions of roads and highways, deficiencies in traffic inspection, and lack of structural adaptations on highways and cities[11,15].

In large cities or metropolises, the increase of the motorcycle fleet occurs both from the low cost of acquiring and maintaining the vehicle and from the speed of travel that the motorcycle promotes when compared to other vehicles, especially in the face of tumultuous traffic in these cities[17,18]. On the other hand, the increase in flow at peak times associated with structural deficiencies in the roads, deficits in the inspection mechanisms, and tiredness/fatigue of drivers create a scenario determinant to the occurrence of injuries involving motorcyclists[18].

Motorcycles have taken on a new role in Brazilian society and in many other low- and middle-income countries. The motorcycle went from a leisure vehicle used on weekends to a working instrument for thousands of individuals[11]. The professions of *motorcycle courier* and *motorcycle taxi* and, more recently the delivery of parcels by apps, can have substantial impacts on the occurrence of injuries involving motorcyclists[9,11,19]. Studies on the working conditions of *motorcycle couriers* have shown that the indiscriminate demand for services causes them to institute an exacerbated work rhythm that leads them to violate traffic laws in order to be able to fulfill deliveries in a timely manner[20]. In addition, these professionals largely neglect the use of personal protective equipment[19].

This process is potentially influenced by the working relationship to which these professionals are exposed[19]. As both *motorcycle taxi*s and *motorcycle couriers* are self-managed, they have no formal employment relationship and their financial gain is dependent only on their work capacity, which results in an intensification of the workday in the search for compensation for the low added value of each task completed[19,20].

Even with methodological care, this study has the following limitations: i) use of secondary data whose quality can be questioned; ii) the inadequate filling out of the death certificate (DO) with the presence of the garbage code, and cases that occurred in hospitals whose underlying cause was not registered as a motorcycle injury; and iv) the underreporting of deaths.

CONCLUSION

The context shown in this study is worrying. Twelve of the 27 capitals showed an increasing trend in mortality. We advocate that broad public policies that include multisectoral actions, strengthening and guaranteeing the application of traffic legislation, structural improvements in the Brazilian road network, and consistent educational actions can contribute to the reduction of the problem in Brasil.

Author's Contribution
Carlos Dornels Freire de Souza, Leonardo Feitosa da Silva, Thiago Cavalcanti Leal, João Paulo Silva de Paiva, Gibson Barros de Almeida Santana: Participated in the development of the concept, planning of the study, data collection and analysis, discussion of the results, scientific writing, as well as in the review and approval of the final version of the work.

Michael Ferreira Machado, Maria Deysiane Porto de Araújo, Divanise Suruagy Correia, Roberto Andrade Medronho, Victor Santana Santos, Mônica de Avelar Figueiredo Mafra Magalhães: Participated in the writing of the results, discussion, scientific writing, as well as in the review and approval of the final version of the work.

RESUMO

OBJETIVO: *Analisar a tendência temporal da mortalidade de homens jovens vítimas de acidente de trânsito envolvendo motocicletas em todas as capitais brasileiras de 2001 a 2015.*

MÉTODOS: *Estudo de séries temporais incluindo as mortes de homens de 20 a 39 anos por lesões no trânsito envolvendo motocicletas nas 27 capitais brasileiras. Para a análise, foi utilizado o modelo de regressão do ponto de inflexão e calculada a Variação Percentual Anual (APC) e a Variação Percentual Anual Média (AAPC).*

RESULTADOS: *Foram registradas 12.058 mortes de homens jovens nas capitais brasileiras durante o período estudado. As maiores taxas de mortalidade foram observadas em Boa Vista/Roraima (34,0/100.000 habitantes) e Palmas/Tocantins (29,80/100.000). Doze capitais apresentaram tendência crescente de mortalidade, sendo o maior aumento percentual em Salvador (APC: 29,0%) e São Paulo (APC: 13,1%). Nenhuma das capitais mostrou declínio nas taxas.*

CONCLUSÕES: *A mortalidade de jovens por lesões no trânsito envolvendo motocicletas tem mostrado uma tendência crescente em 12 capitais, o que representa um problema de saúde pública que requer a implementação de políticas públicas mais eficazes.*

PALAVRAS-CHAVES: *Acidentes de trânsito. Mortalidade. Epidemiologia. Saúde pública. Motocicletas.*

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Impact of the COVID-19 pandemic in patient admission to a high-complexity cancer center in Southern Brasil

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SUMMARY

OBJECTIVE: *The aim of our study was to investigate whether there has been a reduction in patient admission to a high-complexity cancer care center in Brasil during the COVID-19 pandemic, similar to what was reported in Europe.*

METHODS: *We reviewed the cancer tracking database of the largest cancer center in southern Brasil and performed statistical tests to compare first-time appointments from the onset of the outbreak until the end of June to those of the equivalent period in 2019.*

RESULTS: *We observed a dramatic reduction (-42%) in first-time appointments during the pandemic compared to the same period in the previous year (P <0.001). This reduction was observed among all medical specialties (P <0.001).*

CONCLUSION: *The onset of COVID-19 was correlated with a reduction in admission to a high-complexity cancer care center in Brasil. Since a delay in diagnosis and treatment may influence prognosis, it is important that cancer centers and public health strategies reinforce care for non-COVID-19 patients to prevent potentially unnecessary deaths.*

KEYWORDS: *Coronavirus Infections. Medical oncology. Delivery of Healthcare. Public Health. Pandemics.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has transformed how healthcare is delivered globally and has relegated many medical activities to second priority, oncology included. Cancer care consumes significant healthcare resources, and cancer patients not only are frequently exposed to medical facilities but are also at significant risk for bad outcomes with COVID-19[1,2]. Due to that, caregivers are forced to make difficult decisions regarding the allocation of limited resources and to weigh the risk from a delay of cancer management versus the harm of COVID-19 exposure[3]. As a possible consequence of this scenario, data from

European countries showed a significant decrease in cancer referrals and diagnoses during the outbreak[4-6].

In Brasil, the first case of COVID-19 was confirmed on February 25, and on March 20, the Ministry of Health reported the onset of community transmission of the disease all over the national territory[7]. To slow disease spread, governmental organs advised citizens to stay at home and adopt the social distancing strategy. Despite this measure, more than 1.8 million cases of COVID-19 had been reported by July 13[8]. As for the impact of the pandemic on the care for non-COVID-19 patients, a study suggests a reduction in hospital admission for emergency conditions in Brasil[9]. However, national data of admission to cancer care are lacking in the literature.

In Brasil's Unified Health System (SUS), which provides universal access to healthcare, general practitioners are responsible for referring patients with a suspected cancer diagnosis to High-Complexity Oncology Assistance Units (UNACONs) or High-Complexity Oncology Centers (CACONs) to definite the diagnosis and treatment. The aim of this study was to analyze the epidemiologic impact of the COVID-19 pandemic on admission for high-complexity cancer care in Brasil.

METHODS

We conducted a single-institution, observational, retrospective study at a CACON located in the city of Curitiba. This CACON is the largest cancer center in southern Brasil and provides care for more than 430,000 patients per year through SUS. We performed a review of its cancer tracking database aimed at evaluating the number of patients newly referred through the public sector who attended a first-time medical appointment in the period between March and June. The same data were also collected for the same period of 2019. We included patients over 18 years old who presented to a non-hematological oncology service. If the same patient was referred to first-time appointments by different medical services, each clinical visit was counted as a different episode. Data was also analyzed in groups according to medical specialty: gastrointestinal/ urogenital, breast, gynecology, head and neck, skin, thoracic, and "other specialties", which included neurology, orthopedy, and ophthalmology services. Data about COVID-19 incidence in Brasil were obtained from official governmental websites[8]. This study was approved by the institutional ethical committee (CAAE 33544820.4.0000.0098).

Statistical analysis

Data from the pandemic period was compared with that of the equivalent period of 2019 by the Chi-squared test and differences with P <0.05 were considered statistically significant. March 20 was chosen as the cut-off date for the statistical analysis because it was the day of the onset of community transmission of COVID-19 in Brasil[7].

RESULTS

Overall, from March 20, 2020 to June 30, 2020, 1,002 newly referred patients attended a medical appointment versus 1,717 during the same period last year, which represents 715 fewer patients (-42%) (P <0.001). Comparing appointments in 2020 to those in 2019 (Figure 1), respectively, there were 122 versus 196 appointments in the period from 20 to 31 March (-38%), 278 versus 538 in April (-48%), 339 versus 501 in May (-32%), and 263 versus 482 in June (-45%). The number of appointments per week decreased in the period between March and June 2020, as the number of COVID-19 cases in Brasil increased (Figure 2). Between March 20 and June 30, a decrease in appointments was observed for all medical specialties (Figure 3): 361 versus 215 for gastrointestinal/urogenital (-40%) (P <0.001), 206 versus 122 for breast (-41%) (P <0.001), 526 versus 235 for gynecology (-55%) (P < 0.001), 145 versus 121 for head and neck (-17%) (P <0.001), 300 versus 193 for skin (-36%) (P <0.001), 87 versus 64 for thoracic (-26%) (P <0.001), and 92 versus 52 for other specialties (-43%) (P <0.001).

DISCUSSION

The main finding of the present study is the dramatic reduction (42%) in the number of first-time appointments during the COVID-19 pandemic compared to the same period the year before (Figure 1). A weekly reduction in appointments was observed as the number of COVID-19 cases increased in Brasil (Figure 2). The impact was observed for all medical specialties but was more pronounced for gynecology (Figure 3). Our data is in accordance with previous studies that identified a reduction in overall cancer referrals and in cancer diagnoses during the pandemic in the United Kingdom[4,5] and in the Netherlands[6], countries that
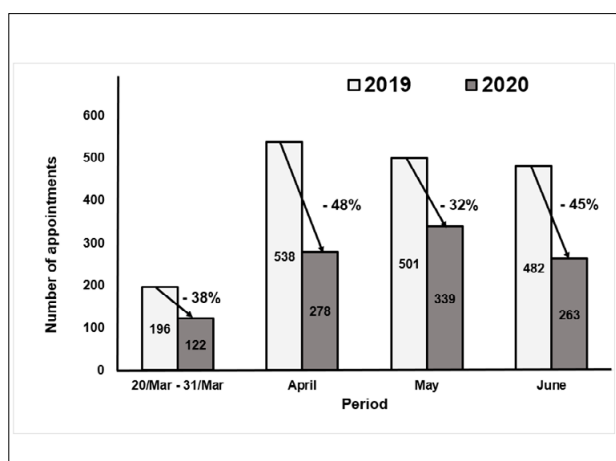
FIGURE 1.
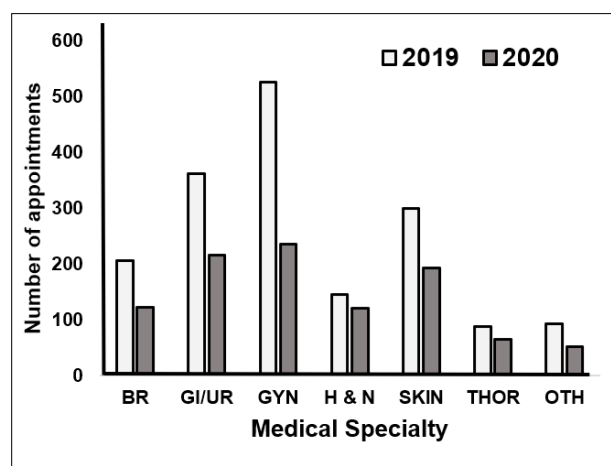
FIGURE 3.
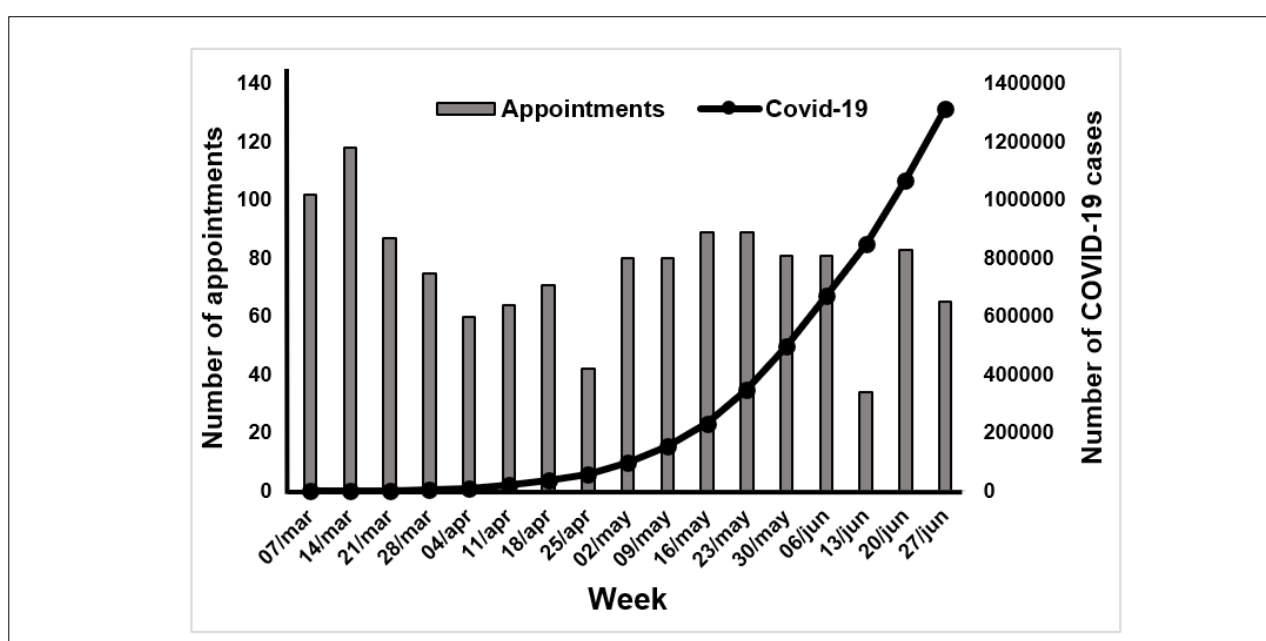
FIGURE 2.

have a public health system that provides universal access to healthcare and adopts the gatekeeping principle, similar to the SUS in Brasil.

Identifying the causes that lead to this decrease is beyond the scope of this work; however, we suggest five possible explanations. First, there may have been a reduction in cancer detection among asymptomatic individuals since the National Institute of Cancer in Brasil has issued a recommendation for physicians to postpone cancer screening exams during the outbreak. Second, potential oncology patients may have downplayed symptoms that would otherwise lead them to seek medical attention due to fear of COVID-19 or confusion about stay-at-home orders. Third, general practitioners might have postponed cancer investigations and specialized-center referrals to save healthcare resources for the management of

the COVID-19 pandemic. Fourth, the cancer center has postponed appointments considered non-urgent to minimize patient exposure. Fifth, patients may have missed medical appointments at the cancer center due to the anxiety of becoming infected at a healthcare facility. All this combined may explain fewer patients effectively getting specialized oncological care during the pandemic. Of note, despite the remarkable reduction in appointments, there was a period of slight increase and stability during the month of May (Figure 2). We suppose that this is due to a policy adopted by this CACON of using virtual means to contact patients whose appointments could not be postponed.

Cancer care delay may have a significant impact on the oncological scenario in the near future. Firstly, it is known that some tumors require immediate

diagnosis and treatment and that even short delays may impact significantly life expectancy[3,10]. Although other tumors have a lower risk of progression and can tolerate a certain delay in cancer treatment, a model-based analysis showed that a delay of six months in those cases results in a significant amount of cancer-attributable deaths since many of those tumors are common[3,10]. Secondly, postponing cancer care may cause a rebound effect and create an epidemic of cancer cases in the near future, a significant part of them upstaged, which are more expensive to treat. This has a tremendous potential to overwhelm a healthcare system that was already burdened before COVID-19.

Cancer accounts for significant morbimortality and this scenario may be worsened as a consequence of the COVID-19 pandemic[11]. A model estimated additional 6,270 deaths in England and 33,890 in the United States for new cancer cases in 1 year due to the outbreak[5]. In Brasil, cancer is also a major health issue; 626,000 new cases are expected for 2020, and 224,000 deaths were registered in 2018[12]. Since the number of COVID-19 cases is still on the rise in our country, cancer management will continue to face challenges and will require individualized decisions based on each patient's condition and each hospital's resources[8]. It is important for cancer centers to set a proactive approach for diminishing patient's exposure to COVID-19 by adapting oncological care during this unusual period, as recommended by national[13] and international[14] entities. Contacting patients to minimize their behavior changes towards cancer care is also necessary. In this pandemic context, a rapid and well-structured response is needed, as already reported by institutions in Brasil[15].

CONCLUSIONS

In conclusion, our data suggest a significant negative impact of the COVID-19 pandemic in patient admission for cancer care. Its consequences on cancer prognosis and mortality will be evaluated in the near future. As for now, it is important that cancer centers and public health strategies reinforce care for non-COVID-19 patients to prevent potentially unnecessary deaths.

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Author's Contribution

Jacqueline Nabhen: conceptualization (Lead), Data curation (Lead), Formal analysis (Lead), Investigation (Lead), Methodology (Lead), Project administration (Lead), Validation (Lead), Visualization (Lead), Writing of the Original Draft (Lead). Tayza Ostroski; Milena Kozonoe; Tiago Tormen: conceptualization (Supporting), Investigation (Supporting), Methodology (Supporting), Validation (Equal), Visualization (Equal), Review & Editing (Equal). Dinarte Orlandi: conceptualization (Equal), Data curation (Lead), Formal analysis (Lead), Methodology (Lead), Validation (Equal), Visualization (Equal), Review & Editing (Equal). Sérgio Ossamu Ioshii: conceptualization (Lead), Data curation (Lead), Formal analysis (Lead), Investigation (Lead), Methodology (Lead), Project administration (Lead), Resources (Lead), Supervision (Lead), Validation (Lead), Visualization (Lead), Review & Editing (Lead).

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The teaching of Medical Law in Brasil

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SUMMARY

OBJECTIVE: *To provide a brief overview of the teaching of medical law in Brazilian law schools, proposing a syllabus if needed.*

METHODS: *Survey the curricula of the best-ranked Law Schools in the country and reference Law Schools in the USA and Europe. Analyze the disciplines offered and their relation to the actual demands of the industry.*

RESULTS: *The offer of medical law disciplines in Brasil is very scarce and concentrated in one city (São Paulo). Most of the few existing disciplines focus on bioethical issues rather than law and lawsuits.*

CONCLUSION: *There is a need to reformulate the teaching of medical law in Brasil by including new disciplines and broadening the subjects approached.*

KEYWORDS: *Legislation. Jurisprudence. Education. Malpractice.*

INTRODUCTION

Medicine is a science that is constantly improving and evolving. But despite such innovations, practical and adequate performance in Medical Sciences still depend, primarily, on the age-old relationship between doctor and patient; thus, the lack of a consistent, durable and respectful doctor-patient relationship, allied with the belief in the ability of doctors to save lives, especially with all the technological advances, has been the source of a huge increase on the number of administrative procedures and lawsuits against physicians.

In order to investigate the increase in lawsuits in the past decade, the Regional Council of Medicine of São Paulo concluded a survey on the relationship between the medical class and the Judiciary[1], finding that there were six new lawsuits in each month of the surveyed period (the 2010s).

Subsequently, in 2018, the National Council of Justice found that claims related to medical errors totaled 70 new lawsuits per day in the country during 2017, with the caveat that the number may be higher due to methodological inconsistencies between the databases[2]. The numbers of cases in some courts, in particular, convey the size of the trend over the years: in the Superior Court of Justice, new cases about medical errors went from 466 in 2015 to 542 in 2017. In the Court of Justice of São Paulo, the largest appeal

court in the country, that number increased from 2,600 (2015) to 4,600 (2017).

In this scenario, adequate performance of lawyers is fundamental, as they should be able to confidently analyze the possibility of medical malpractice and the scope of civil, criminal, and/or administrative liabilities, knowing how to differentiate between medical error and the normal occurrences of the daily practice of an inherently inaccurate science.

Despite the importance of the subject and the broad scope of practice of lawyers who enter the field of medical law, undergraduate medical and law courses offer little to no teaching on the subject.

METHODS

The current scenario of Medical Law instruction in Brasil was obtained through a survey of various Brazilian law schools, selected by their prominent position in the national scenario according to the national university rankings and carried out by analyzing the curriculum and syllabus of the courses,

as made available on the online portal of each of the faculties. For Law Schools abroad, the same approach was used.

The results were selected and discussed under the optics of the Brazilian scenario on medical malpractice lawsuits and Brazilian law.

RESULTS

In the United States, of the 27 disciplines of Medical Law being offered, eighteen are about public policy issues on health, health care, and the national health system. There are also disciplines that deal with themes of bioethics - 08 - and technological innovation in medicine and its consequences - 07.

On the European front, the disciplines were found to be offered in only five countries - England (two), Germany, Spain, Italy, and Switzerland (one each), and the prevalent theme in the courses was bioethics. Other topics, such as public health, medical liability, forensic practice, and aspects of medical innovation, are also taught to a lesser extent.

Number of Medical Law Courses

Subjects taught (Brazil only)

Courses per state

Courses per city
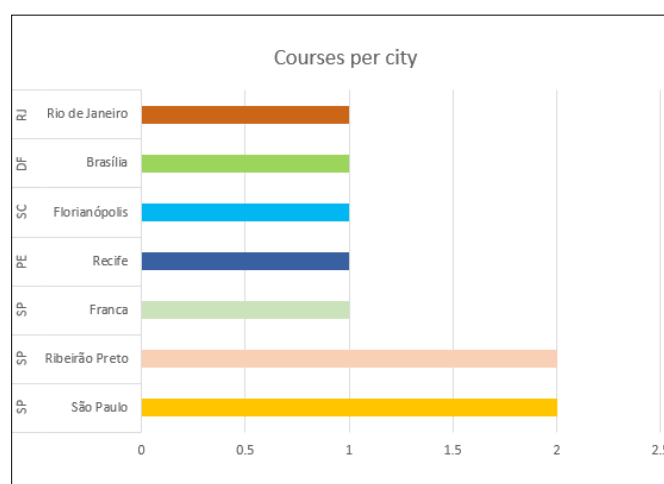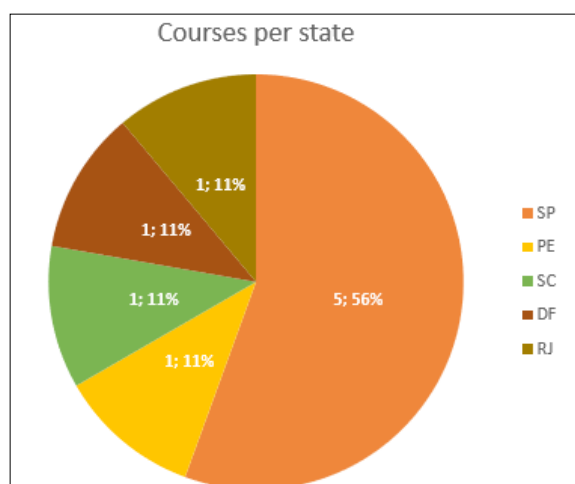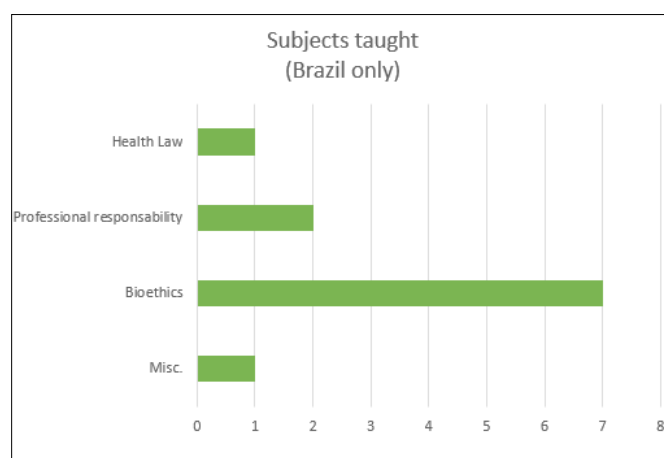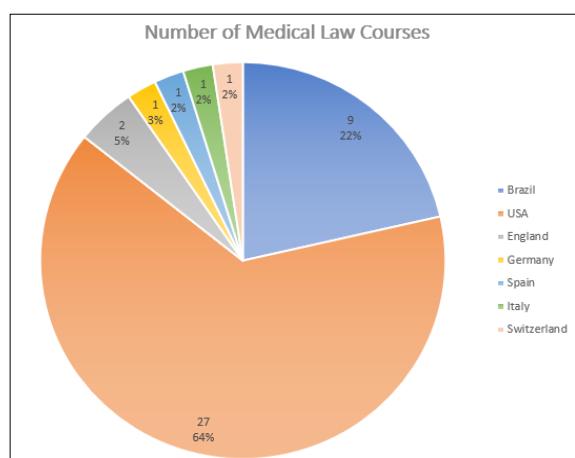
Of these nine disciplines found in Brasil, the most covered topic is bioethics. Medical liability, including the allegation, characterization, and accountability of medical error, and confidentiality issues, are addressed in only one-third of the disciplines.

Of all the nine courses offering undergraduate medical law and/or bioethical disciplines, it is of note that five (approx. 55%) are in the state of São Paulo – two of which are in the capital, meaning that the city of São Paulo concentrates approximately 22% of all undergraduate courses that offer subjects related to the theme at hand. Of the ones that were considered adequate, 2/3 are located in the state of São Paulo.

DISCUSSION

Concerning the development of students to act in the defense of medical professionals, only three courses provide adequate subsidies: the University of São Paulo School of Law – São Paulo *campus*, Federal University of Pernambuco School of Law, and São Paulo State University School of Law – Franca *campus*.

On all nine disciplines that were considered, the topic of bioethics deals with issues such as the beginning and end of life, questions on organ transplantation and fertilization treatments, all important issues that bring controversial topics to law students, all of which can be answered in various ways from the medical point of view.

On the other hand, professional liability and health law issues are addressed in only one-third of the disciplines, a worrying scenario, since this is the main theme which lawyers will come across, as well as the one that has the greatest repercussions on the personal and professional life of medical professionals.

Another much-missed point in the legal curriculum is the specific approach to judicial and administrative proceedings. Only two undergraduate disciplines provide students with insight into the specifics of judicial proceedings in medical matters, while only one of them presents the issue of the administrative procedures involved.

Thus, it is clear that the focus of the - incipient - teaching of medical law in the country is the discussion around bioethical themes, which serves more to the creation of jurists than working lawyers. In order to verify how much this profile differs - or not - from the scenario of international medical law teaching, we present these points in other western countries.

This is a worrisome scenario, as the offer of Medical Law disciplines in undergraduate courses in Brazilian institutions is very meager, hindering the formation of qualified professionals to meet a demand constantly on the rise and which deals with rather specific issues and involves individuals who deal daily with the lives of individuals.

The lawyers' responsibility in defending a doctor is inarguably high. Not only because of the seriousness of the offenses that are often involved in the matter, including manslaughter, but also because the entire career and reputation of another professional is at stake.

Thus, as noted, professionals who choose this path, being under-served in terms of academic education at the undergraduate level, need to search for specializations or even learn the subject during the unforgiving day-to-day forensic activities.

Regarding the results around this matter in the United States, one can assume the focus found may be due to the intense debate that ensued after the 2010 approval of the *Patient Care and Affordable Care Act* and the subsequent changes to the public health system with Medicare and Medicaid. In addition, these are themes that are strongly linked to the US research and development industry, which is a center of innovation in both diagnostic technologies and pharmaceutical advances.

As occurs in Brasil, disciplines of Medical Law and medical liability in cases of error, so common in the medical and legal professional practice in the United States, have little presence - approximately 14% and 10%, respectively, despite the strong litigious culture of the country.

Interestingly, there are two subjects - one at Harvard School of Law and the other at Stanford School of Law - which are open to both medical and law students, providing an extremely healthy exchange of experiences and expectations.

In the survey of the main European Universities, it can be theorized that the scenario found is due to the fact that the curriculum in such countries follows a more traditional line, with a theory-oriented formation, in countries that do not have intense debates about access to public health, nor an exacerbated litigation scenario like the United States of America.

It is interesting to note that in Germany there is an area of Medical Law that addresses civil and criminal issues, as well as public health and bioethical issues. It is an interesting option for a more complete and

focused formation and was a unique occurrence in the present survey.

There are some points in our legislation that are worth discussing when it comes to medical law since it adds to the importance of the theme as an autonomous discipline. Students and lawyers must be equipped with knowledge in various areas since there are peculiarities to the medical profession that permeate multiple sectors of the law.

In the criminal area, for example, it is relevant to note that there is the so-called "duty of guarantor" by the medical professional - pursuant to art. 13, §2º of the Criminal Code - which generates several consequences in the field of criminal authorship and culpability, especially when acts practiced by a medical team are added to the mix.

Still in the criminal sphere, there are some crimes in the Criminal Code that are called specific, that is, can only be committed by health professionals, such as the omission of notification of disease (art. 269), the illegal exercise of medicine (art. 282), the falsehood of medical certificate (art. 302), and a specific form of violation of preventative sanitary measure (sole paragraph of art. 268).

In the civil sphere, issues regarding the definition of medical liability as contractual or non-contractual, objective or subjective should be debated. Another point of extreme importance - and which was not found in any curriculum - is the determination if the obligation of professionals is based on the use of the adequate means or the final result, a distinction that has numerous repercussions in the spheres of responsibility and probative burden, for example.

In close relation to the above theme, there is a need to discuss the framing of the medical activity as the provision of services that can be protected by the Consumer Protection Code, and the various consequences stemming from this.

Still, there is room for discussion of a recent issue, which is the field of compliance and its possible application to medical professionals, being the lawyer then able to create standards of conduct that enable the prevention of errors, distribute responsibilities appropriately, and conduct investigations and evidence production in the best possible way.

Another innovative issue is the possibility of using Mediation, which may revolutionize civil forensic practice regarding the composition of damages and the reaching of agreements.

In addition to the topics mentioned, the procedural consequences are numerous, ranging from administrative procedures (within the scope of class bodies or public administration), which have specific rules, to legal proceedings that may involve both the Special Courts (civil or criminal) as well as, eventually, proceedings before a Jury.

In addition, and to name but a few, the need to discuss public health policies at Universities, such as access to basic health and the issue of drug addiction, should not be overlooked.

This brief exposition shows that topics are varied and go far beyond the ever-present bioethical discussions, with a wide field of professional practice to be explored in the formation of lawyers, with diverse peculiarities and unique procedural developments, including the possibility of breaking new ground - such as the use of *compliance* and mediation.

What is missing, therefore, is not the possibility or breadth of activity in the field of medical law, but a less shortsighted view of undergraduate curriculums to these possibilities.

Given the above, the question that remains is: how can the scarcity of medical law disciplines and the superficiality of the curricula be solved?

Clearly, the first step should be to broaden the range of law schools that have medical law disciplines in their curricula. Also, the disciplines dealing with medical law and bioethics, especially with regards to professional liability, must be expanded.

Such basic training is relevant not only for the defense of professionals - pre-emptively or in the course of procedures - but also for enforcing the rights of patients or their families.

In addition to the dissemination of medical law teaching in the country, it is also interesting to include some topics in the curriculum, such as the relationship between patients' demands and public health policies, the rights of consumers and doctors regarding health plans, and the application of the law on medical innovation.

Another relevant point is the constant updating of curricula, with the inclusion of topics such as mediation and *compliance*, and the discussion of political and social issues.

CONCLUSION

Given the above, we suggest a brief draft of a syllabus in medical law that provides a broad background for undergraduate students.

Block 1: Bioethics

- Principles of Bioethics
- Themes on the beginning and end of life: abortion, euthanasia, dystania, assisted suicide, etc.
- Human reproduction, fertility, and sterilization
- Research in humans and animals
- Organ donation and transplantation
- Genetic and drug patenting
- Patient autonomy and freedom of treatment
- The relationship with the pharmaceutical industry and hospitals

Block 2: Medical Responsibility
- Concept of liability: civil law, criminal law, and administrative law
- Criminal liability: duty of guarantor
- Crimes specific to health professionals
- Liability: obligation of means or of outcome?
- Medical error: main causes and consequences

Block 3: Procedures - General
- Administrative Procedures: Class Organs
- Administrative Procedures: Public Sector Inquiries
- Civil proceedings: specials courts and indemnity actions
- Criminal Proceedings: From Special Courts to the Jury Court
- The state interfering with medical care: do's and don'ts
- Collaboration with authorities: police inquiries and lawsuits

Block 4: Prevention and Containment of Damage
- Medical records: concept and use as a protection tool
- Compliance: Concepts and application possibilities
- Composition through mediation

Block 5: Discussion of topics of interest
- Technological advances against the principles of bioethics
- Neuroscience and culpability: definition of free will
- Issues of public health: National Health Service, epidemics, primary medicine
- Debates about legislative changes and public policy
- The society of risk: judicialization

As can be seen, the subjects to be addressed are several, requiring a curriculum space of at least two semesters. Still, Block 5 can, at the teacher's discretion, be divided into optional subjects, enriching the undergraduate curriculum and fostering debate and the generation of ideas. This can, if applied well, put the country at the forefront in teaching and applying medical law, ensuring a healthier environment for patients and health professionals.

Notes

There were no financial or any other relationships linked to the work done in this manuscript. There are no conflicts of interest.

Author's Contribution

All authors have contributed equally

RESUMO

OBJETIVO: *Apresentar um breve panorama da situação do ensino do direito médico nas faculdades de direito brasileiras, com a proposta de uma matriz curricular, se necessário.*

MÉTODO: *Levantamento dos currículos das Faculdades de Direito mais bem classificadas do país e das Faculdades de Direito de referência nos EUA e Europa. Análise das disciplinas oferecidas e sua relação com as reais demandas da área.*

RESULTADOS: *A oferta de disciplinas de direito médico no Brasil é muito escassa e concentrada em uma cidade (São Paulo). A maioria das poucas disciplinas existentes enfoca questões bioéticas, em vez de leis e ações judiciais.*

CONCLUSÃO: *há necessidade de reformulação do ensino do direito médico no Brasil, com inclusão de novas disciplinas e ampliação das disciplinas abordadas.*

PALAVRAS-CHAVE: *Legislação. Jurisprudência. Educação. Imperícia.*

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Assessment of the hemogram parameters in patients with paroxysmal supraventricular tachycardia: a retrospective study

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SUMMARY

OBJECTIVE: *Inflammation has been suggested as a potential mechanism in the pathogenesis of arrhythmia. Hemogram parameters such as monocyte count to high-density lipoprotein cholesterol ratio (MHR), neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) have been considered to be markers of inflammation and new cardiovascular risk predictors. This retrospective study aimed to investigate the relationship between MHR, NLR, and MLR in patients with paroxysmal supraventricular tachycardia (PSVT).*

METHODS: *A retrospective study conducted at a university hospital in Bolu, Turkey, between 2017 and 2019. Our study included 196 patients who underwent electrophysiological study (EPS) due to palpitation or documented PSVT on electrocardiography (ECG). Patients having documented atrioventricular nodal re-entrant tachycardia (AVNRT) on ECG or inducible AVNRT on EPS were included in the PSVT group (n=130), and patients with palpitation but without inducible arrhythmia on EPS (n=66) were included in the control group. Routine biochemical and hemogram tests were performed before the EPS procedure.*

RESULTS: *When hemogram parameters were compared, there was no statistically significant difference in MHR values [0.010 (0.001-0.030) vs 0.010 (0.001-0.020) p =0.67]. Additionally, both NLR [2.21(0.74-11.36) vs 1.98(0.72-24.87) p=0.13] and MLR [0.25 (0.03-1.05) vs 0.24(0.07-1.39) p=0.41] were not statistically significant between the two groups.*

CONCLUSION: *There is no significant difference in PSVT patients regarding hemogram parameters including white blood cell subtypes, MLR, NLR, and MHR. Therefore the evaluation of hemogram parameters may not be clinically relevant for PSVT patients.*

KEYWORDS: *Inflammation. Tachycardia, supraventricular. Blood cell count. Monocytes. Lipoproteins, HDL.*

INTRODUCTION

Paroxysmal supraventricular tachycardia (PSVT) is characterized by the sudden onset and abrupt termination of tachycardia[1]. Most patients have no associated structural heart disease. Enhanced automaticity, triggered activity, and re-entry are among the mechanisms for PSVT[2]. The mechanism for tachycardia may be induced by pharmacologic and pacing maneuvers[3]. Atrioventricular nodal re-entrant tachycardia (AVNRT) is the most common type of PSVT[2].

Inflammation has been suggested as a potential mechanism in the pathogenesis of arrhythmia[4,5]. White blood cells (WBC) and their subtypes are among inflammatory markers and have been associated with cardiovascular disorders[6]. Recently, monocyte count to HDL-C ratio (MHR), which is obtained by dividing monocyte count by HDL cholesterol, has been reported to be a novel indicator in cardiovascular diseases[7]. There are few and contradictory reports about the association of PSVT and hemogram parameters[8-10]. And, as far as we know, there is no data for MHR and PSVT association.

OBJECTIVE

In this study, we aimed to investigate the relationship between PSVT and hemogram parameters and MHR.

METHODS

A retrospective cross-sectional design was used. After institutional approval, patients who underwent electrophysiological study (EPS) and catheter ablation of PSVT between December 2017 and September 2019 at our center were included. Patients' data were obtained from the computer records and files of our hospital. The study was approved by the institutional board (33443051-903.99).

We included 196 patients who underwent EPS due to palpitation or documented SVT on ECG. Patients having documented AVNRT on ECG or inducible AVNRT on EPS were included in the PSVT group, and patients with palpitation and without inducible arrhythmia on EPS were included in the control group.

The exclusion criteria included recent infection or surgery, morbid obesity (body mass index ≥35 kg/m2), severe renal or liver dysfunction, heart failure, coronary artery disease, moderate to severe valvular diseases, chronic obstructive pulmonary disease, peripheral or cerebral vascular disease, hematological disorders, malignancies, inflammatory diseases, and drug use (including antiarrhythmic agents).

Venous blood samples were drawn from the antecubital vein at the initial presentation before the EPS procedure. In order to determine hemogram parameter values, the blood samples were analyzed in the Beckman Coulter Device (Beckman Coulter In.; Bre CA) within 15 minutes. Basic biochemical tests and several hemogram parameters like WBC, leukocyte subtypes [neutrophil (NEU), monocyte (MONO), and lymphocyte (LYM) counts], hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), red blood cell distribution width (RDW), platelet (PLT) count, platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT) were measured, and neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), RDW/platelet ratio (RPR), mean platelet volume/platelet ratio (MPR), and monocyte/lymphocyte ratio (MLR) and monocyte count/HDL cholesterol ratio (MHR) were calculated.

STATISTICAL ANALYSIS

Data were evaluated using SPSS version 16.0 (SPSS 16.0; SPSS Inc., Chicago, IL, USA). The normality of the variables was tested with the Kolmogorov-Smirnov method. The student t-test was used for the comparison of normally distributed variables, and these data were expressed as mean ± standard deviation (SD). The Mann-Whitney U test was used for the comparison of non-normally distributed variables, and these data were expressed as median (min-max). The Chi-square test was used for the comparison of categorical variables. P<0.05 values were considered statistically significant.

RESULTS

A total of 196 patients were included in the study. There were 130 patients in the PSVT group (Group 1) and 66 patients in the control group (Group 2). Baseline demographic variables including age, sex, frequencies of hypertension, and diabetes were not significantly different between the groups (Table 1).

TABLE 1. DEMOGRAPHICS AND CLINICAL

Characteristics of the patients			
	Study Group	Control Group	P-value
Number of patients (n)	130	66	
Age (years)	51±15	48±18	0.24
Gender			0.48
Male	56 (%43.0)	25 (%38.0)	
Female	74 (%57.0)	41 (%62.0)	
Comorbid Disease			
Hypertension (%)	40 (31%)	23(35%)	0.56
Diabetes mellitus (%)	17(13%)	15(23%)	0.08

Values are expressed as mean (SD) or n (%).

Laboratory findings and studied hemogram parameters were also not significantly different between the groups (Table 2, Figure 1).

DISCUSSION

In this study, we have found that hemogram parameters including MPV, NLR, monocyte count, and MHR were not significantly different in the PSVT

FIGURE 1. MHR, NLR, MPV AND MONOCYTE COUNT DISTRIBUTION OF THE SVT AND CONTROL GROUPS
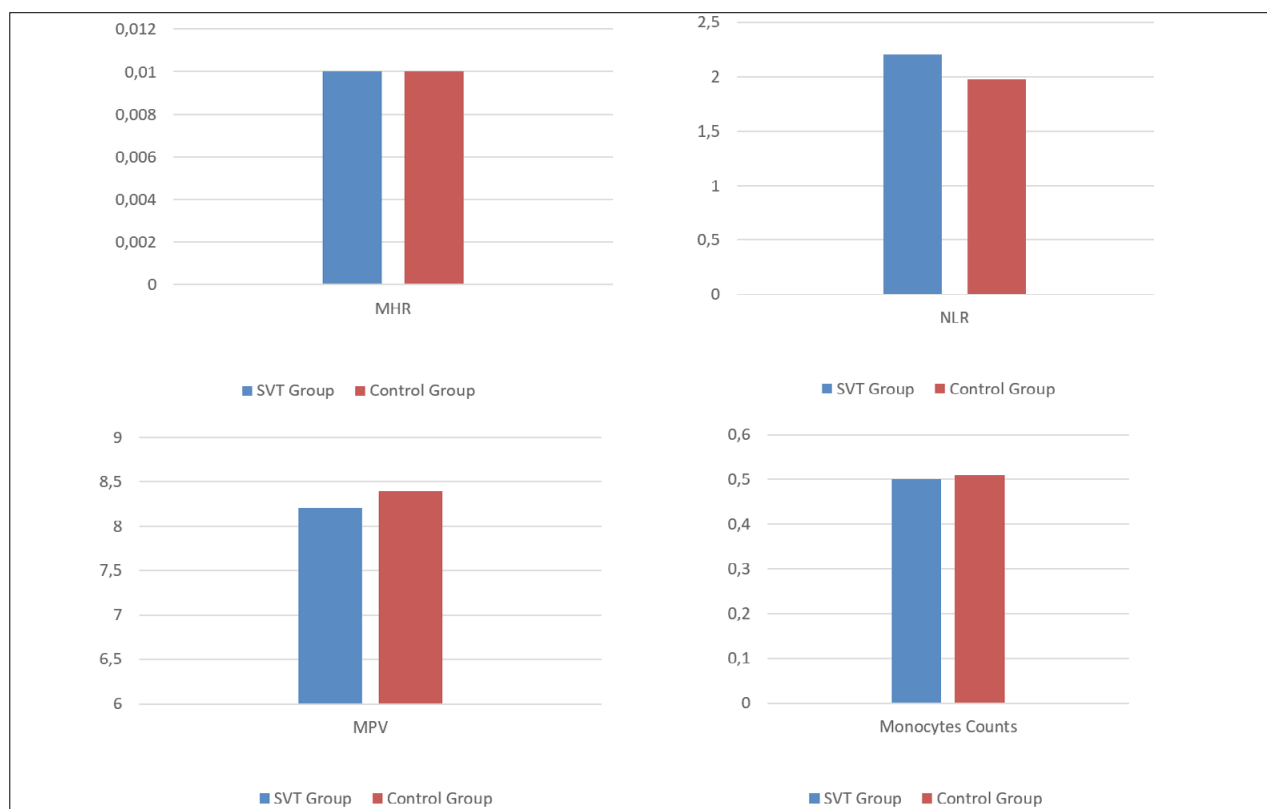
MHR, monocyte/high-density lipoprotein cholesterol ratio; NLR, neutrophil/lymphocyte ratio ; MPV, mean platelet volume.

TABLE 2. LABORATORY DATA OF THE STUDY COHORT

	Study Group	Control Group	P-value
Hemoglobin (gr/dl)	13.7±1.5	13.5±1.6	0.31
Platelet counts (k/mm3)	247±56	253±56	0.48
RDW	14.64±1.28	15.72±1.43	0.69
PDW	17.6±1.2	17.5±1.4	0.68
MPV	8.2±1.3	8.4±1.4	0.39
PCT	0.21±0.04	0.21±0.05	0.38
Monocytes, ×109/L	0.50(0.04-0.92)	0.51(0.23-0.94)	0.62
NLR	2.21(0.74-11.36)	1.98(0.72-24.87)	0.13
MHR	0.010(0.001-0.030)	0.010(0.001-0.020)	0.67
MLR	0.25(0.03-1.05)	0.24(0.07-1.39)	0.41
MPR	0.03(0.02-0.11)	0.03(0.02-0.07)	0.84
PLR	117.2(38.5-656.08)	108.5(48.3-1492.2)	0.34
Creatinine (mg/dl)	0.80 (0.57-1.48)	0.79(0.45-1.44)	0.88
Fasting plasma glucose (mg/dl)	90(70-240)	91(71-216)	0.31
HDL-cholesterol (mg/dl)	50(27-89)	49(32-84)	0.82

Values are expressed as mean (SD) or Median (Min-Max). HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TG, triglyceride; WBC, White blood cell; RDW, Red blood cell distribution width; PDW, Platelet distribution width; MPV, Mean platelet volume; PCT, Plateletcrit; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; MPR, Mean platelet volume/platelet ratio; MLR, Monocyte/lymphocyte ratio; MHR, Monocyte/high-density lipoprotein cholesterol ratio.

patient and control groups. Inflammation is a common condition seen in many pathological states. Inflammatory pathogenesis has also been claimed for coronary artery disease, heart failure, and arrhythmias[5,11]. Likewise, inflammation has been suggested to have an important role in PSVTs[12].

Several mechanisms have been accused of an association between systemic inflammation and arrhythmogenesis. Inflammatory cytokines may play a particular role in arrhythmogenesis through a potential reduction in the arrhythmogenic threshold in arrhythmia-prone patients[4,13,14]. For instance, TNF-α was suggested to exert its arrhythmogenic effects at the cellular level through electrophysiological abnormalities, which may be associated with enhanced automaticity and reentrant loops, like the hyperactivation of sodium channels with abnormal calcium handling and increased action potential duration[15].

Currently, hemogram parameters are, in general, recognized as inflammatory markers and prognostic determinants in a wide spectrum of diseases. These hemogram parameters have been evaluated as new predictors of cardiovascular risk[6,7].

It has been suggested that increased MPV was correlated with inflammation in several conditions[16]. Ocak et al.[9] demonstrated that MPV was significantly higher in patients with documented SVT. In this retrospective study, 122 patients arriving at the emergency department with documented SVT on ECG and 100 healthy adults were analyzed. They found that, among hemogram parameters, hemoglobin, neutrophil count, MCV, RDW, platelet, WBC, and lymphocyte counts were similar to the control group, whereas MPV was significantly higher in SVT patients. However, we couldn't confirm their finding in the present study.

NLR has been suggested as an indicator of inflammation[17]. Aydın et al.[10] studied 150 patients who underwent catheter ablation of SVT and 98 healthy subjects. In this retrospective cross-sectional study, they reported that higher values of NLR were associated with SVT. Furthermore, NLR values were higher in patients in whom tachycardia was induced during EPS than those in whom tachycardia was not induced. However, Küçük et al.[8] recently studied 33 SVT patients and 26 control subjects who underwent EPS and suggested that NLR and MLR values were not significantly different. In accordance with Küçük et al.[8], we have also found similar NLR values in PSVT patients and in the control group.

Monocytes are the largest type of WBC and have a major role in the inflammatory process of atherosclerosis[18]. High-density lipoprotein cholesterol (HDL-C) shows anti-inflammatory and anti-oxidant properties by inhibiting the transmigration of monocytes. Higher levels of HDL-C are associated with reduced cardiovascular disease risk[19]. Therefore, the integration of these two measurements as MHR can be used as an indicator of inflammation[6,20-23]. Accordingly, MHR has been suggested as a new prognostic marker in several cardiovascular disorders[23-25]. Regarding monocyte counts, Küçük et al.[8] have found no significant difference in SVT patients. In the present study, we have also found that MHR was not increased in SVT patients.

Limitations

This is a single-center, retrospective small study. Lack of measurement of other inflammation markers like CRP, TNF-α, and interleukins is another major limitation.

CONCLUSION

We have found no significant difference in PSVT patients regarding none of the hemogram parameters including WBC subtypes, MPV, NLR, and MHR. Therefore, the evaluation of hemogram parameters may not be clinically relevant for PSVT patients.

Potential Conflicts of Interest

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

Sources of Funding/ Study Association

There were no external funding sources for this study.

This study is not associated with any thesis or dissertation work.

Author's Contribution

Concept and design of the research: Cosgun M. Acquisition of data and financing: Cosgun M. Analysis and interpretation of the data, statistical analysis, and critical revision of the manuscript for intellectual content: Cosgun M, Yilmaz Gunes, Isa Sincer, Asli Kurtar Mansiroglu. Writing of the manuscript: Cosgun M, Yilmaz Gunes.

Place or institution where the work was developed, city and country: Bolu Abant Izzet Baysal University, Gölköy, Bolu/Turkey

RESUMO

OBJETIVO: *A inflamação tem sido sugerida como um mecanismo potencial na patogênese da arritmia. Parâmetros do hemograma, como contagem de monócitos e razão de colesterol lipoproteína de alta densidade (MHP), proporção de neutrófilos / linfócitos (NLP) e proporção de monócitos / linfócitos (MLR), foram considerados marcadores de inflamação e novos preditores de risco cardiovascular. Este estudo retrospectivo teve como objetivo investigar a relação entre MHP, NLP e MLP em pacientes com taquicardia paroxística supraventricular (PSVT).*

MÉTODOS: *Estudo retrospectivo realizado em um hospital universitário em Bolu, Turquia, entre 2017 e 2019. Nosso estudo incluiu 196 pacientes submetidos a estudo eletrofisiológico (EPS) devido a palpitações ou PSVT documentada na eletrocardiografia (ECG). Os pacientes com taquicardia nodal atrioventricular reentrante (AVNRT) no ECG ou AVNRT indutível no EPS foram incluídos no grupo PSVT (n = 130) e os pacientes com palpitações sem arritmia induzível no EPS (n = 66) foram incluídos no grupo controle. Testes bioquímicos e de hemograma de rotina foram realizados antes do procedimento de EPS.*

RESULTADOS: *Quando os parâmetros do hemograma foram comparados, não houve diferença estatisticamente significante nos valores de MHP (0,010 (0,001-0,030) vs 0,010 (0,001-0,020) p = 0,67). Além disso, tanto o NLP (2,21 (0,74-11,36) vs 1,98 (0,72-24,87) p = 0,13) quanto o MLP (0,25 (0,03-1,05) vs 0,24 (0,07-1,39) p = 0,41) não foram estatisticamente significantes entre os dois grupos.*

CONCLUSÃO: *Não há diferença significativa nos pacientes com PSVT em relação aos parâmetros do hemograma, incluindo os subtipos de glóbulos brancos, MHP, NLP e MHP. Portanto, a avaliação dos parâmetros do hemograma pode não ser clinicamente relevante para pacientes com PSVT.*

PALAVRAS-CHAVE: *Inflamação. Taquicardia supraventricular. Contagem de células sanguíneas. Monócitos. Lipoproteínas HDL.*

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Factors associated with student performance on the medical residency test

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SUMMARY

OBJECTIVE: *To determine whether the scores of the Progress test, the Skills and Attitude test, and the medical internship are correlated with the medical residency exam performance of students who started medical school at the Federal University of São Paulo in 2009*

METHODS: *The scores of 684 Progress tests from years 1-6 of medical school, 111 Skills and Attitude exams (5th year), 228 performance coefficients for the 5th and 6th years of internship, and 211 scores on the medical residency exam were analyzed longitudinally. Correlations between scores were assessed by Pearson's correlation. Factors associated with medical residency scores were analyzed by linear regression.*

RESULTS: *Scores of Progress tests from years 1-6 and the Skills and Attitude test showed at least one moderate and significant correlation with each other. The theoretical exam and final exam scores in the medical residency had a moderate correlation with performance in the internship. The score of the theoretical medical residency exam was associated with performance in internship year 6 (β=0.833; p<0.001), and the final medical residency exam score was associated with the Skills and Attitude score (β=0.587; p<0.001), 5th-year internship score, (β=0.060; p=0.025), and 6th-year Progress test score (β=0.038; p=0.061).*

CONCLUSIONS: *The scores of these tests showed significant correlations. The medical residency exam scores were positively associated with the student's performance in the internship and on the Skills test, with a tendency for the final medical residency exam score to be associated with the 6th-year Progress test.*

KEYWORDS: *Medical school; Progress test; Medical internship; Medical residency.*

INTRODUCTION

The form and content of medical student evaluations of should cover the acquired knowledge as well as specific skills and elements of their affective nature, such as attitudes towards professional practice.[1] The "Miller pyramid" is a model to define the learning outcomes in terms of the skills students should acquire, and it provides the cognitive bases ("knows" and "knows how") of professional practice ("does") and the need to evaluate practical skills and competencies ("shows how").[2]

"Knows" refers to methods that evaluate knowledge, which can be recovered from memory, and supports the construction of more complex capabilities. Both "knows" and "knows how" belong to the cognitive domain and therefore should be evaluated by appropriate methods for measuring knowledge

acquisition. However, they differ in the nature of the knowledge they refer to: "Knows" is more related to the theoretical domain, whereas "knows how" is an applied type of knowledge. Thus, the tests proposed for this stratum should target the use of knowledge for decision-making and problem-solving within a clinical context. The "shows how" refers to the evaluation of clinical skills and competencies that are performed in the context of training. This skill set is usually evaluated through practical exams involving clinical tasks. The evaluation of "does" corresponds to the practice in the work environment. It is tested in the student at the end of the course, in the professional training stages, where training targets the practice of "does", with the student exercising the clinical practice under supervision.

Among the various forms of applied evaluations, the Paulista School of Medicine of the Federal University of São Paulo (EPM-UNIFESP) has evaluated the performance of students using the Progress test (PT), the Skills and Attitude test (SA), and the performance coefficient (PC) during the medical internship.

In this context, the objective of this study was to determine whether the PT scores from the first to the sixth year of medical school, the SA score, and the PC during the medical internship were correlated with the medical residency (MR) scores of the students who started medical school at the Paulista School of Medicine - Federal University of São Paulo (EPM-UNIFESP) in 2009.

METHODS

This was a retrospective study that employed a longitudinal analysis of the PT scores, SA score, and PC during the 5th and 6th medical school years (PC 5th and PC 6th) and the exam of the MR. This study was approved by the Research Ethics Committee of UNIFESP. The data included the scores on the PT from the 1st to the 6th medical school years, the score on the SA performed in the 5th year, the PC in the 5th and 6th years, and the score on the theoretical test and the final test result of the 2015 MR among the students who in 2009 were enrolled in the 1st year of medical school at EPM-UNIFESP.

The PT, which was voluntarily taken by the students, consisted of 120 multiple-choice questions about medicine and was written and administered together with the institutions that are part of the Núcleo Interinstitucional de Estudos e Práticas de

Avaliação em Educação Médica (Interinstitutional Center for Studies and Practices of Medical Training Evaluation).

The voluntary SA consisted of 10 stations with different clinical tasks, such as obtaining a clinical history, performing the clinical examination, evaluating a radiograph or electrocardiographic tracing, and giving the diagnosis and/or instructing the patient. This test was designed and administered similarly to the Objective Structured Clinical Examination (OSCE).

The PC is an index that measures academic performance at the end of each academic period. It is calculated based on the final grade and workload in each curricular unit.

The MR test was performed in two phases. The first phase had a theoretical test with 100 assertive questions with short answers and a computerized test with 50 questions with images. The second phase was in the form of four practical stations (12 boxes). The final result of the MR test was the sum of the theoretical test score (weight 5), the practical test score (weight 4), and the interview score (weight 1).

The scores of students who did not complete the PT in all years of the medical course were excluded.

Reliability analysis of the collected data was performed, the correlations between the scores of all tests were calculated, and the factors associated with the scores of the theoretical test and the final result of the MR test were identified.

Statistical analysis

The numerical variables are expressed as the mean and standard deviation and were compared by the paired t-test. Data reliability was assessed by Cronbach's α coefficient,[3] which was considered adequate when > 0.7.[4] For the correlation analysis, Pearson's correlation coefficient was calculated, where 0.1 to 0.3 was considered a weak correlation, 0.3 to 0.6 was considered a moderate correlation, and 0.7 to 1.0 was considered a strong correlation. [5]

Two linear regression models were constructed. The dependent variable of one of the models was the theoretical test score, while the dependent variable of the other model was the final result of the MR test. In the univariate linear regressions, the scores of the various tests were regressed on, and those with $p < 0.2$ were included in the multiple linear regression model.

Statistical analyses were performed in SPSS® software (IBM SPSS Statistics, Somers, NY, USA), with a significance level of $p < 0.05$.

RESULTS

In 2009, 123 students enrolled in the 1st year of the medical school at EPM-UNIFESP. Of these, 114 (92.7%) performed all PT tests from 2009 to 2014, and 111 (90.2%) performed the SA in the 5th year. Of the 114 students included in the study, 106 (93.0%) completed the theoretical MR test, and 105 (92.1%) completed all stages of the MR tests at EPM-UNIFESP (Figure 1).

The data reliability analysis showed internal consistency between the scores of all tests analyzed (0.730, 95% CI: 0.646 to 0.802 (p <0.001)). The data reliability had an α of 0.749 (95% CI: 0.669 to 0.815 (p < 0.001)) if the scores of the 1st-year PT or the SA score were deleted. This difference was small, so the scores of all tests were included in the analysis.

Some students received a score of 0 on the PT, to wit, four students in the 1st school year, one student in the 2nd year, one student in the 3rd year, two students in the 4th year, six students in the 5th year, and five students in the 6th year. The mean ± SD of PT scores (n = 114 for each year) were as follows: 1st year (2.67 ± 0.97), 2nd year (3.01 ± 0.70), 3rd year (4.19 ± 1.13), 4th year (4.01 ± 1.05), 5th year (5.19 ± 1.56), and 6th year (6.38 ± 1.80) (Figure 2). There was a significant increase (p <0.05) between the PT scores of consecutive years, except from the 3rd to the 4th school year. Between the 1st and 6th school years, there was a considerable increase in the PT score (Figure 3).

The mean of the 111 SA scores was 7.53 ± 0.56. The scores of PC 5th (n = 114) were 8.32 ± 0.29 and PC 6th (n = 114) were 8.26 ± 0.28 (p <0.001) (Figure 2).

Of the 114 students included in the study, 106
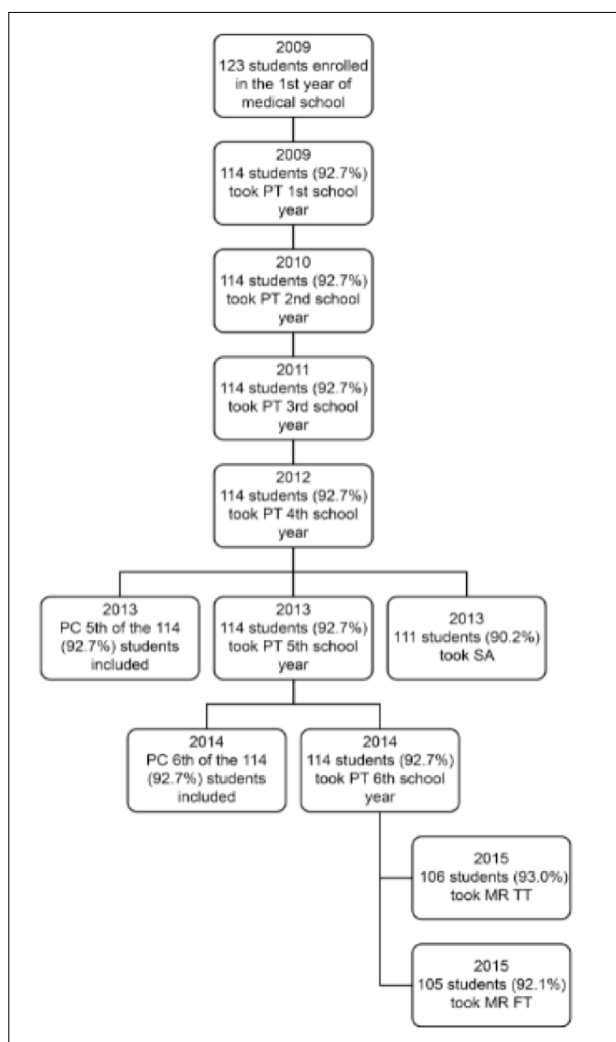
FIGURE 1. FLOWCHART OF THE STUDENTS INCLUDED IN THE STUDY. PT: PROGRESS TEST; PC: PERFORMANCE COEFFICIENT DURING THE INTERNSHIP; SA: SKILLS AND ATTITUDE TEST; MR TT: MEDICAL RESIDENCY THEORETICAL TEST; MR FT: MEDICAL RESIDENCY FINAL TEST.
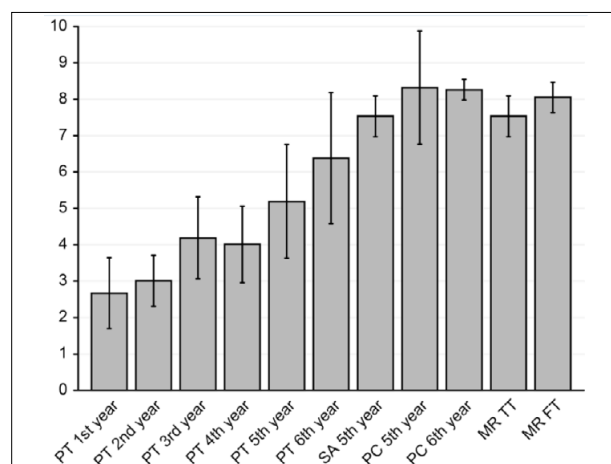
FIGURE 2. MEAN ± STANDARD DEVIATION OF THE STUDENTS' SCORES ON THE PROGRESS TEST (PT) FROM THE 1ST TO THE 6TH SCHOOL YEAR, SKILLS AND ATTITUDE TEST (SA), PERFORMANCE COEFFICIENT (PC) OF THE 5TH AND 6TH SCHOOL YEARS, MEDICAL RESIDENCY THEORETICAL TEST (MR TT), AND MEDICAL RESIDENCY FINAL TEST (MR FT) (P < 0.05).
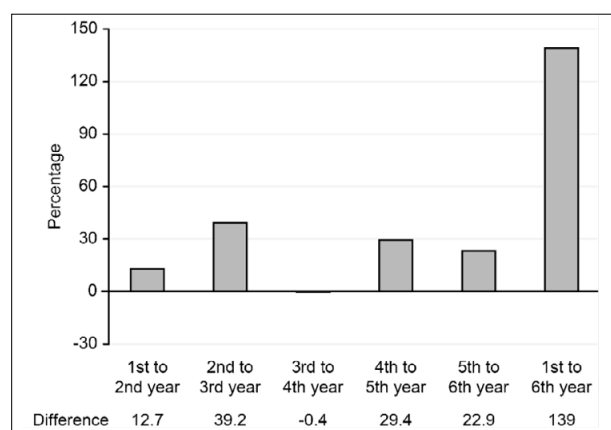
FIGURE 3. DIFFERENCE ON THE PROGRESS TEST MEANS (%) Y-AXIS: PERCENTAGE

TABLE 1. PEARSON'S CORRELATION BETWEEN THE SCORES OF THE PROGRESS TEST, THE SKILLS AND ATTITUDE TEST, THE PERFORMANCE COEFFICIENTS AT THE 5TH AND 6TH SCHOOL YEARS, AND THE SCORES OF THE THEORETICAL AND FINAL MEDICAL RESIDENCY TEST.

		1st year (n=114)	2nd year (n=114)	3rd year (n=114)	4th year (n=114)	5th year (n=114)	6th year (n=114)	Skills (n=111)	PC 5th (n=115)	PC 6th (n=115)	Theoretical MR (n=106)	FINAL MR (n=105)
1st Year	Pearson correlation	1										
	Sig. (2-tailed)											
2nd Year	Pearson correlation	.375	1									
	Sig. (2-tailed)	.000										
3rd Year	Pearson correlation	.116	.351	1								
	Sig. (2-tailed)	.220	.000									
4th year	Pearson correlation	.084	.386	.695	1							
	Sig. (2-tailed)	.374	.000	.000								
5th Year	Pearson correlation	.141	.109	.397	.369	1						
	Sig. (2-tailed)	.135	.247	.000	.000							
6th Year	Pearson correlation	.032	.118	.439	.424	.695	1					
	Sig. (2-tailed)	.739	.210	.000	.000	.000						
Skills	Pearson correlation	.041	.168	.100	.324	.140	.057	1				
	Sig. (2-tailed)	.669	.079	.296	.001	.142	.552					
PC 5th	Pearson correlation	.292	.252	.280	.380	.228	.187	.138	1			
	Sig. (2-tailed)	.002	.007	.003	.000	.015	.046	.149				
PC 6th	Pearson correlation	.345	.389	.414	.445	.337	.270	.198	.802	1		
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.004	.037	.000			
Theoretical score	Pearson correlation	.134	.062	.069	.129	.156	.139	.187	.404	.412	1	
	Sig. (2-tailed)	.172	.527	.479	.188	.111	.156	.057	.000	.000		
Final score	Pearson correlation	.083	.041	.109	.254	.259	.255	.266	.450	.466	.782	1
	Sig. (2-tailed)	.398	.682	.267	.009	.008	.009	.007	.000	.000	.000	

TABLE 2. UNIVARIATE LINEAR REGRESSION FOR FACTORS ASSOCIATED WITH THE SCORE ON THE THEORETICAL EXAMINATION AND THE SCORE ON THE FINAL MEDICAL RESIDENCY EXAMINATION AT UNIFESP.

Variables associated with the theoretical MR test	β	95% CI	p
1st year Progress	0.081	-0.036 to 0.198	0.172
2nd year Progress	0.049	-0.104 to 0.203	0.527
3rd year Progress	0.034	-0.061 to 0.128	0.479
4th year Progress	0.070	-0.035 to 0.175	0.188
5th year Progress	0.058	-0.013 to 0.129	0.111
6th year Progress	0.043	0.015 to -0.102	0.156
Skills and Attitude	0.077	-0002 to 0.156	0.057
PC 5th	0.763	0.427 to 1.099	<0.001
PC 6th	0.835	0.478 to 1.194	<0.001

Variables associated with the final MR result	β	95% CI	p
1st year Progress	0.038	-0.051 to 0.127	0.398
2nd year Progress	-0.024	-0.092 to 0.140	0.682
3rd year Progress	0.040	-0.031 to 0.111	0.267
4th year Progress	0.103	-0.026 to 0.181	0.009
5th year Progress	0.072	0.020 to 0.014	0.008
6th year Progress	0.060	0.015 to 0.1104	0.009
Skills and Attitude	0.082	0023 to 0.141	0.009
PC 5th	0.629	0.394 to 0.887	<0.001
PC 6th	0.707	0.444 to 0.969	<0.001

β: regression coefficient; PC: performance coefficient; MR: medical residency

(93.0%) took the theoretical MR test. One student withdrew from the practical test and interview, although this student had a high enough mean score in the theoretical test to progress in the evaluation process. The 105 (100%) students who completed the evaluation passed the MR test, with a mean score on the theoretical test of 7.53 ± 0.56 and a final MR result of 8.05 ± 0.42 (p <0.001) (Figure 2).

The correlations between the scores obtained are shown in Table 1. The factors associated with the MR score were tested through two linear regression models. The first model considered the score of the theoretical MR test as the dependent variable, while the other model considered the final result of the MR test as the dependent variable (Tables 2 and 3). The final model of multiple linear regression, which was

TABLE 3. FINAL LINEAR REGRESSION MODEL OF VARIABLES ASSOCIATED WITH THE SCORES OF THE THEORETICAL EXAMINATION AND FINAL EXAMINATION OF MEDICAL RESIDENCY

Variable associated with the theoretical MR test	β	95% CI	p
PC 6th	0.833	0.470 to 1.196	<0.001

Variables associated with the MR final result	β	95% CI	p
PC 5th	0.587	0.332 to 0.825	<0.001
Skills	0.060	0.008 to 0.113	0.025
6th-year Progress	0.038	-0.002 to 0.079	0.061

β: regression coefficient; PC: performance coefficient; MR: medical residency.

included the PT scores from the 4th to the 6th school year, the SA score, and the performance in the medical internship because they met the cutoff in the univariate linear regression model (Table 2), showed that each additional point in PC 6th increased the theoretical test score by 0.833 points (Table 3). In the second multivariate regression model, which included the same variables mentioned above (Table 2), each additional point in PC 5th increased the final MR score by 0.587, and each additional point on the SA increased the final MR score by 0.06. The PT of the 6th school year showed an association trend without statistical significance (Table 3).

DISCUSSION

In the present study, the PT scores showed a progressive increase over time, except between the 3rd and 4th years. Between the 1st and the 6th years, there was a substantial increase of 3.71 points on the PT, which was an increase of 139%. This highlights the degree of knowledge acquisition in the medical school period. Similarly, a study conducted in the EPM from 1996 to 2001 showed a similar increase of 2.79 points to 3.90 points in the PT score from the 1st to the 6th school year.[6] At the University of Londrina, there was an average increase of 2.89 points in the PT from the 1st to the 6th school year from 1998 to 2006.[7]

In general, the PT scores obtained in the present study were similar to those of other institutions. The national 2015 PT conducted in 23,065 students at 57 medical schools and showed pass rates of 32.38%, 35.23%, 39.71%, 44.85%, 51.98%, and 61.28% from the 1st to the 6th school year, respectively, which were higher than those at UNIFESP in the first two school years and lower than that at UNIFESP in the 6th school year.[8] At the State University of Campinas (UNICAMP), the PT grades from 2011 to 2014 among the 6th-year students had a mean of 6.7 ± 0.7, 6.1 ± 1.0, 6.6 ± 0.7, and 7.1 ± 0.7, respectively, which were slightly lower than

the means of the present study.[9] A study at the University of Missouri, USA, reported lower percentages of correct answers on the PT than those of the present study for the 1st to the 6th school years, with percentages of 6.1%, 16.1%, 30.7%, 41.6%, 50.9%, and 56.0%, respectively.[10] Blake et al[11] reported the PT scores of three classes of students at McMaster University, which were 10-20% at the beginning of the course but increased almost linearly until reaching 50% on the 5th exam 20 months later. The scores of the theoretical MR test in this study were similar to those observed at UNICAMP, which were 6.8 ± 0.8, 7.6 ± 0.9, 7.3 ± 0.8, and 7.5 ± 0.9 from 2011 to 2014, respectively.[9]

In this study, there was a weak correlation between the PT scores of the 1st and 2nd school years. From the 2nd school year, the most relevant correlations occurred between the closest years. There was a strong correlation between the 3rd and 4th school years and between the 5th and 6th school years, which suggests greater consistency in the knowledge acquired in the clinical area. However, the strength of correlations decreased for the MR tests, which might show the insufficient preparedness for that test at that time.

Ferreira[9] compared the PT score during the 6th school year with the score on the MR theoretical examination of UNICAMP students and observed moderate correlations of 0.588 in 2011, 0.610 in 2012, 0.671 in 2013, and 0.476 in 2014, in contrast to the present study, which showed a significant but weak correlation between the 6th school year PT score and the final MR score.

The analysis of internal consistency showed that the scores of PT, SA, PC 5th, PC 6th, and MR together showed an α coefficient greater than 0.7. Another study showed that PT scores in medical school had a predictive validity of 0.6 for success on the medical licensing exam.[11]

In the present study, the removal of the 1st-year PT score or the SA score from the analysis increased the internal consistency of the study. This result suggests

that the PT has a large number of questions considered "difficult" for the 1st-year students and therefore has less discriminatory power for student performance. Regarding the SA test, a possible explanation would be the diverse nature of this test in comparison to PT test, in addition to the small number of questions, since studies have highlighted the importance of the number of questions on this test.[12]

Other studies have found stronger predictive relationships between the clinical performance of the student and OSCE when the test had 18 5-minute stations[13] or 35 2-minute stations,[14] which suggests that longer OSCE assessments may be better predictors of performance. A systematic review reinforced this hypothesis, finding that the best reliability was associated with a greater number of stations.[15] In another systematic review, 12 of the 15 reviewed articles that reported the best relationships between OSCE scores and clinical performance were precisely those with the most questions.[16]

In the literature, the importance of OSCE in health education programs is well established. It is an evaluation mode specifically designed to provide a valid and reliable measure of the clinical competence of students in a simulated environment.[17] Reinforcing this idea, the final linear regression model obtained in the present study showed the importance of the SA score to the final result of the MR test. Each additional point on the SA increased the final MR test score by 0.060 points. However, the variable most strongly associated with performance on the final exam of the MR was PC 5th, each point of which increased the score on the final MR exam by 0.58 points. Likewise, PC 6th was significantly associated with the score of the theoretical MR exam, each point of which increased the theoretical MR exam score by 0.83 points. A study at São Paulo State University from 2009 to 2011 showed a moderate correlation between PT 6th and the score on the first phase of the multiple-choice MR test, but this correlation did not persist in the second phase of the test, which consisted of the OSCE and an interview.[18] Another study[19] showed an association between good performance on the medical internship exam and student performance in clinical practice (0.8 points), in the theoretical course of clinical medicine (0.5 points), and in basic science (0.4 points). Similarly, other authors found that performance on previous tests influenced future results.[20,21]

The results of the present study suggest that students should be encouraged to take the PT and SA seriously to improve their performance year by year. In addition, greater participation in practical activities, especially in medical internships, can improve the final result on the MR test.

The strength of this study was the longitudinal analysis of the scores of the tests taken during the medical course and the statistical treatment applied, which showed results that would be expected in practice but were reinforced by the relevant statistical analysis. The limitations of the study were the inclusion of student grades in only a certain period, and in the linear regression, external factors were not considered, such as having taken preparatory courses, which could interfere in the performance on the MR test.

CONCLUSION

The data reliability obtained in this study was adequate and showed a significant correlation between the scores of the tests analyzed. The performance on the SA and in the internship was positively associated with the performance on the MR tests.

Author's Contribution

Maria Cristina de Andrade: Study design, data collection and analysis, manuscript writing, critical review, and final approval of the manuscript.

Maria Wany Louzada Strufaldi; Rimarcs Gomes Ferreira; Gilmar Fernandes do Prado; Rosana Fiorini Puccini: Data collection and analysis, critical review, and final approval of the manuscript.

Amélia Miyashiro Nunes dos Santos: Study design, statistical analysis of data, writing of the manuscript, critical review, and final approval of the manuscript.

RESUMO

OBJETIVO: *Analisar a presença de correlação e associação entre as notas dos Testes de Progresso, provas de Habilidades e Atitudes e notas de desempenho no internato em relação às notas de Residência Médica (RM) de alunos ingressantes em 2009 no curso médico da Universidade Federal de São Paulo.*

MÉTODOS: *análise longitudinal de 684 notas de Testes de Progresso do 1º ao 6º ano, 111 de Habilidades e Atitudes (5º ano), 228 coeficientes de rendimento do 5º e 6º anos e 211 notas da Prova de Residência Médica. Analisou-se a correlação de Pearson entre as notas e os fatores associados às notas da RM por regressão linear.*

RESULTADOS: *Os Testes de Progresso do 1º ao 6º ano e Habilidades apresentaram pelo menos uma correlação moderada e significante entre si. As notas da prova teórica e nota final da RM tiveram correlação moderada com as notas de desempenho no internato. A nota teórica da Prova de RM se associou ao desempenho no internato no 6º ano (β=0,833; p<0,001) e nota final da Prova de RM se associou às notas da prova de Habilidades e Atitudes (β=0,587; p<0,001), desempenho no 5º ano (β=0,060, p=0,025) e Testes de Progresso do 6º ano (β=0,038; p=0,061).*

CONCLUSÕES: *Houve correlação significante entre as notas das diversas provas. A nota da prova de Residência Médica se associou positivamente ao desempenho do aluno no internato e prova de Habilidades, com tendência de associação do Teste de Progresso do 6º ano com o desempenho final na prova de RM.*

PALAVRAS-CHAVE: *Faculdade de medicina, Teste de Progresso, Internato médico, Residência Médica.*

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Cross-cultural adaptation of the NoMAD questionnaire to Brazilian Portuguese

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SUMMARY

BACKGROUND: *The Normalization Measure Development (NoMAD) tool is used to determine the contextual determinants in the process of implementing complex health interventions. The aim of this study is to translate and culturally adapt NoMAD to Brazilian Portuguese.*

METHODS: *The cross-cultural adaptation was performed in five steps: 1) translation of the questionnaire into Portuguese; 2) synthesis and creation of the first version; 3) back-translation of the instrument into the source language; 4) review of the instrument by a group of experts and target professionals; and 5) pretesting. A final version of the questionnaire was answered by users of a clinical monitoring system in specialist care services for people living with HIV/AIDS, and the internal consistency of the questionnaire was assessed using Cronbach's alpha.*

RESULTS: *The questionnaire was answered by 188 health professionals, of which 87.7% were female, and the average age was 45.2 years. For the final version of the questionnaire, Cronbach's alpha was over 0.70 for the construct's coherence (0.74), collective action (0.70), cognitive participation (0.71), and reflexive monitoring (0.81).*

CONCLUSION: *The NoMAD questionnaire was cross-culturally adapted and can be used to evaluate the implementation of complex health care interventions.*

KEYWORDS: *Implementation Science, Implementation process, NoMAD, Cross-cultural adaptation.*

INTRODUCTION

One aim in implementing new health interventions is to maximize the intended benefits with the provision of services and patient care. However, this process is generally designed and executed without considering the characteristics of the intervention's context, which could lead to underuse of the intervention, regardless of its potential to produce better health outcomes[1-3]. The aim of implementation science is to understand the contextual factors that influence the implementation of health interventions. This field is defined as the "scientific study of methods to promote the systematic incorporation of research results and other evidence-based practices into routine practice and, consequently, improve the quality and effectiveness of health services" (Eccles & Mittman, 2006. p.1)[4]. To instrumentalize studies

developed from this perspective, researchers in the area have developed theories, models, and approaches with three main objectives: 1) describing or guide the process of translating evidence into practice; 2) understanding or explaining the facts that influence the results of the implementation; and 3) evaluating the implementation[5].

Normalization Process Theory (NPT) is an implementation theory that seeks to explain the contextual factors that influence the implementation of complex health interventions. It is concerned with the social organization of work (implementation), integrating routine elements of everyday life into practice (incorporation), and sustaining practices incorporated into social contexts (integration). The theory assumes that a successful implementation of new health care practices is dynamic, non-linear, and dependent on the collective and coordinated behavior of individuals who work within the limits of health care contexts[6-9].

NPT explains four constructs that determine collective behavior for the incorporation of complex interventions in practice: coherence, participation or cognitive engagement, collective action, and reflective monitoring[10, 11]. The coherence construct evaluates how a new practice to be implemented is evaluated by the participants, whether it can bring about changes in the work processes performed, and the users' perception of its purpose. The cognitive participation construct assesses the individual and collective involvement of professionals with the new intervention and their motivation to ensure the day-to-day implementation of the service.

The collective action construct assesses professionals' perception of the intervention's implementation process in pre-existing routine while considering the capacity and interaction with other professionals, the availability of resources, and technical and administrative support provided by the service coordination. The fourth and final construct, reflective monitoring, assesses how participants evaluate the new practice or intervention, whether it can be improved, and whether it causes changes in work processes in the day-to-day services [10, 11].

The Normalization Measure Development (NoMAD) tool is a developed, validated, NPT-based questionnaire[11, 12]. The questionnaire evaluates contextual factors that are seen as barriers or facilitators for the implementation of interventions in day-to-day services by professionals. The aim of this study is to present the process of cross-cultural adaptation of the NoMAD questionnaire and a final version in Brazilian Portuguese.

METHODS
The NoMAD questionnaire

NoMAD is available for free[13] and consists of 23 items that are divided into three sections, as shown in Figure 1. It starts with section A, which consists of two questions about the participant, followed by section B, which has three items that provide an overall assessment of participants' expectations and their experience with the intervention's implementation process. The items in section B are answered on two 10-point Likert scales ranging from "Not at all" to "Completely" and from "Still feels very new" to "Feels completely familiar."

Section C contains 20 specific items on the intervention, which correspond to the four constructs of the NPT: Coherence and Cognitive Participation with four items each, seven items for Collective Action, and five items for Reflective Monitoring. The items in part C are answered using a 5-point Likert scale ranging from "Strongly disagree" to "Strongly agree." If participants consider that any of the 20 items is not relevant to expressing their experience with the intervention, they can respond to one of three "Neutral" options: "Not relevant to my role;" "Not relevant at this stage;" and "Not relevant to the intervention" (Figure 1).

NoMAD does not offer specific instructions for scoring or creating measurements for each construct. However, when assessments are required at the level of the four NPT constructs, it is recommended that the average of the items for each construct be calculated with the aim of creating "'scores" that can be compared between constructs, groups, or locations if appropriate for the purpose of the study[12].

Cross-cultural adaptation

The cross-cultural adaptation was carried out by following the methodological steps used in the translation of NoMAD into seven other languages within the scope of the European collaboration project "ImpleMentAll" for the implementation of e-health interventions (https://www.implementall.eu/). The steps were made available by the questionnaire authors in a methodological guide and validation articles [11, 12]. In step 1, the questionnaire was translated by two Brazilian translators independently. This step provided versions T1 and T2 versions of the Portuguese questionnaire.

FIGURE 1. ORIGINAL AND BRAZILIAN PORTUGUESE FINAL VERSION OF THE NOMAD QUESTIONNAIRE AFTER CROSS-CULTURAL ADAPTATION

	Original questionnaire	Br-Pt-NoMAD
Part A: Characterization of the participant	1. How many years have you worked for this [name of organization/department]? Answer: Less than one; 1-2 years; 3-5 years; 6-10 years year; 11-15 years; More than 15 years	1. Há quantos anos você trabalha na (o) [organização/departamento/serviço de saúde] Respostas: Menos de um ano; De 1 a 2 anos; De 3 a 5 anos; De 6 a 10 anos; De 11 a 15 anos; Mais de 15 anos.
	2. How would you describe your professional job category?	2. Como você descreveria sua função?
Part B: General questions about the intervention not scored	1. When you use [the intervention], how familiar does it feel? Likert scale: 0-Still feels very new;1-9;10- Feels completely familiar	B1. Ao fazer uso [da intervenção], quão familiarizado (a) você se sente com ela? Escala: 0-ainda pouco familiarizado; 1-9; 10- totalmente familiarizado.
	2. Do you feel [the intervention] is currently a normal part of your work? Likert scale: 0- Not at all; 1-4; 5-Somewhat;6-9; 10-Completely	B2. Você acha que [a intervenção] é atualmente utilizada de forma rotineira no seu trabalho? Escala: 0-de maneira nenhuma; 1-4; 5- até certo ponto; 6-9; 10-definitivamente, sim.
	3. Do you feel [the intervention] will become a normal part of your work? Likert scale: 1-Not at all; 2-4; 5-Somewhat;6-9; 10-Completely	B3. Você acha que [a intervenção] se tornará rotina no seu trabalho? Escala: 0-de maneira nenhuma; 1-4; 5- até certo ponto; 6-9; 10-definitivamente, sim.
Part C1: Coherence Construct (CO)	1. I can see how [the intervention] differs from usual ways of working. 2. Staff in this organization have a shared understanding of the purpose of [the intervention]. 3. I understand how [the intervention] affects the nature of my own work. 4. I can see the potential value of [the intervention] for my work.	CO1. Percebo como [a intervenção] pode trazer mudanças na atual rotina de trabalho. CO2. Os funcionários desta organização compartilham uma compreensão comum da finalidade do uso [da intervenção] CO3. Entendo como [a intervenção] influencia a realização das atividades essenciais do meu trabalho. CO4. Consigo entender o quanto [a intervenção] melhora e facilita meu trabalho.
Part C2: Cognitive Participation (CP) construct	1. There are key people who drive [the intervention] forward and get others involved 2. I believe that participating in [the intervention] is a legitimate part of my role 3. I'm open to working with colleagues in new ways to use [the intervention] 4. I will continue to support [the intervention]	PC1. Há pessoas que impulsionam de modo decisivo o uso [da intervenção] e engajam os demais. PC2. Acredito que participar [da intervenção] constitui uma parte legítima da minha função. PC3. Estou disposto a adotar novas formas de trabalhar com meus colegas visando o uso [da intervenção]. PC4. Continuarei a dar apoio [a intervenção].
Part C3: Construct Collective action (AC)	1. I can easily integrate [the intervention] into my existing work 2. [The intervention] disrupts working relationships 3. I have confidence in other people's ability to use [the intervention] 4. Work is assigned to those with skills appropriate to [the intervention] 5. Sufficient training is provided to enable staff to implement [the intervention] 6. Sufficient resources are available to support [the intervention] 7. Management adequately supports [the intervention]	AC1. Consigo integrar facilmente [a intervenção] ao meu trabalho atual. AC2. [A intervenção] prejudica as relações de trabalho entre os profissionais. AC3. Tenho confiança na capacidade dos demais em fazer uso [da intervenção]. AC4. As atividades/funções relacionadas ao uso [da intervenção] são dadas a profissionais com capacidade adequada para executá-las. AC5. Os funcionários recebem treinamento suficiente para habilitá-los a implementar [a intervenção]. AC6. Os recursos disponíveis são suficientes para dar suporte [a intervenção]. AC7. A coordenação/gerência dá apoio adequado [a intervenção].
Part C4: Construct Reflective monitoring (MR)	1. I am aware of reports about the effects of [the intervention] 2. The staff agree that [the intervention] is worthwhile 3. I value the effects that [the intervention] has had on my work 4. Feedback about [the intervention] can be used to improve it in the future 5. I can modify how I work with [the intervention]	MR1. Estou ciente dos relatos realizados por profissionais na (o) [organização/departamento/serviço de saúde] a respeito do impacto na utilização [da intervenção]. MR2. Os funcionários envolvidos concordam que [a intervenção] vale a pena. MR3. Valorizo os efeitos que [a intervenção] vem tendo sobre o meu trabalho. MR4. É possível utilizar o *feedback* da equipe a respeito [da intervenção] para aprimorá-la no futuro. MR5. Sou capaz de modificar minha forma de trabalhar com [a intervenção].
Response scale for items from C1 to C4	5- Strongly agree; 4- Agree; 3- Neither agree nor disagree; 2- Disagree; 1- Strongly disagree; Not relevant to my role; Not relevant at this stage; Not relevant to the intervention.	5- Concordo totalmente; 4- Concordo; 3- Nem concordo nem discordo; 2- Não concordo; 1- Discordo totalmente; Não é relevante para minha função; Não é relevante no estágio atual; Não é relevante para a intervenção.

In step 2, T1 and T2 were evaluated and compared with the original version by researchers who have good knowledge of English, which gave rise to version T3. Version T3 was back-translated into English by two independent and native English translators in step 3, which generated versions T4 and T5. A committee of experts reviewed these versions to reach a consensus on the differences found and prepare

a pre-test version. The committee was composed of two methodologists, two health professionals, and authors of the questionnaire. The committee members were also fluent in the English language and native speakers of Brazilian Portuguese. None of them participated as translators of the questionnaire. The authors responsible for developing the NoMAD questionnaire collaborated directly in the translation and back-translation process.

Before applying the pre-test, 30 health professionals were invited to assess the clarity and understanding of the questionnaire items through three questions: 1) "Write in your words how you understood the previous question;" 2) "Did you fully understand this questionnaire item (yes/no)?" and, 3) "How would you rewrite this question to make it more understandable?" The answers to the first question were evaluated to ensure that the adapted version maintained its equivalence with the original version of the questionnaire. If a participant declared that the item in the second question was not understood, an open field was made available (if not, the participant was asked to write the word or phrase that was not understood) so that the participant could signal which word or expression had not been understood. Items not understood by more than 90% of the participants were restructured, translated, and evaluated by the committee.

The pre-test was answered online by health professionals who participated in the implementation of the Clinical Monitoring System (SIMC) for people living with HIV/AIDS (PLWHIV). SIMC is an individual management support system that was developed by the Ministry of Health in 2013. The system identifies PLWHIV with difficulties in the continuum of care: a) PLWHIV who perform CD4 tests and viral load tests and are not starting antiretroviral treatment; b) PLWHA under treatment who had a detectable viral load after six months of treatment; c) PLWHIV in loss of follow-up; and d) pregnant women with HIV and a detectable viral load[14].

The choice of this sample was due to the low implementation of SIMC in the state of São Paulo. Analysis of the use of SIMC in September 2019 showed that among the 10,561 patients in the treatment gap in the state of São Paulo, 89.3% (n = 9,151 patients) were cases not analyzed by the services. Therefore, 409 professionals with an approved login to use the system in the state were invited to answer NoMAD on an online platform between May and July 2019.

The characterization of the participants and their responses to NoMAD were described using simple and relative frequencies. The mean and standard deviation of the set of respondents in each item of the four constructs were also calculated. The calculation of the average considered the responses on a 5-point Likert scale ranging from "1 - Strongly disagree" to "5 - Strongly agree".

The internal consistency of the items of each construct was assessed using Cronbach's alpha and considered satisfactory when the values were ≥0.7. All analyses were conducted using the software Stata/IC 14.0®. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine of the University of São Paulo (opinion number 3.033.064).

RESULTS

Figure 1 presents the items from the original questionnaire and the culturally adapted version. The 23 items of the questionnaire and two other questions for the characterization of the respondent were maintained (Chart 1). Of the 30 professionals invited to assess the clarity and understanding of the questionnaire items, 29 participated.

Items C01, C03, AC4, and MR1 were not understood by 90% of the health professionals. The participants reported doubts about the meaning of the expression, "nature of my own work," and proposed replacing it with the expression, "essential activities of my own work." The expression, "appropriate skills," was replaced by "adequate capacity," and there was a need to modify the phrase "differs from usual ways of working" to "brings changes in the current work routine." Suggestions for changes were also made to replace the phrase "about the effects of" with "regarding the impact." After restructuring, the items were answered by 14 other health professionals and were understood by more than 90% of the participants.

Considering SIMC as the implemented intervention, the NoMAD questionnaire was answered by 188 professionals in specialized care services who used the clinical monitoring system. Most participants were female (87.2%) and had higher education with specialization (54.8%) (Table 1). The average age was 45 years, and 28.2% of the participants reported working for more than 15 years in health services. Managers of health services and nurses were the most frequent professions (25% and 22.9%, respectively).

The professionals reported little familiarity and low use of the system in their routine (average=2.5 and 2.9, respectively). On the other hand, professionals believed that the system would become routine in their work (average=7.1) (Table 1).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND RESPONSES OF PARTICIPANTS TRAINED TO USE SIMC (N = 188).

Characteristics	N (%)
Gender	
Female	164 (87.7)
Male	23 (12.3)
Age	
Mean (minimum - maximum)	45.2 (20.6 – 75.6)
Education	
Elementary School	1 (0.5)
High school	7 (3.7)
Technical high school	4 (2.1)
Incomplete higher education	5 (2.7)
Higher education	47 (25.0)
Higher education with specialization	92 (48.9)
Master degree	10 (5.3)
PhD	2 (1.1)
Not filled	20 (10.6)
Working time in the health service	
Less than one year	8 (4.3)
From 1 to 2 years	33 (17.6)
From 3 to 5 years	33 (17.6)
From 6 to 10 years	33 (17.6)
From 11 to 15 years	24 (12.8)
More than 15 years	53 (28.2)
Not filled	4 (2.1)
Occupation	
Manager	47 (25)
Nurse	43 (22.9)
Pharmacist	19 (10.1)
Doctor	14 (7.4)
Administrative assistant	9 (4.8)
Nursing technician	9 (4.8)
Social worker	6 (3.2)
Psychologist	6 (3.2)
Pharmacy assistant	5 (2.7)
Health agent	4 (2.1)
Nursing assistant	2 (1.1)
Dentist	1 (0.5)
Intern	1 (0.5)
Others	22 (11.7)
General questions about the intervention:	
Q1. When you use SIMC, how familiar does it feel?	2.5 (3.4)
Q2. Do you think that the SIMC is currently used regularly as part of your job?	2.9 (3.2)
Q3. Do you think that the SIMC will become a regular part of your job?	7.1 (2.8)

Table 2 shows the answers to the items corresponding to the four questionnaire constructs. In the coherence dimension, the averages varied between 3.5 and 4.1. The lowest average was found for item CO2. This item assessed whether there is a common understanding among the service employees about the purpose of the SIMC. 30.3% of the participants responded that the disagreed with the statement, and another 50.7% neither disagreed nor agreed. However, the participants were aware of the possibilities of SIMC offering to bring changes in the work routine (CO1=4.1), in the performance of essential activities (CO3 = 3.9), and in the improvement of work (CO4=3.9).

In the cognitive participation construct, only item PC1 had an average lower than 4.0. This item assesses whether there are professionals in the service who decisively encourage others to use SIMC. However, items PC3 and PC4 refer to the participant's willingness to contribute to colleagues and individually support the system. More than 90% of respondents agreed with these items, presenting the highest averages among all NoMAD items in this sample (average=4.2) (Table 2).

The collective action construct demonstrated that 76% of the participants disagreed that the system can cause possible losses in the working relationships between service professionals (average=2.0). The proportion of professionals who trust the ability of others to use SIMC was also above 70% (average=3.8). Less than 50% agreed that the available resources are sufficient to support the use of SIMC, and only 41% reported that employees receive training to enable them to implement SIMC (Table 2).

The reflexive monitoring construct showed that 70.4% of the participants agreed that the system is worthwhile, and almost 80% of the professionals believed they are able to modify their work processes using the system (items MR1 and MR5). The lowest average observed in this construct (MR1=3.5) refers to the professional's perception of the reports made by other colleagues about the impact of using the system. The evaluation of internal consistency indicated Cronbach's α greater than 0.70 in all constructs: coherence (α: 0.74), collective action (α: 0.70) reflective monitoring (α: 0.81), and cognitive participation (α: 0.71). The constructs "reflective monitoring and collective action" (α: 0.87) and "coherence and collective action" (α: 0.81) showed a strong correlation.

TABLE 2. RESPONSES OF PROFESSIONALS INVOLVED IN THE IMPLEMENTATION OF SIMC TO THE NoMAD QUESTIONNAIRE.

NoMAD item according to the theoretical construct	Mean (Standard Deviation)	1- Strongly disagree	2- Disagree	3- Neither agree nor disagree	4- Agree	5- Strongly agree
Coherence						
CO1. I am able to perceive how the SIMC can bring changes in the current work routine. (n=176; 12 Neutral).	4.1 (0.6)		-	21 (11.9%)	109 (61.9%)	46 (26.1%)
CO2. The employees of this organization have a shared understanding of the purpose of the SIMC (n=169; 19 Neutral).	3.5 (0.9)	-	46 (30.3%)	77 (50.7%)	4 (2.6%)	25 (16.5%)
CO3. I understand how the SIMC affects the essential activities of my own work (n=174; 14 Neutral).	3.9 (0.6)	-	4 (2.3%)	32 (18.4%)	109 (62.6%)	29 (16.7%)
CO4. I can see how the SIMC improves and facilitates my work. (n=171; 17 Neutral).	3.9 (0.7)	-	6 (3.5%)	37 (21.6%)	96 (56.1%)	32 (18.7%)
Cognitive Participation						
PC1. There are people who decisively boost the use of the SIMC and get others involved. (n=169; 19 Neutral).	3.7 (0.8)	-	40 (24.4%)	86 (61%)	1 (0.7%)	14 (9.9%)
PC2. I believe that participating in the SIMC is a legitimate part of my role (n=180; 8 Neutral).	4.0 (0.7)	-	5 (2.8%)	26 (14.4%)	106 (58.9%)	43 (23.9%)
PC3. I am willing to take up new ways of working with my colleagues, with a view to using the SIMC. (n=181; 7 Neutral).	4.2 (0.5)	-	1 (0.6)	11(6.1%)	124 (68.5%)	45 (24.9%)
PC4. I shall continue to give my support for the SIMC (n=176; 12 Neutral).	4.2 (0.5)	-	-	9 (5.1%)	113 (64.2%)	54 (30.7%)
Collective action						
AC1. I can easily integrate the SIMC into my existing work (n=170; 18 Neutral).	3.6 (0.8)	1 (0.6%)	20 (11.8%)	46 (27%)	85 (50%)	18 (10.6%)
AC2. The SIMC hinders labor relations between workers (n=171; 17 Neutral).	2.0 (0.8)	46 (26.9%)	87 (50.9%)	32 (18.7%)	6 (3.5%)	-
AC3. I trust the abilities of other people to use the SIMC (n=172; 16 Neutral).	3.8 (0.7)	1 (0.6%)	9 (5.2%)	38 (22.1%)	101 (58.7%)	23 (13.4%)
AC4. The activities/functions related to the use of the SIMC are given to professionals with adequate capacity to perform them (n=172; 16 Neutral).	3.9 (0.6)	-	2 (1.2%)	35 (20.3%)	107 (62.2%)	28 (16.3%)
AC5. Staff receives sufficient training to enable them to implement the SIMC (n=165; 23 Neutral).	3.1 (1.1)	14 (8.5%)	36 (21.8%)	46 (27.9%)	57 (34.5%)	12 (7.3%)
AC6. The resources available suffice to give due support to the SIMC (n=168; 20 Neutral).	3.4 (0.9)	3 (1.8%)	25 (14.9%)	62 (36.9%)	65 (38.7%)	13 (7.7%)
AC7. The management gives appropriate support to the SIMC (n=171; 17 Neutral).	3.8 (0.9)	2 (1.2%)	11 (6.4%)	42 (24.6%)	76 (44.4%)	40 (23.4%)
Reflexive Monitoring						
MR1. I am aware of the reports made by professionals in [organization/department/health service] regarding the impact on the use of the SIMC (n=165; 23 Neutral).	3.5 (0.9)	5 (3%)	19 (11.5%)	39 (23.6%)	86 (52.1%)	16 (9.7%)
MR2. The employees involved agree that the SIMC is worthwhile (n=169; 19 Neutral).	3.8 (0.7)	-	6 (3.6%)	44 (26%)	89 (52.7%)	30 (17.7%)
MR3. I value the effects that the SIMC has had upon my work (n=158; 30 Neutral).	3.7 (0.8)	-	9 (5.7%)	59 (37.3%)	61 (38.6%)	29 (18.3%)
MR4. It is possible to use the team's feedback with regard to the SIMC to further improve it in the future (n=167; 21 Neutral)	3.9 (0.7)	-	7 (4.1%)	34(20.4%)	100 (59.9%)	26 (15.6%)
MR5 I am able to change my own way of working with the SIMC (n=172; 16 Neutral).	3.9 (0.6)	1 (0.6%)	2 (1.2%)	32 (18.6%)	118 (68.6%)	19 (11%)

DISCUSSION

This study presents the cross-cultural adaptation of the NoMAD questionnaire and provides a questionnaire to assess the implementation of complex health care interventions in a Brazilian context. The methodology used to carry out this study was carefully chosen to guarantee reliable results and the maintenance of the original meaning of the questionnaire built from the NPT. The translation and back-translation process, the participation of an expert committee, and the pre-testing are steps that have been used and recommended in the literature since 1993[15]. The

questionnaire showed good reliability in the internal consistency test. All four theoretical constructs of the NoMAD questionnaire showed good reliability, with α values between 0.70 and 0.81. The internal consistency result was similar to that found in the validation study of the original instrument, which had α values between 0.78 and 0.83[12].

This study provides a questionnaire that is capable of assessing involvement, the perception of individual and collective participation, and the reflection of professionals participating in the implementation of complex interventions based on evidence in the context of health care. NoMAD can be used before or after the implementation of an intervention and can assist managers and professionals who are conducting an implementation process in understanding contextual factors that interfere with the implementation[13]. Confirmatory factor analysis was not performed due to a sample size of less than 10 cases for each variable, which is recommended as the minimum[16]. However, Acuardo et al. showed a consensus in the literature regarding the completion of the cross-cultural adaptation process after the pre-test stage[17].

CONCLUSION

This article study has provided a Brazilian Portuguese adaptation of the NoMAD questionnaire to evaluate the implementation of complex interventions in health care. The 23 items from NoMAD contribute to the identification and evaluation of contextual factors involved in the social organization of the work of professionals participating in the implementation.

Author's Contribution
All authors have contributed equal to work.

RESUMO

INTRODUÇÃO: *O questionário Normalisation Measure Development (NoMAD) tool busca identificar os fatores contextuais determinantes no processo de implementação de intervenções complexas em saúde. Este artigo tem por objetivo traduzir e adaptar culturalmente o NoMAD para o português do Brasil.*

MÉTODOS: *A adaptação transcultural foi realizada em cinco etapas: 1-Tradução do questionário para o português; 2-Síntese e criação da primeira versão; 3-Retro-tradução do instrumento para a língua de origem; 4-Revisão por grupo de especialista e profissionais-alvo do instrumento; e 5-Pré-teste. A versão final do questionário foi respondida por usuários do sistema de monitoramento clínico em serviços de assistência especializada às pessoas vivendo com HIV/AIDS e sua consistência interna foi avaliada por meio de alpha de Cronbach.*

RESULTADOS: *O questionário foi respondido por 188 profissionais, 87,7% eram do sexo feminino e média de idade de 45,2 anos. A versão final do questionário apresentou α de Cronbach superiores a 0.70 nos construtos coerência (0.74), ação coletiva (0.70), participação cognitiva (0,71) e monitoramento reflexivo (0.81).*

CONCLUSÃO: *O questionário NoMAD foi adaptado transculturalmente e pode ser utilizado para avaliar a implementação de intervenções complexas no cuidado em saúde.*

PALAVRAS-CHAVE: *Ciência da implementação. Inquéritos e Questionários. Promoção da Saúde/organização & administração.*

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Clinicopathological analysis of acral melanoma in a single center: a study of 45 cases

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SUMMARY

OBJECTIVE: The relationship between the clinicopathological and sociodemographics characteristics of acral melanomas diagnosed at the Hospital do Servidor Público Estadual de São Paulo was analyzed and traced between 1997 and 2016.

METHODS: An observational, descriptive, and retrospective study of patients diagnosed with acral melanoma was performed at Hospital do Servidor Público Estadual de São Paulo. Sociodemographic and clinicopathological characteristics were collected and analyzed.

RESULTS: Forty-five patients with acral melanomas were found during the evaluation period. Thirty-one were females, and 14 were males (68.89% and 31.3%, respectively). Most of the cases were invasive (88.37%), and the predominant histological subtype was the acral lentiginous (91.11%). The plantar region was the most prevalent (64.44%). The median Breslow index was 3 mm, and there was a tendency towards greater severity in male patients.

CONCLUSIONS: Acral site melanomas are detected diagnosed when they reach more advanced stages, which leads to a worse prognosis for patients. Late detection assumes even greater importance in highly mixed and black populations, such as the Brazilian population.

KEYWORDS: Melanoma/epidemiology. Melanoma/pathology. Skin neoplasms.

INTRODUCTION

Despite the tremendous therapeutic advance of oncology, melanoma remains a neoplasm with a high mortality rate.[1,2] A progressive increase in the incidence of this pathology has been reported. Despite efforts and campaigns, many cases are still diagnosed when they are already in the invasive phase.[3] From a clinical and pathological point of view, primary cutaneous melanoma is divided into extensive superficial, nodular, malignant lentigo melanoma and acral lentiginous.

Such subtypes, in addition to histopathological differences, present different risk factors and clinical and demographic characteristics. With the advancement in molecular and genetic techniques, it was noticed that they also have divergences in oncogenic mutations.[4,5] This finding has led to therapeutic

implications with the development of targeted therapies and immunotherapies.[6–8]

Any skin surface can be a primary melanoma site. The most frequent site of involvement depends directly on the skin color of the affected individual. In Caucasians, the head, neck, trunk, and limbs are the preferred places, whereas in Asians and blacks, melanomas more frequently affect acral locations (mainly hands and feet).[9–12] All histological subtypes may have an acral origin (except for malignant lentigo as the lentigo occurs in photodamaged skin) with the acral lentiginous subtype being the most common in such locations.

Brasil is a country with a highly miscegenated population with the majority of the population composed of blacks, so it is a territory with a large number of acral cutaneous melanomas.[13] However, despite this diverse population, few studies have specifically focused on these cases. Thus, cases of acral melanoma in a single center in the city of São Paulo are described.

METHODS

An observational, descriptive, retrospective study of patients diagnosed with melanoma in an acral site (feet and hands) was carried out between 1997 and 2016 at Hospital do Servidor Público Estadual de São Paulo.

Sociodemographic and clinicopathological characteristics, including sex, age, anatomical site, histological type, tumor thickness, ulceration, mitotic index, and 5-year survival, were collected and analyzed.

Statistical analysis was performed with STATA version 13 (STATA Corp., Texas, United States). The Shapiro–Wilk normality test showed that all quantitative data were non-parametric. Thus, the median and interquartile range (IQR) and the Wilcoxon rank-sum test were used to describe the data and associations. Qualitative data are shown as frequency and percentages, and analyses were performed using the chi-square or Fisher's exact test. Statistical significance was considered to be P ≤ 0.05.

RESULTS

Of the 386 cases of primary cutaneous melanoma, 52 were located in the acral region (hands and feet). According to the classification of cutaneous tumors of the World Health Organization (WHO), acral cutaneous melanoma is located in non-exposed areas such as hands and feet (palmar, plantar, and nail apparatus).[14]

Thus, excluding patients with the ankle[4] and dorsum of the foot[3] melanomas, a statistical analysis was performed with 45 patients.

Tumor characteristics and the demographic variables of each patient included in this study are shown in Table 1. Among 45 patients included in the analysis, 31 were female (68.89%) and 14 were males (31.11%). Most melanomas were invasive (38 patients, 88.37%), and only 5 (11.63%) of the cases were melanoma *in situ*. The histological subtype acral lentiginous melanoma was found in 41 cases (91.11%). Four patients (8.89%) did not have the specified histological type (melanoma, NOS). The median age at diagnosis was 69 years (IQR: 61–77 years).

TABLE 1. PATIENT CHARACTERISTICS

Gender [n (%)]	
Female	31 (68.89%)
Male	14 (31.11%)
Age (years)	
Mean (SD)	68.71 (11.13)
Median (IQR)	69 (77-61)
Anatomical Site [n (%)]	
Plantar Region	29 (64.44%)
Subungual (Pododactyl)	8 (18.00%)
Subungual (Quirodactyl)	6 (13.33%)
Palmar Region	1 (2.22%)
Unspecified	1 (2.22%)
Histological Type [n (%)]	
Acrolentiginous	41 (91.11%)
Unspecified	4 (8.89%)
Breslow (mm)	
Average	5.09
Median (IQR)	3 (5.5-1)
Invasion [n (%)]	
Invasive	38 (88.37%)
In situ	5 (11.63%)
Ulceration [n (%)]	
Yes	19 (42.22%)
No	26 (57.78%)
Mitosis greater than 1 [n (%)]	
Yes	23 (52.27%)
No	21 (47.73%)
Clark's index [n (%)]	
I	4 (8.89%)
II	5 (11.11%)
III	7 (15.56%)
IV	26 (51.11%)
V	6 (13.33%)
5-year survival [n (%)]	
Yes	23 (67.65%)
No	11 (32.35%)

SD = Standard Deviation; IQR = Interval between 25th and 75th quartiles

In terms of location, the lesions were from the plantar region in 29 cases (64.44%), subungual in 14 patients (of these, eight located in toes and six in fingers), and only one case in the palmar region (2.22%). The median Breslow index was 3 mm.

As for histological characteristics, 19 patients had tumors with ulceration (42.22%), and 23 (52.27%) had more than one mitosis per field. Most patients (23, 51.11%) had melanomas with Clark IV.

Table 2 shows histological characteristic distribution of melanomas according to patient sex. Mean age at diagnosis was similar in both groups, 68 years for women, and 69.5 years for men. Tumors were located on the feet in 26 cases (83.87%) in women and 11 (78.57%) among men. Similar behavior between the sexes was also found regarding the histological subtype with the majority of patients presenting acrolentiginous melanoma (28 patients, 90.32% of women and 13 patients, 92.86% of men) and regarding the presence of invasion. No statistical difference regarding five-year mortality (50.00% x 22.73%; p = 0.104), ulcerations (57.14% x 35.48%; p = 0.173), and mitosis (71.43% x 43.3%; p = 0.082) between the sexes were noted.

TABLE 2. CHARACTERISTICS OF TUMORS ACCORDING TO SEX.

Variables	Gender		value P
	Female	Male	
Anatomical Site			0.667
Hand	16.13%	21.43%	
Foot	83.87%	78.57%	
Histological Subtype			0.782
Acrolentiginous	90.32%	92.86%	
Not specified	9.68%	7.14%	
Invasion			0.524
In situ	13.79%	7.14%	
Invasive	86.21%	92.86%	
Ulceration			0.173
Yes	35.48%	57.14%	
No	64.52%	42.86%	
Mitosis			0.082
Yes	43.33%	57.14%	
No	56.67%	42.86%	
5-year survival			0.104
Yes	77.27%	50.00%	
No	22.73%	50.00%	
Breslow			0.459
Average	4.12	6.97	
Median (IQR)	3 (5-1)	3 (6-1.3)	
Age (years)			0.854
Mean (SD)	69.06 (11.55)	68.00 (10.54)	
Median (IQR)	68.00 (78-60)	69.50 (74-61)	

When analyzing the anatomical sites and the different characteristics of the tumors (figure 1), similar behavior was observed in terms of invasion since most tumors were invasive, both in the subgroup of tumors located in the feet (91.67%) and in the hands (71.43%). The 5-year survival also showed no statistical difference between the two groups (hands and feet). No statistical difference in thickness between the tumors located on the hands (mean and median 6 mm) in relation to those present on the feet (mean and median 4.96 and 3 mm, respectively).

FIGURE 1. CHARACTERISTICS OF MELANOMAS IN TERMS OF LOCATION (FEET X HANDS).
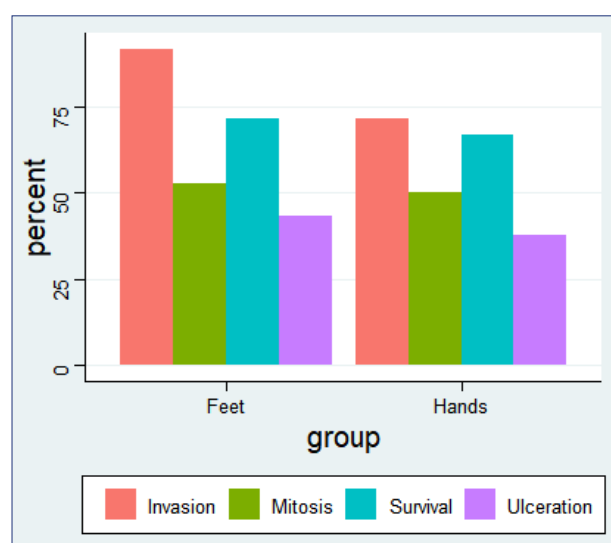
DISCUSSION

We present a series of 45 cases of acral melanoma diagnosed between 1997 and 2016 at the Hospital do Servidor Público Estadual de São Paulo (HSPE). In this study, we correlated the demographic characteristics of each patient with the clinical and histopathological findings.

The acral location corresponds to body extremities, such as the hands and feet. Such anatomical sites can be the site of melanomas of different histological types, the most common being the so-called acral lentiginous melanoma.[11] These names lead to errors since many dermatologists confuse the anatomical location with the histological subtype, a finidng that is reflected in scientific studies. In the present study, we included all primary cutaneous melanomas that appeared in the glabrous skin of the hands and feet in addition to melanomas originating from the nail apparatus according to the WHO's definition of acral melanoma. Despite

being located in an acral site, the melanomas arising in the dorsum of the foot and hands are not included in WHO's definition of acral melanoma.

In accordance with already published studies, most patients had tumors on the soles of their feet, whose involvement was 3 to 10 times more common than that found on the hands.[13–16] The lentiginous acral histological type was found in 91.11% of the cases and was the predominant one in both sexes in this study in agreement with the international and national literature.

Only one case of melanoma was diagnosed in the palmar region during this study period, confirming the rarity of this involvement as described in other studies.[13,15] Besides, the tumors located in the hands showed a larger thickness at diagnosis than the observed in melanomas diagnosed in the feet. However, we did not demonstrate statistical significance for this data.

Due to this preference for the plantar region, it has been postulated that lentiginous acral melanoma has different behavior and risk factors in relation to other histological subtypes, including repetitive trauma as a predisposing factor[13,16,18] since different from other histological types, ultraviolet radiation seems to have little influence as a risk factor for lentiginous acral melanoma.[17,18]

Subungual melanoma accounted for an important percentage of acral tumors as it was the second most common location. Ultraviolet radiation also seems to have little influence on the development of these neoplasms. A compact layer of keratin works as a protective factor for matrix melanocytes, the source of this type of melanoma.[18] In our sample, we found a higher amount of melanomas in the toenail apparatus[8] in the fingers.[6] In the literature, nail melanoma is more frequent in the fingers; however when the melanoma returns, it occurs more in the plantar region. This finding suggests that the factors involved in the oncogenesis of nail melanomas and those located on the plantar/palmar face may be different.[19,20]

When compared to the other melanoma subtypes, especially in photoexposed areas, lentiginous acral presents a lower incidence of BRAF activating mutations, accounting for only 17% of cases.[19–28]

Most tumors are already diagnosed when they are invasive in the vertical growth phase. The median Breslow index of 3 mm and most of the cases being Clark's level IV corroborate this observation. The average thickness of the tumors at diagnosis was similar to that found in the national study and is classically associated with poor prognosis.[13–18]

We also demonstrated that most tumors had mitoses at diagnosis, and almost half of the tumors contained ulcerations. These are significant findings since both are markers of worse prognosis, indicating a higher risk of metastasis.[19,20]

Thus, these data support the fact that melanoma in the acral region, regardless of the histological subtype, is usually diagnosed late in relation to melanomas in other locations. A complete physical examination, including inspection of the palmar and plantar regions and the education of patients can reduce these indicators.[17,21]

The sex ratio found in this series (1 man for every 1.36 women) is similar to that previously reported.[13–15] Nunes et al. (2018) demonstrated a mean age at diagnosis similar to that shown in this study (68.71 years).[13]

The data collected in our study show a trend toward greater severity in male patients since they have a higher number of mitoses, thickness, ulcerations, and, consequently, a lower five year survival rate. Sex has been recognized in other studies as an independent prognostic factor for melanoma although the reasons for longer prolonged survival in women remain unclear.[13,22] Although the diagnosis is made earlier in women, who usually practice better self-care, this finding does not seem to be sufficient to explain the difference in prognosis between the sexes. Some theories about the difference between genders suggest a role for oxidative stress and estrogen as a protective factor in women at menarche.[20,23,24].

The challenge of early acral melanoma diagnosis, especially the lentiginous subtype, has prompted further studies to better understand the pathogenesis of this nosological entity. A promising área is the development of target therapies since new studies have elucidated the molecular and genetic aspects of acral lentiginous melanoma.[18,23] It is postulated that kinase-dependent cyclin (cyclin D1) acts as an oncogene in this melanoma subtype as identified early by the *in situ* hybridization technique (FISH).[18] Also, acral lentiginous melanoma presents a higher frequency of mutations in tyrosine kinase receptors (KIT), which has even been associated with the advanced Clark level.[17,25] These findings are relevant since therapies aimed at these KIT mutations are already available for other neoplasms.[25]

CONCLUSION

Melanomas that develop in acral sites have a very high average thickness at diagnosis, which reinforces the importance of redoubling our efforts to establish public policies for the earlier recognition of this condition. Gender also seems to influence the prognosis of these patients, and larger studies need to be conducted for better definition.

Author's Contribution

All authors have contributed equal to work.

RESUMO

OBJETIVO: *Analisar e traçar uma relação entre as características clinicopatológicas e sociodemográficas dos melanomas acrais diagnosticados no Hospital do Servidor Público Estadual de São Paulo.*

MÉTODOS: *Fez-se um estudo observacional, descritivo e retrospectivo de pacientes diagnosticados com melanoma em sítio acral entre 1997 e 2016 no Hospital do Servidor Público Estadual de São Paulo. Características sociodemográficas e clinicopatológicas foram coletadas e analisadas.*

RESULTADOS: *Foram encontrados 45 pacientes com melanoma acral no período avaliado. Trinta e um eram do sexo feminino (68,89%) e 14 masculino (31,11%). A maioria dos casos diagnosticados eram invasivos (88,37%) e o subtipo histológico predominante foi o lentiginoso acral (91,11%). A região plantar foi a mais prevalente (64,44%). A mediana do índice de Breslow foi de 3 mm. Houve uma tendência a maior gravidade nos pacientes do sexo masculino.*

CONCLUSÕES: *Os melanomas de sítio acral são diagnosticados em fases mais avançadas o que acarreta pior prognóstico dos pacientes. Assume ainda maior importância em populações altamente miscigenadas e negras como a brasileira.*

PALAVRAS-CHAVE: *Melanoma/epidemiologia. Melanoma/patologia. Neoplasias cutâneas.*

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VEGF gene rs35569394 polymorphism in patients with Polycystic Ovary Syndrome

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SUMMARY

OBJECTIVE: The relationship between the clinicopathological and sociodemographics characteristics of acral melanomas diagnosed at BACKGROUND: This study aimed to investigate the frequency of VEGF gene insertion (I) / deletion (D) polymorphism (rs35569394) in patients with Polycystic Ovarian Syndrome (PCOS) and to compare with a control population to verify its association with the pathology.

METHODS: 206 women participated in this study, 103 with PCOS (group of patients) and 103 without the disease (control group). After extraction of genomic DNA from the samples, molecular analysis was performed by Polymerase Chain Reaction (PCR) and electrophoresis in polycrylamide. Descriptive analysis, univariate analysis and logistic regression model were used. Results were presented in odds ratio (OR) and 95% confidence interval (95% CI), considering the significance of $p < 0.05$.

RESULTS: There were no statistical differences between patients and controls for allele frequencies ($\chi 2 = 1.16$, $p = 0.56$). The genotypic frequency distribution was in Hardy Weinberg equilibrium for the patients ($\chi 2 = 2.42$; $p < 0.05$), but not for the control group ($\chi 2 = 7.26$; $p < 0.05$). Regarding risk factors for the syndrome, a history of familial PCOS is more frequent among women with the syndrome.

CONCLUSIONS: In the present study, there is no association between VEGF gene I / D polymorphism and PCOS.

KEYWORDS: Polycystic ovary syndrome. Polymorphism, Genetic. Polymerase chain reaction.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is an endocrine metabolic pathology that affects 5% to 20% of women of reproductive age and is considered one of the main causes of female infertility.[1] The diagnosis of this condition is based on the Rotterdam criteria that consists of at least two of the following three findings: (1) oligoovulation or chronic anovulation, (2) clinical and/or laboratory evidence of hyperandrogenism and (3) pelvic ultrasound indicative of polycystic ovaries.[2] Secondary manifestations may also

occur, such as metabolic disorders related to obesity, insulin resistance, type II diabetes mellitus, cardiovascular disease, endometrial carcinoma and dyslipidemia. Women with PCOS are also at increased risk for gestational diabetes, pre-eclampsia and pregnancy complications with early pregnancy loss and / or neonatal complications.[3]

PCOS is a multifactorial disease and studies show that genetic predisposition and exposureto environmental factors such as toxins, diet, nutrition and ethnicity are in the etiology of this pathology.[3,4]

Among the genes studied in PCOS, changes in the Vascular Endothelial Growth Factor/VEGF gene, which encodes a protein that participates in the physiological regulation of ovarian angiogenesis, stabilization of blood vessels, formation, function and regression of the corpus luteum, can play an important role in the etiology of the syndrome.[5] The correct formation and regression of vascular vessels during each ovarian cycle is important for proper follicular development, ovulation and formation of the corpus luteum. The small follicles are avascular and depend on stromal vessels for nutrition and hormonal supply. Blood vessels develop within the ovarian theca, regulated by angiogenic factors, and each follicle depends on its thecal vascular pathway to survive and mature.[1] Studies have shown an association of alterations in the VEGF gene when abnormalities occur in the angiogenesis process.[6,7] Another study also showed that changes in ovarian angiogenesis in different gynecological conditions may contribute to an increased risk of ovulation disorders, hyperandrogenism and infertility, which are characteristics of PCOS.[5]

This gene is highly polymorphic and is located in the chromosomal region 6p21.3.It consists of eight exons and seven introns, exhibiting alternative splicing to form a family of proteins.[6] An 18 base pair insertion/deletion (I/D) polymorphism was located in the promoter region at position -2549 of the *VEGFA* gene (rs35569394). This alteration affects the gene expression and the increased transcriptional activity by allele D (deletion) compared to allele I (insertion).[8] This genetic variant was associated to some gynecological conditions, such as risk of recurrent spontaneous abortion,[8] severe pre-eclampsia,[9] uterine leiomyoma[10] and susceptibility to breast cancer.[11] However, recent bibliographic surveys do not show published data on the rs35569394 polymorphism in PCOS. In spite of that, it is known that patients with PCOS have increased VEGF protein expression

and *VEGF* polymorphisms contribute to the etiology of this endocrine metabolic condition.[7,12-15] Recent studies conducted by our group have shown that the VEGF gene rs1570360 polymorphism is associated with PCOS and the TGC haplotype may be associated with protective factors.[13] A meta-analysis included 29 case-control studies of 11 polymorphisms of the VEGF gene and concluded that such genetic variants may become early biomarkers of PCOS.[16]

In view of the above, this study aimed to determine the frequency of the polymorphism of the VEGF gene (rs3569394) in patients with PCOS and to compare it with a control population in order to verify the association of this polymorphism with the syndrome.

METHODS

This is a case-control study approved by the Research Ethics Committee (CEP) of the Federal University of Triângulo Mineiro (UFTM), protocol nº 1796. The sample consisted of 206 women from the Gynecology and Obstetrics Clinics at UFTM, 103 diagnosed with PCOS and 103 women of reproductive age, between 14 and 53 years old, with no history of hyperandrogenism, menstrual dysfunction, infertility or sonographic sign of PCOS, metabolic disorders, which constituted the control group.

Rotterdam criteria were used for the diagnosis of PCOS. Exclusion criteria were applied to women with Cushing's syndrome, 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia, diabetes, androgen-secreting tumors, antiandrogens, statins, glucocorticoids or infertility medications. Patients with the mentioned pathologies or in use of these drugs were excluded from the sample, as these conditions may cause hormonal changes and be conflicting factors for the diagnosis of PCOS. The patients were considered "smokers" when at least 100 cigarettes were consumed during their lifetime. With regards to alcohol, those who consume at least four doses per week were considered "alcohol users"..[17]

The genomic DNA was extracted from 5mL of peripheral blood using the salting-out procedure, described by Miller *et al.* (1988)[18]. This technique is fast, simple and very efficient for obtaining high quality DNA. The quantification of genomic DNA was performed by spectrophotometry and the ratio between the A260 / A280 readings was approximately to 1.8. The rs 35569394 polymorphism was analysed by Polymerase Chain Reaction (PCR) using the following

sequences of the primers sense 5'GCT GAG AGT GGG GCT GAC GAG TAG GTA 3' and antisense 5 'GTT TCT GAC CTG GCT ATT TCC AGG 3'.

The genomic DNA was amplified in a final volume of 25 μL containing approximately 100 ng of genomic DNA, 1X PCR buffer, 2m M of MgCl2, 2 uM de dNTP and 1 U of Taq DNA polymerase (Invitrogen, Brasil). To the reaction, 20 pmol of each primer (Exxtend, Brasil) were also used. All PCR experiments were performed with negative control, that is, the components of the reaction without genomic DNA. Amplification conditions were: initial denaturation at 95°C for 10 minutes, followed by 35 cycles with denaturation at 95°C for 45 seconds, annealing at 60°C for 45 seconds, extension at 72°C for 45 seconds and final extension at 72°C for 10 minutes. PCR products were visualized on 10% polycrylamide gel, coloured with ethidium bromide for 10 minutes and visualized in UV light for genetic determination, with the 229 bp products corresponding to the insertion of 18 bp (allele I) and the 211 bp the deletion (allele D). Thus, three genotypes can be found: II (one band in the electroforesis of 229 bp), ID (two bands, one of 229 bp and other of 211 bp) and DD (one band of 211 bp) (Figure 1).

In the statistical analysis, the chi-square test was used to analyse the genotypic and allelic distribution of the polymorphisms and the Hardy Weinberg equilibrium was also tested by the same test, considering the significance of p<0.05. The multiple logistic regression model was used to determine the effect of risk factors on PCOS (family history of PCOS, smoking, alcoholism and the presence of polymorphism) and was analysed in 94 patients and 83 controls who had complete data for all variables analysed. Multiple logistic regression was performed only for the patients and the model included the clinical consequences of PCOS and the polymorphism studied.

RESULTS

In the control group (n = 103), 6.8% (7/103) had genotype II, 58.2% (60/103) had ID genotype and 35% (36/103) presented the DD genotype. In the patients group (n=103), the genotype frequencies were 9.7% (10/103); 53.3% (55/103) and 37% (38/103), for genotypes II, ID and DD, respectively. No statistical differences were observed between patients and controls for genotype frequencies (χ2 = 0.80; p = 0.67). Allelic

FIGURE 1. PCR AMPLIFICATION PATTERNS FOR GENOTYPES II (A SINGLE BAND OF 229 BP IN THE ELECTROPHORESIS), ID (TWO BANDS, ONE WITH 229 BP AND THE OTHER WITH 211 BP) AND DD (ONE 211 BP BAND) IN ONE 10% POLYACRYLAMIDE GEL STAINED WITH ETHIDIUM BROMIDE. COLUMN 5 REPRESENTS GENOTYPE II; COLUMNS 2, 3, 4 AND 7 REPRESENT THE HETEROZYGOUS ID GENOTYPE AND COLUMNS 1 AND 6, THE DD GENOTYPE.

TABLE 1. DISTRIBUTION OF POLYMORPHISM OF RS35569394 OF *VEGF* GENE AND RISK FACTORS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS, N = 94) AND CONTROLS (SPCOS, N = 93), THAT HAD COMPLETE DATA FOR THE ANALYZED VARIABLES.

VARIABLE ANALYZED	PCOS n (%)	CPCOS n (%)	O.R (CI-95%)	p
Smoker				<0.05
Yes	06 (6.38)	21 (28.09)	0.28 (0.10-0.78)	
No	88 (93.62)	72 (71.91)		
Alcohol consumption				0.68
Yes	25 (26.59)	31 (33.33)	0.86 (0.43-1.73)	
No	69 (73.41)	62 (66.64)		
PCOS Family History			3.87 (1.85-8.11)	<0.05
Yes	38 (40.42)	15 (16.13)		
No	56 (59.58)	78 (83.87)	0.89 (0.30-2.62)	
Polimorphism of VEGF gene				0.83
II	9 (9.57)	7 (7.52)		
ID/ DD	85 (90.43)	86 (92.48)		

TABLE 2. DISTRIBUTION OF POLYMORPHISM OF RS35569394 OF *VEGF* GENE AND CLINICAL OUTCOMES IN PATIENTS (N = 94) WITH GENOTYPE II VERSUS PATIENTS WITH GENOTYPES ID OU DD.

VARIABLE ANALYZED	Patients with genotype II, n (%)	Patiens with genotypes ID or DD, n (%)	O.R (CI 95%)	p
Absence of Pregnancy			3.60 (0.26-48.89)	
Yes	02 (22.2)	65 (76.5)		0.33
No	07 (77.8)	20 (23.5)		
Abortation			0.21 (0.12-3.86)	
Yes	01 (11.1)	05 (5.9)		0.30
No	08 (88.9)	80 (94.1)		
Menstrual Irregularity			2.83 (0.47-16.76)	0.25
Yes	04 (44.4)	54 (63.5)		
No	05 (55.6)	31 (36.5)		
Hirsutism			3.20 (0.55-18.47)	0.19
Yes	03 (33.3)	51 (60)		
No	06 (66.7)	34 (40)		
Acne			1.19 (0.17-8.10)	0.85
Yes	04 (44.4)	55 (64.9)		
No	05 (55.6)	30 (35.1)		
Oiliness			1.44 (0.12-16.40)	0.76
Yes	07 (77.8)	64 (75.3)		
No	02 (22.2)	21 (24.7)		
Hair Loss			1.42 (0.23-8.71)	0.70
Yes	04 (44.4)	56 (65.9)		
No	05 (55.6)	29 (34.1)		

TABLE 3. RECENT STUDIES PUBLISHED IN THE LITERATURE ON THE *VEGF* - 2549 I / D POLYMORPHISM IN DIFFERENT GYNECOLOGICAL CONDITIONS.

Author	Condition	Conclusion
Keshavarzi et al., (2017)[10]	Uterine leiomyomas	Significant association between genotype II.
Bruno et al., (2018)[19]	Endometriosis	Variant was not associated with the investigated condition.
Hashemi et al., (2018)[8]	Recurrent spontaneous abortion	Significant association between polymorphism and the risk of recurrent miscarriage.
Gala-Bladzinska et al.., (2019)[24]	Vascular complications in patients with type 2 diabetes mellitus	The presence of the I / D allele may be associated with heart failure and strokes.
Keshavarzi et al., (2019)[9]	Pre eclampsia	No association was found between the studied polymorphisms.
Vidyadhari et al., (2019)[25]	Recurrent pregnancy loss	Polymorphism was associated with aborted fetuses.

frequencies were 0.36 and 0.64 for alleles I and D in both groups. The distribution of genotypic frequencies was in HWE to the patients ($\chi 2= 2.42$; p<0.12), but not to the control group ($\chi 2= 7.26$; p<0.05). There were also no differences between allele frequencies ($\chi 2=1.16$, p=0.56).

In the multiple logistic regression model (Table 1) it was evidenced that family history was more frequent in patients with PCOS (OR=3.87, 95% CI: 1.85-8.11, p <0.05), smoking was more frequent in controls (OR=0.28; 95% CI: 0.10-0.78, p<0.05) and there were no differences in alcohol consumption (OR=0.86, 95% CI: 0.43.1.73, p=0.68) and in the distribution of polymorphism (OR=0.89, 95% CI: 0.30-2.62, p= 0.83). There were no differences between patients with the presence of polymorphism and clinical consequences of disease (Table 2).

DISCUSSION

The VEGF gene is expressed and secreted in the human ovary and plays an important role in the folliculogenesis of the ovarian cycle. Deregulation of ovarian angiogenesis contributes to abnormal follicular development in women with PCOS, with an imbalance in angiogenic factors.[1] Two recent studies evaluated polymorphisms of the VEGF gene in patients with PCOS, one of which evaluated Single Nucleotide Polymorphisms/SNPs in 55 patients and 52 controls[12] and the other, two SNPs (rs2010963 and rs833061) in 118 and 130 patients and controls, respectively[14]. Both confirmed the participation of genetic variants of the VEGF gene for the pathogenesis of the syndrome. However, there are no published studies on the contribution of the rs35569394 polymorphism of the VEGF gene to the development of PCOS. In addition, a previous study conducted by our group also showed that the rs1570360 polymorphism is associated with PCOS and the TGC haplotype is associated with protective factors[13], which made us investigate the contribution of this other SNP of the VEGF gene to the development of this condition.

The absence of studies of this SNP in PCOS makes it difficult to discuss the results obtained, but it highlights the originality of our research. In the present study, according to the univariate analysis (103 patients and 103 controls), the rs35569394 polymorphism did not show statistically significant differences in the distribution of genotypic frequencies between patients with PCOS and controls. Similar results have been reported in other studies conducted

in patients with endometriosis[19] and hepatocellular carcinoma.[20] The present study observed that the genotypic frequency of the control group was not in HWE as in the study by Bruno and collaborators in 2018[19], which suggests a protective effect of the polymorphic allele.

It has been reported that the presence of the D allele in the -2549 promoter region leads to a 1.95-fold increase in transcriptional activity, increasing the expression of VEGF.[8] Our results showed high frequencies in both ID and DD genotypes, and the literature has associated the frequency of the D allele to cases of diabetic nephropathy[21] and severe pre-eclampsia.[9] According to previous research[22], the inheritance of the D allele can alter the VEGFA in the gene expression of the embryo, causing abnormalities in protein levels that may lead to spontaneous abortion and abnormal angiogenesis. However, it is important to highlight that there are controversies regarding the potential of the D allele as a risk factor for clinical conditions, since a published study positively associated genotype II and/or allele I with pathologies such as uterine leiomyoma.[10]

The increase in the frequency of smoking in the control group is not in accordance with a previous study[23], in which women with PCOS showed higher frequency in relation to smoking, as well as a greater risk of worsening the metabolic profile. The increased frequency of family recurrence of PCOS in the study group is supported by the literature that evidences genetic factors in the etiology of this pathology, leading to a shared genetic predisposition.[3] The risk factors established for PCOS are related to the increased risk to develop infertility, cardiovascular disease, metabolic syndrome, type 2 diabetes and endometrial cancer. Pregnant women with PCOS have a higher risk of pregnancy complications, such as pre-eclampsia, spontaneous abortion, gestational diabetes and premature birth.[1] No differences were found between clinical manifestations of PCOS and the analyzed polymorphism. It is known that hyperandrogenism is characterized by an increase in the production of ovarian androgen due to the increased synthesis of the hormone by follicular theca cells, which shows an increased expression of several genes that encode these steroids.[3] However, in the study analyzed, no associations were found between these parameters and the investigated polymorphism.

PCOS is multifactorial and the presence of the D allele can be a risk factor for the clinical consequences of the pathology, as it leads to the overproduction of androgen hormones responsible for the clinical manifestations of this condition, such as menstrual irregularity, acne, hirsutism, polycystic ovarian morphology, insulin resistance and obesity.[1,3] The literature reports that the high vascularization promoted by high levels of VEGF in the stroma can lead to abnormal growth of the theca - an important site for androgenic steroidogenesis.[6]

In the present study, this genetic polymorphism was not associated with PCOS. However, previous studies on other gynecological conditions have shown divergent results (Table 3).

The present study faced a certain limitation because there was no dosage of the various biochemical parameters related to PCOS and VEGF serum levels to assess the association between genotypes. However, it is important mentioning that our study so far is the only one to evaluate this polymorphism in PCOS and, although it has not been individually associated with PCOS, the study in (of?) haplotypes may present significant effects. Previous studies[13,25] show the importance of this type of analysis to help understanding the etiology of complex diseases. In conclusion, the VEGF -2549 I/D polymorphism is not associated with PCOS in the investigated sample.

Financial Suport

Authors' contributions

Sheila Silveira Fernandes: project design, data collection and analysis, article writing; Alessandra Bernadete Trovó de Marqui: project design, data collection and analysis, article writing; Daniela Reis Fernandes Teles: data collection and analysis; Elisabete Aparecida Montovani Rodrigues Resende: data collection and analysis; Marco Fábio Prata Lima: data collection and analysis; Mariana Kefalas Oliveira Gomes: data collection and analysis; Mariangela Torreglosa Ruiz Cintra: project design, data collection and analysis, article writing. All authors participated in the final analysis of the article.

RESUMO

OBJETIVO: *Este estudo teve como objetivo investigar a frequência do polimorfismo de inserção (I)/ deleção (D) do gene VEGF (rs35569394) em pacientes com Síndrome dos Ovários Policísticos (SOP) e comparar com uma população controle para verificar sua associação com a patologia.*

MÉTODOS: *Participaram desse estudo 206 mulheres sendo 103 com SOP (grupo de pacientes) e 103 sem a doença (grupo controle). Após extração do DNA genômico das amostras, a análise molecular foi realizada por Reação em Cadeia da Polimerase e eletroforese em gel de poliacrilamida. Utilizou-se análise descritiva, análise univariada e modelo de regressão logística. Os resultados foram apresentados em odds ratio (OR) e intervalo de confiança de 95% (IC-95%), considerando a significância de p < 0,05.*

RESULTADOS: *Não houve diferenças estatísticas entre as pacientes e controles para as frequências alélicas (χ^2 = 1,16, p = 0,56). A distribuição da frequência genotípica estava em equilíbrio de Hardy Weinberg para as pacientes ($\chi 2$= 2,42; p<0,12), mas não para o grupo controle ($\chi 2$= 7,26; p<0,05). Em relação aos fatores de risco para a síndrome, a história de SOP familiar é mais frequente entre as mulheres com a síndrome.*

CONCLUSÕES: *Na casuística estudada, não há associação entre o polimorfismo I/D do gene da **VEGF** e a SOP.*

PALAVRAS CHAVE: *Síndrome do ovário policístico. Polimorfismo genético. Reação em cadeia da polimerase.*

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Evaluation of the frequency of patients with cancer presenting to an emergency department

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SUMMARY

OBJECTIVE: *This study aims to determine the demographic characteristics of cancer patients admitted to an emergency department and determine the relationship between the frequency of admission to the emergency department and oncological emergencies and their effect on mortality.*

METHODS: *This observational, prospective, diagnostic accuracy study was performed in the ED of a tertiary care hospital. Patients over the age of 18 who were previously diagnosed with cancer and admitted to the emergency service for medical reasons were included in the study. We recorded baseline characteristics including age, gender, complaints, oncological diagnosis, metastasis status, cancer treatments received, the number of ED admissions, structural and metabolic oncological emergency diagnoses in the ED, discharge status, length of hospital stay, and mortality status.*

RESULTS: *In our study, 1205 applications related to the oncological diagnosis of 261 patients were examined. 55.6% of the patients were male, and 44.4% were female. The most common metabolic oncological emergency was anemia (19.5%), and the most common structural oncological emergency was bone metastasis-fracture (4.6%.) The mean score of admission of patients to the emergency department was four times (min: 1 max: 29) during the study period. A total of 49.4% (n: 129) of the patients included in the study died during follow-up, and the median time of death was 13 days after the last ED admission.*

CONCLUSION: *The palliation of patient symptoms in infusion centers that will be established in the palliative care center will contribute to the decrease in the frequency of use of emergency services.*

KEYWORDS: *Emergency Service, Hospital. Palliative care. Hospitalization. Neoplasms.*

INTRODUCTION

Cancer is a severe disease that presents a physical burden as well as social, economic, and mental aspects[1]. It is observed that cancer patients present to emergency departments (ED) more frequently in the last six months before the death, primarily because of their decreased functional capacity, pain control deterioration, and changes in consciousness[2]. More than 4.5 million cancer patients annually present to

EDs in the USA[3]. Cancer patients present to EDs due to the course of their oncological disease or complications related to their treatment. Due to many reasons such as increasing early diagnosis rates, increasing knowledge of patients about malignancy, changing treatment approaches, and prolonging follow-up periods, the life expectancy increases; thus, the number of cancer patients admitted to the emergency department increases too[4].

This study aims to determine the demographic characteristics of cancer patients admitted to the emergency department and the relationship between the frequency of admission to the emergency department and oncological emergencies and their effect on mortality.

METHODS

This observational, prospective, diagnostic accuracy study was performed between July 01, 2016, and June 30, 2017, in the ED of a tertiary care hospital in Adana, Turkey. Patients over the age of 18 who were previously diagnosed with cancer and were under treatment (chemotherapy, radiotherapy) and admitted to the emergency service for medical reasons were included in the study. Patients with hematological malignancies (since there was no hematology specialist in our hospital at the time of the study), cancer patients admitted with trauma, and patients under 18 years old were excluded from the study. Ethics approval from the local ethics committee was obtained before the study process. A total of 1,205 emergency applications of 261 patients who met the inclusion criteria were examined. We recorded baseline characteristics including age, gender, complaints, the primary system involved (oncological diagnosis), metastasis status, cancer treatments received, the number of ED admissions, structural and metabolic oncological emergency diagnoses in the ED, discharge status, length of hospital stay, and mortality status. Patients were followed up regarding mortality throughout the study. Gender, age, treatments, oncological diagnosis, metastases, the number of ED admissions, and mortality status were evaluated according to the number of patients; other parameters were evaluated according to the number of applications. The primary outcome of the study was to determine the frequency of application to the emergency department and the outcome of cancer patients. The secondary outcome was to determine the structural and metabolic oncological

emergencies that caused the patients' to apply to the emergency department.

Statistical Analysis

The data were analyzed with IBM V22 SPSS[5]. The appropriateness of quantitative measurements to normal distribution was examined by Shapiro-Wilk and Kolmogorov Smirnov tests. Mann Whitney U test and Kruskal Wallis test were used to compare the data with abnormal distribution. A chi-square test was used to analyze categorical data. Categorical data were presented as frequency (percentage), and quantitative data were presented as mean ± deviation, and median (min-max). A p-value of <0.05 was set as the significance level.

RESULTS

In our study, 1205 applications related to the oncological diagnosis of 261 patients were examined. 55.6% (n=145) of the patients were male, and 44.4% (n=116) were female. 60% (n=723) of the applications were from males, and 40% (n=482) were from female patients. The average age of women was 57.5 ± 13.1, while it was 63.3 ± 12 in men, and there was a statistically significant difference between the genders (p <0.001). It was found that the most common reason for admission was related to the gastrointestinal tract (liver, gallbladder, pancreas, stomach, intestine). Considering the distribution by gender, the most common primary diagnosis was breast cancer in women (17.6%, n=46) and lung cancer (19.5%, n=51) in men. Metastasis was present in 36.4% (n=95) of the patients (Table 1). The most common reason for ED admission was the progression of the disease in 53% (n=639) of the patients. 37.9% (n=457) of the patients applied to the ED with pain. Common body pain was the most commonly seen pain type with 14.6% (n=176), and abdominal pain was present in 14.6% (n=176). When the frequency of admission of patients to the emergency department was evaluated, it was observed that the mean was four times (min: 1, max: 29) during the study period. 28% (n=73) of the patients had six or more admissions (Table 1).

There was no statistically significant relationship between the frequency of admission to the ED and the primary oncological diagnosis (p=0.339). The median value of admission to the emergency department for patients with gynecological malignancy was significantly statistically different for patients with head

TABLE 1. PATIENT DEMOGRAPHICS AND ADMISSION DETAILS

	Female	Male	Total
Gender n (%)	116 (44.44)	145 (55.55)	261 (100)
Age (yr, mean±SD) (min-max)	57.5±13.1 (24-82)	63.3±12 (25-91)	60.7±12.8 (24-91)
Localization of malignancies n (%)			
Gastrointestinal	35 (13.4)	40 (15.3)	75 (28.7)
Lung	11 (4.2)	51 (19.5)	62(23.8)
Breast	46 (17.6)	3 (1.1)	49(18.8)
Genitourinary	2 (0.8)	30 (11.5)	32(12.3)
Gynecological	13 (5.0)	0 (0)	13 (5)
Head and neck	1 (0.4)	7 (2.7)	8 (3.1)
Central nerve system	3 (1.1)	5 (1.9)	8 (3.1)
Lymphoma	3 (1.1)	5 (1.9)	8 (3.1)
Primary unknown	2 (0.8)	3 (1.1)	5 (1.9)
Skin	0 (0)	1 (0.4)	1 (0.4)
Metastase n (%)			
Yes	36 (13.8)	59 (22.6)	95 (36.4)
No	80 (30.7)	86 (33.0)	166 (63.6)
Cancer treatment			
Chemotherapy	84 (72.4)	103 (71)	187 (71.64)
Radiotherapy	3 (2.6)	3 (2.1)	6 (2.29)
Chemotherapy and Radiotherapy	29 (25)	39 (26.9)	68 (26.25)
Number of presenting to the ED n (%)			
1	16	21	37 (14.2)
2	26	25	51 (19.5)
3	20	21	41 (15.7)
4	18	17	35 (13.4)
5	9	15	24 (9.2)
≥6	27	46	73 (28)
Reason of ED visits n (%)			
Progressive disease	237 (19.7)	402 (33.4)	639 (53)
Chemotherapy effects	202 (16.8)	255 (21.2)	457 (37.9)
Infections	31 (2.6)	58 (4.8)	89 (7.4)
Radiotherapy effects	12 (1.0)	8 (0.7)	20 (1.7)
Result of ED visits n (%)			
Discharge from the ED	364 (30.2)	505 (41.9)	869 (72.1)
Hospitalization	116 (9.6)	213 (17.7)	329 (27.3)
Discharge	108 (9)	188 (15.6)	296 (24.6)
Mortality	8 (0.6)	25 (2.1)	33 (2.7)
Mortality at emergency department	2 (0.2)	5 (0.4)	7 (0.6)
Length of hospital stay (day, mean ±SD)	6.8±6.3	7.1 ±8.9	7 ±8.1
Mortality n (%)			
Death during follow-up	39 (14.9)	90 (34.5)	129 (49.4)
Alive at end of follow-up	77 (29.5)	55 (21.1)	132 (50.6)

and neck cancer (p=0.007). Patients who were under chemotherapy were admitted to ED with an average of 3 times (min: 1, max: 18), while patients under radiotherapy had an average of 3 times (min: 1, max: 17). The average admission was four times for patients who received both treatments (min: 1, max: 29). There was no statistically significant difference between the frequency of admission to the ED and the received cancer treatment (p= 0.319). The patients who did not die during the study period were admitted to the ED with an average of 3 times (min: 1 max: 29), and the patients who died had an average admission of 4 times (min: 1, max: 22). There was no statistically significant difference between the frequency of admission to the ED and mortality (p= 0.100) (Table 2).

Metabolic oncological emergencies were detected in 71.9% (n=866) of all the admissions. When metabolic oncological emergencies were evaluated, the most common hematological disorder was anemia with 19.5% (n=236), while the most common biochemical disorder was hyponatremia with 5.1% (n=61). There was a marginally significant effect between the presence of metabolic oncologic emergencies and the frequency of admission to the ED (p=0.050) (Table 3).

Structural oncological emergencies were detected in 15.4% (n=185) of all the admissions. The most common structural oncological emergencies in patients were fractures due to bone metastasis with 4.6% (n=56) and increased intracranial pressure (ICP) syndrome

TABLE 2. THE RELATIONSHIP BETWEEN THE FREQUENCY OF PATIENTS PRESENTING TO EMERGENCY DEPARTMENT AND MORTALITY, PRIMARY CANCER DIAGNOSIS AND CANCER TREATMENT

	The frequency of patients presenting to emergecny department		
	Median (min-max)	Test statistics	p
Primary cancer diagnosis			
Head-neck	7.5 (3-15)	χ^2=22.528	0.339
Skin	6 (6 - 6)		
Lung	4.5 (1 - 29)		
Central nervous system malignancy	4.5 (1 - 17)		
Gastrointestinal system malignancy	3 (1 - 15)		
Breast	3 (1 - 15)		
Lymphoma	3 (1 - 15)		
Genitourinary system malignancy	3 (1 - 18)		
Gynecological	3 (1 - 5)		
Unknown primary	1 (1 - 5)		
Cancer treatment			
Chemotherapy	3 (1 - 18)	2.285	0.319
Radiotherapy	3 (1 - 17)		
Chemotherapy + Radiotherapy	4 (1 - 29)		
Mortality			
Dead patients	4 (1 - 22)	U= 9507	0.100
Alive patients	3 (1 - 29)		

: Chi square test statistics, U: Mann Whitney U Test statistics

TABLE 3. DISTRIBUTION OF METABOLIC AND STRUCTURAL ONCOLOGICAL EMERGENCY DIAGNOSES ACCORDING TO THE FREQUENCY OF PATIENTS PRESENTING TO EMERGENCY DEPARTMENT

	The frequency of patients presenting to emergecny department			
	n (%)	Median (min-max)	Test statistics	p value
Metabolic Oncological Emergencies				
Anemia	236 (19.58)	6 (1 - 29)	= 25.280	0.050
Thrombocytopenia	136 (11.28)	6 (1 - 29)		
Leukocytosis	119 (9.87)	5 (1 - 15)		
Febrile neutropenia	64 (5.31)	5 (1 - 14)		
Hyponatremia	61 (5.06)	5 (1 - 14)		
Hyperglycemia	56 (4.64)	5 (1 - 17)		
Leukopenia	53 (4.39)	5 (1 - 15)		
Hyperpotassemia	30 (2.48)	6 (1 - 18)		
Hypercalcemia	28 (2.32)	4 (1 - 15)		
Hypopotassemia	23 (1.90)	6 (2 - 12)		
Hyperuricemia	19 (1.57)	6 (1 - 29)		
Hypoglycemia	17 (1.41)	5 (1 - 15)		
Hypernatremia	13 (1.07)	6 (1 - 17)		
Hypocalcemia	11 (0.91)	18 (1 -29)		
Structural Oncological Emergencies				
Bone Metastasis-Fracture	56 (4.64)	4 (1-29)	χ2= 15.310	0.121
Brain Metastasis-ICP syndrome	41 (3.40)	4 (1-29)		
Malignant Pleural Effusion	25 (2.07)	6 (2-15)		
Obstructive Uropathy	19 (1.57)	6 (1-18)		
Ileus	17 (1.41)	4 (1-13)		
Malignant pericardial effusion	8 (0.66)	5.5 (1-14)		
Spinal Cord Compression	5 (0.41)	4 (2-4)		
Gastrointestinal Bleeding	4 (0.33)	4.5 (2-7)		
Vena Cava Superior Syndrome	3 (0.24)	13 (6-22)		
Pancreatitis-Hepatitis-Cholecystitis	3 (0.24)	10 (9-11)		
Airway Obstruction	3 (0.24)	6 (6-10)		
None	1020 (84.64)	-	-	-

χ^2: Chi square test statistics. ICP: Increased intracranial pressure

due to brain metastasis with 3.4% (n=41). There was no statistically significant difference between the frequency of admission to the ED and the structural oncological emergencies (p=0.121) (Table 3). Structural oncological emergencies were detected in 31.7% (n=41) of patients who died during the study period and in 14.3% (n=19) of patients who remained alive. There was a marginally significant effect between the presence of structural oncological emergencies and mortality. (p=0.054)

While 72.1% of the patients were discharged, 27.3% were hospitalized, and 0.6% died in the ED (Table 1). 49.4% (n=129) of the patients included in the study died during the follow-up. 2.7% (n=7) of the patients died in the ED, and 12.6% (n=33) died in the clinic where they were hospitalized; the median time for death was 13 days after the last ED admission.

The mean length of hospital stay was 7±8.1 days for 329 admissions. There was no statistically significant difference between the length of hospital stay and the cancer treatment received (p=0.272). There was no statistically significant difference between the length of hospital stay and metabolic oncologic emergencies (p=0.259) and structural oncological emergencies (p=0.095).

DISCUSSION

In our study, we observed that cancer patients applied to the emergency department four times on average during the study, and 72.1% of all admissions resulted in discharge from the ED. Metabolic emergencies were detected in 71.9% of all admissions, and structural oncological emergencies in 15.4%. There was no statistically significant effect of structural oncological emergencies and a marginally significant effect of metabolic oncological emergencies on the frequency of admission to the ED. There was no statistically significant difference between the frequency of admission to the ED and mortality.

Cancer is an increasing clinical health problem worldwide and leads to significant socioeconomic issues in communities and spiritual losses in individuals. Emergency admission of cancer patients may be related to oncological emergencies or other existing comorbidities due to the increased frequency of old-aged cancer patients. In both cases, it is life-threatening and has a high mortality. For this reason, early diagnosis and appropriate treatment in the ED are vital in reducing morbidity and mortality[6].

According to 2018 data of GLOBOCAN, the three most common cancer types in men worldwide are lung cancer (31.5%), prostate cancer (29.3%), and colorectal cancers (23.6%); in women, they are breast cancer (46.3%), colorectal cancers (16.3%), and lung cancer (14.6%)[7]. Similar to the literature, in our study, we found that the most commonly seen cancer in men was lung cancer, and breast cancer in women. The most common complaints expressed to the emergency department are compatible with the three most common primary cancer etiologies (gastrointestinal malignancies, lung, and breast cancer). While abdominal pain, nausea, and vomiting were admission causes of gastrointestinal malignancies, the cause was dyspnea in lung carcinomas and metastasis in breast carcinomas.

Chronic widespread pain and fatigue complaints are thought to be due to systemic metastases, and anemia, both of which are common metabolic oncological emergencies. Anemia can occur due to primary cancer, as well as due to malnutrition or hemolysis and bone marrow infiltration caused by immunosuppressive treatments[8]. Hyponatremia, the most common biochemical impairment, can be seen due to cancer progression, inappropriate ADH syndrome, which is a paraneoplastic syndrome, side effects of chemotherapy, resistant vomiting, and low oral intake[9]. The most common metastasis occurs in the lungs, liver, and bones, respectively. Although all types of cancer can metastasize to the bone, 80% of bone metastases are primarily caused by prostate, breast, lung, kidney, and thyroid cancers[10]. Since the most common malignancies in the community are breast and lung cancers, we think that fracture due to bone metastasis is the most common structural oncological emergency.

Patients with oncological diseases are admitted to the ED due to the course of their existing malignancies (pressure symptoms, pain, bleeding, respiratory distress, etc.), indirect causes of the diseases (metabolic, endocrine, hematological, infectious, etc.), adverse effects of antitumor treatment (such as febrile neutropenia), or several acute problems caused by the patient's social conditions (such as lack of care and nutrition)[11]. In our study, 39.6% of all admission was due to the side effects of the treatments (chemotherapy + radiotherapy). We think that outpatient units that will be established in chemotherapy units can help patients with pain management and provide symptomatic parenteral

treatment. Also, the registration of cancer patients to a palliative care unit and follow-up of these patients by the palliative care team will reduce ED application of cancer patients[12]. With this solution, cancer patients who are also under immune suppression can be kept away from the emergency rooms that are the focus of a wide range of infectious agents. Also, we think that the intensity of the emergency department can be reduced by using emergency resources more effectively.

The frequency of admission to the emergency service in our study was higher than the other conducted studies in the literature[13,14]. It may be due to the fact that the study population consisted of patients in the active treatment period. According to the results of our study, the presence of metabolic oncological emergencies had a marginally significant effect on the frequency of emergency department admissions, whereas structural oncological emergencies had no statistically significant effect. This finding suggests that cancer patients were admitted to the ED instead of the primary care center or palliative care center for their simple complaints. As a result of advancing age and increased diagnostic possibilities, the incidence and follow-up time of oncological diseases have increased, and these patients apply to the emergency departments more than expected. The reasons for recurrent emergency admission were thought as follows: easy and faster accessibility to the ED, the fact that this group of patients did not want to wait in the outpatient queue for reasons such as chronic body pain, the emergency department services are available uninterruptedly, and the hospitalization of some of those patients from the outpatient clinic was delayed due to the lack of hospital rooms.

In studies, the rate of hospitalization in the general population was reported as 12-13% in ED of tertiary care hospitals[15,16]. In our study, 27.3% of all admissions were hospitalized. When assessed in comparison to all emergency admissions, the rate of hospitalization in oncological patients is high. Difficulties of care and low pain control for cancer patients at home are among the reasons for this high rate. According to other studies[17,18] the high rate of discharge from the emergency department can be explained by the absence of palliative care and infusion centers for pain palliation and symptomatic treatment. Problems that can be easily, cheaply, and quickly solved by family doctors and home care services in the places where patients live increase the burden of EDs. Also, hospitalization of these patients for pain palliation or parenteral fluid treatment alone is more harmful than beneficial due to hospital-acquired infections, deep venous thrombosis, etc.[12]

In one study, cancer patients' one-year mortality was determined as 39%, and in another, the mortality rate was 70.6%[14,19]. In our study, the one-year mortality rate was 49.4%, and the median duration until death after the last emergency admission was 13 days. Due to the deterioration of their general condition, frequent complaints, and psychosocial conditions, patients are admitted to emergency services that provide uninterrupted treatment and are easily accessible in the terminal period. EDs have great importance for cancer patients because, with the emergency department interventions, they can relieve their pain in the last stages of their lives and improve their quality of life. However, even if the emergency services provide medical support to cancer patients, they are insufficient for psychosocial and moral support due to their current patient loads. End-stage cancer patients need palliative care centers where their relatives can be with them before death. Also, in palliative care units, pain management, and additional treatments can be provided.

CONCLUSION

As a result, starting from the time of the definite diagnosis, follow-up of cancer patients by a team of oncologists, emergency specialists, family doctors, palliative care specialists, and other health care providers will help patients reach appropriate medical help in every stage of the disease. Home care service, palliative care, and effective use of the primary care system, and appropriate and sufficient care are vital for end-stage patients and increase the comfort of patients.

We think that the palliation of the symptoms that may occur in patients under active treatment period in infusion centers that will be established in chemotherapy units or in palliative care centers will contribute to the decrease in the frequency of emergency services.

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Ethics Approval

This study started after obtaining ethics approval from the T. C. Ministry of Health, Health Sciences University Adana Numune Training and Research Hospital Scientific Research Evaluation Commission.

Author's Contribution

Study concept and design: CI, MG, SS. Acquisition of data: CI, MG, GGI, AA, OY, SA. Analysis and interpretation of data: CI, MG, GGI, AA, OY. Drafting of the manuscript: CI, MG, SS, SA, AA. Critical revision: CI, MG, SS, GGI, OY, SA. All the authors approved the final version to be published; all authors agreed to all aspects of the work.

RESUMO

OBJETIVO: Este estudo tem como objetivo determinar as características demográficas dos pacientes com câncer admitidos no setor de emergência e determinar a relação entre a frequência de admissão no setor de emergência e emergências oncológicas e seus efeitos na mortalidade.

MÉTODOS: Este estudo observacional, prospectivo e de precisão diagnóstica foi realizado no pronto-socorro de um hospital terciário. Pacientes com idade superior a 18 anos que foram previamente diagnosticados com câncer e admitidos no serviço de emergência por razões médicas foram incluídos no estudo. Registramos características basais, incluindo idade, sexo, queixas, diagnóstico oncológico, status de metástase, tratamentos de câncer recebidos, número de admissões ao DE, diagnósticos de emergência oncológicos estruturais e metabólicos no DE, status de alta, tempo de internação e estado de mortalidade.

RESULTADOS: Em nosso estudo, foram examinadas 1205 aplicações relacionadas ao diagnóstico oncológico de 261 pacientes. 55,6% dos pacientes eram do sexo masculino e 44,4% eram do sexo feminino. A emergência oncológica metabólica mais comum foi anemia (19,5%) e a emergência oncológica estrutural mais comum foi fratura óssea causada por metástase (4,6%). A média de admissão dos pacientes no pronto-socorro foi de quatro vezes (min: 1 máx: 29) durante o período do estudo. Um total de 49,4% (n: 129) dos pacientes incluídos no estudo morreram durante o acompanhamento, e a mediana para o tempo de morte foi de 13 dias após a última admissão ao ED.

CONCLUSÃO: A paliação dos sintomas de pacientes nos centros de infusão que serão estabelecidos nos centros de cuidados paliativos contribuirá para a diminuição da frequência de uso dos serviços de emergência.

PALAVRAS-CHAVE: Serviço Hospitalar de Emergência. Cuidados paliativos. Hospitalização. Neoplasias.

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Comparison of three methods for teaching mechanical ventilation in an emergency setting to sixth-year medical students: a randomized trial

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SUMMARY

OBJECTIVE: To determine if there are significant differences between the tutorial, simulation, or clinical-case-based discussion teaching methods regarding the transmission of medical knowledge on mechanical ventilation.

METHODS: A randomized, multicenter, open-label controlled trial was carried out using 3 teaching methods on mechanical ventilation: clinical-case-based discussion, simulation, and online tutorial. Voluntary students of the sixth year of medical school from 11 medical colleges answered a validated questionnaire on knowledge about mechanical ventilation for medical students before, immediately after, and 6 months after in-person training consisting of 20 multiple-choice questions, and 5 questions about the participants' demographic profile.

RESULTS: Immediately after the test there was no difference between the scores in the simulation and clinical case groups,[15,06 vs 14,63] whereas, after some time, there was a significant difference in retention between the case-based and simulation groups, with the score in the simulation group 1.46 [1.31; 1.64] times higher than the score of the case group (p-value < 0.001). In the multivariate analysis, an individual who had received more than 4 hours of information showed an increase of 20.0% [09.0%; 33.0%] in the score (p-value = 0.001).

CONCLUSIONS: Our results indicate that, in comparison with other forms of training, simulation in mechanical ventilation provides long-lasting knowledge in the medium term. Further studies are needed to improve the designing and evaluation of training that provides minimal mechanical ventilation skills.

KEYWORDS: Respiration, Artificial. Emergencies. Students, Medical. Teaching.

INTRODUCTION

The increased number of patients on mechanical ventilation, most of whom are not in an ICU, requires, from general practitioners, special skills on the subject[1,2]. Moreover, the increase in costs and mortality is related to the increase in the time of mechanical ventilation and its complications[3]. However, despite evidence showing that evidence-based practices can decrease these, such practices have low compliance and are underused in clinical practice[4-7].

There is a large number of non-specialist physicians working in emergency and pre-hospital services attending patients who need to be intubated and kept

on mechanical ventilation[8]. However, the teaching of these skills is very deficient[9,10]. There are few studies about teaching and assessment methods of these skills among resident physicians, and there are no studies in the literature for undergraduate medical students.

Our study compares simulation methods, case-based discussions, and online remote education methods on artificial ventilation, and uses a validated tool for assessing knowledge on mechanical ventilation among students in the last semester of medical graduation[11]. The objective is to determine if there are, among the teaching methods, significant differences regarding the transmission of medical knowledge on mechanical ventilation.

METHODS

A randomized, multicenter, open-label controlled trial was carried out using 3 teaching methods on mechanical ventilation: clinical case-based discussion, simulation, online tutorial. A simple randomization using an electronic method was applied for each group of 10 students for each teaching method, and one group remained as the control. All participants answered a validated questionnaire on knowledge about mechanical ventilation for medical students before, immediately after training, and 6 months after it[12], consisting of 20 multiple-choice questions, and 5 questions about the participants' demographic profile. Figure I

The participants were voluntary students of the sixth year of medical school from 11 medical colleges, out of 53 invited, who accepted the researcher's invitation. All of them were in the second semester of the course and had already participated in training sessions on adult intensive care, emergency room, and anesthesiology. The training sessions were offered at the headquarters of the participating universities by the same researcher in all groups.

All training was based on the basic objectives of knowledge on mechanical ventilation, divided into 55 items developed by Goligher et al.[13]. Four clinical cases were used for the simulation, case-based discussion, and online tutorial scenarios. The "control" groups attended an 8-hour course that was not related to mechanical ventilation and answered the questionnaire as well.

A training session based on 4 clinical cases with a structured sequence of questions was created for each case. The schedule was divided into two methods: in

the simulation, students handled the artificial ventilator and observed the effects of its changes with the simulator. In the discussion-based format, the same sequence was followed, but there was no "hands-on" practice, only the demonstration by the instructor; both methods were recorded and saved on DVDs to be presented to a random group as an online Tutorial.

Using the simulation taxonomy, Chiniara et al.[14] used a high-fidelity scenario, emergency room, respiratory system simulator, and instructor-based debriefing; the instructor evaluated the response of each handling action of the group of students and made comments simultaneously. (Annex 1) The case-based discussion[11] was based on fundamental principles of structured discussion, realism, relevance, need to trigger the learner's involvement, challenging problem, and instructional methods such as equipment, simulators, and theatricalization of scenarios. The same sequence of structured questions was used for each scenario, but students had no direct contact with the ventilator, everything was demonstrated by the instructor. The online modality recorded the case-based modality, suppressing the interaction of the students and the instructor, and providing DVDs to the participants. The artificial ventilator iX5 was used in all training groups, the technical name of which is pressure and volume ventilator (registered with the Brazilian Health Regulatory Agency – Anvisa under no. 10243240052; manufacturer: Intermed Equipamento Médico Hospitalar Ltda). The simulator used was the PneuView® 3 Advanced Simulation Software (Michigan Instruments, Grand Rapids, Michigan, USA).

A Quasipoisson Regression (Wedderburn, 1974; McCullagh and Nelder, 1989) was used to compare the score between groups over time, with an interaction between the variables group and time, with the necessary contrasts being calculated. The software used in the analyses was R (version 3.4.1).

RESULTS

Most students reported not having attended a mechanical ventilation course as part of their undergraduate program (294, 89.1%); most of them never participated effectively in the approach to mechanical ventilation in a patient (282, 75.2%); and reported that the participation of the physical therapist prevailed in the approach to mechanical ventilation in emergency settings (213, 70.5%). The Case and Simulation groups had the highest scores for overtime retention (Table 1).

TABLE 1. DESCRIPTIVE ANALYSIS OF THE SCORE BY TIME AND GROUP

Group	Time	Average	SD	Min.	1st Q	2nd Q	3rd Q	Max.
Control	Pre-test	3.73	3.38	0.00	1.00	3.00	6.00	14.00
	Post-test	3.71	3.06	0.00	1.00	3.00	5.00	14.00
	Retention	3.83	3.08	0.00	1.00	4.00	6.00	16.00
Case	Pre-test	3.30	3.28	0.00	0.50	2.50	5.00	16.00
	Post-test	14.63	2.29	8.00	13.00	15.00	16.00	20.00
	Retention	10.96	1.89	5.00	10.00	11.00	12.00	16.00
Simulation	Pre-test	3.40	3.00	0.00	1.00	3.00	6.00	13.00
	Post-test	15.06	2.39	6.00	15.00	15.00	16.00	20.00
	Retention	14.60	2.82	3.00	14.00	15.00	16.00	20.00
Online tutorial	Pre-test	4.38	3.73	0.00	2.00	4.00	7.00	15.00
	Post-test	5.38	4.47	0.00	2.00	4.00	7.00	20.00
	Retention	4.68	3.96	0.00	2.00	4.00	6.00	20.00

TABLE 2. MULTIVARIATE ANALYSIS OF MECHANICAL VENTILATION CLASSES AND INFORMATION TIME

Variables		Initial model			Final model		
		Exp (β)	95% CI	P-value	Exp (β)	95% CI	P-value
Time = Pre	Group = Control	1.00	-	-	1.00	-	-
	Group = Case	0.87	[0.70; 1.07]	0.194	0.87	[0.71; 1.07]	0.198
	Group = Simulation	0.95	[0.77; 1.16]	0.601	0.95	[0.77; 1.16]	0.610
	Group = Tutorial	1.15	[0.93; 1.41]	0.190	1.15	[0.94; 1.41]	0.181
Time = Post-test	Group = Control	1.00	-	-	1.00	-	-
	Group = Case	3.58	[2.98; 4.30]	0.000	3.58	[2.98; 4.30]	0.000
	Group = Simulation	3.68	[3.08; 4.40]	0.000	3.67	[3.07; 4.38]	0.000
	Group = Tutorial	1.61	[1.33; 1.96]	0.000	1.60	[1.32; 1.94]	0.000
Time = Retention	Group = Control	1.00	-	-	1.00	-	-
	Group = Case	2.80	[2.36; 3.33]	0.000	2.81	[2.36; 3.33]	0.000
	Group = Simulation	4.08	[3.46; 4.82]	0.000	4.12	[3.49; 4.85]	0.000
	Group = Tutorial	1.29	[1.05; 1.58]	0.017	1.29	[1.05; 1.58]	0.016
Course = No		1.00	-	-	1.00	-	-
Course = Yes		1.26	[1.16; 1.38]	0.000	1.27	[1.17; 1.39]	0.000

FIGURE 1. COMPARISON BETWEEN GROUPS OVER TIME
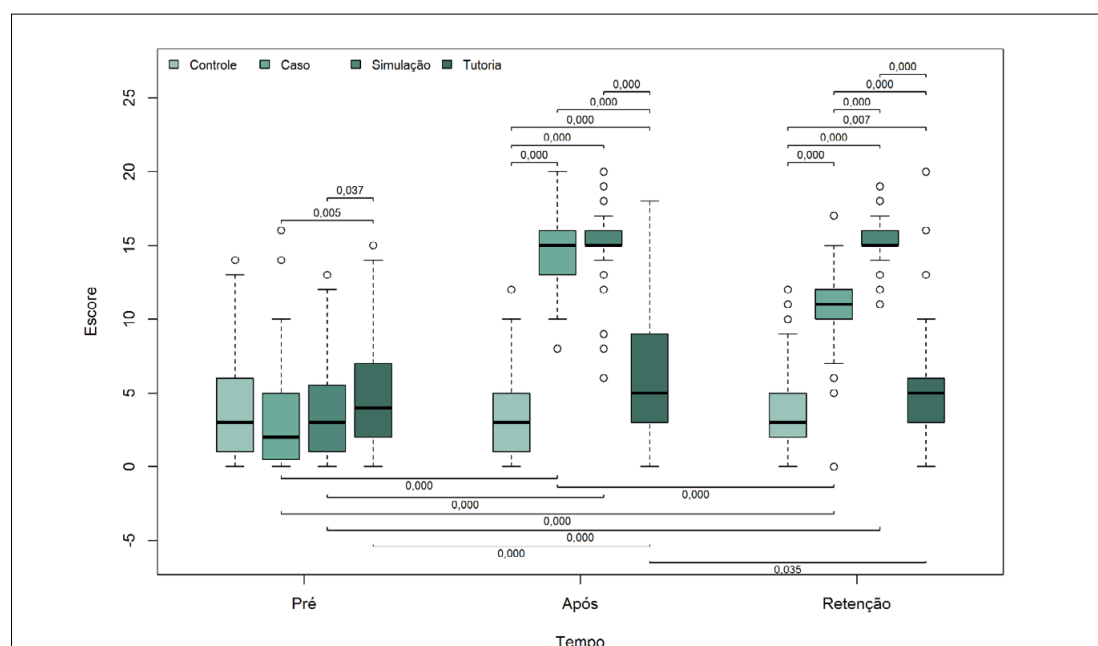
Immediately after the training (POST-TEST), there was no difference between the scores in the simulation and clinical case groups, whereas over time (RETENTION) there was a significant difference between the case-based and simulation groups, with the score in the simulation group 1.46 [1.31; 1.64] times higher than the score of the case group (p-value < 0.001).

In the multivariate analysis (Table 2) when individuals who had not had classes of mechanical ventilation as part of their undergraduate program are compared to those who had, the latter shows an increase of 27.0% [17.0%; 39.0%] in the score (p-value = 0.001); and when compared to individuals who had 0 to 1 hour of training, individuals who had more than 4 hours of training show an increase of 20.0% [09.0%; 33.0%] in the score (p-value = 0.001).

DISCUSSION

Our study was the first multicenter study that evaluated the influence of different teaching methods on the knowledge about mechanical ventilation among medical students with a validated instrument. A teaching program standardized in simulation and case-based discussion achieved significant results in the acquisition and retention of knowledge in the short- and medium-term. Few studies have evaluated the teaching of mechanical ventilation; among them, most did not use validated assessment instruments[15,16], and among those using them, none approached medical students[17,18].

The common concept that simulation methods are associated with better results for medical students' knowledge and skill acquisition is controversial. Our study showed no significant difference in specific knowledge in terms of the method of discussion of clinical cases. Few studies have shown similar results[19,20]. In addition, the level of fidelity, in general, correlates with the success in the acquisition of knowledge; the more sophisticated the mannequin, the better the learning result. A recent study did not show this association, and the use of high-fidelity simulation led to a performance equal to or worse of knowledge improvement if compared to low-fidelity simulation, besides inducing undesirable effects, such as overconfidence[21].

Some studies have demonstrated the utility of using simulation in mechanical ventilation training.

A study compared simulation training of mechanical ventilation for first-year residents to what the authors called "traditional bedside training" for third-year residents. Similar to our study, the simulation group (n = 40) scored significantly higher in the assessment of clinical skills than the traditional group (n = 27) (91.3% [95% CI 88.2% to 94.3 %] versus 80.9% [95% CI 76.8% to 85.0%], P = <0.001)[22]. Important limitations to the study are influences on the variation of patients at the bedside in the evaluation, and the lack of formal validation of the instrument, as well as the single center. Another study using a simulation of mechanical ventilation showed an improvement in knowledge and skills with an average of 40 to 67%, respectively. However, there are limitations to the study because of the use of an assessment instrument that has not been validated[23]. A randomized trial evaluated the mannequin-based simulation versus computer-based simulation. The mannequin-based group had a higher overall score and key action scores than the computer-based group (3.0 versus 2.0, and 82% versus 71%, respectively). The study was carried out in a single center with a non-validated instrument[24]. Only one study approached a tutorial form of teaching about ventilation, similarly to ours, and compared it to a method that added simulation training. Using a non-validated instrument and a small, non-randomized number of participants, the "hands-on" method achieved a higher assessment score than the tutorial alone (25% vs. 10%, p = 0.07)[25]. Our results using an online tutorial showed no difference in the acquisition of knowledge in relation to the control group.

CONCLUSIONS

Our results indicate that, in comparison with other forms of training, simulation of mechanical ventilation provides long-lasting knowledge in the medium term. Further studies are needed to improve the design and evaluation of training to provide minimal mechanical ventilation skills.

Author's Contributions

Fernando Tallo: project design, data collection and analysis, and drafting of the text.

Letícia Sandre Vendrame: data analysis and drafting of the text

Andre Luciano Baitello: data review and analysis

RESUMO

OBJETIVO: *Determinar se existem diferenças significativas entre os métodos de ensino tutorial, simulação ou discussão de casos clínicos relativos à transmissão de conhecimentos médicos sobre ventilação mecânica.*

MÉTODOS: *Um ensaio clínico randomizado, multicêntrico, aberto e controlado foi realizado usando três métodos de ensino em ventilação mecânica: discussão baseada em casos clínicos, simulação e tutorial on-line. Alunos voluntários do sexto ano de medicina de 11 faculdades responderam a um questionário validado abordando o conhecimento sobre ventilação mecânica para estudantes de medicina antes, imediatamente após e seis meses depois do treinamento presencial, composto por 20 questões de múltipla escolha e cinco questões sobre perfil demográfico dos participantes.*

RESULTADOS: *Imediatamente após o teste, não houve diferença entre as pontuações nos grupos de simulação e caso clínico [15,06 vs 14,63], ao passo que, após algum tempo, houve uma diferença significativa na retenção entre o baseado em caso e a simulação grupos, com a pontuação no grupo simulação 1,46 [1,31; 1,64] vez maior que a pontuação do grupo caso (p-valor <0,001). Na análise multivariada, um indivíduo que recebeu mais de quatro horas de informação apresentou aumento de 20,0% [09,0%; 33,0%] no escore (p-valor=0,001).*

CONCLUSÕES: *Nossos resultados indicam que, em comparação com outras formas de treinamento, a simulação em ventilação mecânica proporciona um conhecimento duradouro a médio prazo. Mais estudos são necessários para melhorar o desenho e a avaliação do treinamento que forneça habilidades mínimas de ventilação mecânica.*

PALAVRAS-CHAVE: *Respiração Artificial. Emergências. Estudantes de Medicina. Ensino.*

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Corticosteroid associated lupus pancreatitis

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SUMMARY

The relationship between acute pancreatitis and the administration of glucocorticoids is unclear because most reported cases have been diagnosed with systemic vascular diseases, such as systemic lupus erythematosus, which may be responsible for pancreatitis.

A 22-year-old woman with eye involvement of a newly diagnosed systemic lupus erythematosus was admitted to our hospital. Pulse intravenous methylprednisolone therapy was given at 1mg/kg day for 3 days, and oral prednisolone at 40 mg/day thereafter. During pulse steroid therapy, she had abdominal pain, back pain, distention, nausea, and vomiting. Her physical examination was compatible with acute abdomen and peritonitis. Abdomen Computerized Tomography scan revealed diffuse liquid perihepatic and perisplenic area with heterogeneity around the mesentery. Due to the symptoms of acute abdomen, explorative laparotomy was performed. There was diffuse free fluid in the abdomen and edematous changes were observed around the pancreas. Amylase and lipase from intraabdominal fluid were studied and found to be high. The postoperative prednol dose was reduced carefully. On the sixth postoperative day, the drain was removed, and the patient was discharged without any problem.

Physicians should keep in mind that acute pancreatitis may also be a cause of differential diagnosis of newly developed abdominal pain in patients receiving pulse steroid therapy with a normal level of serum amylase and lipase.

KEYWORDS: Lupus Erythematosus, Systemic. Pancreatitis. Pulse Therapy, Drug. Steroids.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect any part of the gastrointestinal system, from the oral mucosa to the rectum[1]. Acute pancreatitis is an uncommon complication that occurs in 0.85% to 4% of patients with SLE and is reported to be a rare adverse reaction associated with the administration of corticosteroids[2]. The relationship between acute pancreatitis and administration of glucocorticoids is unclear because most reported cases have been diagnosed with systemic vascular diseases, such as systemic lupus erythematosus, which may be responsible for pancreatitis[2].Here,

we report a 22-year-old woman who developed acute pancreatitis after receiving steroid pulse therapy for the treatment of eye involvement in SLE.

Case presentation

A 22-year-old woman was admitted to our hospital because of eye and neurological involvement of newly diagnosed systemic lupus erythematosus. She had no gallstone on imaging methods and no history of hypertriglyceridemia and alcohol intake. She was given intravenous methylprednisolone pulse therapy at 1mg/kg day for 3 days, and oral prednisolone at 40

mg/day thereafter. During pulse steroid therapy she had abdominal pain, back pain, distention, nausea, and vomiting. Her physical examination was compatible with acute abdomen and peritonitis. The patient was consulted with general surgery. While her leucocytes increased rapidly (11.100x10 3/uL to 29.800x10 3/uL), she started complaining of mild back pain with normal serum amylase (31U/L) and lipase levels (40U/L). Abdomen Computerized Tomography scan revealed diffuse liquid perihepatic and perisplenic area with heterogeneity around the mesentery (Figure 1). Due to the symptoms of acute abdomen, explorative laparotomy was performed. No perforation was detected during explorative laparotomy. There was diffuse free fluid in the abdomen and edematous changes were observed around the pancreas (Figure 2). Amylase and lipase from intra-abdominal fluid were studied and found to be higher (1190 U/L and 2040 U/L). The abdomen was irrigated with plenty of saline solution and drains were placed. Although the blood amylase and lipase levels were normal in the preoperative laboratory tests, postoperative control tests were found to be high. The patients' preoperative albumin ratio, Complements C3 and C4 levels were low with an elevated anti-dsDNA. The postoperative prednol dose was reduced carefully. On the sixth postoperative day, the patient was discharged without any problems. The patient continues to use low-dose steroids in the postoperative 8th month and is followed up without any problems.

FIGURE 1. COMPUTERIZED TOMOGRAPHY SCAN OF THE ABDOMEN REVEALED DIFFUSE LIQUID PERIHEPATIC AND PERISPLENIC AREA WITH HETEROGENEITY AROUND THE MESENTERY

DISCUSSION AND CONCLUSION

Acute pancreatitis is a rarely seen clinical entity among patients with SLE. Lupus associated pancreatitis (LAP) occurs within days to weeks of starting medium-to-high dose corticosteroids. Dwivedi et al have used the term 'corticosteroid-associated lupus pancreatitis' (CALP) the point at which it happened inside 3 weeks[3].

CALP had a female predominance[3]. The most frequent symptom of CALP was abdominal pain, followed by vomiting, paralytic ileus, and fever, which generally present under the corticosteroid therapy[3]. Imaging methods such as ultrasound or computed tomography may be helpful for the diagnosis, with the appearance of the heterogeneous pancreas and peripancreatic fluid collection[3].

The role of corticosteroids in the etiology of lupus pancreatitis is controversial and not clear. Animal studies have shown that corticosteroids can induce pancreatitis and are generally useful in the treatment of acute pancreatitis[3,4]. Although, multiple factors such as the activity of disease, gallstones, drugs, alcohol,

FIGURE 2. THERE WAS DIFFUSE FREE FLUID IN THE ABDOMEN, AND EDEMATOUS CHANGES WERE OBSERVED AROUND THE PANCREAS

and hypertriglyceridemia may play a role in the pathogenesis of pancreatitis with SLE[1,2]. In previous studies, high amylase and lipase levels were frequently found in patients associated with SLE pancreatitis[3,4]. To our knowledge, a case of CALP with normal preoperative lipase and amylase levels has not been reported as in our case.

As Dwivedi et al.[3] reported after the occurrence of acute pancreatitis, for the treatment of CALP, corticosteroids were continued or a dose of corticosteroid was increased, such as our presented case. It is difficult to ascribe sole responsibility for pancreatitis to either disease activity or corticosteroids in these SLE patients[3]. The pathogenesis of pancreatitis in SLE is complex and difficult to relate to a single factor. It has

been suggested that vasculitis, thrombosis secondary to antiphospholipid antibodies, vascular intimal thickening, and accumulation of immune complexes, as well as autoantibodies directly targeting the pancreas, may play a role in the etiology of cellular immune response[3,4].

In conclusion, physicians should keep in mind that acute pancreatitis may also be a cause of differential diagnosis of newly developed abdominal pain in patients receiving pulse steroid therapy with a normal level of serum amylase and lipase. It's difficult to differentiate pancreatitis due to SLE or CALP. Due to the rarity of CALP, for a better understanding of the importance of etiopathogenesis, a larger case series may be better fitting.

RESUMO

A relação entre pancreatite aguda e a administração de glicocorticoides é incerta pois a maioria dos casos relatados foram diagnosticados com doenças vasculares sistêmicas, como lúpus eritematoso sistêmico, que pode causar pancreatite.

Uma paciente de 22 anos com envolvimento ocular e lúpus eritematoso sistêmico recém-diagnosticado foi admitida em nosso hospital. Pulsoterapia intravenosa com metilprednisolona 1mg/kg foi administrada por 3 dias. Depois disso, a paciente foi tratada com prednisolona oral 40 mg/dia. Durante a pulsoterapia com corticoides, a paciente apresentava dor abdominal, dor nas costas, distensão, náusea e vômitos. O exame físico era compatível com quadro de abdome agudo e peritonite. Tomografia computadorizada do abdome revelou líquido difuso na região perihepática e periesplênica, com heterogeneidade ao redor do mesentério. Devido aos sintomas de abdome agudo, foi realizada laparotomia exploradora. Havia líquido livre difuso no abdome e alterações edematosas foram observadas em torno do pâncreas. A amilase e lipase do líquido intra-abdominal foram analisadas e consideradas elevadas. A dose pós-operatória de prednol foi reduzida com cuidado. No sexto dia de pós-operatório, o dreno foi retirado, e a paciente recebeu alta sem qualquer problema.

Médicos devem lembrar que a pancreatite aguda também pode ser uma causa de diagnóstico diferencial para dor abdominal recém-desenvolvida em pacientes recebendo pulsoterapia com corticoides e com níveis normais de amilase e lipase séricas.

PALAVRAS CHAVE: *Lúpus Eritematoso Sistêmico. Pancreatite. Pulsoterapia. Esteroides.*

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Good practices in the recovery of ambulation in octogenarian women with hip fractures

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SUMMARY

OBJECTIVE: *Determine good recovery practices for ambulation of octogenarian women after hospital discharge after being operated on for hip fracture.*

METHODS: *Prospective study during the second half of 2019, with 192 women (85.95 ± 5.1 years) with hip fracture. A medical history, fracture types, complications, surgical treatment, and assessment of the level of ambulation were recorded before and after six months of hospital discharge.*

RESULTS: *100 patients lived in the family home and 92 in an institutional center, 68.2% provided pertrochanteric fracture and a total of 3.7 comorbidities, all of them received spinal anesthesia and were admitted an average of 11.4 days. After six months, the patients showed a significant loss of functional independence with respect to the situation prior to the fracture, both for the ability to wander and for activities of daily living. It is noteworthy that the worst prognosis in the recovery of ambulation has to do with intermediate levels of ambulation and that the functional level of departure influences to a lesser extent than the place where they perform the recovery.*

CONCLUSIONS: *Age is a factor that influences the recovery of hip fracture, but there are other influential factors since patients who remain in the family home have a better functional prognosis than those who recover in institutionalized centers, after six months of hospital discharge.*

KEYWORDS: *ambulation; frail elderly; hip fractures; residence.*

INTRODUCTION

It is estimated that the average age individuals who suffer from hip fractures (HF) is 81.4 ± 8.1 years, and they are more frequent in women than in men[1,2]. At the same time, it is evident that this type of fracture causes a high comorbidity rate, with an average of 3.7 comorbidities per patient, with a high incidence of signs of cognitive deterioration and a state of acute confusion[3,4].

Osteopenia is the most serious consequence of osteoporosis, and fractures of the femur represent the highest rate of morbidity and mortality. In addition, osteoporosis fractures represent a great economic burden on health systems[5]. It is estimated that by the year 2050, if the number of fractures continues to grow at the current rate, the incidence of HFs throughout the world will increase by up to

310% in men and 240% in women, surpassing 4.5 and 6.3 million fractures per year, respectively[6,7].

In the octogenarian population, the risk factors for this type of fracture are attributed to physical impairments, such as a reduction of visual acuity, peripheral vision, presbycusis, increased reaction time, metabolic changes, increased joint stiffness, increased joint instability, skin changes, and the onset of diseases such as sarcopenia[8]. At the same time, for all purposes, there are other risk factors that are "extrinsic" or environmental, such as poor lighting, obstacles in transition zones, badly placed carpets, lack of architectural barriers, flooring with different levels, among other inappropriate practices[9].

Good healthcare practices[10], as well as family support[11] and social resources, influence the outcomes of maintenance and recovery, after an intervention, of the ambulation of elderly people. In particular, the duration of hospitalization, the type of surgical intervention, recovery through physical therapy sessions, or the absence of the need for commuting to recovery units outside the usual residence act as protective factors for recovery[12]. Therefore, the key is to properly coordinate between the different levels of health and social care to ensure comprehensive care[13] (Figure 1).

This study is part of a broader research, whose goal is to find evidence of factors that contribute to the preservation of functional independence in the elderly during the final stage of life[14]. In particular, in this research, we aimed to determine the best practices for the recovery of ambulation in octogenarian women after hospital discharge after undergoing surgery for a HF.

METHODS

This is a prospective, cross-sectional, observational study using a convenience sample. We included 192 women (mean age 85.95 ± 5.1 years) who were admitted to the León University Hospital with a diagnose of hip fracture from June to November of 2019.

Exclusion criteria: HF caused by an accident, oncological bone pathologies, and HF secondary to other systemic diseases.

The sociodemographic and clinical data were obtained from the clinical histories. The assessment of the ambulation ability was recorded using the following categories: independent/use of a cane; walker/use of two canes; a lot of help and not walking.

All participants were informed about the study objectives and procedures and provided their informed consent. The study was approved by the Ethics Committee for Clinical Research of the León Hospital and was carried out according to the ethical standards of the Declaration of Helsinki of 1975 (revised in the 52nd General Assembly of Edinburgh, Scotland, October 2000), the standards of Good Clinical Practice, and in compliance with the Spanish legislation and regulations for human clinical research (Royal Decree 223/2004 for clinical trials).

The data were analyzed using SPSS v 22.0. Inc., Chicago, IL, USA, for Windows, and the significance level was established at $P<0.05$. The descriptive data were presented as mean values, quantitative variables as standard deviation, and qualitative variables as percentages and frequencies. For qualitative results, we used percentages and frequencies, as well as the Chi-square test (χ^2). The magnitude of the effect was calculated by the coefficient R^2. The data analysis showed a normal distribution assessed by the Kolmogorov-Smirnov test.

RESULTS

Of the 192 octogenarian women (85.95 ± 5.1 years), 100 lived with their family, and 92 in some institution. A total of 68.2% presented a peritrochanteric fracture and 31.8% subcapital. 96.3% of the patients

FIGURE 1. INTERVENTION PROCESSES FOR HFs AND THE DIFFERENT CARE LEVELS IN GERIATRICS (ADAPTED FROM ABIZANDA, 2012).
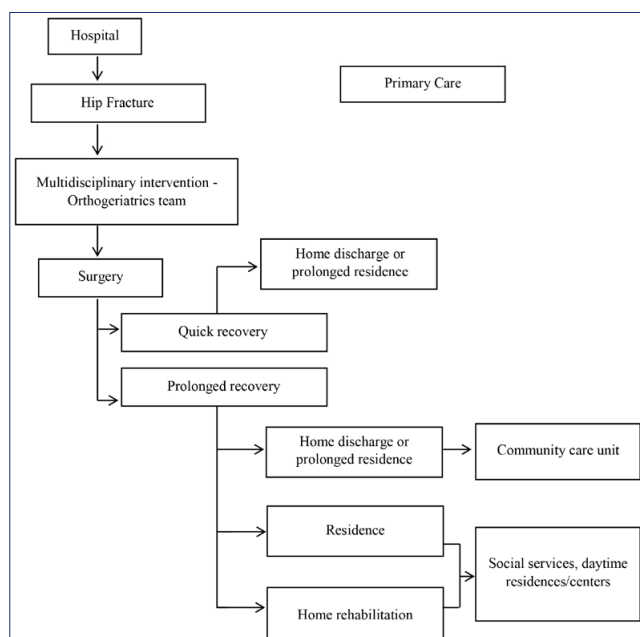
were submitted to surgery, three of them in the emergency service (intervention in the first 24-hours after admission), and 1.7% had exitus They all received spinal anesthesia; in 62.5% of the patients intramedullary nails were used, in 21.7% bipolar partial prosthesis, and in 15.8% unipolar prosthesis.

Most patients had multiple comorbid conditions at the time of admission and, during their stay, developed other clinical complications and disorders such as delirium (Table 1). 71.1% of the patients showed independence to walk or needed to use a cane to walk,

in comparison with 42.35% six months after hospital discharge; six of them died after a month and a half.

The results based on groups according to patient domicile highlight the significative differences in functionality and comorbidities at baseline. In particular, regarding depression (X^2=7.10; p<.05); R^2=.011), dementia (X^2=49.10; p<.001; R^2=.072), diabetes (X^2=7.34; p<.05); R^2=.010), right-sided cerebrovascular accident (X^2=15.41; p<.005; R^2=.026), chronic kidney failure (X^2=2.31; p<.005; R^2=.013), previous hip fracture hip (X^2=7.12; p<.005; R^2=.012), and

TABLE 1. CHI-SQUARED TEST. COMORBIDITIES AND COMPLICATIONS BASED ON THE PLACE OF RESIDENCE BEFORE THE INTERVENTION.

COMORBIDITIES							
Variable	N	(N=50) Own/family home	(N=46) Institution	Chi^2	gl	P	Size of effect: R2
Cardiopathy	82	74.2%	72.4%	0.24	2	.795	.000
Hypertension	72	71.3%	71.6%	0.16	2	.901	.000
Depression	21	26.7%	28.4%	7.10	2	.040 *	.011
Dementia	21	16.2%	30.1%	49.10	2	.000**	.072
Diabetes	15	17.4%	30.4%	7.34	2	.032 *	.010
Arthrosis	19	18.4%	26.5%	1.22	2	.620	.002
Change in sight	15	17.1%	18.8%	0.99	2	.720	.002
Cerebrovascular Ac.	8	11.6%	20.1%	15.41	2	.005*	.026
Chronic kidney failure	14	9.6%	18.2%	2.31	2	.022 *	.013
COPD	6	12.7%	16.4%	1.88	2	.460	.003
Cancer	12	12.1%	18.3%	2.72	2	.071	.013
Multiple falls	10	10.6%	15.4%	3.10	2	.052	.004
Anemia	2	7.1%	15.1%	6.21	2	.054	.008
Osteoporosis	6	9.4%	13.8%	6.28	2	.053	.015
Previous hip fracture	4	6.3%	15.4%	7.12	2	.005**	.012
Parkinson's Disease	2	0.1%	6.1%	10.21	2	.003**	.024
Dysphagia	2	0.4%	4.8%	--	--	--	--
COMPLICATIONS							
	N	(N=50) Own/family home	(N=46) Institution	Chi^2	gl	P	Size of effect: R2
Anemia	87	84.3%	90.2%	5.52	2	.030*	.010
Transfusion	46	38.0%	34.2%	3.62	2	.310	.005
Acute confusion syndrome/Delirium	36	37.3%	33.2%	1.55	2	.457	.006
Constipation	26	23.5%	26.2%	2.06	2	.322	.004
Changed kidney function	8	13.4%	23.7%	5.02	2	.051	.007
Urinary tract infection	34	16.3%	12.4%	4.12	2	.143	.006
Respiratory infection/failure	12	12.6%	17.6%	3.86	2	.141	.005
Malnourishment	11	13.7%	15.1%	1.02	2	.473	.002
Heart failure	6	9.1%	12.1%	2.37	2	.212	.006
Acute urinary retention	5	9.0%	11.4%	0.50	2	.621	.001
Ischemic heart disease	2	7.2%	4.3%	2.62	2	.261	.005
Exitus	3	3.1%	12.4%	7.81	2	.023*	.014
Pressure ulcers	3	4.1%	2.9%	0.90	2	.625 NS	.002
Infection of Qx wound	4	0.9%	0%	--	--	--	--
Cerebrovascular Ac.	2	0.9%	0%	--	--	--	--
PV Thrombosis	2	0%	1.4%	--	--	--	--

Parkinson's disease (X^2=10.21; p<.005; R^2=.024). In addition, we found that the type of anesthesia used produces significant differences in functionality and mobility after the intervention, with better results from local anesthesia (spinal) (X^2=4.80; p<.002; R^2=.038) (Table 2).

Complications and characteristics at hospital admission and discharge are presented in Table 1, according to the place of residence of patients. There are statistically significant differences in favor of the group who lived with a family member in variables such as anemia (X^2=5.52; p<.005 R^2=.010) or exitus (X^2=7.81; p<.005; R^2=.014); for all other variables there were no statistically significant measurements based on the place of residence (P >.05).

As shown in Table 2, there are significant differences in the recovery of the ambulation ability depending on the patients' place of residence (X^2=17.32; p<.004; R^2=.042). Finally, age, regardless of the place of residence, is linked to the ambulatory ability after an intervention due to a HF. Our data make it clear that nonagenarian patients have a worse recovery of ambulation (Table 2).

TABLE 2

Age ranges	General Population (IU)	Risk Population (IU)
0-12 months	400	400- 1,000
1 - 8 years	400	600- 1,000
9-18 years	600	600- 1,000
19-70 years	600	1,500-2,000
>70 years	800	1,500-2,000
Pregnant women 14-18 years	600	600- 1000
Pregnant women > 18 years	600	1,500-2,000
Breastfeeding women 14-18 years	600	600- 1,000
Breastfeeding women > 18 years	600	1,500-2,000

IU = International Units.

DISCUSSION

The results make it clear that the place of residence of octogenarians (with family or some institution) is correlated with the type of clinical and functional comorbidity before, during, and after discharge from hospital. After six months from hospital discharge, the ambulatory had better recovery in the group of women who live with their families. In particular, patients who came from some institution and returned to it after hospital discharge had up to 64% of loss of independent ambulation or with the use of a cane, compared to only 32.8% of those who returned to their family home.

Age is a determining factor for the length of hospital stay, which is shorter for younger patients, in agreement with the findings of other studies[15]. The mean hospital stay was 11.44 days, in line with the research by Bellas, which found a stay between ten and fourteen days,[16] and slightly longer than the average stay recently of ten days found by Castilla y León[14]. Despite that, early surgery is recommended for hip fractures, within the first 24-36 hours; the pre-surgical stay for patients in this study was 5.78 days, higher than the national average (4.31 days)[17] and the average found by Castilla y León (3 days)[14]. Patients who received general anesthesia (21.7%) spent an average of 10.4 days hospitalized and presented a greater number of complications compared to patients who received local anesthesia (74.2%), who had an average of 8.2 days and showed a better recovery of independent functionality, data similar to those obtained in other studies[18]. Overall, in the studies reviewed, it is recommended to minimize the overall days of hospital stay, surgical and post-surgical, to avoid increasing the average stay, with a higher risk of infection of the joint prosthesis, an increase of readmissions during the first month after discharge, and increased health costs[6].

Regarding the functional anatomy by groups of patients, the data show a clear advantage of women who remain home before and after the hospital stay. In this sense, according to the study by Sanclemente-Boli and collaborators, the better recovery of ambulation in these patients can be explained by the support provided by a family caregiver[19]. The family caregiver receives instructions from the orthogeriatric team, in which nurses play a fundamental role, also performing household monitoring, which contributes to the reduction of hospital complications[20]. However, institutionalized patients do not have the advantage of having a family member as a permanent caregiver, which is essential in the recovery of ambulation. In addition, the physical therapy rehabilitation received by these women is insufficient since some institutions where they reside have an on-site physical therapist for only 5 hours a week to service an average of 50 residents. However, patients who live with their families receive customized rehabilitation at the hospital center, and the family caregiver who accompanies them receives instructions on exercises to complete at home.

CONCLUSIONS

Age may be an influencing factor in the recovery of older patients. However, there are other influencing factors, such as their place of residence and follow-up. Patients who live with their families have a family member as a permanent caregiver, which positively impacts the recovery of the ambulation ability in patients with a HF six months after hospital discharge. In future research, it would be interesting to draw up a guide for good infirmary practices to handle the social and health problems that hinder a good recovery of patients with HFs.

Conflict of interests

The authors declare there are no conflicts of interest.

Author's Contribution

MPC: made substantial contributions to the project concept and design, data acquisition, analysis, and interpretation; CRH: made substantial contributions to the project concept and design, data analysis, and interpretation; SJM: made substantial contributions to the project concept and design, data acquisition, analysis, and interpretation.

RESUMO

OBJETIVO: *Determinar boas práticas para a recuperação da ambulação de octogenárias posterior à alta hospitalar após cirurgia por fratura da pelve.*

METODOLOGIA: *Um estudo prospectivo realizado no segundo semestre de 2019 com 192 mulheres (85,95 ± 5,1 anos) com fratura da pelve. O histórico médico, tipo de fratura, complicações, tratamento cirúrgico, e avaliação do nível de ambulação foram registrados antes da alta hospitalar e após seis meses.*

RESULTADOS: *De todas as pacientes, 100 viviam com a família e 92 em alguma instituição, 68.2% tinham fratura peritrocantérica e uma média de 3,7 comorbidades; todas receberam anastesia espinhal e ficaram internadas por 11,4 dias em média. Após seis meses, as pacientes apresentaram uma perda significativa da independência funcional em relação à situação anterior à fratura, tanto em relação à capacidade de ambulação e atividades cotidianas. É importante ressaltar que o prognóstico negativo em relação à recuperação da ambulação está relacionado a níveis intermediários de ambulação e que o nível funcional de saída tem menor influência do que o local onde a recuperação é feita.*

CONCLUSÃO: *A idade é um fator que influencia a recuperação de fraturas da pelve. Porém, há outros fatores com influência, já que as pacientes que ficam com familiares têm um prognostico funcional melhor do que aquelas que se recuperam em instituições, após seis meses da alta hospitalar.*

PALAVRAS-CHAVE: *ambulação; idosos frágeis; fraturas da pelve; residência.*

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Assessment of costs related to cancer treatment

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SUMMARY

INTRODUCTION: *Cancer patients and their caregivers incur costs not covered by the Sistema Único de Saúde – SUS(Unified Health System) during their treatment, with expenses related to transportation, symptomatic medications, food, loss of working days, and others.*

OBJECTIVE: *To evaluate the costs incurred and not covered for cancer patients and their caregivers during cancer treatment at SUS.*

METHODS: *This is a cross-sectional study of 110 cancer patients undergoing chemotherapy, radiotherapy, and 88 caregivers in the last month prior to their inclusion in the study. We correlated costs with clinical and sociodemographic variables such as gender, race, age, marital status, education, occupation, place of birth, origin, monthly income, family income, housing, comorbidities, types of cancer, and staging.*

RESULTS: *We observed that the average cost for study patients was R$ 747.92, which corresponds to 78.4% of the minimum wage, and the average cost for caregivers was R$ 118.86, which is 12.46% of the minimum wage. Among all variables analyzed, the average overall monthly cost for patients was positively correlated with the occupation (p = 0.021) and origin (p = 0.038) variables. For the other variables, no significant associations were detected.*

CONCLUSION: *The positive correlation found between occupation and origin variables with costs incurred and not covered for patients suggests that the creation of programs that enable the payment of costs not covered by SUS and the decentralization of access to cancer treatment could potentially facilitate patients' adherence to cancer treatment.*

KEYWORDS: *Neoplasms. Medical oncology. Health expenditures. Unified Health System. Caregivers.*

INTRODUCTION

Every year, there are approximately 12.7 million new cancer cases worldwide. It is estimated that, in Brasil, in the 2018-2019 biennium, there were 600,000 new cases[1].

In this context, major advances in the early diagnosis of certain types of cancer and a greater understanding of the pathogenesis of neoplasms have led to the development of strategies to prevent and reduce the

risk of death of cancer patients. However, this success has been accompanied by a substantial increase in healthcare costs for cancer treatment[2]. In fact, cancer is currently the second most expensive disease in the United States, behind heart disease, with an annual cost estimated at 157 billion for 2020[3]. Therefore, with the increasing costs for the diagnosis and treatment of cancer, the financial concerns of patients, families, physicians, health systems, and contributors have been progressively accentuated[4].

Cancer patients are particularly under personal financial risk of new financial charges not covered by insurance sources and associated with their treatment, such as transport, symptomatic medications, inputs, etc[5]. This financial burden caused by the treatment is part of what we currently call "financial toxicity". These costs can have significant negative consequences for patients and their families[6] that are comparable to other toxic and devastating effects from the diagnosis and treatment of cancer[7].

To assess the total costs of disease, both the direct (those directly associated with the diagnosis and treatment of cancer) and indirect costs (economic losses caused by cancer, such as loss of productivity) need to be evaluated. By ignoring productivity losses, we may underestimate the true cost of a disease. Likewise, the informal care provided by family members or friends also leads to a loss of productivity and, therefore, should also be considered since this is an important element of care for many cancer patients[8].

The objective of this study was to evaluate the indirect and not covered costs of cancer treatment in a population of cancer patients in the northeast of Brasil treated in the Single Health System (SUS) and their caregivers.

METHODS

This is a cross-sectional study that was conducted in the clinical oncology service of the Cancer Hospital of Maranhão Dr. Tarquínio Lopes Filho, located in the city of São Luís - MA, after approval by the Medical Ethics Committee of the Faculty of Medicine of ABC (CAAE: 79225417.1.0000.0082).

We included in the study patients over 18 years, with a good understanding of the Portuguese language and with a confirmed diagnosis of a malignant neoplasm. We admitted patients on free demand under chemotherapy or chemotherapy combined with radiotherapy treatment. We also included the

caregivers of these cancer patients, aged over 18 years, with a good understanding of the Portuguese language and who accompanied the patients during the cancer treatment (chemotherapy/radiotherapy sessions).

Patients who agreed to participate in the research signed the Informed Consent Form and filled out a form with their socioeconomic and demographic data. The patient data form included identification data (initials, gender, age, race, marital status, education, occupation, nationality, origin, comorbidities, and medications in use) and socioeconomic information (the type of occupation, aid from the INSS, number of dependents, monthly income, family income, housing, and means of transport). Patients and caregivers answered a detailed questionnaire to analyze the time spent on and the financial costs of transportation, food, oral medications not covered or provided by SUS, housing, and other inputs required during the last month of treatment.

The cost-time questionnaire comprises the evaluation of the amounts spent on transportation, medicines, food, and raw materials and the time (minutes or hours) spent in activities related to the cancer treatment. The time was converted into money by the calculation of the average value of an hour of work, using as a basis the minimum wage in 2018, which corresponds to R$ 954.00. Thus, for example, we assumed that a work month comprised a maximum of 40 hours/week for 4 weeks. A similar procedure was used to calculate the value of the caregivers' time. This conversion of hours into reais was made so that we could include the hours spent as part of the additional total costs incurred and not covered.

Regarding the transport, for patients who used a car, the conversion was made by dividing the mileage from their residence to the treatment locations (hospitals, pharmacies, and health care units) by the fuel price in 2018. As for public transport (bus, alternative transportation), the value considered was the transport fee multiplied by the number of trips; for taxi rides, we considered the amount charged by the professional for each commuting; for cyclists or for those who walked, no expense was computed.

We only included the cost of medicines bought by the patients; those obtained from health units were not considered. For the calculation, the patients filled out the name of the medication, dosage, and amount used per month. For raw materials, the patients listed and filled out the amount spent related to the treatment

in the last month. The currency used for all items was real and, for the conversion, we used as a basis the minimum wage in 2018.

The survey data were organized in descriptive tables for better visualization. For data analysis, we used the statistical software SPSS v. 19, considering a significance level of 5%. To compare the averages of the final overall monthly cost for patients between the groups regarding caregivers, INSS, origin, type of neoplasia, staging, occupation, and educational level, we used the statistical one-way ANOVA test. Previously, we tested the data homogeneity of variances (Levene test) and normality (Shapiro-Wilk test) as assumptions of the ANOVA technique.

RESULTS

The clinical and pathological characteristics of the 110 patients included in this study are described in Table 1. Approximately 69 patients (62.73%) were females, with a mean age of 55.45 years. The patients had a variety of solid tumors, and the most predominant type of neoplasia was in the GIT (n=47; 42.73%), and staging 4 was the most frequent (n= 64; 58.19%). Regarding the level of schooling, most patients had up to incomplete secondary education, i.e., 59.09% (n=65). In relation to the occupation, the group that includes unemployed individuals/home-makers/informally employed individuals was the most prominent (n=56; 50.91%). The low educational level and the high percentage of patients without a fixed income (formal work/ retirement), in this population, reflect the low Human Development Index of Mara-nhão, considered the 2° (second) worse among the states of the federation[9].

In Table 2 it is possible to see the overall average of hours spent by patients, in a month, on transportation, consultations, treatment with chemotherapy and radiotherapy, purchase of medicines, and other activities and their proportional relationship with the minimum wage in 2018. The total average of hours was 17.45 ± 11.69 (4.50 - 114.50 hours).

After converting time into money, we obtained a general average of 134.15 ± 142.63 reais (0 - 840.71

TABLE 1. GENERAL PROFILE OF CANCER PATIENTS TREATED IN THE PUBLIC SERVICE OF THE CITY OF SÃO LUÍS - MA.

Variable		N (Total = 110)	% (Total = 100%)
Sex	Female	69	62.73
	Male	41	37.27
Type of neoplasms	Head and neck CA	3	2.73
	Lung CA	8	7.27
	Genitourinary CA	23	20.91
	Breast CA	20	18.18
	Sarcoma	5	4.54
	CNS	4	3.64
	GIT	47	42.73
Staging	2	13	11.82
	3	33	30.00
	4	64	58.19
Follow-up	With a caregiver	88	80.00
	Without a caregiver	22	20.00
Time of diagnosis	<6 months	43	39.09
	6-12 months	36	32.73
	> 12 months	31	28.18
Ethnicity	White	34	30.91
	Non-white	76	68.09
Formal education	Up to incomplete secondary	65	59.09
	Complete secondary Up to complete tertiary	27 18	24.55 16.37
Occupation	Formal employment	13	11.82
	Unemployed/Homemaker/Informally employed	56	50.91
	Retired	41	37.27

Variable		N (Total = 110)	% (Total = 100%)
Natural from	Maranhão	106	96.63
	Others	4	3.64
Origin	Capital	55	50.00
	Interior	55	50.00
Associated diseases	DM	8	7.27
	SAH	27	24.55
	SAH + DM	9	8.18
	SAH + Hypercholesterolemia	1	0.91
	Hyper-Hypothyroidism	3	2.73
	Hypercholesterolemia	1	0.91
	Others	3	2.73
	No Comorbidities	58	52.73
INSS	No	85	77.27
	Yes	25	22.73
Car	No	90	81.82
	Yes	20	18.18
Housing	Rented	14	12.73
	Financed	1	0.91
	Owned	95	86.36
Monthly income	Up to 1 minimum wage	67	60.91
	2-3 Minimum wages	22	20.00
	3-6 Minimum wages	3	2.73
	No income	18	16.36
Family income	Up to 1 minimum wage	13	11.82
	2-3 Minimum wages	54	49.09
	3-6 Minimum wages	40	36.36
	No income	1	0.91
Transportation	Car	56	50.91
	Bus	54	49.09
Variable		Mean ± SD	Min. - Max.
Age (years)	Female (n=69)	53.80 ± 12.70	24 – 81
	Male (n=41)	58.24 ± 14.34	26 – 84
	Overall (n=110)	55.45 ± 13.44	24 – 84

TABLE 2. IMPACT OF DIRECT AND INDIRECT COSTS OF CANCER TREATMENT IN HOURS/MONTH BASED ON THE MINIMUM WAGE (2018) FOR PATIENTS. SÃO LUÍS - MA.

Variable (patients)		Mean ± SD	Min. - Max.	% Minimum wage [1]
Transport (h/month)	Female (n=69)	7.57 ± 6.18	0.66 – 31	35.81%
	Male (n=41)	7.70 ± 6.35	0.66 – 28	37%
	Overall (n=110)	7.62 ± 6.22	0.66 – 31	36.29%
Consultations (h/month)	Female (n=69)	2.70 ± 2.06	0.33 - 12	4.55%
	Male (n=41)	2.55 ± 1.84	0.16 - 7	4.06%
	Overall (n=110)	2.64 ± 1.97	0.16 - 12	4.35%
CT and RT (h/month)	Staging 2 (n= 13)	11.36 ± 29.68	0 - 110	80.7%
	Staging 3 (n= 33)	6.68 ± 3.98	1 - 18	27.89%
	Staging 4 (n= 64)	5.24 ± 2.55	0 - 16	17.16%
	Overall (n=110)	6.40 ± 10.45	0 - 110	25.6%
Purchase of medication (h/month)		0.62 ± 0.65	0 - 3	0.24%
Other activities (h/month)		0.17 ± 0.76	0 - 6	0.02%
Total (h/month)		17.45 ± 11.69	4.50 - 114.50	190.3%

Legend: 1 = Minimum wage in 2018 - R$ 954.00

reais), which corresponds to 14.06% of the minimum wage (Table 3). The overall average cost for patients, in reais, regarding transportation, medication, raw materials, alternative therapies, telephone, food, housing, and exams was R$ 613.76 ± 662.03 reais (0 - 5,390 reais) corresponding to 64.33% of the minimum wage. The average total cost (time + money) was 747.92 ± 693.78 reais (103.84 - 5,475.44 reais), which corresponds to 78.40% of the minimum wage. The final average total cost (time + money + companion) reached 89.06% of the minimum wage, with an average expense of 849.65 ± 103.84 reais (751.69 - 5,474.44), as shown in Table 3.

When we correlated the cost incurred by patients with other clinical and socioeconomic variables presented in Table 4, we found a statistically significant difference for the "occupation" (p = 0.021) and "origin" (p = 0.038) variables. For the other variables, no statistically significant associations with costs incurred by patients were found.

DISCUSSION

Several risk factors have been described for the development of financial toxicity, such as female gender, younger age, non-white race/ethnicity, greater distance from treatment centers, and unemployment[3]. In the present study, patients analyzed predominantly presented some of these risk factors: 62.73% were

females, 69.09% were non-white, 50.91% were unemployed/homemakers/informally employed, and 50% were from the interior of the state of Maranhão.

A cross-sectional study involving 334 women with cervical cancer carried out in the Kisumu on Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) showed that patients who had formal employment had proportionally less financial challenges, while participants who had completed only primary education reported greater financial challenges in comparison with those with other levels of education[10]. The occupation variable in this study was also statistically significant (Table 4), and this finding was also observed in a cross-sectional analysis carried out on women with metastatic breast cancer (n=145). This study showed that financial toxicity is common among low-income women with the disease and is directly related to a worse quality of life and general distress related to cancer[7].

Most cancer patients were at the same level of staging, i.e., 4 (58.19%), something that is also considered a risk factor for increased costs with cancer treatment. Although all cancer patients are vulnerable to financial toxicity, patients with advanced or metastatic cancer seem to be particularly sensitive to it[7]. The paradigm for metastatic cancer treatment is often sequential and involves chemotherapy or immunotherapy that lasts for several months to years for continued treatment. Its diagnosis and treatment have

TABLE 3. IMPACT OF DIRECT AND INDIRECT COSTS OF CANCER TREATMENT IN REAIS BASED ON THE MINIMUM WAGE (2018) FOR PATIENTS AND CAREGIVERS. SÃO LUÍS - MA.

Variable (patients)		Mean ± SD	Min. - Max.	% Minimum wage [1]
Time in cash		134.15 ± 142.63	0 - 840.71	14.06%
Transport (real)		188.46 ± 160.97	0 - 800	19.75%
Medications (real)		106.38 ± 143.97	0 - 800	11.15%
Raw materials (real)		21.51 ± 112.93	0 - 900	2.25%
Alternative therapy (real)		12.82 ± 115.26	0 -1200	1.34%
Telephone (real)		23.74 ± 26.99	0 – 167	2.49%
Food (real)		48.32 ± 69.09	0 – 427	5.06%
Housing (real)		24.58 ± 107.64	0 – 720	2.58%
Exams (real)		187.95 ± 554.82	0 – 4,700	19.70%
Cost in cash (real)		613.76 ± 662.03	0 – 5,390	64.33%
Overall cost (time + money) (real)		747.92 ± 693.78	103.84 – 5,475.44	78.40%
Variable (caregivers)		Mean ± SD	Min. - Max.	% Minimum wage [1]
Total (real)	Female (n=72)	111.91 ± 209.12	0 – 1,180.58	11.73%
	Male (n=16)	150.09 ± 110.20	0 – 304.09	15.73%
	Overall (n=88)	118.86 ± 194.94	0 – 1,180.58	12.46%
Final overall cost (Patients + Caregivers) 849.65 ± 103.84 751.69 - 5,474.44 89.06%				

Legend: 1 = Minimum wage in 2018 - R$ 954.00

TABLE 4. COMPARISON OF AVERAGES OF THE MONTHLY FINAL OVERALL COST (IN REAIS) FOR PATIENTS BASED ON THE QUALITATIVE VARIABLES OF THE STUDY.

Variable		Mean ± SD	p-value[*]
Follow-up	With a caregiver (n = 88)	908.66 ± 795.76	0.100
	Without a caregiver (n = 22)	613.62 ± 486.23	
INSS	Yes (n = 25)	840.87 ± 781.98	0.823
	No (n = 85)	879.47 ± 651.73	
Occupation	Formal employment (n=13)	869.13 ± 755.44	0.021
	Unemployed/Homemaker/Informally employed (n=56)	570.24 ± 470.85	
	Retired (n=41)	579.12 ± 751.62	
Formal education	Up to incomplete secondary (n=65)	621.17 ± 649.64	0.450
	Complete secondary (n=27)	664.11 ± 675.89	
	Up to complete tertiary (n=18)	494.89 ± 440.56	
Type of neoplasm	Head and neck CA (n=3)	506.86 ± 194.57	0.212
	Lung CA (n = 8)	821.24 ± 653.07	
	Genitourinary CA (n = 23)	872.75 ± 670.78	
	Breast CA (n = 20)	636.65 ± 415.94	
	Sarcoma (n = 5)	459.39 ± 362.56	
	CNS (n = 4)	352.54 ± 240, 72	
	GIT (n = 47)	849.65 ± 751.68	
Staging	2 (n=13)	717.26 ± 619.56	0.412
	3 (n=33)	744.60 ± 456.78	
	4 (n=64)	930.71 ± 884.55	
Origin	Capital (n=55)	998.19 ± 889.55	0.038
	Interior (n=55)	701.11 ± 551.61	

[*] ANOVA one-way test.

unique financial implications due to the chronicity of therapy, the costs incurred and not covered by insurance or SUS, the cumulative effects associated with the treatment, additional expenses, difficulty in maintaining employment when undergoing this therapy, and the decline of health[8]. However, this variable did not present a "p" value statistically significant in this study. Some factors that could have interfered in this outcome were the limitation of patient assessment (which comprised only 1 month of treatment), the inclusion of patients in the initial stages (2 and 3), in addition to the sample size.

In the analysis of the average monthly costs for patients, the final value of R$ 849.65 is very representative of their average monthly income, considering the receipt of up to one minimum wage of R$ 954.00, in 2018 (60.91% of the cases), as shown in Table 3. In a Swedish study, indirect costs (work hours lost) were responsible for more than 50% of the total costs incurred and not covered for patients aged less than 65 years[11]. In a study conducted in Australia, the indirect costs for the treatment of breast cancer (e.g., custom wigs, bras, prostheses, etc.) totaled up to 62% of the total cost and were even greater in younger women[12].

Of the indirect costs analyzed, the transport was the highest, i.e., R$ 188.46 per month (Table 3). When a patient is submitted to radiotherapy and chemotherapy, travel expenses constitute the main component of the overall cost[13] which, among others, corroborates the findings of the present study, in which patients coming from the interior of the state had increased costs, with a statistically significant difference in overall costs in comparison with patients from the capital (Table 4; p=0.038).

The percentage of indirect costs varies according to the methods used and differences in health systems between countries. As is in many studies, indirect costs amount to up to half of the total costs, which are essential to evaluate the total costs incurred and not covered in the cancer treatment[14].

In 2011, a study carried out in the department of pulmonary diseases of a University in Greece with 128 patients with lung cancer followed-up for 32 months showed that patients lost a total of 27,050 days of productivity and their caregivers lost a total of 1,337 days of productivity. Although no monetary value was assigned to this loss of productivity, certainly the potential for monetary gain by the patient and caregiver were affected[15].

Our study was the first step to identify possible factors related to direct and indirect costs not covered during cancer treatment in a state of the northeast

region of Brasil. However, the cross-sectional approach did not allow for the follow-up of patients during the entire course of the disease, which can be seen as a limitation. In the present study, all methods of therapy were analyzed jointly. Therefore, any differences in costs incurred and not covered by patients or carers could not be evidenced for specific treatments. The small sample size also had no statistical power for detecting small differences in costs incurred and not covered for patients and caregivers based on several of their socio-demographic and clinical variables.

CONCLUSION

The direct and indirect healthcare costs are quite significant for cancer patients and their caregivers considering the low average monthly income found in the study sample. The prevention of cancer or its early detection is, without a doubt, the best alternative for the reduction of costs incurred and not covered associated with cancer treatment. As strategies to tackle this public health problem, we can mention the strengthening of treatment financing programs for patients and caregivers, as well as the decentralization of access to cancer treatments in order to reduce the commuting of patients from the interior of the state to the capital in order to undergo treatment.

Author's Contribution

JKLA: Data curatorship (Lead)/Writing - original draft (Lead); LMS: Data Curatorship (Lead)/Supervision (Equal); CAS: Research (Equal); ISO: Research (Equal); GMF: Research (Equal); ADG: Supervision (Equal)/Writing - revision and editing (Equal).

RESUMO

INTRODUÇÃO: *Pacientes oncológicos e seus acompanhantes incorrem em custos não cobertos pelo Sistema Único de Saúde (SUS) durante o seu tratamento, com gastos relacionados a transporte, medicações sintomáticas, alimentação, perda de dias de trabalho dentre outros.*

OBJETIVO: *Avaliar os custos incorridos e não cobertos pelo SUS por pacientes com câncer e seus acompanhantes durante a realização do tratamento, oncológico.*

MÉTODOS: *Trata-se de um estudo transversal realizado com 110 pacientes oncológicos em tratamento com quimioterapia ou quimioterapia e radioterapia e 88 acompanhantes, no último mês, antes de sua inclusão no estudo. Correlacionamos os custos dispendidos com variáveis clínicas e sociodemográficas como sexo, idade, raça, estado civil, escolaridade, ocupação, naturalidade, procedência, renda mensal, renda familiar, moradia, comorbidades, tipo de neoplasia e estadiamento.*

RESULTADOS: *Observamos que a média do custo global dos pacientes do estudo foi de R$ 747,92, que corresponde a 78,4% do salário mínimo e a média do custo dos acompanhantes foi de R$ 118,86 reais que equivale a 12,46% do salário mínimo. Dentre todas as variáveis analisadas, a média do custo global mensal dos pacientes correlacionou-se positivamente com a variável ocupação (p=0,021) assim como com a variável procedência (p = 0,038). Para as demais variáveis, não foram detectadas associações significativas.*

CONCLUSÃO: *A correlação positiva encontrada entre ocupação e procedência com custos incorridos e não cobertos por pacientes sugere a criação de programas que viabilizem o pagamento dos custos não cobertos pelo SUS e a descentralização do acesso ao tratamento oncológico podem potencialmente facilitar a aderência do paciente ao tratamento oncológico.*

PALAVRAS-CHAVES: *Neoplasias. Oncologia. Gastos em saúde. Sistema Único de Saúde. Cuidadores.*

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Seasonal variation of vitamin D among healthy adult men in a subtropical region

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SUMMARY

OBJECTIVE: *To evaluate seasonal variation of 25(OH)vitamin D [25(OH)D3] levels, and factors associated with it, in healthy adult men, who exercised outdoors for 50 min., at least twice a week, from 10AM to 4PM, in a Brazilian semitropical region.*

METHODS: *Blood samples were collected at the end of each season for 25(OH)D3, measured by liquid chromatography with tandem mass spectrometry. Ultraviolet irradiation was estimated by radiometer, calculating the daily photobiological response to vitamin D synthesis in human skin (D-VitD). The prevalence of 25(OH)D3 <20ng/mL changed with the seasons (p=0.000): 8.7% (n=6/69), 1.5% (n=1/66), 0 (n=0/64), and 21.7% (n=13/60), respectively, at the end of winter, spring, summer, and autumn. The prevalence, adjusted for multiple comparisons, was higher in winter than summer (p=0.026), and in autumn than spring (p=0.001) and summer (p=0.000). There were no associations of 25(OH) D3 levels with BMI (p=0.207), body fat (p=0.064), and phototype (p=0.485), in univariate analysis. It was associated with D-VitD in the 30 days before blood sampling (p=0.000), after adjustment to body fat. The prevalence of 25(OH) D3 <30ng/mL varied seasonally (p=0.000): 69.6% (n=48/69), 68.2% (n=45/66), 43.8% (n=28/64), and 88.4% (n=53/60), respectively, in winter, spring, summer, and autumn.*

CONCLUSIONS: *In a Brazilian subtropical region, a seasonal variation in 25(OH)D3 was observed in healthy adult males, although they spent at least 50 min outdoors twice a week, wearing shorts and T-shirts. 25(OH)D3 <20ng/mL was 21.7% in autumn; D-vitD 30 days prior to blood sampling was the only factor independently associated with 25(OH)D3 levels.*

KEYWORDS: *Cholecalciferol. Vitamin D. Vitamin D deficiency. Seasons. Ultraviolet rays.*

INTRODUCTION

Vitamin D deficiency has been associated with several diseases[1,2], and it has been observed in sunny areas, such as the semitropical region of the southern hemisphere[3-5]. Human vitamin D sources are food intake or ultraviolet B radiation (UVB)-induced skin production, which has been associated to its content of 7-dehydrocholesterol, UVB wavelength, phototype, sunblock use, latitude, season, time of the day, weather conditions, area and length of exposure, and age[2,6]. Our aim was to evaluate the seasonal variation of 25-hydroxyvitamin D3 [25(OH)D3 in Porto Alegre, RS, Brasil (30° 1'40" S and 51° 13'43" W), and its associated factors in healthy male adults who practiced regular outdoor activities.

METHODS
Ethics statement

All procedures were approved by the Ethics Committee in Research of the Hospital de Clinicas de Porto Alegre, under number 14-0173, and CAEE number 28822014.5.0000.5327. Written informed consent was obtained from all subjects. All authors declare no conflicts of interest.

Subjects

Male military police officers of Porto Alegre/RS/Brasil, aged ≥18 years to ≤55 years were invited to participate. The exclusion criteria were body mass index (BMI) ≥39 Kg/m², travel within the last 3 months, use of vitamin D supplements or diuretics, anticonvulsants, glucocorticoids, anti-HIV or anti-fungal medications, history of bariatric surgery, and known diseases, which could interfere with vitamin D metabolism. As part of their professional duties, they performed outdoor physical activities wearing shorts and T-shirts at least twice a week from 10 AM to 4 PM.

Experimental design: four cross-sectional studies.

Logistics

Participants were evaluated by a trained healthcare professional, who measured their weight and height, while barefoot, on a standing stadiometer and a digital scale, and body fat content was calculated by the measurement of seven cutaneous folds with a caliper. They were divided into 3 groups, according to the Fitzpatrick phototype classification: 1= I+II, 2= III+IV, and 3=V+VI. All participants answered a questionnaire about current tobacco use, alcohol intake (frequent or not), use of prescription drugs, vitamin D supplements or sunblock, and known diseases.

Biochemical data

Blood samples were collected on the last day of each season for 25(OH)D$_3$ measurements. In autumn, blood was collected after overnight fast to measure plasma PTH, and serum total calcium, creatinine, and albumin. Serum and plasma were kept at -70ºC. Total serum calcium, creatinine, and albumin levels were measured by routine assays. Intact PTH was measured by chemiluminescence (ARCHITECT, Abbott Diagnostics, Wiesbaden, Germany) with an intra-assay variation of 4.1%. All samples were measured in the same assay.

Plasma concentrations of 25(OH)D$_3$ were measured by Liquid Chromatography with tandem mass spectrometry after protein precipitation. Briefly, 100µL of plasma was transferred to a 2mL polypropylene tube with 200µl of acetonitrile and the 20ng/mL internal standard of D6-25(OH)D$_3$, and Vortex mixed for 1 minute. After centrifugation at 12,000g for 15 minutes, 15µL of the supernatant was injected into an Ultimate 3000 XRS UHPLC system (Thermo Scientific, San Jose, USA). The separation was performed in an Acquity C18 column (150 × 2.6 mm, p.d. 1.7 µm) from Waters (Milford, USA), maintained at 40°C. The mobile phase was a mixture of 0.1% formic acid in water and methanol (20:80, v/v), eluted at a flow rate of 0.25mL min-1. Detection was performed in a TSQ Quantum Access triple quadrupole mass spectrometer (Thermo Scientific, San Jose, USA) with an atmospheric-pressure chemical ionization (*APCI*) probe. The MS settings were: positive ionization mode, corona discharge needle voltage 7 kV; sheath gas, nitrogen at a flow rate of 60 arbitrary units; auxiliary gas, nitrogen at a flow rate of 5 arbitrary units; collision gas, argon; vaporizer temperature at 390°C; and ion transfer capillary temperature at 202°C. The scan time was set to 0.3 seconds per transition. The following transitions were used for MRM acquisition: m/z 401 → 365 (quantification), 401 → 159, and 401 → 105 (qualification) for 25(OH)D$_3$; and m/z 407 → 371 (quantification), and m/z 407 → 105, and 401 → 91 (qualification) of internal standard. The method was linear from 5.0 to 100.0 ng mL-1 (r=0.999). Accuracy and imprecision were acceptable with an accuracy between 90.7 and 103.4%, and within and between assay coefficients of variation in the range of 2.8-7.5% and 3.9-7.8%,

respectively. Daily calibration curves were included in all analytical batches. Commercial quality control samples from Chromsystem® (Munich, Germany) were processed every 20 samples.

Two 25(OH)D cut-off levels were used to classify vitamin D status: <20ng/mL and <30ng/mL[7,8].

Ultraviolet radiation measurement

UV-R was measured from solar radiation using the Model 501 calibrated radiometer of Solarlight (https://solarlight.com/product/uvb-biometer-model-501-radiometer/), which has a normalized spectral response for the 297nm unit, simulating skin response to the formation of erythema[9]. The equipment was stabilized at 25°C in order to prevent changes in spectral response and in sensitivity to variations in ambient conditions. The irradiances [Wm^{-2}], weighted by the photobiological response to erythema formation (D-Ery), were collected at 1-second intervals, and the mean of these values was recorded every 10 minutes. Irradiances were integrated between 07:00 AM and 5:00 PM (local time) in order to evaluate the amount of UV-R accumulated in daily exposures, and total daily doses (D-Ery) [Jm^{-2}] were determined. From the D-Ery, UV-R doses weighted by the photobiological response for vitamin D synthesis in human skin (D-VitD) were calculated. Since this photobiological response depends almost exclusively on UVB-R, a conversion factor based on the total ozone content and the position of the sun was used to determine it[10]. This conversion factor aims to represent the UVB-R attenuation processes caused by both meteorological parameters.

Statistical analysis

The distribution of data was evaluated by the Kolmogorov-Smirnov test. Mean 25(OH)D$_3$ levels for the 4 seasons and their associated factors were compared by the Generalised Estimating Equation method, adjusted to multiple comparisons by the Bonferroni test. Mean seasonal doses of D-VitD were compared by one-way analysis of variance (ANOVA), adjusted for multiple comparisons by the Tukey HSD test. The prevalence of 25(OH)D <20ng/ml and <30ng/mL at the end of each season was calculated by the likelihood-ratio chi-square test, adjusted for multiple pairwise comparisons by the Bonferroni test. The PTH and 25(OH)D correlation was evaluated by the Pearson test. All analyses were made in the SPSS (Statistical Package for Social Studies) software,

version 18.0, except for the analysis of the prevalence of low vitamin D, which was conducted in the WIN-PEPI software, version 11.65.

RESULTS

One hundred and ten men were invited to participate and 71 accepted. Two were excluded: 1 for using a vitamin D supplement, and 1 for having a BMI ≥39Kg/m², so 69 were included in the 1st evaluation. In the 2nd evaluation, 3 were excluded for traveling, so 66 were included; in the 3rd evaluation, 2 were excluded (1 suffered a gunshot wound and 1 gave up participating), so 64 were included; and in the 4th evaluation, 4 gave up participating, so 60 were included. The clinical characteristics of the participants are shown in Table 1.

TABLE 1. CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

	Mean± SD or n	n
Age (years)	34.3±6.8	69
BMI (Kg/m²)	25.2±2.5	69
Body fat (%)	17.8±3.2	62
Phototype*	1: 35, 2: 31, and 3: 3	69
Use of sunscreen	2	69
Smoking	4	69
Frequent alcohol intake	0	69
Chronic use of medications	7	69
Known diseases	3	69

Phototype*: 1 = Fitzpatrick phototype I + II; 2 = Fitzpatrick phototype III + IV; 3 = Fitzpatrick phototype V + VI. Data are shown as mean ± SD or number (n)

Plasma 25(OH)D3 levels

Mean 25(OH)D$_3$ levels changed with seasons (p<0.001), respectively, 27.2 ± 6.6ng/mL (n=69), 28.9 ± 6.1ng/mL (n=66), 31.7 ± 6.4ng/mL (n=64), and 23.3 ± 5.2ng/mL (n=60), in winter, spring, summer, and autumn. Pairwise comparisons were all different (p<0.000), adjusted by the Bonferroni test, except when comparing levels at the end of summer and spring (p=0.139), as shown in table 2. In autumn, mean serum albumin, total calcium, PTH, and creatinine levels were 4.4±1.3g/dL, 8.9±2.3mg/dL, 59.2±22.8pg/mL, and 1.03±0.24mg/dL, respectively.

There was a seasonal variation in the 25(OH)D$_3$ <20ng/mL prevalence (p=0.000): 8.7% (n=6), 1.5% (n=1), zero, and 21.7% (n=13), respectively, at the end of winter, spring, summer, and autumn. Prevalence was higher in winter than in summer (p=0.026), and

TABLE 2. MEAN 25(OH)VITAMIN D3 [25(OH)D3] LEVELS AND ITS CORRELATION WITH THE MEAN ULTRAVIOLET LIGHT RESPONSIBLE FOR VITAMIN D SYNTHESIS IN HUMAN SKIN (D-VITD) IN THE 30, 45, AND 90 DAYS BEFORE BLOOD SAMPLING

	25(OH)D_3 (ng/mL)*	D-vitD 30 days (Jm^{-2})	D-vitD 45 days (Jm^{-2})	D-vitD 90 days (Jm^{-2})
Winter	27.2 ± 6.6	1038.5 ± 301.8	950.1 ± 165.9	626.1 ± 406.6
Spring	28.9 ± 6.1	1488.4±1016.2	1485.8±1328.7	1036.7 ± 584.5
Summer	31.7 ± 6.4	2192.2 ± 492.5	1876.0 ± 521.4	2326.9±1057.9
Autumn	23.3 ± 5.2	606.7±285.5	630.9 ± 294.9	1779.3 ± 102.7
r**		0.982; p= 0.018	0.972; p= 0.024	0.276; p= 0.723

*Mean 25(OH)D3 were compared by the Generalised Estimating Equation method: p=0.000, when comparing all four seasons, and all pairwise comparisons adjusted to multiple comparisons by the Bonferroni test, except between spring and summer (p=0.139). ** Pearson correlation test between mean 25(OH)D3 and mean D-VitD before blood sampling

in autumn than in spring (p=0.001) and in summer (p=0.000); it was similar in winter and in spring (p=0.283), in winter and in autumn (p=0.227), and in spring and in summer (p=1). The prevalence of 25(OH)D_3 <30ng/mL changed with the seasons (p=0.000), and it was 69.6% (n=48), 68.2% (n=45), 43.8% (n=28), and 88.4% (n=53), respectively, in winter, spring, summer, and autumn. It was higher in autumn than in spring (p=0.033) or in summer (p=0.000); it was also higher in winter (p=0.015) and in spring (p=0.029) than in summer. It was similar in winter and in spring (p=1.000), and in winter and in autumn (p=0.05). These data are shown in Figure 1.

FIGURE 1
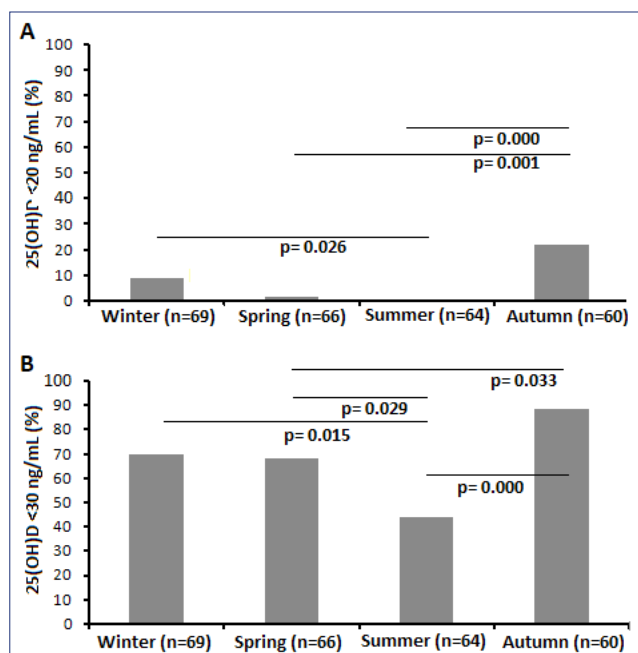
Prevalence of vitamin 25(OH)D3 changed at the end of seasons, for both cut-off points, <20 ng/mL (A) and <30 ng/mL (B), (p=0.000), by the likelihood-ratio chi-square test. The prevalence of vitamin 25(OH)D3 <20 ng/mL was similar in autumn (21.7%) vs. winter (8.7%), p=0.227, in spring (1.5%) vs. summer (0%), p=1.000, and in winter vs. spring, p=0.285. The prevalence of vitamin 25(OH)D3 <30 ng/mL was 43.8%, in summer, it was similar in winter (69.6%) vs. spring (68.2%), p=1.000, and autumn (88.4%), p=0.050. Other multiple pairwise comparisons are shown in the panels, and all were adjusted by the Bonferroni test.

Measurement of UV-R

There was a seasonal variation in mean D-vitD (p=0.000), which was 913.3±383.9, 1937.8±934.0, 1945.9±1180.0, and 903.6±507.2 Jm^{-2}, in winter, spring, summer, and autumn, respectively. D-vitD was higher in spring than in winter (p=0.000) and in autumn (p=0.000); and in summer than in winter (p=0.000) and in autumn (p=0.000); it was similar when comparing winter and autumn (p=1.000), and spring and summer (p=1.000). Mean D-VitD measured in periods prior to blood sampling are shown in Table 2.

Factors associated with 25(OH)D3

Correlations between mean 25(OH)D_3 levels at the end of each season and mean D-VitD before blood sampling are shown in table 2.

There was no association between 25(OH)D_3 levels and BMI (p=0.207), body fat content (p=0.064), and phototype (p=0.485). In a multivariate regression model including mean D-vitD and body fat content, mean D-vitD in the 30 days before blood sampling was independently associated with 25(OH)D_3 levels. These data are shown in Table 3. PTH and 25(OH)D_3 levels were inversely correlated (r=-0.308, p=0.019) at the end of autumn.

TABLE 3. FACTORS ASSOCIATED WITH 25(OH)D3 LEVELS, MULTIVARIATE MODEL

Parameter	B	p
Intercept	26.146	0.000
Mean UVB 30 days before blood sampling	0.004	0.000
Body fat (%)	−0.212	0.097

Dependent variable: 25(OH)D3. Model (intercept), UVB 30 days before blood sampling, body fat content

DISCUSSION

Our results have shown a seasonal variation of $25(OH)D_3$ in healthy adult men, living in a semitropical region, which was associated with the mean D-vitD in the 30 and 45 previous days. These data are in line with studies conducted in subtropical areas with the elderly[4,5], and in two large studies, one including subjects aged from 2-95 years[11], and another with children[12], with vitamin D peaks in autumn and troughs in spring.

In our study, peak vitamin D was observed in summer and spring, and a quite unexpected trough in autumn. Nevertheless, these results are in agreement with the low levels of D-VitD measured at 30 and 45 days before blood sampling in the autumn. Besides, they are in accordance with the D-VitD, which peaked in summer and spring, and was lower in autumn and winter. As data were collected in just one year, we cannot exclude a shifting in D-vitD in the earth's surface, in a given season, caused by meteorological variables as cloud coverage, aerosol pollution, or local ozone content variation[13].

A surprising aspect of our study was the high prevalence of $25(OH)D_3$ <30ng/mL, which ranged from 43.8% in summer to 88.4% in autumn. There was no inflammation[14], nor hypoalbuminemia, which could have been implicated[15], and they exercised outdoors regularly with light clothing, exposing a skin area considered to provide enough vitamin D[2]. Genetic factors, which appear to contribute 70% to the seasonal variation of $25(OH)D_3$ levels, could have been implicated[3,16]. Nevertheless, even with the cut-off of <20ng/mL, which has been deemed sufficient by the Institute of Medicine of the USA for practically all persons, when considering bone health[7], 21.7% of the subjects had low vitamin D at the end of autumn. Probably, at this time of the year, there was not enough D-vitD to provide the needed synthesis of vitamin D.

Several factors have been shown to influence the amount of solar UVB-R which reaches the surface of the earth, such as atmospheric dispersion of solar rays, air attenuation, absorption by molecular oxygen and ozone, and the line structure in the solar spectrum[2].

In addition to UVB-R indices, other factors might affect $25(OH)D$ levels, such as clothing and the time spent outdoors[17,18]. Although our subjects exercised at least twice a week outdoors wearing light clothing, as part of their professional schedule, this was not enough to keep $25(OH)D$ in the recommended levels[7], so probably the amount of D-vitD was not sufficient to provide adequate vitamin D. Vitamin D has been shown to increase with exposed body area[2,19-21], although a plateau in its response has been suggested when more than 33% of body area was irradiated[19]. Nevertheless, in a more recent study, a positive association was found between $25(OH)D_3$ levels and exposed body area[20]. In another study, biweekly exposure of 88% of body area to 1 Standard Erythemal Dose treatment was sufficient to maintain appropriate levels of $25(OH)D_3$[22].

In our study, only two participants used sunscreen, so it was not possible to evaluate its association with vitamin D. Also, there was no association between $25(OH)D_3$ levels and body fat content, which could have been due to the small sample, since low vitamin D levels have been consistently reported in obesity[3,23]. As expected, PTH levels were inversely proportional to $25(OH)D_3$ levels.

The strengths of our work were the prospective collection and measurements on the same individuals in the 4 cross-sections; its weaknesses were no individual UV-R measurements and no assessment of dietary factors, which could contribute to $25(OH)D_3$ levels variability.

CONCLUSIONS

$25(OH)D_3$ levels changed seasonally in healthy adult males in Southern Brasil, which was strongly and independently associated with UV-R indexes 30 days before blood sampling. The prevalence of $25(OH)D_3$ <20ng/mL in late summer and spring was nil or low; however, it increased in late autumn and winter, although our subjects spent at least 50 min outdoors twice a week with light clothing, from 10 AM to 4 PM. Therefore, probably, D-vitD at this time of the year was not sufficient to provide adequate vitamin D. The prevalence of $25(OH)D_3$ <30ng/mL was high during all seasons of the year, especially in autumn.

Author's Contribution

Project design: Tiago O. Fontanive, Marina V. Antunes, Rafael Linden, Marcelo de P. Corrêa, Rita de C. M. Alves, and Tania W.Furlanetto; Data collection: Tiago O.Fontanive, Nidea R. M. Dick, Mariana C. S. Valente, and Vani dos S. Laranjeira; 25(OH)D and UV measurements and calculations: Marina V. Antunes and Rafael Linden, and Marcelo de P. Corrêa; Paper writing: Tiago O. Fontanive, Marina V.Antunes, Marcelo de P. Corrêa, and Tania W.Furlanetto.

RESUMO

OBJETIVOS: *Avaliar a sazonalidade da 25(OH)vitamina D3 [25(OH)D3] e fatores associados em homens adultos saudáveis, que se exercitavam ao ar livre pelo menos 50 min duas vezes por semana, das 10 às 16h, em uma região subtropical.*

MÉTODOS: *Sangue foi colhido no fim das estações para medir 25(OH)D3, por cromatografia líquida em tandem com espectroscopia de massas. A radiação ultravioleta foi estimada por radiômetro, calculando diariamente a resposta fotobiológica para sintetizar vitamina D na pele humana (D-VitD).*

RESULTADOS: *A prevalência de 25(OH)D3 <20ng/mL foi sazonal (p=0.000): 8.7% (n=6/69), 1.5% (n=1/66), 0% (n= 0/64), e 21.7% (n=13/60), respectivamente, no final do inverno, primavera, verão e outono. A prevalência, ajustada para comparações múltiplas, foi maior no inverno do que no verão (p=0.026) e no outono do que na primavera (p=0.001) e verão (p=0.000). A 25(OH)D3 não se associou com o índice de massa corporal (p=0.207), gordura corporal (p=0.064) ou fototipo (p=0.485), na análise univariada. Associou-se à D-VitD nos 30 dias antes da coleta de sangue (p=0.000), ajustada para gordura corporal. Houve sazonalidade na prevalência de 25(OH)D3 <30ng/mL (p=0.000): 69.6% (n=48/69), 68.2% (n=45/66), 43.8% (n=28/64), e 88.4% (n=53/60), respectivamente, no inverno, primavera, verão e outono.*

CONCLUSÕES: *Em uma região subtropical, houve sazonalidade na 25(OH)D3 em homens adultos, saudáveis, embora se exercitassem ao ar livre pelo menos 50 minutos duas vezes por semana, usando shorts e camiseta. 25(OH)D3 <20ng/mL foi 21.7% no outono e a D-vitD 30 dias antes da coleta do sangue foi o único fator associado de modo independente à 25(OH)D3.*

PALAVRAS-CHAVE: *Colecalciferol. Vitamina D. Deficiência de vitamina D. Estações do ano. Raios ultravioleta.*

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Predictors of left atrial thrombus in acute ischemic stroke patients without atrial fibrillation: A single-center cross-sectional study

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SUMMARY

INTRODUCTION: The present study aimed to determine independent predictors of left atrial thrombus (LAT) in acute ischemic stroke (AIS) patients without atrial fibrillation (AF) using transesophageal echocardiography (TEE).

METHODS: In this single-center, retrospective study, we enrolled 149 consecutive AIS patients. All of the patients underwent a TEE examination to detect LAT within 10 days following admission. Multivariate logistic regression analysis was performed to assess independent predictors of LAT.

RESULTS: Among all cases, 14 patients (9.3%) had a diagnosis of LAT based on the TEE examination. In a multivariate analysis, elevated mean platelet volume (MPV), low left-ventricle ejection fraction (EF), creatinine, and reduced left-atrium appendix (LAA) peak emptying velocity were independent predictors of LAT. The area under the receiver operating characteristic curve analysis for MPV was 0.70 (95%CI: 0.57-0.83; p = 0.011). With the optimal cut-off value of 9.45, MPV had a sensitivity of 71.4% and a specificity of 63% to predict LAT.

CONCLUSION: AIS patients with low ventricle EF and elevated MPV should undergo further TEE examination to verify the possibility of a cardio-embolic source. In addition, this research may provide novel information with respect to the applicability of MPV to predict LAT in such patients without AF.

KEYWORDS: Stroke. Heart atria. Thrombosis. Mean platelet volume.

INTRODUCTION

Stroke is a leading cause of morbidity and disability in both developed and developing countries and is the second most common cause of death worldwide[1]. Acute ischemic stroke (AIS) accounts for approximately 85% of all cases and can be classified into five main subtypes based on their etiopathogeneses: I) small vessel occlusion (lacunar infarction), II) large artery atherosclerosis (atherothrombotic),

III) cardio-embolism, IV) stroke of other determined etiology, and V) stroke of undetermined etiology[2]. In particular, patients with cardio-embolic stroke usually have high mortality, disability, and poor neurological outcomes compared to the other types of ischemic stroke[3]. Although previous studies have demonstrated that atrial fibrillation (AF) is the most common source of cardio-embolism due to the formation of left atrial thrombi (LAT)[3]. The data regarding predictors of LAT in AIS patients without AF is not clearly defined in the current literature.

In current practice, transthoracic echocardiography (TTE) is the initial imaging modality in patients with AIS[4]. However, it is not usually possible to exclude all causes of cardio-embolism using TTE alone. In addition, there is no strong recommendation in the current guideline on whether patients with normal TTE findings must undergo further transesophageal echocardiography (TEE) examination to verify potential sources of cardio-embolism in AIS patients with undetermined etiology[4]. Besides that, because TEE is a semi-invasive procedure and carries some risk of complications in patients with recent ischemic stroke, identifying the patients who will most benefit from this examination would be useful in clinical practice.

In light of these data, the present study aimed to determine predictors of LAT that were not detected on TTE but confirmed only using TEE in AIS patients without AF.

METHODS
Patient selection

In this single-center, retrospective, and cross-sectional study, we enrolled 149 consecutive AIS patients who had undergone a TEE examination with a preliminary diagnosis of cardio-embolic source in a tertiary center. Patients who had AF (paroxysmal or persistent) and stroke of other identifiable etiology were excluded from the study. Also, 2 patients who were diagnosed with left-ventricle thrombosis and 4 patients with right-atrial thrombosis were not included in the study. In all of the patients, cranial magnetic resonance imaging, including diffusion-weighted imaging and T2-weighted imaging, was used to confirm the diagnosis of AIS or transient ischemic attack (TIA). In order to rule out a stroke of atherothrombotic sources, either magnetic resonance angiography or computed tomography angiography was ordered in all patients. Per hospital protocol, all patients with signs and symptoms of stroke were evaluated by an experienced neurologist following admission. A 24-72h Holter monitoring was routinely applied to all the patients to rule out any possible arrhythmias, including AF. The clinical data of all patients were collected from the hospital electronic database. The independent local ethics committee approved the design of the present study (approval number: HNEAH/KAEK/2019/KK/171), which was conducted in accordance with the ''Good Clinical Practice'' guidelines of the Declaration of Helsinki.

TEE examination
After overnight fasting of 8h, all of the patients underwent TEE examination to detect LAT 10 days after admission. Informed consent was obtained from all patients or patients' relatives to perform the TEE examination. All TEE procedures were performed by two experienced echocardiographers in the left lateral decubitus position. In all patients, a local anesthetic was given to anesthetize the oropharynx. If indicated, intravenous diazepam was given for sedation. Images were obtained using an iE33 ultrasound system with a multiplane 5 MHz probe (Philips Med. Sys., Massachusetts, USA). On the TEE examination, the left atrium (LA) and left atrium appendix (LAA) were assessed in different planes to determine the presence of LAT. We evaluated the LAA flow velocities by placing a pulsed Doppler from the beginning of the LAA to the body of the LA. Figure 1 displays a case of AIS patient with a thrombus found in the LAA.

Laboratory analysis
All blood samples were collected on admission before TEE examination. Hematologic parameters, including hemoglobin, white blood cell, and platelet counts were measured as a part of the automated complete blood count, using the Sysmex XN 9000 hematology analyzers (Sysmex Corporation, Kobe, Japan). Biochemical measurements were performed using Beckman Coulter, Inc. kits and calibrators. The normal range for the mean platelet volume (MPV) in our institution was between 7 and 11 fL.

Definitions
Cranial infarction was accepted as an acute neurological incident continuing ≥24h[5]. TIA was defined as an abrupt onset of neurological events or amaurosis fugax lasting <24h[5]. LAT was defined as a circumscribed homogenous mass attaching to the LA wall or LAA which was seen in at least two different degrees

FIGURE 1.
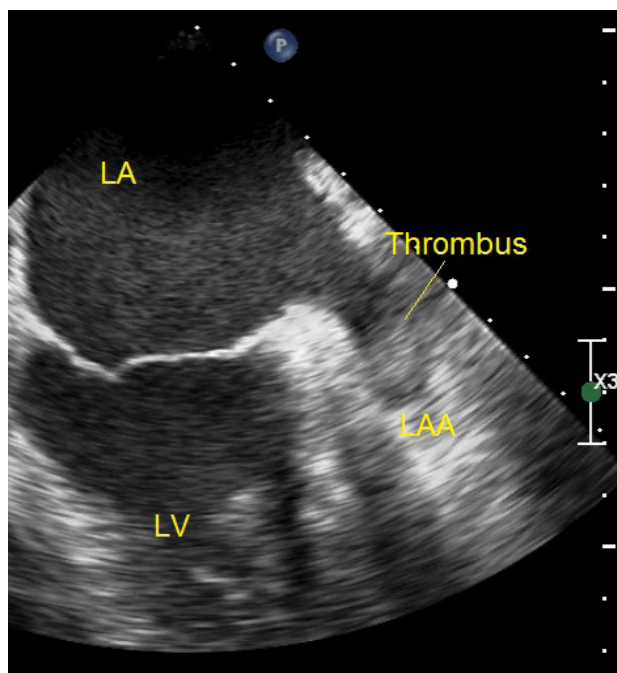
of mobility and echogenicity compared to myocardial texture. LA spontaneous echo contrast (SCE) was graded from I to III. Patent foramen ovale (PFO) was confirmed if microbubbles were spontaneously seen in the LA or after performing the Valsalva maneuver.

Statistical analysis

All statistical analyses were done using SPSS software, IBM, version 21.0. To test if the variables were normally distributed, the Kolmogorov-Smirnov test was performed. For continuous parameters, the data were presented as mean ± standard deviation or median, while the data were provided as percentage and number values for categorical parameters. To determine the difference between the groups of continuous parameters with normal distribution, the independent t-test was performed. The Mann–Whitney U-test was used in the analysis of continuous parameters without normal distribution. For categorical variables, the Chi-square test was used. In order to determine the predictors of LAT, we first performed univariate analysis. The variables with a significance of $p < 0.05$ were used in the multivariate analysis. After that, the multivariate logistic regression analysis was used to assess independent predictors of LAT. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and was satisfied when the p-value was >0.05. The Hosmer–Lemeshow statistic of multivariate analysis did not suggest a lack of fit

($\chi 2 = 13.818$, $p = 0.087$). The effect size (Cohen's d) and power value (1- β) were calculated using G*Power software (version 3.1.9.2.). The effect size and power value were 0.86 and 0.97, respectively. The optimal cut-off value of MPV for LAT was evaluated using the receiver operating curve (ROC) analysis. A p-value <0.05 was considered statistically significant.

RESULTS

In the present study, the mean age was 64±13 years and 76 (51%) of the patients were male. Among all patients, 14 (9.3%) had a diagnosis of LAT on the TEE examination. We classified the study cohort into two groups: Patients with thrombus (+) and without thrombus (-).

The baseline clinical features of all patients are displayed in Table 1. The study results show that patients who had LAT had an older age and higher prevalence of diabetes. No significant differences in terms of other baseline clinical features were found between the groups. We observed that 5 patients (3.7%) without LAT (3 patients with grade III, 1 patient with grade II, and 1 patient with grade I) and 5 patients (35.7%) with LAT (2 patients with grade III, 3 patients with grade II) had SCE on the TEE examination.

Laboratory and echocardiographic findings of the study population are depicted in Table 2. Red blood cell distribution width, MPV, creatinine, and blood urea nitrogen (BUN) levels were significantly elevated in patients with LAT. In terms of echocardiographic parameters, patients with LAT had lower left-ventricle ejection fraction (EF) and LAA peak emptying velocity. We found that the frequency of tricuspid regurgitation was significantly higher in cases with LAT. In comparison, the other echocardiographic parameters were not different between the groups.

The independent predictors of LAT were identified using univariate and multivariate logistic regression analysis as shown in Table 3. A logistic regression analysis using the backward LR method was done for multivariate analysis of the variables that were found significant in the univariate analyses (p<0.05). According to the multivariate analysis, elevated MPV, low ventricle EF, creatinine, and a reduced LAA peak emptying velocity were independent predictors of LAT.

The optimal value of MPV to predict LAT revealed by ROC analysis is shown in Figure 2. The area of MPV under the ROC analysis was 0.70 (95%CI: 0.57-0.83; p = 0.011). With the optimal cut-off value of 9.45, MPV

TABLE 1. COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS ACCORDING TO THE PRESENCE OF THROMBUS

	Thrombus (-), (n=135)	Thrombus (+), (n=14)	P value
Age, y	57.7 (46.0–72.0)	72.2 (66.0–82.0)	0.007
Male gender, n (%)	68 (50.4)	8 (57.1)	0.629
Hypertension, n (%)	31 (23.0)	5 (35.7)	0.327
Diabetes mellitus, n (%)	78 (57.8)	12 (85.7)	0.030
Hyperlipidemia, n (%)	36 (26.7)	3 (21.4)	1.000
Smoking, n (%)	20 (14.8)	2 (14.3)	1.000
PCI, n (%)	41 (30.4)	6 (42.9)	0.372
CABG, n (%)	12 (8.9)	1 (7.1)	1.000
CVA, n (%)	16 (11.9)	4 (28.6)	0.097
CRF, n (%)	65 (48.1)	9 (64.3)	0.247
CHF, n (%)	16 (11.9)	4 (28.6)	0.097
COPD, n (%)	23 (17.0)	4 (28.6)	0.284
MVR, n (%)	9 (6.7)	1 (7.1)	1.000
AVR, n (%)	14 (10.4)	3 (21.4)	0.202
Tricuspid anuloplasty, n (%)	6 (4.4)	1 (7.1)	0.506
Medical treatment Acetylsalicylic acid, n (%) Clopidogrel, n (%) Beta-blocker, n (%) Ca channel blocker, n (%) Statin, n (%) Ace inhibitor/ARB, n (%) Warfarin, n (%)	49 (36.3) 26 (19.3) 49 (36.3) 22 (16.7) 31 (23.0) 45 (33.3) 23 (17.0)	5 (35.7) 4 (28.6) 6 (42.9) 4 (28.6) 5 (35.7) 7 (50.0) 5 (35.7)	0.966 0.482 0.631 0.276 0.327 0.245 0.141

Continuous variables are presented as mean ± SD or median, nominal variables are presented as frequency (%). Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; CRF, chronic renal failure; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MVR, mitral valve replacement; AVR, aortic valve replacement.

FIGURE 2.

AUC for MPV: 0.70; 95% CI:0.57 – 0.83; p=0.011

had a sensitivity of 71.4% and a specificity of 63% to predict LAT.

DISCUSSION

In AIS patients, AF is the most well-defined risk factor for cardio-embolism. However, a prior case-control TEE-based study showed that the thrombus formation might occur in subjects with sinus rhythm due to the impairment of the flow velocities in the LAA[6]. In this study, Agmon et al.[6] reported that sinus rhythm was present in 20 patients (6.3%) out of 314 with LAT during TEE evaluation. Additionally, Karabay et al.[7] investigated LA deformations using speckle tracking echocardiography to predict LAT in patients with suspected cardioembolic stroke who had normal sinus rhythm. They found that the frequency of LAT in AIS patients without AF was 6.2% (9 out of 144 patients). In our study, the frequency of LAT was 9.3% (14 out of 149 patients), which was slightly higher.
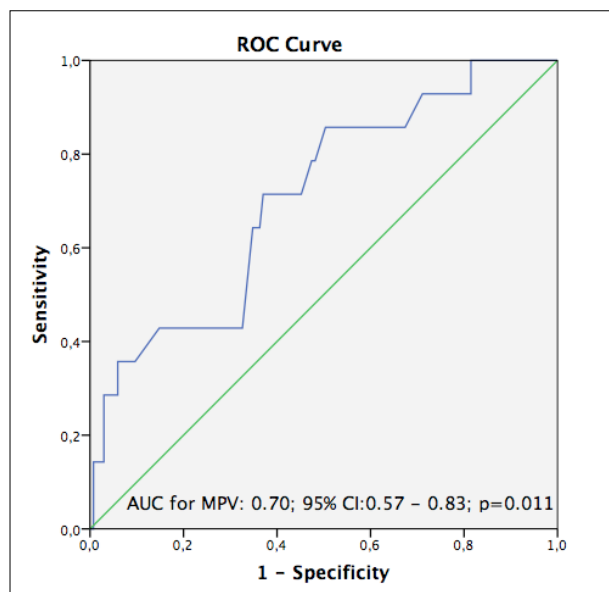
A number of recent studies have demonstrated that the left ventricle EF is strongly correlated with the formation of LAT in patients with AF undergoing TEE examination. Ayirala et al.[8] performed a case-control study in 334 consecutive patients with AF who had undergone TEE examination for the presence of LAT. In their multivariate analysis, left ventricle EF was found to be an independent predictor of LAT. Moreover, Rader et al.[9] found that solely left ventricle EF <40% was an independent predictor of LAT in 524 patients with AF who underwent TEE. Although our data were consistent with the findings of those published case-control studies, we were also able to demonstrate that left ventricle EF was an independent predictor of LAT in AIS patients without AF in our study. As a possible explanation of this finding, we considered that patients with low ventricle EF had usually hypercoagulable status due to increased platelet activation and elevation of coagulation parameters such as thromboglobulin and thrombin-antithrombin III, which might cause thrombus formation[10].

The second important predictor of LAT in our study was the presence of low LAA peak emptying velocity. We thought that the presence of LAA dysfunction in such patients may play a key role in the formation of LAT. Besides that, atrial cardiopathy, which might cause a reduced LAA peak emptying velocity, might be another potential cause of cardio-embolism among the groups of patients with AIS in the study[11]. Based on their results, Yaghi et al.[11] have suggested that a reduced LAA peak flow velocity might be correlated

TABLE 2. COMPARISON OF LABORATORY AND ECHOCARDIOGRAPHY PARAMETERS OF PATIENTS ACCORDING TO THE PRESENCE OF THROMBUS

	Thrombus (-) (n=135)	Thrombus (+) (n=14)	P value
Laboratory variables			
Hematocrit, (%)	38.0 (33.4–43.0)	36.7 (33.0–41.0)	0.530
Hemoglobin, g/dL	12.5 (10.9–14.4)	11.7 (10.3–13.9)	0.273
Red blood cell distribution width, %	14.7 (12.5–14.8)	15.5 (14.5–15.9)	0.003
WBC, cells/µL	8.0 (6.0–9.6)	8.5 (7.0–10.0)	0.513
Platelet count, mm³	245.0 (192.0–284.0)	217.9 (126.0–323.0)	0.350
MPV, fL	8.8 (7.5–10.4)	11.0 (9.5–12.1)	0.001
Plateletcrit, %	1.24 (0.88–1.25)	1.81 (1.04–2.54)	0.743
Creatinine, mg/dL	1.23 (0.88–1.22)	1.78 (1.10–2.50)	0.001
BUN, mg/dL	41.2 (26.0–49.0)	58.4 (40.0–72.0)	0.004
TSH, U/L	2.13 (0.60–1.83)	1.67 (0.50–2.61)	0.996
T4, U/L	1.03 (0.93–1.12)	1.06 (0.91–1.21)	0.516
AST, U/L	27.2 (18.0–31.0)	26.4 (16.0–23.0)	0.165
ALT, U/L	28.1 (15.0–34.0)	27.2 (11.0–34.0)	0.220
INR	1.57 (1.10–1.80)	1.85 (1.25–2.33)	0.050
Glucose, mg/dl	111.1 (85.0–120.0)	111.4 (96.5–121.5)	0.425
C-reactive protein, mg/dL	27.4 (2.00–24.00)	37.4 (2.30–46.40)	0.233
Echocardiography variables			
Ejection fraction, %	53.4 (50.0–60.0)	39.6 (30.0–45.0)	<0.001
LA anterior-posterior diameter, mm	42.0 (36.0–48.5)	45.2 (40.0–48.0)	0.204
LVEDD, mm	49.1 (46.0–53.0)	52.3 (45.0–59.0)	0.211
LVESD, mm	36.2 (32.0–41.0)	38.6 (33.0–45.0)	0.299
MR ≥+3, n (%)	23 (17.0)	2 (14.3)	1.000
TR ≥+3, n (%)	17 (12.6)	5 (35.7)	0.036
AR ≥+3, n (%)	9 (6.7)	2 (14.3)	0.276
AS ≥+3, n (%)	7 (5.2)	0 (0.0)	1.000
PASP, mm Hg	39.0 (35.0–45.0)	40.5 (30.0–50.0)	0.321
PFO, n (%)	28 (20.7)	2 (14.3)	0.435
Interatrial aneurysm, n (%)	14 (10.4)	3 (21.4)	0.202
LAA peak emptying velocity, cm/s	47.9 (36.0–62.0)	31.9 (20.0–38.0)	0.001

Continuous variables are presented as mean ± SD or median, nominal variables are presented as frequency (%). Abbreviations: WBC, white blood cell; MPV, mean platelet volume; BUN, blood urea nitrogen; TSH, thyroid-stimulating hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; AR, aortic regurgitation; AS, aortic stenosis; PASP, pulmonary artery systolic pressure; PFO, patent foramen ovale; LAA, left atrial appendix.

TABLE 3. UNIVARIATE AND MULTIVARIATE LOGISTIC REGRESSION ANALYSIS FOR THE PREDICTORS OF LEFT ATRIUM THROMBUS*

	Univariate analysis		Multivariate analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Age	0.011	1.063 (1.014 – 1.114)	-	-
MPV	<0.001	1.942 (1.351 – 2.793)	0.007	0.827 (0.723 – 0.947)
Creatinine	0.026	1.729 (1.066 – 2.804)	0.014	2.649 (1.219 – 5.755)
BUN	0.027	1.021 (1.002 – 1.040)	-	-
Ejection fraction	<0.001	0.807 (0.716–0.910)	0.006	1.874 (1.184 – 2.966)
LAA peak emptying velocity	0.008	0.922 (0.869–0.979)	0.043	0.939 (0.884 – 0.998)

*Binary logistic regression analyses using the backward LR method for multivariate analysis of the independent variables that were included if they were significantly different in univariate analyses (p < 0.05). OR: Odds ratio, CI: Confidence interval. Abbreviations: MPV, mean platelet volume; LAA, left atrial appendage.

with cardio-embolic risk in patients with cryptogenic stroke.

In our study, we also observed that MPV was another important predictor of LAT among these patients. MPV, which indicates platelet size, is useful to predict platelet function and activity. In an experimental study, it has been demonstrated that platelets with larger size show greater aggregation and release more thromboxane A2 and beta-thromboglobulin than smaller ones, which in turn result

in high prothrombotic potential[12]. In a single-center study that included 427 consecutive AF patients who had undergone TEE examination for the exclusion of LAT before cardioversion, Providência et al.[13] showed that elevated MPV was related to the presence of left atrial stasis in patients with non-valvular AF. In addition to this study, Turfan et al.[14] have found that AF patients with AIS might have higher MPV compared to those without stroke due to a high risk of cardio-embolism. Besides, in a systematic review and meta-analysis conducted by Chu et al.[15], it was shown that elevated MPV might have a potential link with acute myocardial infarction and restenosis following percutaneous coronary intervention. However, to our knowledge, there are no previous studies regarding the relationship between elevated MPV and LAT in AIS patients with sinus rhythm. This research, therefore, may provide novel information with respect to the applicability of MPV to predict LAT in AIS patients without AF.

We considered that our findings may be useful in terms of clinical applicability. A risk stratification system that enables identifying the patients who would require further TEE examination could be performed based on our study results. Particularly, AIS patients with sinus rhythm who had low left ventricle EF on TTE, higher creatinine value, and elevated MPV represented a high-risk group for LAT. Therefore, these patients should undergo further TEE examination to verify the possibility of a cardio-embolic source.

Study limitations

The present study has the following limitations: first, it was conducted in a single center with a limited number of patients. Second, the major limitation was the retrospective design, which might include selection bias. However, we tried to enroll all consecutive patients. Third, even though some parameters such as D-dimer, fibrinogen, and brain natriuretic peptide were shown to be related with thrombus formation in previous studies, we could not assess these parameters due to missing data. Finally, prospective, multicenter, randomized studies are needed to confirm our results.

CONCLUSION

Based on our study findings, low ventricle EF and elevated MPV were significant predictors for the presence of LAT in AIS patients without AF. Hence, in addition to a TTE evaluation and Holter monitoring, these patients should undergo further TEE examination to verify the possibility of a cardio-embolic source.

Conflict of interest

The authors have no conflicts of interest relevant for this article

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Author's Contribution

Concept: T.Ç. Design: T.Ç., V.Ç., M.İ.H. Supervision: N.K., A.L.O., M.M.A. Funding: M.M.A., V.Ç., N.K. Material: V.Ç., M.M.A. Data collection: V.Ç., T.Ç. Analysis: M.İ.H. Literature review: V.Ç., M.M.A. Writing: T.Ç. Critical review: N.K., A.L.O.

RESUMO

INTRODUÇÃO: *O presente estudo teve como objetivo determinar indicadores independentes do trombo auricular esquerdo (LAT) em doentes com acidente vascular cerebral isquêmico agudo (AIS) sem fibrilação auricular (AF) utilizando ecocardiografia transesofágica (TEE).*

MÉTODOS: *Neste único centro, estudo retrospectivo, inscrevemos 149 pacientes consecutivos com AIS. Todos os pacientes foram submetidos a exame de TEE para detectar LAT no prazo de dez dias após a admissão. A análise de regressão logística multivariada foi realizada para avaliar preditores independentes do final.*

RESULTADO: *Entre todos os casos, 14 pacientes (9,3%) tiveram um diagnóstico de exame tardio no TEE. Numa análise multivariada, volume médio de plaquetas (VMP) elevado, fração de ejeção do ventrículo esquerdo baixo (EF), creatinina e uma velocidade de pico de esvaziamento do átrio esquerdo reduzida (LAA) foram indicadores independentes da LAT. A área sob a análise da curva característica de operação do receptor para VMP foi de 0,70 (95% IC: 0, 57-0, 83; p=0,011). Com o valor-limite ideal de 9,45, o VMP teve uma sensibilidade de 71,4% e uma especificidade de 63% para prever mais tarde.*

CONCLUSÃO: *Os doentes AIS com EF ventricular baixa e VMP elevado devem ser submetidos a um exame de TEE adicional para determinar a possibilidade de origem cardioembólica. Além disso, esta investigação pode fornecer novas informações sobre a aplicabilidade do VMP para prever tardiamente os doentes sem AF.*

PALAVRAS-CHAVE: *Acidente vascular cerebral. Átrios do coração. Trombose. Volume plaquetário médio.*

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Association between vitamin D and cardioprotection in adult patients

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SUMMARY

OBJECTIVE: *To conduct a review of articles which have evaluated the relationship between vitamin D and cardioprotection in adult.*

METHODS: *A literature search was performed in the Pubmed and Scielo databases. The results were extracted from primary and secondary sources and will be presented in the form of a bibliographic review.*

RESULTS: *Twenty-three articles were identified from the electronic search that reported on physiological mechanisms relating the vitamin D axis and the cardiovascular system through receptors. Of the ten studies that evaluated the therapeutic effect of vitamin D in cardiovascular diseases, none reported significant results.*

CONCLUSION: *The articles assessed in this review did not demonstrate a cardioprotective effect of vitamin D, despite the epidemiological correlation of vitamin D deficiency with a higher prevalence of cardiovascular diseases.*

KEYWORDS: *Vitamin D; Cardiovascular disease; Therapeutics; Prognosis.*

INTRODUCTION

Vitamin D is a hormone which along with parathyroid hormone (PTH), is essential for the regulation of calcium and bone metabolism[1]. In addition, there are studies indicating that it is related to the pathogenesis of several diseases[1] (Table 1). In recent times, preliminary epidemiological findings from experimental studies have reported about the association of hypovitaminosis D with non-skeletal diseases. According to the recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) serum concentrations of vitamin D below 20 ng/mL (50 nmol/L) are classified as deficiency, between 20 and 29 ng/mL (50 and 74 nmol/L) as insufficiency and between 30 and 100 ng/mL (75 and 250 nmol/L) as normal[2].

Currently, the measurement of 25(OH)D is not recommended for the general population[2]. However, it is recommended for the diagnosis of disability in individuals belonging to populations at risk or those in whom the clinical situation correlates with vitamin D[2]. According to SBEM, candidates for 25(OH)D measurement would be the following groups: patients with rickets or osteomalacia, osteoporosis, elderly patients with a history of falls and fractures, obese people, pregnant women and infants, patients with malabsorption syndromes (cystic fibrosis, inflammatory bowel disease, Crohn's disease, bariatric surgery), renal or hepatic insufficiency, hyperparathyroidism, patients taking medications that interfere with vitamin D metabolism (anticonvulsants, glucocorticoids, antifungals, antiretrovirals, cholestyramine, orlistat), and those with granulomatous diseases and lymphomas[2].

However, studies indicate that subjects above 35 years of age with vitamin D deficiency had a higher risk of death from cardiovascular disease (CVD) than those with normal level[3]. There is evidence that subjects with chronic conditions had lower levels of vitamin D levels than those without chronic conditions[3]. Some epidemiological studies indicated that vitamin D is a better predictor of risk for coronary disease than

diastolic blood pressure (AP) in the elderly[4]. Vitamin D is inversely proportional to BP, if BP is higher, vit D is lower and vice-versa[4].

The objective of this study was to review the cardioprotective action of vitamin D.

METHODS

Systematic and traditional reviews of the literature, meta-analyses, and major clinical trials about the relationship between vitamin D and cardiovascular diseases were searched in the Pubmed and Scielo databases. The results of information collected from primary and secondary sources, will be presented in the form of a bibliographic review. A search using the terms "Vitamin D" AND "Cardiovascular Diseases" AND "Drug Therapy", and "Vitamin D" AND "Cardiovascular Diseases" AND "Prognosis" was performed.

The inclusion criteria for the articles selected for this review were the presence of the above terms in the title or abstract of the articles; from these, articles published in English or Portuguese with the full text available for selected for the analysis. After analyzing the entire specific bibliography, consolidated findings of the research were grouped by clinical situations; the

TABLE 1

Study	Type of study	Total participants	Posology	Conclusion
Witte, et al[16]	ECR	Group A: Vitamin D3 Group B:Placebo Total: 223 patients	A: Vitamin D3 of 4000 IU daily for one year B: Calcium-free placebo	There was no improvement in the 6-minute walk distance, but vitamin D3 had beneficial effects on the structure and function of the left ventricle in patients under contemporary medical therapy
Gepner D, et al[17]	ECR	Group A: Vitamin D3 Group B:Placebo Total: 114 patients	A: Vitamin D3 2500 IU daily for four weeks B: Placebo	There was no improvement in endothelial function, arterial stiffness or inflammation
Bernini G, et al[18]	ECR	Total: 38 patients	A: Calcitriol 0.25 μg for one week B: Angiotensin II receptor antagonist and a single dose of cholecalciferol at 300,000 IU for eight weeks	Activation of vitamin D receptor does not influence the systemic activity of the renin-angiotensin system
Nsengiyum-va V, et al[19]	RS	Total: 8 articles with 529 participants	Vitamin D3 in the following posologies: 100,000 IU single dose for 8 weeks 200,000 IU single dose for 16 weeks 100,000 IU single dose for 16 weeks 2000 IU daily for 16 weeks 4000 IU daily for 12 weeks 2500 IU daily for 4 months, 5000 IU daily for 12 weeks Only one study described the use of paracalcitriol capsule in the dosage of 2 μg	More clinical trials are necessary to confirm or reject the benefit of vitamin D3 in endothelial dysfunction
Whitham, et al[23]	ECR	Group A: Patients using 3 antihypertensive agents submitted to vitamin D3 therapy Group B: Placebo Total: 68 participants	A: Vitamin D3 at 100,000 IU every two months B: Placebo	No reduction in blood pressure or left ventricular mass in patients with resistant hypertension

ECR: Randomized clinical trial; RS: Systematic review.

findings were then homogenized for presentation of the results and to define the conclusions.

Vitamin D metabolism

The endocrine system of vitamin D is formed by secosteroid molecules derived from 7-hydrocholesterol (7-DHC), its carrier, and receptor proteins[5]. This metabolic axis plays a fundamental role in the regulation of osteomineral physiology, modulation of autoimmunity, synthesis of inflammatory interleukins, blood pressure control, and participates in the process of multiplication and cell differentiation[5]. Synthesis of the active form of vitamin D (1α,25-dihydroxyvitamin D or calcitriol), starts in the epidermis by a photolytic reaction mediated by B5 ultraviolet rays. The precursor of calcitriol reaches the liver through the circulation, where, after conversion of enzymes of the P450 family it becomes 25-hydroxyvitamin D3 or calcidiol[6].

Calcidiol is the most stable metabolite of vitamin D[6]. Calcidiol is converted to calcitriol by the epithelial cells of the renal proximal tubules[6]. Its synthesis is stimulated by PTH and is inhibited by the fibroblast growth factor 23 (FGF23) produced in osteocytes[7]. A fall in 25(OH)D3 stimulates PTH production[7]. Vitamin D is also closely related to factors such as age, obesity, smoking, and a sedentary lifestyle[8]. Besides affecting vitamin D, these are risk factors for cardiovascular disease, which raises the possibility that variations in vitamin D levels are a consequence, not the cause of disease or disease precursor states[8].

The endocrine system of each individual varies according to some external factors, which might be another cause of discrepancy in the data analysis of large populations[8]. Vitamin D levels are impacted by seasonal variation that influences the amount exposure to sunlight, and color of the skin in which melanin influences the photolytic reaction[9]. Hence, the level of vitamin D is lower in people with dark skin[9].

Effect on heart activity

Vitamin D receptor (VDR) exists in several systems[10]. Its spectrum of action is very broad, and studies with microarray show more than 900 potential target genes, corresponding to about 3% of the human genome[10]. Some of the organs and systems it acts on include: brain, parathyroid gland, lung, heart, bones, lymphatic system, arterial system, liver, pancreas, etc[11]. In the cardiovascular system, vitamin D suppresses the renin-angiotensin-aldosterone (SARS) system, thus controlling the increase in blood pressure[11].

In 2002 Li et al. performed an in vivo study of expression of the renin gene in mice by suppressing the VDR, and evaluated the blood pressure (BP) and angiotensin II activity[11]. The analysis revealed significantly higher diastolic BP and systolic BP (> 20 mmHg) in mice with suppressed VDR[12].

The deletion of the VDR can affect the relaxation of blood vessels and increase the hypertensive effects of Angiotensin 2 (AngII) infusion[13]. VDR is present in the myocardium and cells of the coronary arteries, which supports a possible pathophysiological mechanism for the association between hypovitaminosis D and cardiovascular diseases[14]. Vitamin D promotes the proliferation of cardiomio tubules and inhibits the cardiomyoblasts to terminate the cell cycle without inducing apoptosis[15]. VDR also facilitates rapid non-genomic responses by inducing voltage-dependent calcium channels, leading to an increase in the cellular calcium inflow and activation of other messengers, such as cyclic AMP, protein kinase A, and phospholipase C[15]. Cardiovascular reflexes of the dynamic kidney bone influence the renal metabolism of phosphate and vitamin D[14]. The growth factor for fibroblasts, a secretory protein expressed in osteoblasts and osteocytes is associated with vascular dysfunction, ventricular hypertrophy, and incident CVD[10].

What the evidence says

Vitamin D can be found in the form of ergocalciferol or vitamin D2, and cholecalciferol or vitamin D3[2]. Vitamin D2 can be obtained from yeasts and plants, and is produced for commercial use by irradiation of ergosterol present in mushrooms[2]. In Brasil, the most commonly available form of vitamin D for treatment and supplementation is cholecalciferol, and this is the metabolite that has proven to be most effective[2]. As a rule of thumb, it can be predicted that for every 100 IU supplemented, an increase of 0.7 to 1.0 ng/mL in calcidiol concentration is expected[2] (Table 2).

A randomized clinical trial conducted in the United Kingdom by K. Witte et al[16] in 2016, included a total of 223 patients. Two groups were analyzed: placebo group and vitamin D group. Vitamin D3 was administered at a dose of 4,000 IU daily for one year compared to placebo, without calcium. The authors concluded that daily administration of 4,000 IU of vitamin D3 for one year does not improve the 6-minute walking distance, but has beneficial effects on the left ventricular structure and function in patients under contemporary medical therapy.

TABLE 2

Age ranges	General population (IU)	At Risk population (IU)
0 - 12 months	400	400 - 1.000
1 - 8 years	400	600 - 1.000
9 - 18 years	600	600 - 1.000
19 - 70 years	600	1.500 - 2.000
> 70 years	800	1.500 - 2.000
Pregnant women 14 - 18 years	600	600- 1000
Pregnant women >18 years	600	1.500 - 2.000
Infants 14 - 18 years	600	600 - 1.000
Infants > 18 years	600	1.500 - 2.000

IU= International Units

FIGURE 1. ROLE OF VITAMIN D IN THE PATHOPHYSIOLOGY OF THE HEART DISEASES
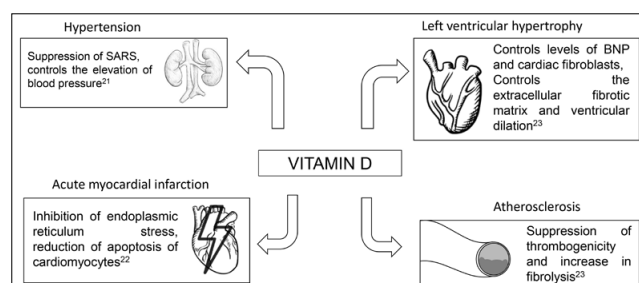
SRAA: Renin-angiotensin-aldosterone system; BNP: Atrial natriuretic peptide.

A randomized clinical trial conducted in the United States by Gepner D et al.[17] in 2012, included a total of 114 participants. Two groups were analyzed: one group received vitamin D3 and the other group received placebo. In the first group, vitamin D3 was administered at a dose of 2,500 IU daily for four weeks. The authors concluded that vitamin D3 supplementation did not improve the endothelial function, arterial stiffness, or inflammation.

A randomized clinical trial conducted in Italy by Bernini G, et al.[18] in 2014 included a total of 38 participants. Two groups were analyzed. One group received calcitriol at a dose of 0.25 μg for one week, while the other group received angiotensin II receptor antagonist therapy and a only one dose of cholecalciferol at a dose of 300,000 IU for eight weeks. The authors concluded that VDR activation does not influence the systemic activity of the renin-angiotensin system.

A systematic review by Nsengiyumya et al.[19], published in 2015, analyzed eight studies with a combined sample size of 529 participants. In these studies vitamin D3 was administered in different dosages: 100,000 IU only one dose for 8 weeks, 200,000 IU only onde dose for 16 weeks, 100,000 IU only one dose for 16 weeks, 2000 IU daily for 16 weeks, 4,000 IU daily for 12 weeks, 2,500 IU daily for 4 months, and 5,000 IU daily for 12 weeks. They concluded that more clinical trials are necessary to confirm or reject the benefit of vitamin D3 in endothelial dysfunction.

A randomized clinical trial conducted by Whitham et al.[23] in the United Kingdom in 2014, included a total of 68 participants. Patients with BP more than 140/90 mm Hg and taking three antihypertensive agents were divided into two groups: one group received vitamin D3 and the other received placebo therapy. Subjects in the first group were administered vitamin D3 at a dose of 100,000 IU every two months. They concluded that oral vitamin D3 did not reduce the BP or left ventricular mass in patients with malignet hypertension.

Concluding remarks

The cardiovascular and renal systems are known to be closely related. The progression of a cardiovascular pathological state involves SARS dysfunction and systemic inflammation that can lead to fluid regulation disorders, which in turn can lead to endothelial dysfunction and myocardial fibrosis. The risk factor in this cycle is a sedentary lifestyle and inadequate nutrition. In addition, the influence of VDR activation on the systemic level of SARS is not well established. It is possible that the supposed causality between vitamin D and CVD is an indicator of active disease. Hypovitaminosis D would actually be a consequence and not a cause of cardiovascular disease. In addition, chronic diseases can lead to reduced exposure to the sun, sedentary lifestyle, poor dietary intake, poor nutritional status, and thus lower vitamin D levels.

Clinical trials in this area show conflicting results and authors differ on the therapeutic window for vitamin D supplementation, age, ethnicity, and region. It is not clear if vitamin D has an effect in cases with already established disease.

CONCLUSION

The articles used in this review did not demonstrate a cardioprotective effect, despite the association of vitamin D deficiency and higher prevalence of cardiovascular diseases in epidemiological studies.

Author's Contribution

Conception of the idea Gabriel Cavalcante Ferraz; Data collect Gabriel Cavalcante Ferraz, Raul Ribeiro de Andrade; Data analysis and interpretation Gabriel

Cavalcante Ferraz, Fernando Minervo Pimentel Reis, Olavo Barbosa de Oliveira Neto; Manuscript writing Gabriel Cavalcante Ferraz, Clisivaldo Oliveira de Omena; Relevant critical review of intelectual contente - Gabriel Cavalcante Ferraz, Mário Jorge Jucá, Célio Fernando de Sousa-Rodrigues; Final approval of the version to be published - Gabriel Cavalcante Ferraz, Fabiano Timbó Barbosa.

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Inflammatory Bowel Diseases and diet: an integrative review

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SUMMARY

OBJECTIVE: *To gather scientific evidence on the role of diet in inflammatory bowel diseases.*

METHODS: *Integrative review with studies published in the last 10 years in national and international journals. Original studies developed with adult human beings aged ≥18 years were included and articles published before 2010, literature reviews, and those that did not focus on elements that answered the guiding question were excluded.*

RESULTS: *14 articles were selected that addressed important dietary elements in inflammatory bowel disease such as fermentable carbohydrates and polyols, foods of animal origin, foods rich in omega 3, consumption of fruits and vegetables, use of probiotic supplements, whey proteins and soy.*

CONCLUSION: *The diet, as a potentially modifiable environmental factor, plays an important role in the prevention and treatment of inflammatory bowel diseases. The reduction in the consumption of fermentable carbohydrates and polyols combined with the increase in the consumption of fruits and vegetables as well as the exclusion of products of animal origin such as beef, pork, milk and eggs can help control inflammation and improve the quality of life of patients with inflammatory bowel diseases. The use of probiotics increases food tolerance and, whey and soy proteins, can alter body composition and reduce inflammation.*

KEY WORDS: *Inflammatory bowel diseases. Diet. Environmental Factors*

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a group of chronic idiopathic inflammatory diseases of the gastrointestinal tract, with symptoms that progressively recur, Crohn's disease (CD) and ulcerative colitis (UC) are the most common clinical forms of IBD[1]. They are diseases distributed worldwide and represent a significant burden on the health systems in the 21st century. The prevalence of IBDs varies considerably between countries, being more in Europe (CD:322/100,000 inhabitants in Germany; UC:505/100,000 inhabitants in Norway) and in North America (CD: 319/ 100,000 inhabitants in Canada; UC: 286/100,000

inhabitants in the United States). However, in recent decades, there have been steady increases in South America, Africa and Asia[2].

The exact etiopathogenic mechanism of IBD remains unclear, however, it is currently believed that homeostasis between microbiota, intestinal epithelium and immune cells is interrupted by genetic and environmental factors, such as the use of antibiotics, smoking, stress and diet, thus possibly leading to a chronic state of unregulated inflammation[3]. The assumption that the pathogenesis of IBD is significantly influenced by environmental factors has aroused great interest in the identification of potentially modifiable factors for the prevention and treatment of IBD. Constituting one of the bases of this assumption is dysbiotic changes in the intestinal microbiota. In this context research with approaches to manipulating microbiomes has been emphasized, such as the use of prebiotics[4], probiotics[5,6], fecal microbiota transplantation[7] and diet, have been emphasized as possible therapeutic strategies [8].

In the universe of environmental factors, diet is believed to play an important role in the development of IBD. Although the precise pathophysiological mechanisms remain unknown, many credible explanations have been proposed. First, the diet plays a fundamental role in defining the composition of the human intestinal microbiota and, thus, microbial metabolites[9]. Second, the foods and nutrients associated with the Western diet, characterized by high consumption of red meats, sugary desserts, and foods high in fat and refined grains, have been linked to increased mucosal inflammation, as measured by the fecal calprotectin in humans[10]. Also, experimental studies have shown that the composition of the diet regulates the function of the mucosal barrier, a crucial factor in the pathogenesis of IBD[11,12].

OBJECTIVE

The aim of this study was to gather scientific evidence on the role of diet in inflammatory bowel diseases.

METHODS

The study consists of an integrative literature review, built from original articles that addressed the role of diet in IBD. The study was conducted from January 5th to 15th, 2020. The elaboration of the manuscript was carried out in stages:

1) Definition of the guiding question: carried out using the PICO strategy, an acronym that represents a problem or population (P), intervention (I), comparison (C) and outcome (O). Thus, the resulting guiding question was: What is the role of diet in inflammatory bowel diseases?

2) Adoption of inclusion and exclusion criteria: Original articles, published in national and international journals, in the last 10 years (2010-2020), carried out with adult human beings (age ≥18 years) were included. Articles published before 2010, literature reviews, and those that did not focus on elements that answered the guiding question were excluded.

3) Search strategy: PubMed, Science Direct and Scielo databases were used to search for articles, using descriptors in Health Sciences (DeCs): Diet and Inflammatory Bowel Disease.

4) Selection of articles: The selection of articles was conducted by two authors independently, and in case of doubt, a third party was consulted. Initially, the titles and abstracts of the selected articles were analyzed to assess whether they met the inclusion and exclusion criteria, and in case of doubt, they were read in full.

RESULTS

According to the pre-established search criteria, the bibliographic search initially resulted in 61 articles (51 from Pub Med, 09 from Science Direct and 01 from Scielo). After reading the title and summary and applying the inclusion and exclusion criteria, 18 articles were selected (14 from Pub Med, 04 from Science Direct). Through the complete reading of the articles, 14 articles were integrated into the study review at the end (12 from Pub Med and 02 from Science Direct) as shown in Figure 1. After the careful selection process of the articles to be included in this review, the main information was extracted from them, which as grouped in Figure 2.

DISCUSSION

The analyzed studies showed that several dietary components play important roles in IBD. The use of prebiotics with a beneficial effect on gastrointestinal symptoms and food tolerance in patients with UC[14], as well as a study by James et al.[21], showed that intestinal fermentation of non-starch polysaccharides and starch is reduced in patients with UC, which was not

FIGURE 1. FLOW DIAGRAM. REGINA MÁRCIA SOARES CAVALCANTE ET AL., 2020.
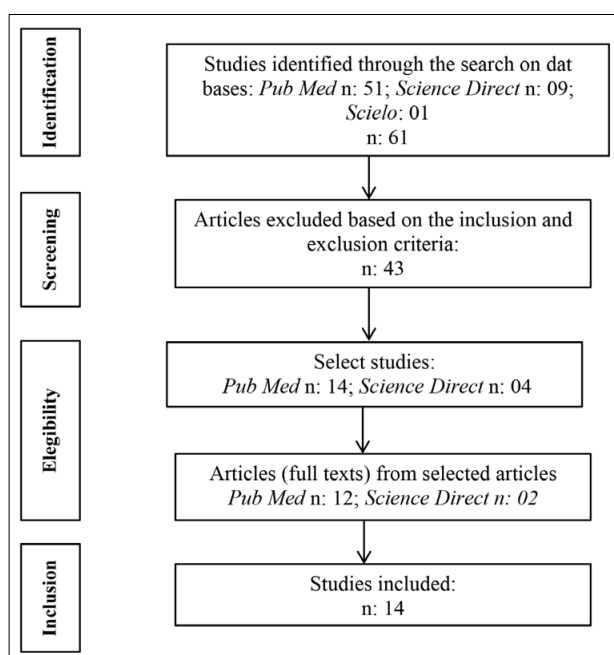
explained by the abnormal intestinal transit and was not corrected by the increased intake of resistant starch/wheat bran. However this can be attributed to the abnormal functioning of the intestinal microbiota.

Diet has a strong connection with the composition of the human intestinal microbiome and microbial metabolites[27]. The genetic *loci* that are related to the risk of developing IBD can be categorized according to abnormalities in the innate and/or adaptive immune response as well as in the function of the mucosal barrier[28]. Experimental data also suggest that many of these pathways are likely to be influenced by dietary factors[29]. Scientific literature has shown in recent years the growing interest in the use of commensal bacteria or bacteria present in fermented foods, called probiotics, to modulate the intestinal microbiota as well as provide positive effects on the immune system[30,31]. A study by Astó et al.[32] showed that the use of probiotics seems to be beneficial in achieving remission in patients with UC, using the UCDAI (Ulcerative Colits Disease Activity Index) and DAI (Disease Activity Index) scales to evaluate disease activity as recommended by the FDA for UC clinical trials with pharmaceuticals. It also revealed that probiotics containing bifidobacteria are apparently the most beneficial.

In addition, diet and prebiotics can affect the microorganism-microorganism and microorganism-host interaction, since in addition to the nutritional functions they can also restore intestinal homeostasis and the integrity of the epithelial barrier [33].

Another highlight among the selected studies was the role of FODMAPs in IBD. A diet low in FODMAPs (oligosaccharides, disaccharides, monosaccharides and fermentable polyols) reduced the typical symptoms of IBDs and increased the quality of life in patients with IBD in remission[16]. From this perspective, a study by Cox et al.[17] demonstrated that the use of relatively high doses of fructans, except GOS (galacto- oligosaccharides) or sorbitol, exacerbated functional gastrointestinal symptoms-FGS in patients with IBD in remission. Following this line, a survey conducted by Racine et al.[19] with 1866 people (376 cases and 1490 controls), revealed that there was a positive association between a pattern of consumption of "high sugar and soft drinks" and the risk of UC. When considering foods more associated with the standard, consumers of foods with high sugar and soft drinks were at a higher risk of UC only if they had a low intake of vegetables.

With regard to sugars, FODMAPs, which are highly fermentable carbohydrates and polyols, but little absorbed, were first described in 2005, when the hypothesis was suggested that the rapid fermentation and passage of these substances led to an increase in intestinal permeability, which has been identified as a predisposing factor to IBD in individuals with a genetic predisposition[34].

With respect to the role of fruits and vegetables, this review presents a study developed by Kim et al.[13], showing that enriching the diet with mango (*Mangifera indica L*) or other foods potentially rich in gallotannin seems to be a promising adjuvant therapy when combined with medications in the treatment of IBD, by reducing inflammation biomarkers and modulating the intestinal microbiota. In this area, a study by Chiba et al.[26] showed that the adoption of a semi-vegetarian diet was highly effective in preventing relapses in patients with CD.

Regarding the consumption of proteins and fats of animal origin, this review found five studies that addressed this topic. Research carried out by Albenberg et al.[15], showed that a substantial reduction in the consumption of red and processed meat among patients with asymptomatic CD was not effective in reducing the time of symptomatic relapse. In contrast, research developed by Gunasekeera et al.[18], concluded that the exclusion diet (milk, beef, pork and egg) guided by IgG4, as an adjuvant, can improve the quality of life and symptoms in patients with CD. In this sense, a study by Machado et al.[20], showed that

FIGURE 2. CHARACTERISTICS OF STUDIES INCLUDED IN THE INTEGRATIVE REVIEW. REGINA MÁRCIA SOARES CAVALCANTE ET AL., 2020.

Authors/year	Sample(n)	Study Design	IBD	Outcomes
Kim et al.[13], 2020	10	Clinical trial	CD UC	The enrichment of the diet with mango (Mangifera indica L) or other foods potentially rich in galotanin seems to be a promising adjuvant therapy combined with conventional drugs in the treatment of IBD, by reducing inflammation biomarkers and modulating the intestinal microbiota.
Sánchez-Morales et al.[14], 2019	34	Clinical trial	UC	The administration of a combination of 6 probiotic strains in patients with UC has shown a short-term beneficial effect on gastrointestinal symptoms, histological findings and food tolerance.
Albenberg et al.[15], 2019	214	Prospective randomized study	CD	The substantial reduction in the consumption of red and processed meat among patients with asymptomatic CD was not effective in reducing the time of symptomatic relapse
Pedersen et al.[16], 2017	99	Randomized controlled study	CD UC	A diet low in FODMAP (Oligosaccharides, Disaccharides, Monosaccharides and fermentable Polyols) reduced the typical symptoms of IBDs and increased the quality of life in patients with IBD in remission.
Cox et al.[17], 2017	32	Randomized, double-blind controlled study	CD UC	The relatively high doses of fructans used, but not GOS (galacto oligosaccharides) or sorbitol, exacerbated FGS (functional gastrointestinal symptoms) in patients with IBD in remission.
Gunasekeera et al.[18], 2015	76	Randomized, double-blind, controlled study	CD	The exclusion diet (milk, beef, pork and egg) guided by IgG4, as an adjuvant, can improve quality of life and symptoms in patients with CD.
Racine et al.[19], 2016	1866	Prospective cohort	CD UC	There was a positive association between a pattern of consumption of "high sugar and soft drinks" and the risk of UC. Consumers of sugar and soft drinks were at higher risk for UC only if they had a low intake of vegetables.
Machado et al.[20], 2015	68	Randomized parallel clinical trial	CD	For patients with CD undergoing anti-TNF-alpha and azathioprine therapies, supplementation with whey and soy proteins alters body composition by reducing body fat and contributes to controlling inflammation.
James et al.[21], 2015	37	Randomized, blinded, crossover clinical trial	UC	Intestinal fermentation of non-starch polysaccharides and starch is decreased in patients with UC, which is not explained by abnormal intestinal transit and has not been corrected by increased intake of resistant starch / wheat bran, which can be attributed to the abnormal functioning of intestinal microbiota.
Kyaw et al.[22], 2014.	112	Clinical trial case-control	UC	A probable link between dietary advice and symptomatic improvement is suggested. The effect of the diet may not occur through the addition or elimination of unique nutrients; instead, each food consumed combines many nutrients that allow synergistic or antagonistic action when present in a given composition.
Brotherton et al.[23], 2014	44	Randomized, blinded, case-control clinical trial	CD	It is suggested that diet modification may be a welcome complementary therapy for individuals who suffer from gastrointestinal disorders associated with CD.
Grimstad et al.[24], 2011	12	Clinical Trial	UC	Ingestion of Atlantic salmon may have beneficial effects on disease activity in patients with mild UC, based on SCCAI (simple clinical colitis activity index) and AIFAI (anti-inflammatory fatty acid index) and a tendency for increased levels of PCR and homocysteine.
Nolan-Clark et al.[25], 2011	165	Analytical observational study	CD	Dairy products in general had no effect on the symptoms of CD, but items with a high fat content were reported more frequently in worsening the perceived symptoms of CD.
Chiba et al.[26], 2010	22	Prospective clinical study	CD	The semi-vegetarian diet was highly effective in preventing recurrences of CD

supplementation with whey and soy proteins altered body composition by reducing body fat and, therefore, contributed to control inflammation in patients with CD submitted to anti-TNF-alpha and azathioprine therapies. Clinical trial developed by Grimstad et al.[24], revealed that the consumption of Atlantic salmon can have beneficial effects on the activity of the disease in patients with mild UC, based on evidence of the simple clinical colitis activity index - SCCAI and anti-inflammatory fatty acid index-AIFAI and a trend towards increased levels of CRP and homocysteine. Research by Nolan-Clark et al.[25] found that dairy products, in general, had no effect on the symptoms of CD. However, items with a high fat content were reported more frequently in worsening the perceived symptoms of the disease.

In the pathogenesis of IBD, the importance of the role played by the diet resides in the impact that it can cause in the modulation of clinical symptoms, in the alteration of the intestinal microbiota, and in the improvement of the style and quality of life of those with these diseases[34]. Studies have shown that the adoption of a "westernized" lifestyle, characterized by a diet with a high content of total fats (especially animal fats rich in saturated fatty acids, such as meat and milk fats; foods rich in fatty acids in the series omega-6), refined sugars (rich in monosaccharides and disaccharides) and proteins, and with a low content of fruits and vegetables, potentially increases the risk of developing IBD[35]. On the other hand, a diet rich in fruits and vegetables, rich in omega-3 fatty acids and low levels of omega-6 fatty acids have been linked to a decrease in the risk of developing CD or UC[36].

In this sense, to assist in the treatment of IBD, changes in the diet as well as nutritional counseling by a professional trained for this purpose, are necessary. The importance of adopting these measures was evidenced in two studies that integrated this review. A case-control study conducted by Brotherton et al.[23], suggested that diet modification may be a welcome complementary therapy for individuals with gastrointestinal disorders associated with CD. A similar study regarding the design, developed by Kyaw et al.[22], suggests that it is likely that there is a link between dietary advice and symptomatic improvement of UC. The effect of the diet may not occur through the addition or elimination of unique nutrients; instead, each food consumed combines many nutrients that allow synergistic or antagonistic action when present in a given composition.

There is growing evidence to suggest a role for diet in the development of IBD, particularly among genetically susceptible individuals[37]. According to Lee et al.[38], dietary interventions can be used to treat patients with active IBD, maintain their remission or even prevent this disease

CONCLUSION

The pathogenesis of inflammatory bowel diseases, despite having numerous gaps is centered on the breakdown of homeostasis between the intestinal microbiota, the epithelial barrier and immune cells. Currently, it is believed that the interruption of homeostasis is caused by genetic and environmental factors (such as the use of antibiotics, smoking, stress and diet). The role of the diet in these inflammatory diseases has been the focus of many studies, considering that it constitutes a potentially modifiable factor both in the prevention and treatment of these pathologies. Scientific evidence from the past ten years has shown that high consumption of fermentable carbohydrates and polyols combined with low consumption of fruits and vegetables can exacerbate functional gastrointestinal symptoms, and increase the risk of developing IBD and that the gallotannin present in mango can help in controlling inflammation and modulating the intestinal microbiota. The consumption of salmon, rich in omega 3, as well as the exclusion of foods of animal origin such as milk, beef, pork and eggs has beneficial effects that can improve the symptoms of the disease and the quality of life. In relation to supplementation, probiotics can be used to alleviate some symptoms, such as increasing food tolerance. Supplements with whey protein and soy can help control inflammation by altering body composition. Therefore, this information can support more precise dietary guidelines and assist in the prevention and treatment of inflammatory bowel diseases.

Author's Contribution

Regina Márcia Soares Cavalcante: conceptualizacion, writing and original draft preparation, research, systematization and analysis of data and final review; Murilo Moura Lima: partial review; José Miguel Luz Parente: partial review; Mayara Storel Beserra de Moura: research, systematization of data; Nadir do Nascimento Nogueira: final review.

RESUMO

OBJETIVO: *Reunir evidências científicas sobre o papel da dieta nas doenças inflamatórias intestinais.*

MÉTODOS: *Revisão integrativa com estudos publicados nos últimos 10 anos em periódicos nacionais e internacionais. Foram incluídos estudos originais desenvolvidos com seres humanos adultos com idade ≥18anos e excluídos artigos publicados antes de 2010, revisões de literatura, e os que não apresentassem como foco elementos que respondessem a pergunta norteadora.*

RESULTADOS: *Foram selecionados 14 artigos que abordaram elementos dietéticos importantes na doença inflamatória intestinal como carboidratos e polióis fermentáveis, alimentos de origem animal, alimentos ricos em ômega 3, consumo de frutas e vegetais, uso de suplementos com probióticos, proteínas do soro do leite e soja.*

CONCLUSÃO: *A dieta, como fator ambiental potencialmente modificável desempenha importante papel na prevenção e tratamento das doenças inflamatórias intestinas. A redução no consumo de carboidratos e polióis fermentáveis aliado ao aumento do consumo de frutas e vegetais como também a exclusão de produtos de origem animal como carne bovina, carne suína, leite e ovo podem auxiliar no controle da inflamação e melhoria da qualidade de vida dos pacientes com doenças inflamatórias intestinais. O uso de probióticos aumenta a tolerância alimentar e, proteínas do soro do leite e soja, podem alterar a composição corporal e reduzir a inflamação.*

PALAVRAS-CHAVE: *Doenças inflamatórias intestinais. Dieta. Fatores Ambientais*

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Scientific production in oncological palliative care with emphasis in communication

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SUMMARY

Communication is a facilitating tool in palliative care, enabling the development of a therapeutic process based on universal humanistic values, with benefits for the team, cancer patient, and family. This theme is of great importance and highlights the significant contributions to clinical practice in the context of palliative care in oncology with an emphasis on communication.

KEYWORDS: *Palliative Care. Medical Oncology. Communication. Review.*

INTRODUCTION

Communication is a fundamental therapeutic modality that goes far beyond words and content, contemplating also non-verbal signs and expressed by attentive listening, eye contact, and professional posture[1]. Communication improves the bond between the patient-team-family triad. In addition, it allows patients to express their decisions and maintain social contact, thus their wishes can be met up to the end of their lives[1].

Considering the importance of palliative care in oncology with an emphasis on communication for healthcare academia, as well as for the medical practice, it is particularly important to develop studies that seek to highlight the scientific production on this subject. Faced with this context, this research aims to: Analyze the scientific production on palliative care in oncology, with an emphasis on communication and contributions to clinical practice.

METHODS

This is an Integrative Literature Review that aims to summarize publications systematically and rigorously, allowing to characterize and disseminate the knowledge produced. This review aimed to answer the following question: what was the scientific production on palliative care in oncology with an emphasis on communication for clinical practice between 2010 and 2017? Works published as scientific articles in the languages: Portuguese, English, and Spanish.

The selection of papers was carried out based on searches in the following databases: *Literatura Latino Americana e do Caribe em Ciências da Saúde* (LILACS) and Public/Publish Medline (PubMed), upon searching the *Biblioteca Virtual em Saúde* (BVS) of the Latin American and Caribbean Center on Health Sciences Information (BIREME). We used the following descriptors of the Database, Cinahl Headings (MeSH), and of the Health Sciences Descriptors (DeCS), all of which were associated with the boolean operator "AND". "Palliative care" "oncology" "communication" "cuidados paliativos" "oncologia" "comunicação". Thus, considering all the publications identified in

previously mentioned databases, 22 publications met our criteria.

Once the study sample was identified, to facilitate the process of organization for the collection of information relevant to the objectives of the present study, we used a form previously prepared by the researchers which allowed obtaining information on the characterization of the studies, approaches to the theme investigated, and contributions for clinical practice.

RESULTS

The study sample was comprised of 22 papers on palliative care in oncology and communication. Most publications were from 2017, i.e., 18.18%. Regarding the databases, most studies were found on LILACS, with a percentage of 72.9%. With respect to journals, important health magazines were the most prominent, most in the medical area, among which the following deserve to be highlighted: Journal of Palliative Medicine, Palliative Support Care, European Journal of Cancer Care, and the Journal of Clinical Oncology,

TABLE 1. DISTRIBUTION OF THE STUDIES PUBLISHED BY TITLE, OBJECTIVES, AND CONCLUSION REGARDING CATEGORY I - PALLIATIVE CARE IN ONCOLOGY: STUDIES ON COMMUNICATION MODALITIES. N=22

Title	Objectives	Conclusion
Communicating bad news: an Integrative Review of the nursing literature	Describe the process of communicating bad news and identify how nurses communicate bad news.	Nurses' approach and ability to transmit messages influence the reaction of patients to information.
Comunicação interpessoal com pacientes oncológicos em cuidados paliativos	Understand the process of interpersonal communication in patients' course of palliative care based on Peplau.	The needs felt by patients were met through effective communication.
A comunicação na transição para os cuidados paliativos: artigo de Revisão	Present a brief Review of the national and international literature on communication during the transition from curative care to palliative care in oncology	The main focus of the published studies was to prepare professionals for better communication and interpersonal relationships, promote greater safety and perception of their self-efficacy regarding patients, family members, and members of multidisciplinary teams.
Comunicação terapêutica na Enfermagem: dificuldades para o cuidar de idosos com câncer	Assess the difficulties and their causes, from the nurses' perspective, in providing assistance to the elderly with oncologic pathologies.	Nurses showed positive feelings, acknowledging the importance of developing skills, such as therapeutic communication, that can help patients to have quality in palliative care.
Compassionate Honesty	Report on communication in palliative care	Honest communication of the clinical reality allows patients to make better-informed decisions about treatment options.
Comunicação de Más Notícias	Present suggestions for action on the verbal and non-verbal dimensions of interpersonal communication that allow reducing patient, family, and professional stress and anxiety.	People need to know the truth throughout their lives, not only in the end, out of respect, so they can develop autonomy and free-will.
Morte: o difícil desfecho a ser comunicado pelos médicos	Understand, from a physicians' perspective, the process of communicating bad news.	Considering the massive denial around death and its interdiction, it is easy to understand how difficult it is to demand a dying patient to look at death and to communicate it to their loved ones.
Comunicação de más notícias pelos médicos no primeiro ano de internato: um estudo exploratório	Explore the perspective of new interns regarding their preparation to communicate bad news and regarding the characteristics of medical programs curricula considered desirable for an adequate formation	To improve the preparation of new interns in communicating bad news the emotional aspects of the process must be approached.

which approach topics on palliative care practice and oncology. Most researchers on the subject were doctors (58%), followed by the nurses.

Regarding the approach adopted in the studies of the sample, qualitative research was the most frequently used (50%). The studies were conducted, in most cases (45%), in hospitals. All of the keywords used in the studies were indexed in the DeCs (*Descritores em Ciências da Saúde*) and/or the Medical Subject Headings (MeSH).

The analysis of the studies allowed us to divide them into thematic categories, namely: communication modalities were emphasized in 36% of the studies; 40% were on communication instruments and strategies; and the communication between patients and family caregivers was the focus of 24% of the publications, as presented in Tables 1, 2, and 3.

DISCUSSION

Based on the analysis of information, the studies were grouped into categories to better understand and analyze the discussion, as shown in Tables 1, 2, and 3. With the purpose of summarizing the findings, we will present a brief discussion of each category listed below.

Regarding the communication modalities (Table 1), the methods for transmitting a message using both verbal and non-verbal communication, and the effectiveness in using them when communicating bad news is a significant ability in clinical practice that should be optimized by professionals in the palliative team.

The communication of bad news causes impacts, but there are meager findings in the literature regarding the performance of nurses in this respect, particularly in publications that relate to chronic, progressive,

TABLE 2. DISTRIBUTION OF THE STUDIES PUBLISHED BY TITLE, OBJECTIVES, AND CONCLUSION REGARDING CATEGORY II - PALLIATIVE CARE IN ONCOLOGY: STUDIES ON COMMUNICATION STRATEGIES AND INSTRUMENTS. N=22

Title	Objectives	Conclusion
Assessment of cancer pain in a patient with communication difficulties: a case report	Use the Abbey Pain Scale to assess cancer pain in patients with communication difficulties	The use of the Abbey Pain Scale assists in the approach to relieve the pain of non-communicative patients with cancer.
Does communication skills training make a difference in patients' experiences of consultations in oncology and palliative care services?	Assess whether advanced training in communication skills enhances the experience of patient consultations.	Training in communication skills reflects greater professional empathy as assessed by patients and enhances the experience during consultations
Association between patient-reported symptoms and nurses' clinical impressions in cancer patients admitted to an acute palliative care unit	Prospectively compare symptoms reported by patients using the Edmonton Symptom Assessment System instrument.	The clinical perspective of nurses highly trained in palliative care showed a weak association with the intensity of symptoms reported by the patient.
Specific training program improves oncologists' palliative care communication skills in a randomized controlled trial.	Demonstrate that concise and individual training in communication skills improves the communication skills of oncologists in consultations focused on the transition to palliative care.	Concise and individual training in communication skills improved specific and general communication skills of quite inexperienced physicians.
Pediatric Palliative Care in the Age of eHealth: Opportunities for Advances in HIT to Improve Patient-Centered Communication	Seeks to identify the effective use of existing and under-development information technology in healthcare to improve communication and care in a clinical setting.	Provides a model for more optimized use of technologies, effectively using technology solutions based on standards to improve communication and the quality of care.
Discussing the transition to palliative care: evaluation of a brief communication skills training program for oncology clinicians.	Develop a brief communication skills workshop to assist oncologist during the transition from active anti-cancer treatment to palliative care	The workshop provided relevant practical information to participants and increased confidence in the communication about the transition to palliative care.
Addressing the transition from curative to palliative care: concept and acceptance of specific communication skills training for physicians in oncology COM-ON-	Evaluate a concise and individual training session on communication skills	The specific, individual, and concise training session on communication skills presented is well accepted, and physicians found there were a high practical relevance and strong personal benefits.
Caracterização dos recursos de comunicação utilizados por pacientes em cuidados paliativos – Revisão integrativa	Complete an integrative review of publications regarding the role of speech therapists on communication strategies in palliative care	Different forms of non-verbal communication are the most frequently used resource, and communication is an important factor for maintaining dignity and comfort in this scenario.
The P-A-C-I-E-N-T-E Protocol: An instrument for breaking bad news adapted to the Brazilian medical reality	Proposes a genuinely Brazilian communication tool and assesses its acceptance among physicians and nurses	The PACIENTE Protocol was proposed as a tool to guide and facilitate communication and proved to be practical and useful for most participants of this study.

TABLE 3. DISTRIBUTION OF THE STUDIES PUBLISHED BY TITLE, OBJECTIVES, AND CONCLUSION REGARDING CATEGORY III - PALLIATIVE CARE IN ONCOLOGY COMMUNICATION: STUDIES ON PATIENTS AND FAMILY CAREGIVERS. N=22

Title	Objectives	Conclusion
De um lado ao outro: o que é essencial? Percepção dos pacientes oncológi-cos e de seus cuidadores ao iniciar o tratamento oncológico e em cuidados paliativos	Assess the perception of oncology patients and their caregivers at the be-ginning of the diagnostic and therapeutic approach, and during palliative care.	Trust mediated by good communication and constan-cy of care are seen as fundamental for the satisfaction of caregivers and cancer patients throughout the course of the disease.
Importância da comunicação nos cuida-dos paliativos em oncologia pediátrica: enfoque na Teoria Hu-manística de Enfermagem	Investigate and analyze communication in palliative care in pediatric oncology, from the perspective of nurses, based on the Humanistic Theory of Nursing.	Communication is considered an effective element in the care of children with cancer and is of the utmost importance to promote palliative care when grounded in the Humanistic Theory of Nursing.
Cuidados paliativos à criança com câncer	Understand the existential experience of nurses when caring for children with cancer without therapeutic possibilities.	Nurses acknowledge the importance of communica-tion with children with cancer undergoing palliative care. There was an emphasis on attention to the non-verbal behavior of children, through eye contact and touch.
Cuidados paliativos sob a ótica de familiares de pacientes com neoplasia de pulmão	Learn what family members of patients with lung cancer understand of this therapy	The research indicates the need for training on and dif-fusion of palliative care practices, particularly regarding communication as a tool for improving care.
Crianças e adolescentes com câncer em cuidados paliativos: experiência de familiares	Investigate the experience of family members when caring for children and adolescents with cancer, undergoing palliative care, particularly in end-of-life care.	Family knowledge and participation in end-of-life care are driven by the communication of difficult updates between health teams, patients, and their families. However, this communication, when present, proved to be ineffective, with confusing and ambiguous information.

and potentially fatal diseases[2]. The communication of bad news may involve not only the disclosure of the diagnosis, but also the disease progression, and the need for referral to palliative care and home care. Communication is understood as a means for achieving and maintaining a more solid and healthy relationship between the health team, patient, and family members. Through effective communication, the team was able to mobilize the best capabilities and potentials of human beings to face stressful situations and preserve the autonomy and dignity of individuals under their care[3,4].

Findings show that the difficulties and causes experienced by nurses in this context of care require emotional control in order to have therapeutic communication between professionals and patients[5].

Research shows that communication should be understood as a resource that aims at creating environments that ensure patients' needs are met satisfactorily by sharing their experiences, anxieties, and insecurities. Thus, care should be focused on the need to communicate as a therapeutic strategy in order to connect the caregiver to the patient[6]. Thus, telling the truth is imperative in this context of care, since the learning of how to prevent a lack of sensitivity requires not only good intentions but strong communication skills[7].

The study is about the communication of difficult news and brings suggestions for verbal and non-verbal

interpersonal communication that aim to minimize the emotional suffering of patients, family members, and professionals, and the difficulties of physicians in the process of communicating bad news, in particular of recently graduated physicians[8,9].

When it comes to communicating difficult news, it is usual for physicians to use phrases in the first person: "I represented a huge hope and, at that moment, I felt like a failure." This feeling of failure is a barrier for physicians when communicating difficult news to family members since physicians themselves see death as a failure[10]. Research highlights that communication or lack thereof between physicians and patients is a constant problem[11]. This problem is a likely reflection of medical training, which is seen as a healing practice, causing many professionals to act mechanically in their daily practices and making them feel powerless in the face of terminality and death.

Non-verbal communication is about decoding relevant emotional information based on the various non-verbal signs, such as facial expressions, body gestures, among others[12,13]. It is important for professionals to understand that the body speaks through words and signs. Communicational interaction should occur in an informative, sensitive, and possible manner to support patients and their family members in understanding and overcoming the difficulties and limiting situations that the disease imposes.

Research in the category of communication

instruments and strategies in oncology (Table 2) focused on the assessment of cancer pain in a patient with communication difficulties using the Abbey Pain Scale, which includes six items to assess pain, including vocal verbal and non-verbal complaints[14]. Another study used the protocol for Consultation Measurement and Relational Empathy, which is a brief questionnaire designed to assess the perceptions of patients on relational empathy during consultations[15]. The research addressed the use of the Edmonton scale for the assessment of symptoms, a self-reporting tool that allows patients with advanced cancer to document the intensity of nine common symptoms[16].

Studies provided a training program with the objective of improving the communication behavior of doctors towards patients with cancer during the transition from curative or oncologic treatment to palliative care. The research used the COM-ON Checklist, which consists of specific items for the transition to palliative care, general communication skills, physicians' skills for handling the emotional needs of patients, and other significant ones[17,18]. The study developed a brief communication skills workshop to assist oncology health professionals during the transition from active anti-cancer treatment to palliative care[19].

In this context, it is necessary to highlight the potential of health information technology (HIT)[20]. E-Health technologies can improve the quality of care provided, reduce medical errors, and allow efficient communication to support joint decision-making. Findings indicate the importance of speech therapists, who allow the maintenance of oral communication as much as possible and work in the transition to alternative communication, protecting patients' right to express themselves, without interruption of the possibility to communicate[21]. Another study used the PACIENTE protocol and found that the worst task to be performed during communication is "talking about death," followed by "discussing the end of attempts to curative treatment," and the "diagnosis" in itself[22].

The studies are unanimous in stating that more research is needed to identify the tools that are suitable for making these assessments in the context of different symptoms and settings and to develop the necessary training by health care providers to integrate these tools and the information they produce into clinical practice.

The category of studies on palliative care with an emphasis on communication carried out with patients and family caregivers (Table 3), found that the most important subsidies for patients, at the start of their treatment, are: the availability of physicians to discuss the disease and answer their questions, trust in the team, and accessible and understandable communication[23]. Studies emphasize that it is essential that nurses, in their practice, identify the needs of children with cancer through verbal communication, characterized as the dialogic aspect of Nursing, and non-verbal communication, in which the child is perceived as a unique being in the relationships of care[24,25].

So the communication between team/family is essential in the construction of care for patients with cancer since the absence of communicative action could compromise the fight against the disease[26]. On the other hand, a study conducted with family members of children and adolescents with cancer noted a feeling of helplessness in the care of children, adolescents, and family members when the expression "there is nothing else we can do" is verbalized, confirming that the clarity, knowledge, and objectivity with which information is passed on to family members are, in general, ambiguous, inaccurate, and often lacking in comparison to the philosophy of palliative care[27].

Findings point to a lack of knowledge by family members when a child and or adolescent with cancer begins palliative care[28]. In these situations, the family notices the team's lack of interest in the continuation of treatment, thus losing trust in information and conducts[29]. Therefore, trust mediated by good communication and constancy of care are seen as fundamental for the satisfaction of caregivers and cancer patients throughout the course of the disease. Thus, in palliative care, assistance to patients with cancer and their families should be more human and holistic, based on strategies such as communication, which can develop a therapeutic process based on universal humanistic values with benefits for all.

CONCLUSION

The present study contributes significantly to clinical practice in the context of palliative care in oncology, with an emphasis on communication. However, considering the reduced number of publications on the subject over a period of eight years, future studies are recommended to subsidize the expansion of knowledge in the area.

Author's Contribution

Fernando André Costa de Souza worked in the drafting of the paper; Alfredo Borreli, Maria Andréa Fernandes, and Solange Fátima Geraldo da Costa worked in the critical review and approval of the version to be published; Cristiani Garrido Andrade and Fernanda Ferreira de Andrade worked on the data analysis and interpretation, and on the drafting of the paper.

RESUMO

A comunicação é uma ferramenta facilitadora nos cuidados paliativos, possibilitando o desenvolvimento de um processo terapêutico baseado em valores humanísticos universais, com benefícios para equipe, paciente oncológico e família. Essa temática é de grande importância e evidencia as contribuições significativas para a prática clínica no contexto dos cuidados paliativos em oncologia com ênfase na comunicação.

PALAVRAS-CHAVE: *Cuidados Paliativos. Oncologia. Comunicação. Revisão.*

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Comment on "Comparison of tru-cut biopsy and fine-needle aspiration cytology in an experimental alcoholic liver disease model"

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Alcohol abuse is a serious cause of morbidity and mortality worldwide[1]. Fatty liver and/or inflammation is observed on the basis of alcoholic liver disease which is one of the conditions caused by alcohol use. In chronic alcohol consumption, steatosis or steatohepatitis can be observed and, in 10% of cases, cirrhosis development is also found[2]. It has been suggested that gender differences, genetic and environmental factors, and personal differences in nutrition and alcohol metabolism play a role in the origin of this different course[3].

While diagnostic imaging methods are more helpful for the evaluation of fatty changes, histopathological examinations are more prominent to determine the degree of inflammation. In histopathological examinations, many pathological processes such as the degree of fatty changes, the location of inflammation and the type of inflammatory cells, the degree and extent of fibrosis, the condition of the biliary tract, and the presence of different deposits can be shown[4]. However, possible complications that may be encountered with histopathological tissue extraction methods such as excisional or incisional biopsy from the liver may have serious consequences in some cases. For this reason, cytopathological examination, which is one of the less invasive methods, comes to the forefront. However, studies on the subject are limited.

In alcoholic liver disease, the histopathological evaluation must be compared with the cytopathological examination, which has fewer complications[5]. Subsequently, if the results of cytopathological studies give similar results to the histopathological examination, it is recommended to increase its use in daily practice. In addition, it is thought that due to the lower risk of complications, repeatability of cytopathological examination may be higher, and it will contribute to the understanding of the pathophysiology of different courses in different cases.

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Comment on "Clinicopathological analysis of acral melanoma in a single center: a study of 45 cases"

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The interesting article "Clinicopathological Analysis of Acral Melanoma in a Single Center: A Study of 45 Cases" by Souza et al. discusses the anatomopathological nuances of one of the most lethal types of skin tumors: the acral melanoma. It is a retrospective study with a considerable time of observation (20 years) and a sample of 45 patients. When compared to other studies involving skin melanomas in Brasil, the series presented by the authors is expressive and possibly the second-largest sample of acral melanomas in a single-center study. The largest national study in number of patients was conducted by Nunes et al. at the National Cancer Institute.[1]

The paper has positively contributed to the profiling of acral melanoma in that population, with a predominance in women, in the plantar region, acral lentiginous histological subtype, invasive tumors, and Clark IV, showing consistent with the existing literature. A curious fact raised by the authors regards the possible worse prognosis in males, which was not confirmed by data presented since men and women did not show statistical differences regarding invasiveness, ulceration, degree of mitosis, Breslow index, and five-year survival rate. Although several studies have indeed demonstrated a worse prognosis in male patients, there is still no clear explanation for this finding [2,3,4]. Often times, this difference is attributed to a greater self-care by females.[2] As well noted by Souza et al.[6], this simplistic explanation should not be accepted as an isolated fact and the absence of better explanations is an invitation to the scientific community for further studies in this respect.

The scientific literature is rich in articles on cutaneous melanoma; however, few focus specifically on assessing the acral subtype. Simultaneously, this subtype of melanoma is diagnosed later, which directly contributes to its poor prognosis[5]. This was observed by the authors, who found high Breslow scores among the patients evaluated. Aware of the positive relationship between delayed diagnosis, Breslow thickness, and the prognosis, the authors accordingly reinforce the need for appropriate dermatological assessment of the palmoplantar and nail regions. It confirms the importance of asking patients to remove footwear during the physical examination of the skin. This simple act, which takes only a few seconds more, can be the difference between an early and late diagnosis or, from a perspective as dramatic as it is true, between life and death.

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Erratum

Regarding the article "Impact of oral hygiene in patients undergoing mechanical ventilation in the COVID-19 pandemic" with DOI number: http://dx.doi.org/10.1590/1806-9282.66.S2.96, published in Journal of the Brazilian Medical Association, 2020;66(SUPPL 2), page 96, authors changed

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Melina de Barros Pinheiro[5]	*Melina de Barros Pinheiro*[6]

Regarding the article "The effects of favıpıravır on hematologıcal parameters of covıd-19 patıents" with DOI number: http://dx.doi.org/10.1590/1806-9282.66.S2.96, published in Journal of the Brazilian Medical Association, 2020;66(SUPPL 2), page 65, Author's Contribution changed:

From: The authors contributed equally to the work.
To: SY: Data collection, Data analysis and interpretation, Conception or design of the work, drafting the article, critical revision of the article, final approval of the version.
HD: DŞ; ABG; HK; DÇ: Data collection, Conception or design of the work, data analysis and interpretation, critical revision of the article, final approval of the version.
CV; AA; MK; OK: Data analysis and interpretation, final approval of the version to be published.

Regarding the article "VALUE OF ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION (EBUS-TBNA) IN THE DIAGNOSIS OF LUNG AND MEDIASTINAL LESIONS" with DOI number: https://dx.doi.org/10.1590/1806-9282.66.9.1210, published in Journal of the Brazilian Medical Association, 2020;66(9), page 1210, changed:

From: Hospital Santa Casa de São Paulo - Departamento de Cirurgia Toráxica, São Paulo, SP, Brasil
To: Hospital Santa Casa de São Paulo - Departamento de Cirurgia Torácica, São Paulo, SP, Brasil.

From: Inclusion criteria
Patients who had normal anatomical findings or vascular interposition that did not indicate nor allowed needle aspiration.
To: Patients who had normal anatomical findings or vascular interposition that did not indicate nor allowed needle aspiration.

From: The following major complications were considered: excessive bleeding that was not self-limiting and that had evident clinical consequences and lung, pneumo-thorax, or pneumomediastinum infections.
To: The following major complications were considered: excessive bleeding that was not self-limiting and that had evident clinical consequences and pneumo-thorax or mediastinitis.

Regarding the article "Bioethical aspects of artificial intelligence: COVID-19 & end of life" with DOI number: http://dx.doi.org/10.1590/1806-9282.66.S2.5 , published in Journal of the Brazilian Medical Association, 2020;66(SUPPL 2):), page 5, title changed:

From: Bioethical aspects of artificial intelligence: COVID-19 & end of life
To: "Artificial intelligence & COVID-19: (bio)ethical aspects of end of life