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Editorial Production

EDITORIAL
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How to treat erectile dysfunction in young patients during the pandemic?

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COVID-19, a disease caused by the novel coronavirus (SARS-CoV-2), has become pandemic, affecting more than 100 million people throughout the world. During March 2021, Brazil occupied second place in the ranking of countries with the highest numbers of confirmed cases, totaling more than 11 million affected people and nearly 300 thousand deaths[1]. With the new increase in the number of cases, cities have once more adopted restrictive measures regarding circulation and social activities, with the shutdown of non-essential services.

The set of measures adopted by the government associated with the dissemination of the disease, with large numbers of infected individuals and deaths, exert a negative impact on individuals and society as a whole[2]. The population finds itself restricted in terms of habitual activities and is constantly exposed to news about the propagation of the disease as well as the accompanying morbidity and mortality rates, which has a negative impact on mental health due to fear, panic, unemployment, a reduction in income, the loss of relatives and friends, and social distancing from family circles[3].

Sexuality is complex and encompasses several aspects, such as attitudes, behaviors, orientation, identity, and beliefs[4]. The negative impact of the pandemic on mental health can significantly affect one's sex life. The few studies that have assessed the effects of the pandemic on sexual behavior demonstrate a reduction in the quality of the sex life of individuals and the number of sexual relations, especially among young, single individuals[5,6].

In urology offices, there has been an increase in the number of young men seeking care for complaints related to reductions in libido and erectile function in this peak period of the pandemic in Brazil. For the most part, these are patients with no other comorbidities or conditions that are harmful to sexual function and no history of sexual problems. Their complaints began precisely during the pandemic. Such patients seek a diagnosis and treatment and are unable to relate the sexual health complaint with a psychological condition of anxiety, fear, and depression caused by COVID-19.

It is of vital importance for urologists to be attentive when examining these patients. It is important to understand the turbulent period in which we find ourselves and its impact on the mental health of patients, bearing in mind the extent to which psychological wellbeing exerts an influence of one's sex life.

Therefore, clinicians should address uncertainties related to the pandemic and its psychological effects by offering online appointments in an effort to clarify issues related to the prescription and doses of medications. Moreover, these young men should have their psychosexual history assessed, as most problems of this type in this population are psychosomatic. In this context, physician–patient dialogue is essential throughout the management of erectile dysfunction.

AUTHORS' CONTRIBUTIONS

GJFA: Conceptualization, Methodology, Writing-original draft. **JFAN:** Data curation, Methodology, Writing-original draft. **LCFS:** Methodology, Writing-review & editing. **JGFA:** Project administration, Supervision, Writing-review & editing. **FNFJ:** Project administration, Supervision, Writing-review & editing.

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EDITORIAL
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University indigenous uses social media to report the impact of COVID-19 on their communities

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The spread of coronavirus disease 2019 (COVID-19) continues to pose a serious threat to 800,000 indigenous people in Brazil. There are 305 tribes who speak 274 languages spread across the remote national territory, who have faced historical inequities related to poverty, health problems, and limited access to health care.

Monitoring the impact of the pandemic among Brazil's indigenous communities is a major challenge due to the lack of adequate surveillance systems. The data collected by[1] Government from March 2021 onward suggested ~50,000 cases and 1,000 deaths among those who live in indigenous lands (except for urban indigenous and those waiting on demarcation of land by the government). Many indigenous people go to urban centers in[2] search of better living conditions[3]. The census of the last Brazilian Institute of Geography and Statistics (IBGE) showed that 49% of the total population of Brazilian Indians live in urban centers, outside demarcated indigenous lands[4].

There have been several structural initiatives to mitigate the impact of COVID-19 including the Emergency Plan to Combat COVID-19 in Indigenous Territories and the National Contingency Plan for Human Infection with the new coronavirus in indigenous people, but there are no known published reports on their impact[5].

Indigenous university students, who returned to their villages after suspension of the university's face-to-face activities, provided a unique opportunity to learn about lived experiences of COVID-19 in their villages through government-sponsored programs. Semi-structured interviews *via* WhatsApp were conducted with 26 indigenous students from 19 villages located in the central-west, south, and northeast regions of Brazil, which has a population of about 54,000 indigenous people.

The topics covered included socio-demographic, access to health care, (i.e., description of the village regarding location, housing, form of subsistence, access to health, education, social organization, and impact of the pandemic on the village). The interviews were conducted in May and June 2020, after authorization from the indigenous leaders, from the Special Indigenous Sanitary District (DSEI) and approval of the study by the Research Ethics Committee (CONEP) with opinion 4.279.173.

To enrich the narratives, prior to the interviews, indigenous students conducted informal dialogues with their village leaders and other members of the community to obtain socio-demographic and access to health care information regarding the impact of the pandemic in their villages. The thematic analysis was used to analyze the data. The ethnic groups in 19 villages were as follows: Atikum and Pankararu (northeast); Terena, Guarani Kaiowa, Pankará, Pitaguary, Tuxi and Pataxó (midwest); and Kaingangi and Guarani (south). In general, houses are made of clay or wood. Sustainable livelihoods are based on farming, fishing, hunting, livestock, and handicrafts. Each village is governed by a chief, 88% of the villages had an elementary school (for 6–14 years old), and 35% had a secondary school (for 17 years old), with classes held in Portuguese in 52% of schools. A total of 100% of villages had at least one Community Agent for Indigenous Health whose role is to 26% had a Health Centre (Base Pole) with nurse, dentist, doctor, some Poles with nutritionist, and psychologist.

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The narratives, although originating from three distinct geographic regions, were convergent and provided contextual insights into the impact of the pandemic on income loss with consequent food insecurity, lack of access to health services, physical and emotional manifestations, and violence and abuse of psychoactive substances.

With deforestation from illegal loggers and miners and climate change, indigenous communities are already vulnerable to food and nutritional insecurity. The loss of income from social isolation preventing the sale of handicrafts exacerbated food and insecurity. Due to the scarce natural resources, these Indians have a diet similar to that of a non-indigenous person, although they still maintain a preference for foods from hunting and fishing. The food is basically purchased from local stores, distributed by the federal government, or generated from subsistence agriculture and the raising of animals such as chickens and pigs.

The "Base Poles" are manned by significant non-indigenous health professionals and struggled to provide a service with reduced visits from non-indigenous professionals, indigenous health professionals' self-isolation because of high risk of the existing comorbidities (i.e., diabetes, hypertension, asthma, and chronic obstructive pulmonary disease) or COVID-19 infections, and with the shortage of personal protective equipment. There was a strong emphasis on the negative impact of social isolation on their communities given multi-generational housing and the fear of losing indigenous elders who are integral to the maintenance of indigenous traditional knowledge, culture, and practices and are the custodians of customary law and governance. There was also a perception of an increase in substance abuse and family conflicts.

Unquestionably, these narratives illustrate that the pandemic is deepening profound systemic inequities, but they also give a strong sense of young indigenous students wanting to maintain their indigenous systems and that the interviews given them an opportunity to advocate for a response to safeguard their communities (Table 1).

Table 1. Themes and illustrations of the narratives.

Themes	Illustrative quotes
Loss of income with consequent food insecurity.	The lack of money and food is very difficult, we can no longer sell our crafts and many were fired, we are in a risk group so we would have to leave and continue paying, but then the boss found it easier to say goodbye. (E8–male, 20 years old) The situation of COVID-19 in Brazil is tense because there is a whole reality in which our society lives, which is very difficult, precarious housing, lack of basic sanitation, health and even food. (E16–male, 24 years old). In the beginning we were left without food, because we had no money and because the basic government Fridays were slow to arrive, then the people who know us started to bring us food. (E3–female, 46 years old). We made signs and banners on the roads asking for food and help. (E9–female, 19 years old).
Lack of access to health services	Particular conditions make us vulnerable, we have difficulty accessing health services due to the geographical distance or unavailability of health teams. (E12—male, 22 years old). The health personnel did not appear here anymore and we know that the indigenous health subsystem created to serve indigenous health suffers from a lack of resources, so we don't even blame it. (E8–male, 31 years old).
Physical and emotional manifestations	[T]he way of life of our people can increase exposure to infectious diseases differently from that of non-indigenous people, as we live in collective houses that can increase contagion. (E16–male, 25 years old). What saddens me most is that we live in community, we've always done everything together, we've shared everything even the food and now we can't do it anymore and it will make people sick with the virus or the head. (E11–male, 23 years old). I am afraid of losing the elderly, they are the living history that cannot die and they are the most at risk. (E7–male, 30 years old). We don't want to be contaminated or contaminate relatives, but it is an anguish, being isolated here makes us sick. (E5–female, 31 years old).
Violence and abuse of psychoactive substances	All of this affects indigenous communities a lot, relatives are drinking, fighting, leaving home and what was happening is getting worse. (E3–female, 26 years old). I think family fights have increased, the lack of money and food makes everyone nervous and angry and then fight. (E17–female, 28 years old). This disease is so strong that you can't even say goodbye to relatives who died. (E8–female, 25 years old). You cannot get the family together to do the rituals with prayers, prayers, so that you can keep your faith steadfast in this difficult time. (E4–female, 71 years old).

CONCLUSIONS

Finally, we alluded that each culture has its shape, patterns, expressions, and structures to know, explain, and predict the state of well-being, as well as behavior patterns related to the health-disease process and the social and cultural universes where they occur. Then, the valorization of traditional knowledge and practices are paramount in the establishment of therapeutic relationships.

Although data on the impact of COVID-19 on indigenous groups around the world are still irregular, it is already worrying how the pandemic has affected indigenous communities and how the situation remains unfavorable for all indigenous people, as the fragility of public policies, the absence of health teams in many communities, the distance from some villages to medical centers, and the natural fragility of this population to respiratory diseases are added to other health problems.

An essential aspect of this study was to ensure that indigenous views of the world are reflected which are centered on the connection between people and nature. Without pretending to exhaust this reflection, we proposed to continue seeking scientific results that reflect the impacts of the pandemic on indigenous communities, the strategies that indigenous people and health workers have adopted in responding to the pandemic, particularly in relation to the use of traditional knowledge and practices, and in addition to their perceptions of priorities for policy responses. Finally, the data have repercussions in the defense of the protection of indigenous rights and in the strengthening of the actions of young indigenous people who seek help for their communities.

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IMAVD: Formal Analysis, Writing – original draft, Writing – review & editing. **FAQ:** Formal Analysis, Writing – original draft, Writing – review & editing. **MGCG:** Formal Analysis, Writing – original draft, Writing – review & editing. **AJG:** Formal Analysis, Writing – original draft, Writing – review & editing. **PTCJ:** Formal Analysis, Writing – original draft, Writing – review & editing. **SH:** Formal Analysis, Writing – original draft, Writing – review & editing.

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LETTER TO THE EDITOR
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Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy

Marcus Zulian Teixeira[1]*

Dear Editors,

In October 2020, a manifesto against European legislation was posted on social networks, which supports the practices of Complementary/Alternative Medicine (CAM; "First worldwide manifesto against pseudosciences in health"), written by "pseudoskeptical" associations or groups without scientific expressiveness, and which present in their associative body individuals who are assumed to have the rights to criticize the health practices that they do not accept by personal, dogmatic, and autocratic opinions, systematically disparaging and denying any scientific evidence that substantiates them. In view of its wide acceptance, use, and worldwide recognition, homeopathy was the preferred target of this manifesto.

I say "pseudoskeptical" associations because the doctrinal current of true "skepticism" (*sképsis* in Greek means "examination" or "evaluation"), founded in ancient Greece by the Philosopher Pyrrhus (4th-century BC), argues, "it is not possible to affirm the absolute truth of anything, with it being necessary to be in constant questioning."[1] The term "pseudoskepticism" emerged in the second half of the 19th century, indicating the explicit tendency toward negationism, instead of evaluation and ethical and objective questioning proposed by Greek skepticism.

In 1987, Marcelo Truzzi (1935–2003), a Danish sociologist and professor of sociology based in the USA (Eastern Michigan University), elaborated a very illuminating analysis of the term "pseudoskepticism" or "pathological skepticism," saying that it is used to denote the forms of skepticism which deviate from objectivity, dogmatically denying everything which is not known, instead of doubting, investigating, and accepting the evidence that appears with an agnostic and neutral position, with an open mind, and free from prejudice[2,3].

"Since 'skepticism' properly refers to doubt rather than denial–nonbelief rather than belief–critics who take the negative rather than an agnostic position but still call themselves 'skeptics' are actually 'pseudoskeptics' and have, I believed, gained a false advantage by usurping that label"[2].

"Critics who assert negative claims, but who mistakenly call themselves 'skeptics,' often act as though they have no burden of proof placed on them at all, though such a stance would be appropriate only for the agnostic or true sceptic. A result of this is that many critics seem to feel it is only necessary to present a case for their counter-claims based upon plausibility rather than empirical evidence. […] Showing evidence is unconvincing is not grounds for completely dismissing it. If a critic asserts that the result was due to artifact X, that critic then has the burden of proof to demonstrate that artifact X can and probably did produce such results under such circumstances."[2]

In his isolated analysis, Marcello Truzzi described the strategies used by pseudoskeptics to deny and disqualify new ideas and their respective scientific evidence: the tendency to deny, rather than doubt; double standards in the application of criticism; the making of judgments without full inquiry; tendency to discredit rather than to investigate; use of ridicule or *ad hominem* attacks; presenting insufficient evidence or proof; pejorative labeling of proponents as "promoters," "pseudoscientists," or practitioners of "pathological science"; assuming criticism requires no burden of proof; making unsubstantiated counter-claims; counter-claims based on plausibility rather than empirical evidence; suggesting that unconvincing studies are grounds for dismissing it; and tendency to dismiss *all* evidence[2,3].

Marcoen Cabbolet, researcher at the Department of Philosophy, Centre for Logic and Philosophy of Science, Vrije Universiteit Brussel, scholar of elementary particle physics[4], in his essay "Tell-Tale Signs of Pseudoskepticism (Bogus Skepticism),"[5] warned that "pseudoscepticism, which typically is portraying someone's work as despicable with scientifically

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unsound polemics, is a modern day threat to the traditional standard of discussion in science and popular science."

Thus, "where the sceptic merely states that he doesn't believe in someone else's claims, the pseudosceptic comes himself up with claims and these are always (very) negative. But pseudoscepticism is not just making negative claims: the keywords are 'dishonesty' and 'foul play'. And it is not aimed at finding out the truth, but at discrediting someone's research."[5]

In another article[6], Cabbolet addressed this "pseudoscience," clearly and objectively describing "scientific misconduct" with several classic examples that lead to "negative conclusions about someone else's work that are downright false." He clarified that "three known issues are identified as specific forms of such scientific misconduct: biased quality assessment, smear, and officially condoning scientific misconduct."

Cabbolet reiterated that pseudoskepticism is the central focus of this scientific misconduct, which has the objective of "uttering negative conclusions about someone else's work that are downright false," further suggesting that this posture may be "a calculated strategy," rather than a passionate attitude, and provides recommendations for preventing and dealing with these three forms of scientific misconduct through educational and punitive measures[6].

In the first quoted essay[5], Cabbolet explains "seven tell-tale signs of pseudoskepticism" in detail (Table 1), most of which were initially described by Marcelo Truzzi, through which the conduct and strategy of pseudoskeptics can be notably recognized.

Expanding the tell-tale signs of pseudoskepticism, Cabbolet also warned of the fact that "pseudosceptics never publish a retraction": "Usually in science, if researcher A publishes a claim and researcher B refutes the proof, then A publishes a retraction of the claim. But not so the pseudosceptic. Even when confronted with conclusive proof that his allegations are false, he will refuse to publish a retraction or to publicly acknowledge that the claims were fabricated: the typical pseudosceptic will stick to his fabrications as if not a word has been said […]"[5].

As Cabbolet described[5], pseudoskepticism is also observed in the reports of peer reviews of scientific publications, in all areas of knowledge, when the prejudiced and pseudoscientific opinion of a reviewer denies the publication of an article which disagrees with their dogmatic view, even if it fulfills all the requirements of the scientific method. This is commonly observed when we forwarded homeopathic scientific articles to non-homeopathic journals. Paradoxically, following a pseudoskeptical ruse (#7: straight to the mass media)[5], the biased and prejudiced allegations against homeopathy are repeatedly transmitted through articles and opinion interviews in newspapers and various popular media, refraining from following the usual scientific path of submitting them to a peer-reviewed scientific journal.

Therefore, pseudoskeptics act according to two weights and two measures: they require homeopathic researchers to publish their studies in non-homeopathic scientific journals (although studies related to any medical specialization are published in specialized journals), but they discard this premise, disseminating their criticisms of homeopathy, propagating them in nonscientific mass media as "double standards in the application of criticism."

Brazilian homeopathy also suffers constant attacks from pseudoskeptical groups just as in Europe. In order to demystify the pseudoskeptical fallacy that "there is no scientific evidence for homeopathy," the Technical Chamber for Homeopathy (TC-Homeopathy), Regional Medical Council of the State of São Paulo (Cremesp, Brazil) prepared a Special Dossier in 2017 entitled "Scientific Evidence for Homeopathy"[7,8], which is available online in Portuguese and English in the *Revista de Homeopatia,* the scientific journal of the São Paulo Homeopathic Medical Association (APH).

The dossier encompasses nine narrative reviews in several lines of homeopathic research (i.e., historical, social, medical education, pharmacological, basics, clinical, patient safety, and pathogenetic) and two randomized clinical trials developed by TC-Homeopathy members contain hundreds of scientific articles published in several peer-reviewed and indexed scientific journals; it seeks to highlight the state-of-the-art in homeopathic research[7,8].

Bothered by the excellence of these lots of evidence, in November 2020, a group of Brazilian pseudoskeptics disclosed a derisory and fallacious manuscript ("Counter-dossier of Evidence on Homeopathy") in the media and social networks to evaluate some of the articles published in the referred dossier according to "the best scientific rigor" and "inform the population about what science says about the supposed effectiveness of Homeopathy."

Unfortunately, none of this happened in the aforementioned manuscript. Contrary to the announced "best scientific rigor" in the analysis of the articles of the dossier, what is observed throughout the text is a set of criticisms based on "pseudoskeptical strategies" to debunk and disqualify any scientific work: the tendency to deny, rather than doubt; double standards in the application of criticism; the making of judgments without full inquiry; use of ridicule or *ad hominem* attacks; presenting insufficient evidence or proof; pejorative labeling of authors; assuming criticism requires no burden of proof (absence of proof); making unsubstantiated counter-claims (nonspecific comments); suggesting that unconvincing studies are grounds for dismissing it; tendency to dismiss *all* evidence; vitriolic tone;

Table 1. Seven tell-tale signs of pseudoskepticism according to Marcoen Cabbolet[5].

Seven tell-tale signs of pseudoskepticism	
#1: *Ad hominem* attacks	Typically, a pseudoskeptic is so eager to portray the author of the targeted work as an amateur that he resorts to *ad hominem* attacks: this is a rhetorical technique that is absolutely inadmissible in a scientific discourse, and therefore this is the number one tell-tale sign that a piece is nothing but a pseudoskeptical attack. It is thus a real giveaway when the author of the targeted work is called "incompetent," an "amateur," a "charlatan," a "crackpot," "ignorant," "only out to brag about it in a pub," etc. So, the occurrence of any of these words alone is already an indication that the entire piece is of doubtful merit.
#2: Vitriolic tone	Typically, a pseudoskeptical attack portrays the targeted work as despicable: usually this is done by riddling the text with belittling phrases and strong pejoratives. Consequently, the piece has a vitriolic or even libelous tone that is immediately evident even from a quick superficial reading: that tone is the tell-tale sign of pseudoskepticism. The archetypical belittling phrase is "every first-year student could have come up with the same thing." Illustrative examples of strong pejoratives are "nonsense," "perverse," "a disgrace," "worthless," "meaningless," "inferior," "devoid of content," "complete rubbish," and the like, which are then typically said about the targeted work as a whole.
#3: Nonspecific comments	In science, when commenting on someone else's work, one very specifically addresses the details of the work in question. A pseudoskeptic, however, typically doesn't go through the hard work of really understanding the targeted work. This feature manifests itself in superficiality of the comments. It is therefore a tell-tale sign of pseudoskepticism when a piece concerns nothing but negative allegations at the metalevel, that is, negative allegations about the targeted work as a whole, without going into the details of the targeted work.
#4: Absence of proof	Another typical feature of pseudoskeptics is that they have no shame: one of the most shameless ways to attack someone else's work is to put forward outright fabrications, which, if true, would imply gross incompetence of the author of the targeted work. But fabrications cannot be proven by their very nature. Consequently, absence of proof of the (usually grave) allegations in a piece is a sure tell-tale sign of pseudoskepticism at its worst, and a strong indication that the piece may contain fabricated allegations. An illustrative example is an absence of proof of the one statement that is probably the most abused phrase of all in modern science: "this work is of insufficient scientific quality." In a pseudoskeptical attack, this is typically said of the targeted work without specifying which criteria of scientific quality are not met, and why or how they are not met–there are peer-reviewed reports that consist of just this one phrase.
#5: False metaphors	In science, comments on someone else's work remain confined to that work: one doesn't indulge oneself in metaphors. In a pseudoskeptical attack, however, often the targeted work is compared with a theory that is known to be false or that is obviously ridiculous, as if it is the same thing. Illustrative examples are phrases like "this is the same as saying that the earth is at," or "this is the same as saying that the phenomenon is caused by angels": these are tell-tale signs of a pseudoskeptical attack. There are more sophisticated cases, but the point is that this use of metaphors is a rhetorical technique that is absolutely inadmissible in a scientific discourse. The error is the same in all these cases: contrary to what is stated by the pseudoskeptic, it is not at all the same.
#6: Contradiction with history and basic principles of science	When attacking a new theory that has not yet been experimentally tested, a pseudoskeptical piece often blatantly contradicts well-known facts from the history of science, as well as basic scientific principles. The three archetypical examples that turn up time and time again are i. stating that scientific discoveries are nowadays only made by large international collaborations, to insinuate that the work of a single author cannot be a scientific discovery; ii. stating that scientific theories are always developed from experimental facts, to insinuate that anything else cannot ever be a scientific theory; and iii. using an accepted model (other than Einstein's Special Relativity) beyond its established area of application as a criterion of truth, to insinuate that a work that contradicts that model cannot be a scientific theory. The arguments (i) and (ii) completely ignore that virtually all of modern science is built on the work of individuals, who more often than not theoretically predicted phenomena before these were experimentally observed (Einstein: time dilation and curvature of space; Dirac: antimatter), and who often did their groundbreaking work in relative isolation (Einstein, Bohr). The argument (iii) ignores the fact that historical breakthroughs in science often went squarely against the accepted model of the time, and contradicts a basic principle of science, put into words by Feynman as follows: "experiment is the sole judge of scientific truth."

Continue...

Table 1. Continuation.

Seven tell-tale signs of pseudoskepticism	
#7: Straight to the mass media	It is a bad sign when a scientific claim is taken straight to the mass media (e.g. the cold nuclear fusion case), but it is an equally bad sign when an attack on someone else's work is taken straight to the mass media. When writing a scientific critical comment on a work, the right method is to first contact its author and discuss the criticism with him/her. When submitting the critical comment for publication in a scientific journal, one is often required to present evidence of such a prior contact with the author of the targeted work. But not so the pseudoskeptic. Typically, he doesn't contact the author of the targeted work, nor does he attempt to publish his "findings" in a peer-reviewed journal: he takes his allegations straight to the mass media. So an editor of a newspaper or university weekly who sees that an attack on someone's work is submitted for publication, can—especially when the piece contains grave accusations—simply ask for evidence of contact with the author of the targeted work: any failure to provide such evidence is then a tell-tale sign that the piece is nothing but a pseudoskeptical attack, and an indication that it may contain fabrications.

false metaphors; and straight to the mass media among others ("Pseudoskeptic and pseudoscientific fallacies of the 'Counter-dossier of Evidence on Homeopathy'")[9].

In highlighting these pseudoskeptical strategies in the detailed analysis of the presented criticisms[9], we unmasked these pseudoskeptics disguised as pseudoscientists as the false and hypocritical image of being the "defenders of science," as they call themselves in the aforementioned contra-dossier. The blindness caused by pseudoskepticism or pathological skepticism caused "experienced and renowned researchers in their areas of concentration" to incur childish errors in their prejudiced analyses, such as simple attentive reading of the texts they attacked in a fallacious way, denoting noncompliance with basic premises of the scientific method.

"The first was never to accept anything for true which I did not clearly know to be such; that is to say, carefully to avoid precipitancy and prejudice, and to comprise nothing more in my judgment than what was presented to my mind so clearly and distinctly as to exclude all ground of doubt" (René Descartes, "Discourse on Method").

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SHORT COMMUNICATION
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Pulmonary rehabilitation: a unfairly forgotten therapeutic tool even in the worst scenarios

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect almost every organ or system. Pleuropulmonary involvement, often underdiagnosed, occurs in about 60–80% of SLE cases[1]. Shrinking lung syndrome (SLS) is one of its rare, although debilitating, complications occurring between 0.5–1.1% of patients[2]. It is characterized by progressive unexplained dyspnea, chest pain, elevated hemidiaphragm, and reduced lung volumes with restrictive pattern on pulmonary function tests (PFTs), but without parenchymal anomalies[2]. Despite being more prevalent during the later stages of the disease, it can manifest at any stage of SLE, even with inactive disease (in more than half of patients, according to SELENA-SLEDAI scores) and usually without prior or simultaneous involvement of other organs[3].

It has been rarely described in other autoimmune disorders and is more prevalent in women (with ratio 6:1)[3]. Differential diagnoses include restrictive respiratory defect due to pulmonary fibrosis, obesity, diaphragmatic palsy, and central nervous system disorders[4]. There are no definite criteria for SLS diagnosis, and it usually relies on the association of reduced lung volumes and restrictive defects on PFTs, together with the exclusion of other causes[4].

Even though its pathophysiology remains unknown, because pleuritic chest pain is a prominent feature of SLS, it has been hypothesized that pleural effusion and inflammation could reduce diaphragmatic mobility. This would inhibit deep inspiration, resulting in chronic lung hypo-inflation, consequently leading to parenchymal remodeling with changes in elasticity and decrease in lung compliance[5,6].

Although the therapeutic approach does not gather consensus, the first-line treatment usually includes corticosteroids with or without immunosuppressants[1,2]. In their review, Duron et al. concluded that there was no prognostic difference between patients receiving isolated steroids or steroids associated with immunosuppressants[4]. Theophylline and beta-agonists alone or in combination with glucocorticoids have been also employed to increase diaphragmatic strength[7,8]. Although the SLS mechanism is poorly understood, there have also been positive outcomes with rituximab and belimumab as B cells may play an important role in SLS pathophysiology[9,10].

Surprisingly, no published literature on SLS patients makes any consistent reference to the benefits of respiratory pulmonary rehabilitation programs as a crucial component of any chronic lung disease management.

DESCRIPTION

The authors present the case of a 57-year-old female, with past medical history significant for SLE with 12 years duration, secondary antiphospholipid syndrome, and chronic pulmonary embolism. In a routine consultation, she had complains of progressive worsening of dyspnea on minor exertion (mMRC grade 2) and intermittent pleuritic chest pain over the past four months, with no extra-thoracic manifestations of SLE, namely, arthralgia or cutaneous involvement. At that time, her therapy consisted of daily prednisolone 10 mg/day, hydroxychloroquine 400 mg/day in addition to azathioprine 50 mg thrice a day, formoterol twice a day, and rivaroxaban 20 mg/day.

The chest X-ray showed small lungs and bilateral elevation of the diaphragm, with no evidence of pleuroparenchymal changes. For better clarification, the patient underwent chest computed tomography to assess the eventual pulmonary

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involvement. As shown in Figure 1, there were only residual linear opacities compatible with fibrotic bands/linear atelectasis with no other relevant parenchymal findings, nor pleural effusion, as commonly reported in SLS cases[11]. Fluoroscopy showed bilateral diaphragmatic paralysis. PFTs confirmed a restrictive ventilatory defect with her forced vital capacity (FVC) being 60.4% of predicted, low total lung capacity (TLC) being 60.3% of predicted, forced expiratory volume (FEV1) being 61.2% of predicted, functional residual capacity (FRC) being 59.8% of predicted, residual volume (RV) being 58.4% of predicted, reduced diffusing capacity for carbon monoxide (DLCO) being 56.8% of predicted, transfer coefficient of the lung for carbon monoxide (KCO) being 91.7% of predicted, and resting gas exchange without significant difference from the age predicted pO_2 being 80.3 mmHg. A 6-min walk test was performed, but the patient only tolerated two min due to excessive dyspnea and desaturation (completed only 142 m; 96–84% oxygen desaturation; maximum exertion on Borg Scale 10/10). Despite having an adequate cardiac response to effort on cardiopulmonary exercise testing (CPET), she presented an important ventilatory limitation (VO_2 17.8 mL/min/kg, 62% of predicted), as her respiratory reserve was depleted, due to a gas exchange compromise with consequent desaturation, probably potentiated by her pulmonary vasculopathy; subsequent lung ventilation-perfusion (V/Q) scintigraphy confirmed evidence of chronic pulmonary thromboembolism,

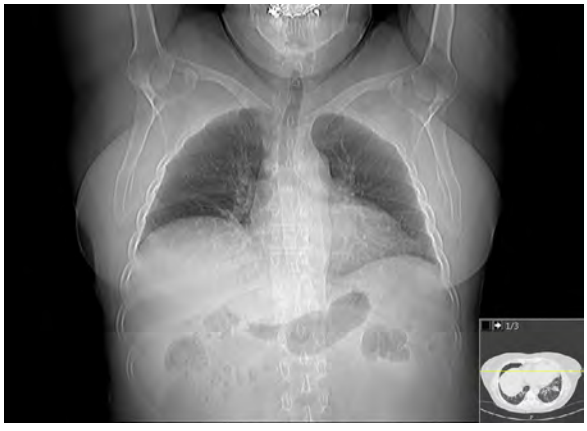

Figure 1. Chest computed tomography shows elevated hemidiaphragms with reduced lung volume, residual linear opacities compatible with fibrotic bands/linear atelectasis in medium lobe, anterior segment of the left upper lobe and lower lobes; right accessory tracheal bronchi directing toward the right upper lobe, with no other parenchymal relevant findings.

although without pulmonary hypertension, and she began full dose rivaroxaban. As reported elsewhere, there was an unusual C-reactive protein elevation, not common on controlled SLE[12]. Considering all these results, SLS diagnosis was assumed, and she initiated aminophylline thrice a day. Noteworthy, as shown in Table 1, when aminophylline was discontinued due to iatrogenic tachycardia, the patient reported worsening of shortness of breath concomitantly with marked decline of her restrictive lung pattern (FVC=36.2%; TLC=40.7%; FEV1=40.3%; FRC=36.7%; RV=46%, of the predicted values). Despite increasing corticosteroid and azathioprine doses, her tolerance to efforts continued to diminish, and she was started on a pulmonary rehabilitation program, twice weekly, for the next five months. The patient performed aerobic exercise training, ventilatory control exercises, and strength training of the upper and lower limbs. She presented a progressive improvement in exercise tolerance with endurance testing showing a significant increase in exercise tolerated time (from 9:25–30 min). The respiratory complains as well as the sequential PFT of patient began to improve progressively (Table 1). At present, her mMRC is grade 1, TLC is 51.6% of predicted, and she completes 462 m on the 6-min walk test, considered a minimal clinically important difference (MCID)[13] with 97–91% oxygen saturation and a Borg Scale 3/10. She is currently maintained on azathioprine 200 mg twice a day and prednisolone 5 mg/day, after a gradual weaning period; aminophylline was also carefully reintroduced. Equally important as exertional tolerance is the unquestionable improvement of patient's quality of life, being now able to restore her professional and normal activities of daily living (ADL), as expressed on The London Chest ADL Scale (LCADL)[14] which score diminished from 26–17, also considered MCID. Furthermore, on the Hospital Anxiety and Depression Scale (HADS)[15], there was also a favorable evolution of clinical importance (Table 1).

CONCLUSIONS

Shrinking lung syndrome is a rare lupus pulmonary manifestation of uncertain etiology whose diagnosis relies on the association of restrictive pulmonary capacity without interstitial lung disease, pleural effusion, or phrenic nerve palsy. Dyspnea, pleuritic chest pain, and elevated diaphragm should raise suspicion for this diagnosis[16]. In most cases, it has a favorable long-term prognosis if detected early and treated properly to avoid irreversible restrictive disturbances sequelae; however, in some case series, only 20% of patients normalize pulmonary function[9,16], while rest of them show only functional improvement or even stabilization of lung function[17].

Table 1. Evolution of the most important parameters.

	Before pulmonary rehabilitation	After aminophylline discontinuation	After pulmonary rehabilitation
FVC (% of predicted)	60.4	36.2	49.7
FEV1 (% of predicted)	61.2	40.3	54.2
TLC (% of predicted)	60.3	40.7	51.2
RV (% of predicted)	58.4	46	60.6
DLCO (% of predicted)	56.8	**	**
KCO (% of predicted)	91.7	**	**
pO_2 (mmHg)	80.3	77.4	77.5
VO_2 (ml/kg/min; % of predicted)	17.8 (62)	–	–
6-min walk test (m)	142	–	462*
Exercise tolerated time (min)	9:25	–	30*
Borg Scale	10	10	3
mMRC	2	3	1
LCADL	26	–	17*
HADS	16	–	12*

FVC: forced vital capacity; TLC: low total lung capacity; FEV1: forced expiratory volume; RV: residual volume; DLCO: reduced diffusing capacity for carbon monoxide; KCO: transfer coefficient of the lung for carbon monoxide; mMRC: modified medical research council dyspnea scale; LCADL: the London chest activities of daily living scale; HADS: hospital anxiety and depression scale. *Considered minimal clinically important difference (MCID). **Not calculated because of low volumes.

This case report is noteworthy, not only due to the rarity of this syndrome and the clear advantages of multidisciplinary management, but also essentially to stress out the core importance of pulmonary rehabilitation as a non-pharmacological tool that unquestionably reinforces therapeutic armamentarium not only on lupus shrinking lung syndrome but also on any chronic lung disease.

AUTHORS' CONTRIBUTIONS

JP: Writing – original draft, Writing – review & editing. **JCC:** Writing – original draft, Writing – review & editing. **CR:** Writing – original draft, Writing – review & editing. **FC:** Writing – original draft, Writing – review & editing. **LA:** Writing – original draft, Writing – review & editing.

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SHORT COMMUNICATION
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Atypical presentation of COVID-19 with multi-organ involvement in a pediatric patient

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Studies have shown that severe cases of COVID-19 are particularly rare in pediatric populations and deaths have been registered in less than 0.1% of infected children[1]. However, there is emerging evidence of systemic inflammatory response in children with COVID-19 which may be associated with a high risk of unusual multi-organ involvement and unfavorable outcomes[2,3].

We described a case of a 6-year-old boy with COVID-19 who was admitted to a pediatric public hospital in Brazil presenting a 5-hour history of acute diarrhea as the first symptom of the disease. On admission, he was afebrile, and his vital signs were unremarkable. Findings on chest radiography were normal (Figure 1A), but laboratory investigation revealed lymphopenia, increased prothrombin time, hypernatremia, hyperkalemia, and metabolic acidosis.

During the first 24 hours of admission, the child progressed to respiratory distress and was admitted to the pediatric intensive care unit (PICU) requiring endotracheal intubation and mechanical ventilation. A nasal swab sample was collected and the result for SARS-CoV-2 testing using RT-PCR assay was positive. After PICU admission, the child presented fever (38.3°C), increased levels of aspartate transaminase (AST), elevated levels of blood urea nitrogen (BUN) and creatinine, high levels of C-reactive protein (CRP), hypernatremia, and hypokalemia. New chest radiography showed no signs of pneumonia (Figure 1B) and blood culture results were negative.

During the clinical course of the disease, the child remained with fever, lymphopenia, liver and kidney impairment, diarrhea, and electrolyte and acid-base imbalance. Moreover, 10 days after PICU admission, a neurological evaluation revealed somnolence, rapidly progressive bilateral limb weakness, generalized hypotonia, hyporeflexia, and a diagnosis of Guillain-Barré syndrome (GBS) was suspected. However, an attempted lumbar puncture was unsuccessful. Transthoracic echocardiography showed normal cardiac anatomy and function (Figure 2). The treatment during the stay in the PICU included antibiotic therapy with meropenem and azithromycin, ivermectin, dexamethasone, red cell concentrates, and peritoneal dialysis due to renal insufficiency. On day 14 of hospitalization, the child died from cardiac arrest. Laboratory examination results are shown in Table 1.

Although most children have a favorable outcome after confirmed COVID-19 possibly due to limited expression of angiotensin-converting enzyme 2 (ACE2)[4], it has been proposed that some cases can present a dysregulated immune response associated with the SARS-CoV-2 infection with multi-organ dysfunction even in the absence of significant respiratory involvement. Gastrointestinal symptoms and urinary complications have been reported[5] and the development of acute kidney injury might be a crucial negative prognostic factor for survival[1]. A "multisystem inflammatory syndrome in children" (MIS-C) has been emerged as a new and potentially life-threatening childhood condition associated with SARS-CoV-2 infection and has been characterized by the persistence of fever, severe illness necessitating hospitalization, the manifestation of signs or symptoms of multi-organ dysfunction, laboratory evidence of inflammation and lacking an alternative diagnosis[2,6]. For these rare cases, it has been proposed the use of steroids and intravenous immunoglobulin, but further clinical trials are needed to implement evidence-based treatment protocols in MIS-C[6].

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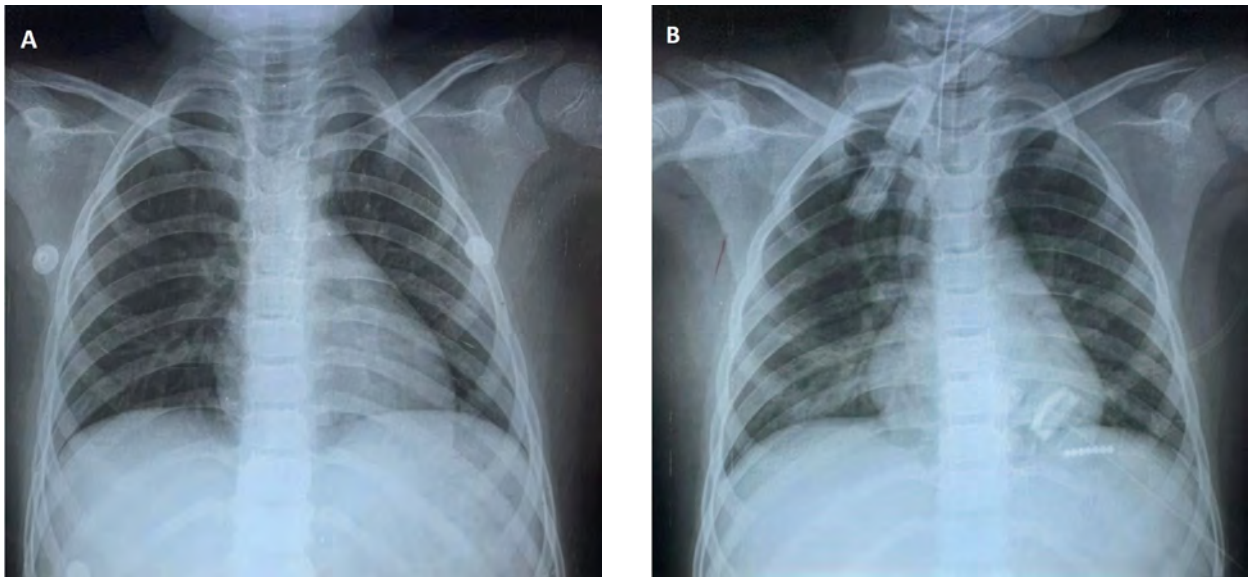

Figure 1. Chest radiographs. No radiological findings of pneumonia were present in the Day 0 (A) and Day 1 (B) of admission.

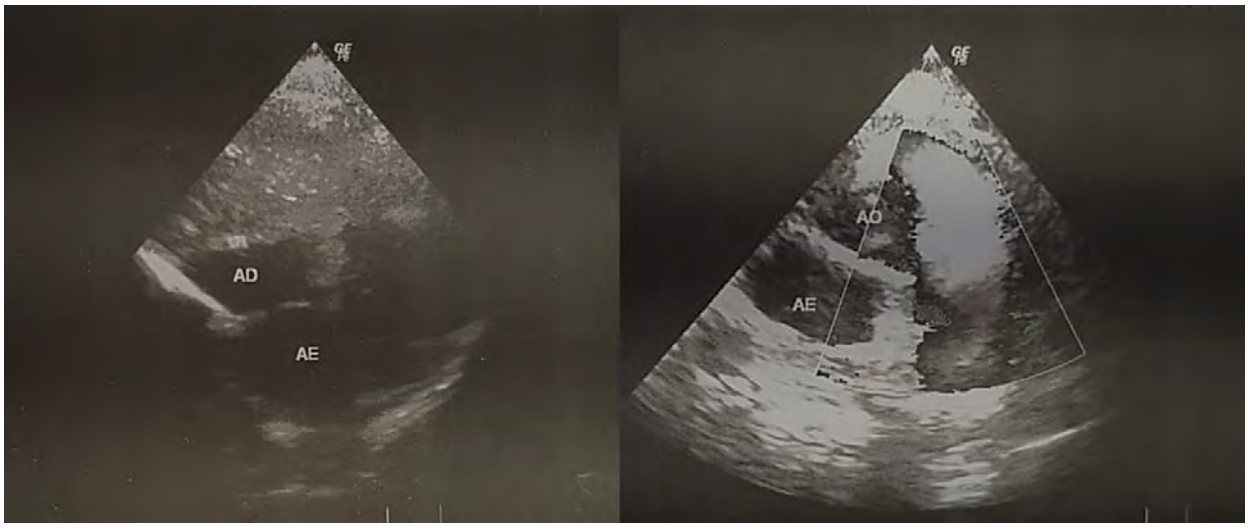

Figure 2. Transthoracic echocardiography. No cardiac morphology and function abnormalities were found previously to the cardiac arrest.

Although a causal association between SARS-CoV-2 infection and neurological symptoms is still unknown, some studies have reported GBS as a complication in adults with COVID-19[7,8]. To date, no cases of GBS have been reported in children with COVID-19. In the present case, the hypothesis of GBS was sustained based on clinical criteria in the absence of alternative diagnosis for weakness and unavailable electrophysiological and cerebrospinal fluid (CSF) evaluation. There is emerging evidence that preceded upper respiratory infection or enteritis increased the risk of GBS9. Pathogenesis of GBS has been associated with increased levels of IL-6 and TNF-alpha which can lead to demyelination and axonal damage[9]. Since SARS-CoV-2 infection is associated with an aberrant systemic inflammatory response, multi-organ complications that can also lead to respiratory failure such as GBS should be investigated during the clinical course of COVID-19.

Table 1. Laboratory findings during the clinical course of disease.

Parameter	Reference	Result							
		Day 0[a]	Day 1[b]	Day 3	Day 4	Day 7	Day 8	Day 10	Day 13
Hematological and coagulation function									
Hemoglobin, g/dL	11.5–14.5	14.1	10.6	10	8.7	16.7	12.3	11.7	10.5
Hematocrit (%)	33–43	41.2	31.4	29.3	25.6	38.1	NA	NA	32.8
WBC, 10^3 cells/mm^3	4–15.5	15	5.4	3.3	4.5	7	11.6	16.3	3.5
Lymphocytes (%)	25–54	8.9	17	30	23	10	11	15	18
Platelet count, 10^3 /mm^3	150–450	300	153	147	83	121	162	253	178
INR	0.9–1.2	1.6	NA	NA	NA	0.9	NA	1.5	NA
PT, seconds	8.7–11.5	19.1	NA	NA	NA	NA	NA	NA	NA
APTT, seconds	26–35	24	NA	NA	NA	NA	NA	NA	NA
Liver function tests									
AST, units/L	15–50	NA	78	94	89	NA	85	NA	NA
ALT, units/L	5–55	NA	10	20	32	NA	78	NA	NA
Albumin, g/dL	3.5–5.6	NA	NA	NA	1.9	NA	NA	NA	2.0
Kidney function tests									
Blood urea nitrogen, mg/dL	2–20	NA	92	93	109	130	147	140	52
Creatinine, mg/dL	0.3–0.7	NA	2.9	3.9	4.7	3.2	1.5	1.7	0.9
Inflammatory marker of myocardial injury									
cTnI	Negative	NA	NA	NA	Negative	NA	NA	NA	NA
Serum electrolytes									
Sodium, mEq/L	130–147	159	157	157	168	149	166	185	154
Potassium, mEq/L	3.5–5.1	7	2.2	3.8	2.9	2.6	2.8	6	3.1
Calcium, mEq/L	8.8–10.8	8.3	8.6	9.8	8.7	8.2	8.4	10.2	8.4
Infection-related indices									
CRP, mg/dL	<0.8	NA	96	48	NA	12	<0.8	<0.8	6
Blood gas analysis									
pH	7.35–7.45	7.09	7.38	7.12	7.08	7.38	7.36	7.22	7.41
PO_2, mmHg	70–108	77	156.4	98.3	95.1	108.8	85	82.1	72.9
PCO_2, mmHg	32–48	39.1	23.5	60.3	58.3	37.3	43	59.4	42
HCO_3^-, mEq/L	19–28	11.6	16.4	16.5	14.4	22	23	20.6	25.5
Base excess, mEq/L	-2 – +2	-18.2	-11.5	-10.1	-13.1	-2.8	-1.2	-3.5	1.7
$SatO_2$ (%)	90–95	91.2	99.2	94	98	97.4	95	92.6	93.2

[a]First 24 hours of hospital admission. [b]Pediatric intensive care unit admission. WBC: white blood cells; INR: international normalized ratio; PT: prothrombin time; APTT: activated partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; cTnI: cardiac troponin I; CRP: C-reactive protein; PO_2: partial pressure of oxygen; PCO_2: partial pressure of carbon dioxide; HCO_3^-: serum bicarbonate; $SatO_2$: oxygen saturation. NA, not evaluated. Values given in this table are commonly accepted reference ranges compiled from many sources.

This unusual case may provide additional data to better understanding the complexity of COVID-19 and to alert pediatricians who attend critically ill children with the disease. Studies are urgently needed to better understand the clinical course of children with COVID-19, particularly of those with multi-organ involvement requiring intensive care.

AUTHORS' CONTRIBUTIONS

PRMF: Conceptualization, Writing – original draft. **CST:** Conceptualization. **SJGSO:** Conceptualization, Data curation, Formal Analysis. **PCNS:** Conceptualization, Data curation, Formal Analysis. **MBBR:** Conceptualization, Data curation, Formal Analysis. **VSS:** Conceptualization, Writing – original draft. **DCFL:** Conceptualization, Data curation, Formal Analysis.

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Evaluation of taste and smell disorders in pediatric COVID-19 Cases

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SUMMARY

OBJECTIVE: Pediatric coronavirus disease 2019 (COVID-19) cases have a high risk of contagiousness, as they usually progress with asymptomatic or mild respiratory symptoms. Disorder in taste and/or smell has rarely been reported in pediatric cases. In our study, early diagnosis and isolation measures were emphasized by evaluating the clinical, laboratory, and radiological imaging findings of pediatric COVID-19 cases presenting with symptoms of taste and/or smell disorder.

METHODS: Seven cases aged 0–18 years were included in the study. The severe acute respiratory syndrome coronavirus-2 polymerase chain reaction test was performed for the seven cases presented with taste and/or smell disorders. Clinical findings, laboratory tests, and radiological imaging of all the cases were evaluated on the day of admission and on the fifth day.

RESULTS: Seven (5.7%) of 122 pediatric COVID-19 cases had disorder in taste and/or smell. In two cases, pneumonia findings were detected in thorax computed tomography imaging. It was observed that all the patients fully recovered at the latest on the 21st day. In the cranial diffusion magnetic resonance imaging of a case, diffusion restriction was detected in the corpus callosum splenium.

CONCLUSION: Although less common than adults, children with COVID-19 may also have taste and smell disorders, and this may be accompanied by central nervous system imaging findings.

KEYWORDS: Child. Coronavirus disease 2019. Smell. Taste.

INTRODUCTION

The new coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) often presents with fever, weakness, dry cough, muscle pain, respiratory distress, vomiting, and diarrhea symptoms[1-3], as well as taste and smell disorders, although these symptoms are less frequently found in adult COVID-19 cases. However, there is insufficient data on the frequency of taste and smell disorders in pediatric COVID-19 cases[3-6].

Angiotensin-converting enzyme 2 (ACE2) is widely available on the oral and nasal mucosa and has been identified as a cellular receptor for SARS-CoV-2[7,8]. It has been reported that SARS-CoV-2 can adhere to the oral mucosa, tongue, nasal respiratory epithelium, and olfactory epithelial support cells;

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and this is associated with taste and smell disorders in COVID-19 cases[8,9]. It is known that ACE2 in the nasal mucosa participates in inflammatory processes through peptides such as bradykinin[10]. However, significant inflammatory and rhinitis symptoms are generally absent in the nasal mucosa of COVID-19 patients[4,5]. Therefore, it is reported that the disorder in the sense of smell may be related to the virus affecting the olfactory pathways[2,11,12]. SARS-CoV-2 binds to the sialic acid receptors on taste pores[2]. Sialic acid is a protector of glycoproteins against the enzymatic effects of taste molecules in taste pores. The decrease in the sialic acid effect causes an increase in the taste threshold[13].

Pediatric COVID-19 cases with asymptomatic or mild clinical symptoms are an important factor in the spread of the virus. The symptoms of COVID-19 are well known, and the early diagnosis of the disease will contribute significantly to the prevention of virus spread. The aim of this study is to investigate the frequency of taste and smell disorders and clinical laboratory findings in pediatric COVID-19 cases.

MATERIALS AND METHODS

The study was performed retrospectively in pediatric COVID-19 cases who were admitted to the Ministry of Health Sakarya University Training and Research Hospital between March 15, 2020 and June 15, 2020. The study included cases who were positive for COVID-19 polymerase chain reaction (PCR) test and admitted to the hospital with taste and/or smell disorder. One of the criteria for inclusion in the study was that the patients were between the ages of 0–18. However, 7 patients included in the study due to taste and smell disorders were between the ages of 11–17. The vital signs and physical examination findings were recorded at the time of admission. In addition, the following test results, which were taken during the time of admission and on the fifth day, were recorded: complete blood count (CBC), C-reactive protein (CRP), procalcitonin (PCT), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase (CPK), lactic dehydrogenase (LDH), ferritin, troponin I, and D-dimer. Chest X-rays, thoracic computed tomography (CT), cranial magnetic resonance (MR), and diffusion MR images were evaluated by the same radiologist. The results are shown as descriptive tables. An Ethics Committee approval from the Sakarya University Medical Faculty was obtained for this study (Ethics Committee Number: 71522473/050.01.04/288).

RESULTS

In this study, taste and/or smell disorder was detected in 7 (5.7%) of 122 pediatric cases who were positive for the COVID-19 PCR test. Two patients had taste disorder, and five patients had taste and smell disorders. It was determined that taste and/or smell disorder started on the day of admission in four cases, 2 days before admission in two cases, and 3 days before admission in one case. The symptoms of the patients during hospital admission are shown in Table 1. The vital and physical examination findings of all the cases were within normal limits during hospital admission. New symptoms or signs were not detected

Table 1. Demographic data and clinical findings of the study group.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gender	Female	Male	Female	Male	Female	Male	Male
Age (year)	17	17	15	15	11	15	16
Reason for admission to the hospital	Headache, sore throat, diarrhea, decreased taste and smell	Decreased taste and smell	Decreased taste and smell	Decreased taste and smell	Headache, sore throat, decreased taste	Headache, decreased taste	Headache, decreased taste and smell
Time to start taste or smell disorder	Admission	Admission	Admission	Admission	3 days before admission	2 days before admission	2 days before admission
Respiratory rate (/min)	24	26	24	24	20	22	16
Disease severity	Moderate	Mild	Mild	Moderate	Mild	Mild	Mild
Time to improve symptoms	21st day	5th day	21st day	5th day	5th day	14th day	5th day

during the 5-day clinical follow-up. It was observed that the symptoms of taste and smell disorders recovered completely on the 5th day in four cases, on the 14th day in one case, and on the 21st day in two cases. Five cases with no findings on thorax CT imaging were evaluated as mild disease, and two cases with unilateral or bilateral ground glass images on thorax CT imaging were evaluated as moderate disease. Three cases were treated with hydroxychloroquine sulfate for 5 days, and three cases were treated with hydroxychloroquine sulfate and azithromycin for 5 days. One case was not treated because the family did not allow it. Demographic characteristics and clinical findings of the cases are shown in Table 1. The COVID-19 PCR test was positive in all cases during hospital admission. Control PCR tests taken on the 14th day were negative for five cases. It was found that one of the cases with positive PCR test on the 14th day became negative on the 22nd day and the other on the 32nd day. In two cases, the lymphocyte count was lower than 1,500/mm^3 during admission, and in two cases, the D-dimer was higher than normal limits. However, both values were within normal limits in the follow-up of all cases. Chest X-ray images of all cases included normal findings. Thorax CT imaging revealed a subpleural ground glass opacity in both lungs in one case and only in the left lung in one case. Cranial diffusion MR imaging was performed in all patients. Diffusion restriction was determined in the corpus callosum splenium section in a case of diffusion MR imaging. It was observed that diffusion restriction improved in control diffusion MR imaging after 14 days (Figure 1). Laboratory examinations and radiological imaging findings of our cases are shown in Table 2.

DISCUSSION

In our study, 5 (4.0%) of 122 pediatric COVID-19 cases had taste and smell disorders and 2 (1.6%) had only taste disorder. Lechien et al. found that taste disorder was 88% and smell disorder was 85.6% in 417 mild-to-moderate COVID-19 adult cases, and they reported a significant relationship between taste and smell disorders[5]. In the meta-analysis conducted by Passarelli et al., it was reported that the taste disorder varied between 5.6% and 88%, and the smell disorder ranged between 5.1% and 85.6%. The taste and smell disorder together was 18.6%[14]. In the literature, there is no study investigating the frequency of taste and smell disorders in pediatric COVID-19 cases. In our study, the taste and smell disorders were found to be very low compared with studies involving adults. It was thought that these low rates may be related to the mild clinical course of the disease in children and difficulties in defining the taste and smell disorders of children. Our results have supported this speculation, five cases had mild disease and two cases had moderate disease.

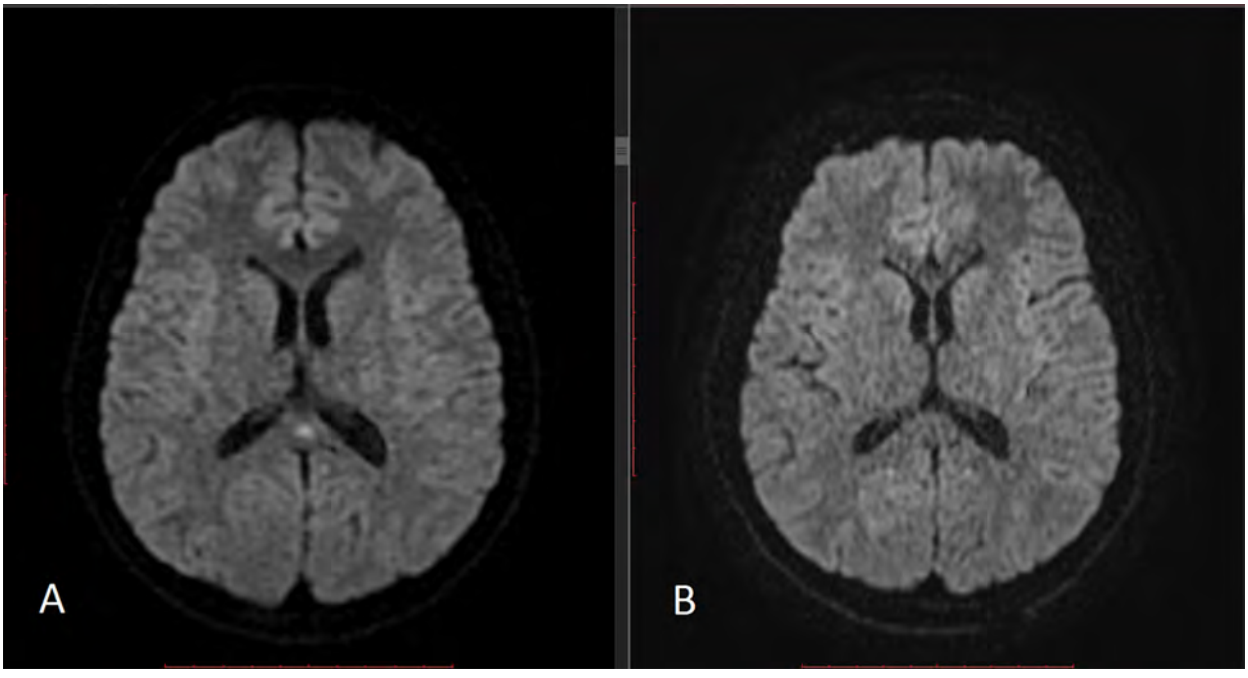

Figure 1. (A) Diffusion restriction in the corpus callosum splenium region (white arrow) in cranial diffusion magnetic resonance imaging of Case 6. (B) Normal findings in control diffusion magnetic resonance imaging of the same case after 14 days.

Table 2. Laboratory examinations and radiological imaging findings of the study group.

	Test time	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
WBC (/ mm^3)	During admission	5,480	4,820	5,520	6,560	8,710	4,780	5,040
	5th day	5,540	6,130	5,300	6,740	5,910	6,740	4,950
LYM (/ mm^3)	During admission	2,510	1,220	1,800	2,010	1,460	1,500	2,080
	5th day	2,620	2,930	1,800	2,750	2,060	2,260	2,080
CRP (mg/L)	During admission	1.23	8.95	0.23	<3.11	<3.11	7.64	5.17
	5th day	<3.11	8.52	0.29	<3.11	<3.11	1.9	1.5
PCT (ng/ mL)	During admission	0.02	0.05		0.03	0.04	0.05	0.02
	5th day	0.02	0.02		0,02	0.03	0.02	0.02
CPK (u/l)	During admission		66	58	91	51	100	111
	5th day	47	42	44	58	28	65	64
LDH (u/l)	During admission	214	203	223	201	228	246	164
	5th day	134	196	175	187	148	227	179
Ferritin (µg/L)	During admission	22.4	16	12.4	70.9	6.5	76.4	88.7
	5th day	15.5	21.5	11.4	75.8	7.3	89	116
Troponin (ng/L)	During admission	0.0	0.0	0.0	0.6	1.1	1.0	0.1
	5th day	0.6	0.8	0.0	1.3	0.3	1.2	76
D-Dimer (FEU µg/L)	During admission	197	669	585	31	85	173	139
	5th day	276	533		115	128	<110	127
SARS-CoV-2 PCR test result	During admission	Positive	Positive	Positive	Positive	Positive	Positive	Positive
	14th day	Positive (22nd negative)	Negative	Negative	Negative	Negative	Positive (32nd negative)	Negative
SARS-CoV-2 Ig G/M test result	14th day	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Cranial diffusion MR imaging	During admission	Normal	Normal	Normal	Normal	Normal	Diffusion restriction in corpus callosum splenium	Normal
Thorax CT imaging	During admission	Subpleural ground glass view in both lungs	Normal	Normal	Subpleural ground glass view in left lungs	Normal	Normal	No screening

WBC: White blood cell count (Normal value: 4.6–10.2 K/µL); LYM: lymphocyte count (Normal value: 0.6–3.4 k/µL); CRP: C-reactive protein (Normal value <3.11 mg/L); PCT: procalcitonin (Normal value <0.5 ng/mL); CPK: creatine phosphokinase (Normal value: 0–145 U/L); LDH: lactate dehydrogenase (Normal value: 180–430 U/L); MR: magnetic resonance; CT: computed tomography.

It is known that taste and smell disorders are related to viral infections. In particular, smell disorders have been associated with nasal congestion, rhinorrhea, and olfactory epithelial involvement[15]. However, symptoms of inflammation and rhinitis are often absent in the nasal mucosa of COVID-19[4,5,16]. Yan et al. evaluated 1,480 patients with influenza-like symptoms. While 68% of 59 COVID-19-positive patients had anosmia and 71% had ageusia, 17% of 203 COVID-19-negative patients had anosmia and 16% had ageusia. It has been shown that smell loss and taste loss independently have a strong relationship with COVID-19 positivity[6]. In our study, the symptoms of nasal obstruction or rhinorrhea were not detected in any case.

It has been reported that taste and smell disorders in adult COVID-19 can be seen before the expected classic symptoms as well as during and after the disease course[17]. Lechien et al. reported that 11.8% of 417 adult COVID-19 cases had smell disorder earlier than other symptoms[5]. In our study, it was determined that taste and smell disorders started at the time of admission in four cases, 2 days before admission in two cases, and 3 days before admission in one case. Taste and smell disorders were earlier than other symptoms in three cases. It was reported by Yan et al. that COVID-19 smell disorder improved in 74% of cases with the disappearance of other symptoms[6].

Lechien et al. reported that 67.8% of adult COVID-19 cases with taste and smell disorders recovered within the first 8 days, and 4% cases took over 15 days to recover[5]. In the literature, there is no data on when the taste and/or smell disorders may improve in pediatric COVID-19 cases. In our study, it was observed that the symptoms of all cases resolved between 5 and 21 days. In our study, three of the five mild cases recovered on the 5th day, one case recovered on the 14th day, one case recovered on the 21st day, one of the two moderate cases improved on the 5th day and the other improved on the 21st day. Therefore, it is thought that it is not possible to comment on the relationship between the clinical severity of the disease and the recovery time of taste and smell disorders.

In COVID-19 studies, it was reported that smell disorder improved significantly within 1–2 weeks, and the frequency of central nervous system symptoms was observed at a much lower rate than smell disorders[5,6,17,18]. It was emphasized that the target of SARS-CoV-2 is not neurons, but may be other non-neuronal cells expressing ACE2 receptors such as olfactory epithelium support cells, microvillus cells, Bowman's gland cells, horizontal basal cells, and olfactory bulbus pericides[9]. For this reason, it seems that smell disorders in COVID-19 are not associated with a viral damage that directly or indirectly affects neuronal cells[2]. In our study, one of the patients with taste disorder had diffusion restriction in the corpus callosum splenium. Control diffusion MR imaging of this case was normal after 14 days. Unlike other cases, it was found that the COVID-19 PCR test became negative on the 32nd day. Since it was a condition detected in one case, no relation could be made about the relationship between pathological MR finding and taste disorder. In the literature, no data with diffusion restriction in the corpus callosum splenium section were found in the diffusion MR images of the adult and pediatric COVID-19 cases. We evaluated the present MR imaging finding as COVID-19 central nervous system involvement. This result suggests that the relationship between the time the virus is present in the body and the central nervous system involvement may be among the research topics in the future.

The most important limitation of our study is that due to the insufficiency in the number of cases, the necessary statistics could not be made in order to detect differences in age, gender, and groups receiving and not receiving antiviral therapy.

CONCLUSIONS

In conclusion, in our study, it was found that taste and smell disorders can be seen alone or with other symptoms in pediatric COVID-19 cases and their frequency is less than that in adults. Although the longer duration of SARS-CoV-2 in children with taste and smell disorders may be associated with the central nervous system imaging findings, further studies are needed.

AUTHORS' CONTRIBUTIONS

BE, PDÇ, MFO, GA, İC, AT, ÖFA, HT: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing, Formal analysis, Funding acquisition, Software, Supervision of the study.

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Ophthalmological knowledge of Family Health Network physicians working as first care providers in Brazil

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SUMMARY

OBJECTIVE: First care providers working in the Brazilian Unified Health System are often physicians from the Family Health Program. Their knowledge on ophthalmology could indicate whether there is a need for training to decrease ophthalmological demands to secondary or tertiary health levels.

METHODS: A cross-sectional observational study based on an electronic questionnaire was conducted to evaluate the ophthalmological knowledge of Family Health Program physicians working at the VI Regional Health Department, Sao Paulo, Brazil. All Family Health Program physicians from this regional health department were invited, and the study included those who responded to the full questionnaire (115 physicians). The data were evaluated using descriptive analysis.

RESULTS: There was no difference in the ophthalmological knowledge between sexes or in relation to undergraduate schools. Only 20% of the interviewees were specialized in Family and Community Medicine, which did not influence the number of correct answers. Only 22 (19.1%) physicians reported having enough knowledge about the main eye disorders, and 82 (71.3%) physicians considered themselves capable of treating ophthalmological emergencies. However, acute glaucoma was recognized by only 51 (44.3%) physicians, and eye perforations could only be handled by 65 (56.5%) of them. In addition, only 47 (40.9%) participants correctly answered that congenital cataracts should be operated right after diagnosis.

CONCLUSIONS: Family Health Program physicians working as first care providers in the Health System in Brazil presented poor ophthalmological knowledge. Providing training on ophthalmology may improve the ophthalmological care at the primary level within SUS and reduce the case demands at other healthcare levels.

KEYWORDS: Ophthalmology. Health personnel. Regional health strategies. Unified health system. Family health strategy.

INTRODUCTION

The Family Health Program (FHP) strategy is considered as the main strand of Primary Health Care (PHC). Effective PHC actions depend on training physicians to perform well in primary care[1-3].

In contrast, ophthalmological care within the Brazilian Unified Health System (SUS) needs improvement, since it is a specialty that often requires the use of expensive equipment[4,5].

Family Health Physicians (FHPh) with basic knowledge to recognize ophthalmological conditions can diagnose and

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treat low-complexity cases, as well as correctly refer patients to specialized services[6-8].

The objective of this study was to evaluate the ophthalmological knowledge of FHPh to build tools that can be used in training.

METHODS

This study considered the ethical principles that guide researches involving human subjects and was approved by the Research Ethics Committee of School of Medicine (FM), UNESP, Sao Paulo, Brazil. All participants signed an informed consent form, and the anonymity of the participants was guaranteed by data masking.

This was a cross-sectional, observational study, based on an electronic questionnaire administered to FHP physicians working at RHD-VI, Sao Paulo, Brazil. The questionnaire was developed by the authors through the Moodle Platform and included personal and medical training data and questions to evaluate the general and emergency ophthalmological knowledge. Sex, age, time of training, type of undergraduate institution, country where they studied, and whether the professional was specialized in Family and Community Medicine (FCM) or not were considered as independent variables[9].

INCLUSION CRITERIA

All physicians who worked in the RHD-VI FHP were invited to participate[10].

EXCLUSION CRITERIA

Physicians acting in other RHD, not working in FHP, and those who did not respond to the questionnaire fully were excluded from the study.

STATISTICAL ANALYSIS

Descriptive statistics was used to analyze the responses. Sex and the undergraduate institution variables were associated using the Goodman's test, which involves contrasts between and within multinomial populations[11,12]. The following expression was used for the percentage of correct answers, p(%)=n/30×100%, where "n" represents the number of correct answers. The Student's *t*-test was used to compare sex, undergraduate institution, and FCM specialization. The Pearson's linear correlation assessed the association of this percentage with time since graduation and patient age[13] (p=5%).

RESULTS

In the study period, the RHD-VI had a total of 214 FHPh, and 115 questionnaires were considered for the survey. Of the participants, 81 (70.4%) were male. The participants presented a mean age of 33.1±7.8 years and a median age of 30.5 years (Table 1).

The duration of the undergraduate course was noted to be 5 years for 64 (55.7%) participants, 58 (50.4%) participants were noted to have studied in a public institution, and 111 (96.5%) participants studied in Brazil. Only 23 (20%) participants were confirmed to have had FCM residence or specialization. The percentage of correct answers to our questionnaire was not related to sex, public or private medical undergraduate course, or having an FCM residence or specialization (Table 1). It was also not associated with training duration, age, or time since graduation. Physicians who graduated in public or private institutions reported having received only notions of ophthalmology in their undergraduate course.

About 58 (50.4%) interviewees reported having treated patients with eye complaints sometimes. Knowledge on the

Table 1. Descriptive measurements of variables by categories and in general.

		Minimum value	Median	Maximum value	Mean	Standard deviation	p-value*
Age (years)		25.0	31.0	62.0	33.1	7.8	–
Years since graduation		0	4.0	36.0	7.0	7.6	–
Correct answers (%)		23.3	66.7	86.7	65.9	13.8	–
Correct answers (%)	Women	30.0	66.7	86.7	63.5	13.4	0.232
	Men	23.3	70.0	86.7	66.9	14.0	
Correct answers (%)	Public	23.3	70.0	86.7	66.9	15.2	0.444
	Private	30.0	66.7	86.7	64.9	12.4	
Correct answers (%)	No FCM specialization	23.3	63.3	83.3	59.9	16.5	0.018
	FCM specialization	30.0	70.0	86.7	67.4	12.8	

*Student's *t*-test for independent samples.
FCM: Family and Community Medicine.

main eye conditions was reported as "reasonable" by 22 (19.1%) physicians, and only 44 (38.3%) physicians considered themselves capable of evaluating visual acuity using tables.

As for general ophthalmology, physicians who did not have an FCM specialization had a significantly higher rate of correct answers than those who had it (p <0.05). However, there was no statistical difference regarding ophthalmological urgencies knowledge (p>0.05) in the percentage of correct answers (Table 2).

As for the ability to identify ophthalmological emergencies, 82 (71.3%) physicians believed they were qualified. Only 18 (15.7%) physicians were able to report the most prevalent cause of irreversible blindness in the world. Most of them (96 physicians, 83.5%) knew that age-related cataract was the leading cause of cataract in the world, and 83 (72.2%) physicians marked the correct response about a clinical case of age-related cataract.

Only 47 (40.9%) physicians can manage correctly a case of congenital cataracts. Most of them (84 physicians, 73%) recognized that the detection and treatment of strabismus in children under seven years of age is important to prevent amblyopia. Seventy-five (65.2%) participants knew that visual deprivation in childhood can lead to amblyopia, and most of them (94 participants, 81.7%) knew the importance of detecting strabismus early in childhood. Refractive errors, such as presbyopia (78 participants, 67.8%) and myopia (95 participants, 82.6%), can also be recognized by most of them.

Most physicians (93, 80.9%) already observed the effects of properly treating diabetic retinopathy and are aware of the time to refer diabetic patients for ophthalmological evaluation (82, 71.3%). However, only 34 (29.6%) physicians correctly answered about the main cause of sudden vision loss in diabetic patients.

Regarding the importance of fundus examination in hypertensive patients, 63 (54.8%) physicians responded correctly, and most of them (94, 81.7%) recognized the most frequent cause of bilateral exophthalmia. The relationship between decompensated diabetes and myopic shift was known by 71 (61.7%) interviewees.

Most of the participants (100, 87%) are able to correctly perform the initial management of trauma in cases of alkali-induced eye burns. However, only 51 (44.3%) participants can recognize the clinical signs of acute glaucoma, 65 (56.5%) participants knew the initial behavior in ocular perforations, and 55 (47.8%) participants knew how to recognize the signs of blunt eye trauma.

Most of the participants can diagnose conjunctivitis (99, 86.1%), recognize the most common type of conjunctivitis (88, 76.5%), and know how to treat acute conjunctivitis (104, 90.4%). In addition, most of the participants (96/83.5%) can differentiate between bacterial and viral conjunctivitis. Most of the participants (99, 86.1%) correctly managed the cases of initial allergic conjunctivitis.

However, signs and symptoms of anterior uveitis and the differential diagnoses of conjunctivitis were only recognized by 28 interviewees (24.3%). Conditions such as retinal detachment (93, 80.9%) and orbital cellulitis (94, 81.7%) were recognized by the majority. In contrast, only 52 physicians (45.2%)

Table 2. Descriptive measurements of the percentage of correct answers by group of physicians with or without specialization in Family and Community Medicine.

Questions	Descriptive measurement	Specialization in Family and Community Medicine		p-value*
		Yes (n=23)	No (n=92)	
General ophthalmology	Mean	56.8	65.9	**<0.05**
	Standard deviation	20.3	15.6	
	Minimum value	6.7	13.3	
	Median	66.7	66.7	
	Maximum value	80	93.3	
Ophthalmological urgent care	Mean	63.7	69.1	**>0.05**
	Standard deviation	14.9	13.7	
	Minimum value	28.6	14.2	
	Median	71.4	71.4	
	Maximum value	85.8	92.9	

*Student's *t*-test for the percentage of correct answers in both study groups.

knew that rural workers can develop with traumatic corneal ulcer in the region.

DISCUSSION

This study evaluated the ophthalmological knowledge of physicians working in FHP at RHD-VI. There are only a few studies on the ophthalmological knowledge of PHC[14,15] professionals, which motivated this research. The results of the study found the need to complement the ophthalmological training of FHPh on several themes.

The physicians adhered to our study, with the research reaching almost all of them. Nevertheless, only fully completed questionnaires were considered in the study. The profile of FHPh working in the FHP in the analyzed region showed that most of them were men (81, 70.4%), which is related to the male predominant profile of the professionals working in FHP at RHD-VI (65.7% male professionals)[16].

The FHPh who participated in the research have a mean age of 33.1 years, and about half of them were trained for about 5 years, showing that the study included a large percentage of young professionals. This emphasized the presence of large number of recently graduated professionals working in PHC, who were there either to acquire more experience or due to a lack of other opportunities.

The number of private schools has increased much more than public schools in Brazil[17], which can be identified by the similar number of physicians coming from the public and private schools in the study. Only 20% of the interviewees were specialized in FCM, confirming the worrisome low demand for this specialization[18], although the consolidation of the FCM medical specialty is an essential condition to strengthen the current PHC guidelines. According to the interviewees, they frequently have ophthalmology cases; however, they evaluated their own knowledge of ophthalmology as poor.

The results showed no significant interference of sex, age, time since graduation, or graduated school in the percentage of correct answers, showing that, regardless of these variables, there is a need to better prepare these professionals in ophthalmological practice.

FCM specialization showed no significant effect on the percentage of correct answers. Although having an FCM specialization is seen as a positive point[1], the teaching of ophthalmology in such courses should be more emphasized.

Eye complaints are relatively frequent, but most physicians reported not being able to identify the main conditions that threaten vision. Questions on systemic diseases and general medicine had more correct answers since these subjects, such as general medical practice, are part of the syllabus, and the daily experience with patients increases the physicians' performance.

Questions about more common subjects in ophthalmology, such as conjunctivitis in general, cataract causes, retinal detachment findings, effects of prolonged steroid therapy, management of orbital cellulitis, concepts of amblyopia, and refractive errors, had a greater chance of correct answers since they were more related to general medicine. However, important causes of blindness and urgent eye conditions had less correct diagnoses and managements, such as congenital cataract, which is often underdiagnosed, affecting prognosis.

The lack of knowledge on ophthalmology affects health promotion and prevention, which is a concern for everyone working with basic health actions given the lack of training on eye conditions[19,20].

The results show that, in general, ophthalmological training is lacking, especially regarding visual disorders that cause irreversible vision consequences such as glaucoma, congenital cataracts, and strabismus, which can also cause uveitis and corneal ulcers. These are frequent disorders encountered in the FCM routine care that require early identification to avoid irreversible complications[21].

A large number of cases that could have been solved with basic care are referred to tertiary hospitals, which was anticipated in the introduction of this study. Undoubtedly, improving the basic care quality can reduce the number of ophthalmological demands resulting from low-complexity conditions in tertiary services[14].

One limiting factor of this research is the fact that it was a regional study, and thus broader studies covering other regions or states of the country are necessary to broaden the knowledge about this subject.

The positive points of this research included the fact that it was based on a questionnaire developed for this specific research, it evaluated a subject scarcely studied in the literature, and it showed that FHP physicians need further ophthalmological training. Based on the results, it was possible to elaborate didactic material directed at professional training to improve eye care at the PHC level and possibly decrease ophthalmological demands. This material can be found at: https://drive.google.com/file/d/1JGBpCvYz0siWUlYMgaNQ1KUeNbukUCXN/view.

CONCLUSIONS

The authors concluded that there is an important gap in the ophthalmological knowledge of FHPh, thus emphasizing the need for training to reduce the ophthalmological demand at other healthcare levels and to decrease the incidence of preventable blindness.

AUTHORS' CONTRIBUTIONS

ILCC, ENJ, SAS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DCMZ:** Software, Writing – original draft, Writing – review & editing. **CRP:** Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **ASSBSF:** Writing – original draft, Writing – review & editing.

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Potentially inappropriate medications, drug-drug interactions, and prescribing practices in elderly patients: a cross-sectional study

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SUMMARY

OBJECTIVE: To evaluate potentially inappropriate medications, potential drug-drug interactions, and prescribing practices in elderly ambulatory patients.

METHODS: We carried out a cross-sectional study on 275 elderly patients attending different outpatient departments. We used the Screening Tool for Older Person's Prescriptions criteria version two to identify potentially inappropriate medications, IBM Micromedex, to categorize potential drug-drug interactions as major and moderate. World Health Organization prescribing indicators were used to evaluate prescribing practices.

RESULTS: The prevalence of potentially inappropriate medications in 275 prescriptions was 21.9%. Diclofenac was the most common inappropriate drug (n=23). Metoprolol is the second most inappropriate drug (n=12). Amlodipine and clopidogrel, aspirin and furosemide, and aspirin and spironolactone together accounted for 71.42% of major interactions (n=15). Atorvastatin and clopidogrel was the most common moderate drug-drug interaction in our study (n=24). The average number of drugs per encounter, the percentage of drugs with a generic name, and the percentage of drugs from the essential drugs list must be improved.

CONCLUSION: There is a need to provide awareness through education about the explicit criteria to identify potentially inappropriate medications and prescribing indicators that aid in rational prescribing in the elderly.

KEYWORDS: Aged. Drug interactions. Potentially inappropriate medication list. STOPP. Inappropriate prescribing.

INTRODUCTION

The aging population across the world is increasing. By 2050, 16% will be elderly, compared to 9% in 2019[1]. Increasing age is a risk factor for chronic diseases and comorbidities. Subsequently, the need to administer drugs to manage them also increases. As a result, the chances of polypharmacy increase and may contribute to drug-related problems such as potential drug-drug interactions, adverse drug reactions, inappropriate prescribing.

Inappropriate prescribing in the elderly is a global concern. The global prevalence of potentially inappropriate prescribing ranges from 13–35%[2]. It is directly linked to substantial morbidity, mortality, and wastage of health resources[3]. The physician's poor choice of medication is a significant cause of ADRs among older people[3]. These adverse effects of inappropriate prescribing need to be prevented, owing to the problem's seriousness. Potentially inappropriate prescribing tools are developed to achieve this goal.

Potential drug-drug interactions due to inappropriate prescribing is another severe problem. Approximately 3–26% of adverse reactions related to hospital admissions are due to drug-drug interactions[4]. Clinically significant drug-drug interactions may occur with narrow therapeutic index, microsomal enzyme inhibitors, severely ill patients, compromised renal and hepatic

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function, and older adults with polypharmacy[5]. The drug-drug interactions can be categorized as major and moderate based on the severity of the interaction. Major drug-drug interaction is life-threatening, whereas moderate interaction exacerbates the patient's clinical condition[IBM]. So, there is a need to promote the rational use of drugs. It helps to eliminate polypharmacy, inappropriate prescribing, and any drug-drug interactions.

Congruent with this, the present study aimed to evaluate the inappropriate prescribing in the elderly using Screening Tool to Older Person's Prescriptions (STOPP) criteria version 2.0, potential drug-drug interactions and their management using IBM Micromedex database, and the rational use of drugs with the help of core drug use indicators by World Health Organization.

METHODS

We conducted a cross-sectional study on elderly patients attending different outpatient departments in a tertiary care hospital. The study was conducted for six months (01/08/2019–31/01/2020). We used a simple random sampling technique to select geriatric patients. Each geriatric patient was allotted a number at the beginning of the consultation with the doctor and using a random number generator, and they are selected randomly. The estimated sample size was 270 (margin of error=5%, 95%CI, population size=900, response distribution=50%).

We included elderly patients (age ≥65 years), prescribed with at least one drug, and excluded inpatients and patients who cannot spare their time due to time constraints. Our study was approved by the Institutional Human Ethics Committee (VIPT/IEC/89/2019). We clearly explained the aim of the study to each participant and obtained written informed consent from them.

Study instruments

We used the Screening Tool for Older Person's Prescriptions criteria version 2.0 to identify potentially inappropriate medications. IBM Micromedex®3 was used to categorize drug-drug interactions (DDI) into major and moderate. Major DDI was any interaction that may be life-threatening and (or) requires medical intervention to minimize or prevent serious adverse effects. Moderate drug interaction was any interaction that may result in exacerbation of the patient's condition and (or) require an alteration in the therapy.

The WHO prescribing indicators help measure the appropriate use of drugs and general prescribing tendencies within a given setting independent of the specific diagnosis. The five indicators measure the degree of polypharmacy, tendency to prescribe by generic name, tendency to prescribe antibiotics, the widespread use of the costly form of drug therapy, and the degrees to which national practices conform to national drug policy.

Data analysis

We calculated frequency and percentages for qualitative data. Based on the normality assumption using the Shapiro-Wilk test, we represented the quantitative data as mean and standard deviation or median and interquartile ranges. A χ^2 test was used to find the association between polypharmacy and inappropriate prescribing. The level of significance was considered at $p<0.05$. Jeffrey's Amazing Statistics Program (JASP, version 0.12.1.0) was used for statistical analysis.

RESULTS

The mean age of elderly patients was 65.90±5.48 years. Males are higher (53.10%) than females. There are 108 patients with comorbidities (39.27%). A total of 1140 drugs were prescribed, and 23 potentially inappropriate medications were distributed across 60 prescriptions. The prevalence of potentially inappropriate medications in 275 prescriptions was 21.9%. Hypertension is the most common comorbidity (45.37%). The majority of the prescriptions contain less than five drugs (65.09%). The majority of the patients (65.09%) visited the department of general medicine (Table 1).

Table 1. Socio-demographic and clinical characteristics of patients.

Characteristic	Frequency (%)
Age (in years)	65.90±5.48
Gender	
Male	146 (53.10)
Female	129 (46.90)
Comorbidities (n=108)	
Hypertension	46 (45.37)
Diabetes Mellitus	37 (36.11)
Hypertension and Diabetes	18 (16.67)
Coronary Artery Disease	02 (1.85)
Others	05 (4.63)
Number of drugs	
<5 drugs	179 (65.09)
≥5 drugs	96 (34.91)
Type of Department	
General Medicine	127 (46.18)
Endocrinology	59 (21.45)
Ortho	43 (15.64)
Pulmonology	26 (9.45)
Others	20 (7.27)

Diclofenac was the most common inappropriate drug (n=23), and Metoprolol is the second most inappropriate drug (n=12). The most commonly prescribed class of inappropriate drugs was Non-Steroidal Anti-Inflammatory Drugs-Diclofenac, Piroxicam, Ibuprofen (Table 2).

We identified 21 major drug-drug interactions (DDI) and 74 moderate interactions. Amlodipine and clopidogrel, aspirin and furosemide, and aspirin and spironolactone together accounted for 71.42% of interactions (n=15). Atorvastatin and clopidogrel was the most moderate drug-drug interaction in our study (n=24) (Table 3).

Table 4 outlined the prescribing indicators along with the World Health Organization reference value. The average number of drugs per encounter, the percentage of drugs prescribed by generic names, and the percentage of drugs from an essential drug list were not within the reference range. We observed a statistically significant association between inappropriate medications and polypharmacy ($p<0.001$), type of department ($p=0.03$).

DISCUSSION

A drug-drug interaction contains an object drug and a precipitant drug. Object drug is a medication that has its therapeutic effect modified by the drug interaction process. The precipitant drug is the medication that affects the pharmacodynamics and pharmacokinetics of the object drug[6]. For example, in the major drug interaction between amlodipine and clopidogrel, amlodipine is the precipitant drug and it decreases the antiplatelet effects of the object drug.i.e., clopidogrel by inhibition of CYP3A-mediated clopidogrel activation[7]. The risk of increased antithrombotic events can be reduced by cilostazol[8].

Drug-Drug interactions can be minimized by choosing alternative drugs that are not affected by the precipitant drug. For example, concurrent use of clopidogrel and CYP3A4 metabolized statins like atorvastatin will result in high on-treatment platelet reactivity[7]. However, substituting the atorvastatin with pravastatin or rosuvastatin that is not metabolized by CYP3A4 will avoid the interaction[9]. We can manage drug interactions by

Table 2. List of potentially inappropriate medications according to screening tool of older person's prescriptions criteria version 2.0.

Name of the drug(s)	Class of the drug(s)	Frequency (n)	Reason for Inappropriateness
Diclofenac	Non-Steroidal Anti-inflammatory Drugs (NSAID)	23	Inappropriate in moderate to severe hypertension as it increases the risk of exacerbation of hypertension
Metoprolol	Beta-Blocker	12	Inappropriate in Diabetes mellitus as it increases the risk of masking hypoglycaemic symptoms
Cinnarizine	1st generation anti-histamine	4	Prolonged use increases the risk of sedation and anticholinergic side effects; Duplication of the drug is inappropriate
Amitriptyline & Amlodipine	TCA; Calcium Channel Blocker	4	Concurrent use increases the risk of severe constipation
Pheniramine Maleate	1st generation anti-histamine	3	Prolonged use increases the risk of sedation and anticholinergic side effects
Telmisartan and Losartan	Angiotensin Receptor Blockers	2	Duplication of the drug class
Chlordiazepoxide (n=2) & Clobazam (n=1) & Clonazepam (n=1)	Benzodiazepines	4	Long-acting benzodiazepine increases the risk of sedation, confusion, impaired balance, falls.
Prednisolone	Systemic Corticosteroid	2	Systemic corticosteroid instead of inhaled corticosteroid for maintenance therapy in moderate to severe COPD is inappropriate
Glibenclamide	Sulfonyl Urea	2	Increased risk of prolonged hypoglycemia
Propranolol (n=1) and Atenolol (n=1)	Beta Blockers	2	Inappropriate in Diabetes Mellitus as it increases the risk of masking hypoglycaemic symptoms
Diclofenac & Piroxicam	NSAID	1	Duplication of the drug class
Hyoscine Butyl Bromide	Anticholinergic	1	Inappropriate in patients with chronic constipation as it exacerbates the constipation

TCA: Tri cyclic antidepressant.

Table 3. Potential drug-drug interactions (major & moderate) that requires a change in the prescription of the elderly patients.

Interaction	Mechanism	Frequency
Major Interactions		
Amlodipine+Clopidogrel	Decreased antiplatelet effect and increased risk of thrombotic events	5
Aspirin+Furosemide	Reduced diuretic effectiveness and possible nephrotoxicity	5
Aspirin+Spironolactone	Hyperkalaemia and possible nephrotoxicity	5
Amitriptyline+Diclofenac	Increased risk of bleeding, including intracranial haemorrhage	2
Ibuprofen+Hydrochlorothiazide	Possible nephrotoxicity	1
Diclofenac+Hydrochlorothiazide	Possible Nephrotoxicity	1
Domperidone+Hydroxychloroquine	Increased risk of QT-interval prolongation, including torsades de pointes	1
Enalapril+Losartan	Increased risk of adverse events, including hypotension, syncope, hyperkalaemia, and changes in renal function	1
Moderate Interactions		
Atorvastatin+Clopidogrel	High-on treatment platelet reactivity	24
Aspirin+Metoprolol	Results in increased blood pressure	16
Azithromycin+Theophylline	Increased serum theophylline concentrations	8
Metoprolol+Metformin	May increase or decrease the blood-glucose-lowering effect of the antidiabetic agent, and may decrease or obscure signs and symptoms of hypoglycemia	7
Glimepiride+Metoprolol	May increase or decrease the blood-glucose-lowering effect of the antidiabetic agent, and may decrease or obscure signs and symptoms of hypoglycemia	7
Diclofenac+Telmisartan	May result in renal dysfunction and/ or increased blood pressure.	6
Aspirin+Atenolol	May result in increased blood pressure	3
Diclofenac+Losartan	May result in renal dysfunction and/ or increased blood pressure.	3

Table 4. World health organisation prescribing indicators.

Name of the indicator	Frequency/ Percentage (%)	WHO reference value (%)
The average number of drugs per encounter	4.23	<2
Percentage of drugs prescribed by generic name	71.85	100
Percentage of encounters with an antibiotic prescribed	18.51	<30
Percentage of encounters with an injection prescribed	4.44	<20
Percentage of drugs from Essential drug list or formulary	96.32	100

avoiding the combination directly, dose adjustment, monitoring for early detection, improved computerized screening systems, proving information about patient risk factors like comorbidities[7].

We compared the indicators of our study with three other studies[10-12]. Comparatively, the percentage of drugs prescribed from the essential drugs list was high in our study (96.32%). The average number of drugs is nearly equal, except for Jyosthna et al.[11] (6.7), who reported polypharmacy. Abdulah et al.[12] reported a higher percentage of prescribed by generic name (98.09%). Jyosthna et al.[11] reported a very high percentage of encounters with an injection (67.5%), which is nearly 15 times of our study.

World Health Organization prescribing indicators measure the appropriate use of medicines. The indicators are aimed to assess the extent of polypharmacy, prescriber's tendency to prescribe medicines using a generic name, frequency of with antibiotics and injections are prescribed, and to assess whether prescribing practices complies with national drug policy[13].

The advantage of using these indicators is, they will give an overview of irrational prescribing irrespective of diagnosis[13].

Inappropriate prescribing results in prescribing medications with higher risk than benefit. For example, cinnarizine is a potentially inappropriate medication; if prescribed to treat menopausal symptoms because it is ineffective[14]. Drugs-to-avoid lists include medications that should be avoided in any circumstance, doses that should not be exceeded, and drugs to avoid in patients with specific disorders[15]. STOPP criteria version 2.0 provides a drugs-to-avoid list for the elderly and is widely accepted as an evaluation tool for potentially inappropriate medications.

A study in a Brazilian hospital reported Omeprazole, Furosemide, Clonazepam, Spironolactone as the most common inappropriate medications at home and the hospital[16]. Three studies[17-19] from Japan reported Benzodiazepines as the most commonly observed potentially inappropriate medication according to STOPP criteria version 2. There are proven interventions to reduce the inappropriate medications in the elderly such as educational interventions[20], pharmaceutical interventions[21], medication review[22], computerized systems[23]. The use of drug reference software such as Micromedex or Lexicomp will aid in good prescribing.

CONCLUSIONS

NSAIDs, Diuretics, and Beta-Blockers are the most commonly observed potentially inappropriate drugs. The major and moderate drug interactions that require a change in the therapy can be minimized using a drug-to-avoid list or criteria. Awareness, accountability of prescribing, and drug utilization evaluation can contribute to the rational use of drugs.

AUTHORS' CONTRIBUTIONS

VM: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – reviewing & editing. **KCB:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **PS:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **KK:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **SR:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **RMK:** Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – reviewing & editing.

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ORIGINAL ARTICLE
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Expression of metalloproteinases 2 and 9 and plasma zinc concentrations in women with fibroadenoma

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SUMMARY

OBJECTIVE: This study aims to investigate the association between the immunohistochemical expression of matrix metalloproteinase-2 and matrix metalloproteinase-9 and plasma zinc in women with fibroadenoma.

METHODS: This cross-sectional study included 37 premenopausal women with fibroadenoma. Waist circumference and body mass index of the participants were measured. Plasma zinc concentrations were determined using atomic flame absorption spectrophotometry. Fragments of breast tissue were fixed and incubated with primary mouse monoclonal antibodies (monoclonal antibodies matrix metalloproteinase -2 -507 and monoclonal antibodies matrix metalloproteinase -9-439). Semi-quantitative analysis of matrix metalloproteinase-2 and matrix metalloproteinase-9 immunoreactivity was performed. Spearman's test and Friedman's test were used for statistical analyses. The $p<0.05$ were considered statistically significant.

RESULTS: The average age of the participants was 32.81±9.51 years. The body mass index and waist circumference values were within the normal range. The mean plasma zinc concentration was 42.73±13.84 µg/dL, with 94.6% inadequacy. A statistically significant difference was found between the positive expression of matrix metalloproteinase-2 and matrix metalloproteinase-9 ($p=0.0184$). There was no significant correlation between the matrix metalloproteinase expression and the plasma zinc levels.

CONCLUSIONS: Women with fibroadenoma had hypozincemia and positive expression of metalloproteinases.

KEYWORDS: Matrix Metalloproteinases. Fibroadenoma. Zinc.

INTRODUCTION

Breast fibroadenomas are benign lesions in the breast tissue characterized by hyperplasia and polyclonal proliferation of the epithelial tissue and stroma. In this type of lesions, the presence of benign nodular masses is common. Its etiology is mainly due to the hormonal influences of estrogen, progesterone, and prolactin[1].

Studies have shown that fibroadenomas rarely cause breast cancer. However, invasive cancer can develop in fibroadenoma[2]. Breast cancer has high metastatic rates and often invades the liver, the brain, and the lungs. Moreover, biomarkers for determining invasiveness and tumor aggressiveness have been studied, especially the analysis of matrix metalloproteinases (MMPs), which are evaluated both in breast carcinoma and in benign tumors such as fibroadenoma[3].

MMPs are involved in the initiation and progression of breast cancer through interactions with tumor suppressor genes involved in the early stages of carcinogenesis. In addition, a

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positive correlation has been demonstrated between increased levels of MMP-2 and MMP-9 and an increased risk of metastasis and reduced survival in cancer patients[4].

MMPs are a family of zinc-dependent endopeptidases that are involved in regulating various physiological events such as cell growth, inflammation, invasion, and angiogenesis. When overexpressed, these enzymes can damage the integrity of the basement membrane and extracellular matrix by proteolysis, which are important barriers against cell invasion[5]. In particular, MMP-2 and MMP-9 favor the metastasis of tumor cells[6].

Zinc participates as a cofactor for MMPs and is essential for regulating their expression and activity. Zinc deficiency can decrease the activity and expression of MMPs; however, an increase in the amount of zinc in the cellular compartments favors the physiological activity of these proteins and their catalytic effects[7].

Considering the importance of zinc in regulating the expression and activity of MMPs, as well as the scarcity of literature on immunohistochemical expression of these proteins in fibroadenoma, this study aimed to investigate the association between the immunohistochemical expression of MMP-2 and MMP-9 and plasma zinc in women with fibroadenoma.

MATERIALS AND METHODS

This was a cross-sectional study involving 37 premenopausal women, aged 20–59 years, with benign fibroadenoma tumors. Moreover, this study is an excerpt from a macro project entitled "Molecular Biomarkers in Women with Mammary Neoplasia" approved by the Ethics Committee of the Federal University of Piauí with opinion 1.022.962. All patients signed an informed consent form prior to the study initiation.

Participants were recruited from the mastology clinic of a public hospital in Teresina-Piauí, according to the following eligibility criteria: premenopausal women with follicle-stimulating hormone (FSH) levels <30 mUI/mL; presence of fibroadenoma; nonsmoker; absence of chronic diseases, liver disease, anemia, or clinical inflammatory processes; and absence of vitamin–mineral supplementation. The participants underwent histological evaluation of the tumors.

The body mass index (BMI) and waist circumference (WC) were calculated and measured[8,9]. Ten milliliters of blood was collected in the morning after a 12-h fast and was transferred to the tubes containing 30% sodium citrate for zinc analysis. Plasma was obtained by centrifuging whole blood at 1,831 g for 15 min at 4°C (CIENTEC® 4K15) and stored in microtubes at -20°C for further analysis. Plasma zinc analysis was performed using atomic flame absorption spectrophotometry[10]. The reference value used was 75–110 µg/dL[11].

Semiquantitative analysis of MMP-2 and MMP-9 immunoreactivity was performed[12], and the following were considered: intensity of cell staining (I) and fraction of stained neoplastic cells (F). The intensity was classified as 0 (negative), 1 (weakly colored), 2 (moderately colored), or 3 (strongly colored). The fraction of stained cells was classified as: I (0–25%), II (25–75%), or III (75–100%). The final result was achieved by a combination of two parameters (I and F) ranging from 0 to 6. Cases with a final score ≥3 were classified as positive for MMP-2 and MMP-9. In all cases, brown cytoplasmic staining was used as the standard of positivity.

Data were analyzed using IBM SPSS statistical software for Windows, version 22 (Armonk, NY: IBM Corp.). Descriptive analyses were used for frequencies, percentages, means, and deviations. The Spearman's test was used to analyze the correlation between the data. For comparisons between the studied variables, the Friedman's test was performed. The $p<0.05$ were considered statistically significant.

RESULTS

The mean age of the participants was 32.81±9.51 years. The average values of the anthropometric parameters used to assess the nutritional status of women with fibroadenomas are shown in Table 1. The average plasma zinc concentration (42.73±13.84 µg/dL) was found below the reference values for plasma zinc, as well as a high percentage of inadequate plasma zinc concentrations in women with fibroadenoma (94.6%) (Figure 1).

Analysis of the immunohistochemical expression of MMP-2 and MMP-9 revealed that a greater number of women showed a negative expression of MMP-2 (n=22) and a positive expression of MMP-9 (n=25). A statistically significant difference was found ($p<0.0184$) between the number of women with positive immunohistochemical expression of MMP-2 and MMP-9 (final score ≥3) (Figure 2). The correlation between the immunohistochemical expression of MMP-2 and MMP-9

Table 1. Mean values and standard deviations of age, weight, height, body mass index and waist circumference of women with fibroadenoma.

Parameters	Women with fibroadenoma (n=37)
	Mean±SD
Age (years)	32.81±9.51
Weight (kg)	57.49±11.33
Height (m)	1.57±0.07
BMI (kg/m²)	23.92±4.76
WC (cm)	79.70±12.13

SD: standard deviation.

with plasma zinc was not statistically significant (r=–0.1252, p=0.4602; r=0.1693, p=0.3164, respectively).

DISCUSSION

In this study, reduced levels of plasma zinc concentrations were found in women with fibroadenoma. Although there were still no data on plasma zinc concentrations in women with fibroadenoma, the reduction in plasma zinc concentrations in women with breast cancer has already been observed[13].

It is noteworthy that hypozincemia present in breast cancer may be the result of changes in the compartmentalization of the mineral. It is likely that zinc is transported from the plasma compartment into the tumor cells and is used to stimulate the catalytic domain of MMPs, which might alter the activity of this enzyme, thereby contributing to the tumor development and progression[14]. Holanda et al. found that reduced concentrations of zinc in plasma and erythrocytes were positively related to the increased plasma concentrations of MMP-2 in patients with breast cancer[13].

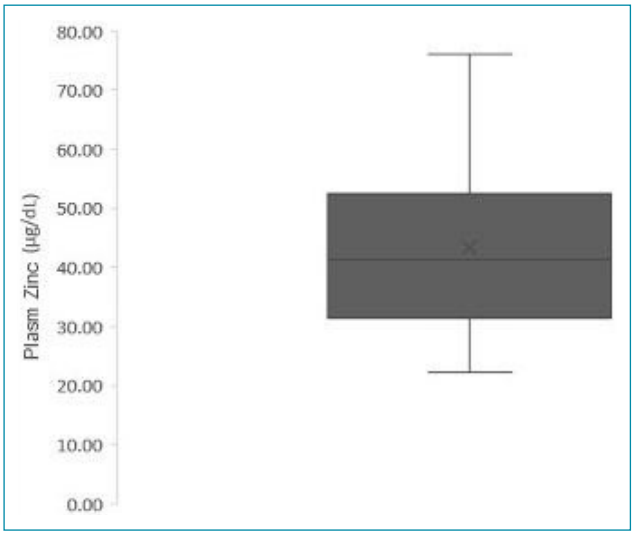
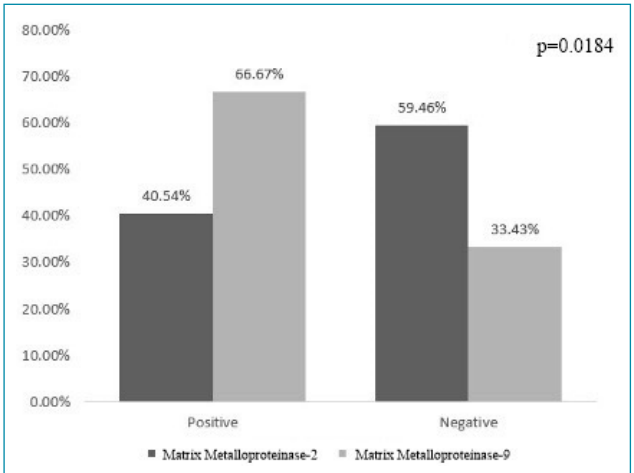


Figure 1. Mean values of plasma zinc concentrations in women with fibroadenoma.



*Statistically significant difference (p<0.05) for Friedman's test comparing the number of cases (%) with cells positively stained for matrix metalloproteinase-2 and matrix metalloproteinase-9.

Figure 2. Percentage of cases with cells expressing matrix metalloproteinase-2 and matrix metalloproteinase-9 in breast fibroadenoma.

Zinc is essential for the cell survival, growth, proliferation, and metabolism. Changes in zinc levels in the body contribute to cellular and metabolic dysfunction with pathophysiologic repercussions[15].

In this study, we evaluated the positive immunostaining of MMP-2 and MMP-9, which showed 40.54 and 67.57% of expression, respectively. Jinga et al. observed that both enzymes were expressed in both malignant and benign tumors, enzymes being more expressed in malignant than in benign tumors[16]. Vasaturo et al. observed that the plasma concentration of MMP-2 was significantly higher in patients with breast carcinoma than in patients with fibroadenoma[17].

MMP-9 participates in the progression of breast cancer; its high expression is associated with a higher incidence of metastasis and a worse prognosis[18]. Although the risk of developing breast cancer is low in fibroadenomas, some authors report the appearance of cancerous lesions within fibroadenomas[19,20]. Thus, investigation of the expression pattern of MMPs may contribute to the early identification of changes that favor carcinogenesis in fibroadenomas.

The change in the dynamics of MMP functioning is a critical factor in the process of tissue integrity; that is, the imbalance in the activity of these enzymes may favor excessive degradation or accumulation of tissues in the extracellular layer. Positive immunostaining for MMP-2 has been proposed as a marker of aggressiveness in breast carcinomas. It has been shown that blocking the secretion and activation of this enzyme can reduce the risk of breast cancer[21].

Although most studies have shown greater expression of these enzymes in breast cancer, the results of some studies have already shown higher MMP expression in women with fibroadenoma[22]. According to Sangma et al., patients with proliferative lesions had risk factors for developing invasive carcinoma[23]. As there is no consensus on the morphological risk markers, molecular and nutritional biomarkers can, therefore, help in risk stratification and improve clinical management.

Thus, MMPs have been evaluated in breast carcinoma, normal breast tissue, and benign tumors, as these proteins are involved in tumor progression[24]. Somiari et al. suggested that the preoperative plasma concentration and the activity of MMP-2 and MMP-9 may allow the subclassification of patients with

breast diseases[25]. In that study, individuals without breast disease and with a low risk for developing breast cancer showed significantly different concentrations and activities of these proteins in the plasma, compared to individuals with high risks for benign disease and breast cancer.

This study had limitations due to the small number of participants; however, it was possible to verify a considerable percentage of cells stained for MMP-2 and MMP-9 and a reduced plasma zinc concentration in women with benign breast tumors.

CONCLUSIONS

The data obtained in this study do not show a correlation between the MMPs evaluated and the plasma zinc concentrations in women with fibroadenoma, despite the low values found for this micronutrient. The study also showed positive expression of gelatinases, particularly MMP-9, which had a higher expression than MMP-2. Thus, it is recommended that further studies should be conducted to obtain more in-depth knowledge on the topic.

AUTHORS' CONTRIBUTION

LMM, ISB, ESF, AGSN, CSMED, VAO, ARSO, JBSM, DNM, BBS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Value of magnetic resonance combined with dual-source spectral computed tomography in improving the clinical diagnosis and treatment efficiency of lumbar disk herniation

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SUMMARY

OBJECTIVE: This study aims to investigate the value of magnetic resonance combined with dual-source spectral computed tomography in improving the clinical diagnosis and treatment efficiency of lumbar disk herniation.

METHODS: Two hundred patients with lumbar disk herniation were enrolled. Magnetic resonance and dual-source spectral computed tomography were used to perform the diagnosis. The treatment efficiency and effectiveness of different diagnostic methods were determined.

Results: Eighty cases of lumbar disk herniation, 40 cases of prolapse, 33 cases of bulge, 27 cases of sequestration, and 20 cases of nodules were diagnosed based on pathologic evaluation. magnetic resonance detected lumbar disk herniation in 172 cases, with a detection rate of 86.00%. Dual-source spectral computed tomography detected 171 cases, with a detection rate of 85.50%. Magnetic resonance combined with dual-source spectral computed tomography detected 195 cases, with a detection rate of 97.50%. There was no significant difference between magnetic resonance and dual-source spectral computed tomography ($p>0.05$), but compared with the combined detection, there was a significant difference ($p<0.05$). One hundred and two cases of calcification, 83 cases of spinal cord deformity, 70 cases of intervertebral disk degeneration, 121 cases of intervertebral disk gas, 85 cases of dural sac compression, and 78 cases of nerve root compression were surgically demonstrated. The detection rate of diagnostic signs based on imaging by magnetic resonance or dual-source spectral computed tomography alone was lower than that of combined detection ($p<0.05$).

Conclusion: Magnetic resonance combined with dual-source spectral computed tomography can improve the diagnosis and treatment efficiency and effectiveness of lumbar disk herniation.

Keywords: Magnetic resonance. X-ray computed tomography. Hernia. Efficiency.

INTRODUCTION

Lumbar disk herniation is a common spinal surgical condition that frequently occurs in males and can be manifested as lumbago, sciatica, and other symptoms[1]. The main underlying mechanism of lumbar disk herniation is that the partial or complete rupture of the annulus fibrosus of the intervertebral disk accompanied by the nucleus pulposus protrusion beyond the normal boundary of the lumbar disk compresses the nerve, thus resulting in a constellation of symptoms[2]. Lumbar disk herniation is undoubtedly an inconvenience with respect to the activities of daily living and work for those affected. Currently, the early diagnostic modes of lumbar disk herniation include computed tomography (CT) and magnetic resonance (MR). Specifically, the direction of lumbar disk herniation and local tissue shadows can be clearly shown by

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imaging examinations, which help physicians detect the changes in lumbar motion from different positions and establish a definite diagnosis[3]. With the progress and development of imaging technology, multispectral CT has replaced the previous mode of blindly increasing the width of the detector, thus significantly improving the temporal resolution[4]. To compare the application effect of different diagnostic modes, a total of 200 patients with lumbar disk herniation between December 2018 – December 2019 were selected as research subjects to discuss and analyze the diagnosis and treatment efficiency of MR combined with dual-source spectral CT.

METHODS

Patients

A total of 200 patients with lumbar disk herniation who were admitted to our hospital between December 2018 – December 2019 were selected as the research subjects. There were 113 males and 87 females, ranging in age from 26–53 years (mean age, 44.5±18.5 years) with disease duration from 1–10 years (mean disease duration, 8.0±2.0 years). All patients were given dual-source spectral CT and MR diagnoses. All subjects participated voluntarily in this study with informed consent from their families and approval by the Ethics Committee of our hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

I. patients presenting typical lumbar disk herniation images on routine CT scanning,
II. patients accompanied by lumbago and symptoms of leg pain and numbness caused by nerve root compression for ≥3 months, and
II. patients without symptoms of lumbar spondylolisthesis or a lumbar compression fracture.

The exclusion criteria were as follows:

I. patients with severe osteoporosis;
II. patients with giant intervertebral disk protrusion or significantly reduced muscle strength;
III. patients with liver, kidney, cardiovascular, or cerebrovascular disease;
IV. patients with rheumatoid arthritis, ankylosing spondylitis, or other spondylitis lesions; and
V. patients with lumbar tuberculosis or tumors.

Dual-source spectral CT diagnosis

A 64-row dual-source CT [SOMATOM Definition Flash; Siemens (China) Co., Ltd., Beijing, China] diagnostic instrument was selected for dynamic continuous scanning. Patients were assisted to assume a supine position, with a soft cushion placed under the sacrococcygeal region at a height of 25 cm. The pelvis was immobilized with a fixing band to maintain lumbar hyperextension, and the motion angle was stretched from an extension position of 20° to a flexed position of 20°. The patient was instructed to get trained before scanning, wherein the center line of the position should be consistent and the speed should be uniform in motion. Scanning parameters were set as follows: tube voltage, 80 kV; tube current, 110 mAs; layer thickness, 0.6 mm; and the rotation speed, 0.5 s/round. The function was reconstructed to 10; the L3–S1 lumbar disk spectral CT scan was performed first, with the obtained images transmitted to an Inspace workstation. The key where the optimal contrast image of the spinal cord near the lumbar protrusion site was located was acquired using the contrast-to-noise ratio. Matter was then separated to obtain single energy images and calcium- and water-based images to find the ideal protrusion area. Then, the core, center, and base of the lumbar disk protrusion with a diameter of 5 mm were measured, and the mean value was taken as the lumbar disk sample value. The content of water and calcium in the lumbar disk was measured, and the protrusion area was measured at the sagittal layer of the lumbar disk protrusion site.

MR diagnosis

A 1.5 T MR equipment (GE Medical Co., Wuhan, China) was selected as the examination instrument. The patient was instructed to be in a supine position, given a three-plane location. Sagittal SE T1 and T2 scans were performed in the lumbar region (Figures 1A and B). A one-layered scan was performed for most of the lumbar disks, and a three-layered scan was performed for a small part of the lumbar disks. All patients were then subjected to transverse and sagittal scans and, if necessary, a coronal scan (Figure 1C). Attention was paid to the changes in spinal stenosis and the lumbar disk signal and whether there was spinal cord compression, a dural sac, or a bulging lumbar disk.

Diagnostic criteria

The detection of patients with lumbar disk herniation by using different diagnostic modes was compared according to the results of the surgical pathology. Two imaging physicians with extensive experience in film reading were selected to evaluate the diagnostic results. The diagnostic standards for lumbar disk herniation were as follows:

I. the patient lost physiologic activity in the lumbar region, had spinal scoliosis, and had obvious tenderness near the affected vertebral region, and the lumbar activities were restricted;

II. the lumbar region was accompanied by a medical history of trauma, cold and damp exposure, and chronic strain;
III. there was muscular atrophy or dysesthesia in the innervation area of the lower limbs, and the patellar reflexes were absent; and
IV. the intervertebral disk was narrowed, and there was proliferation of osteophytes at the edge of the lesion[5].

Statistical analysis

All statistical analyses were carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as number and rate and were compared using χ^2 test. The measurement data were presented as mean±standard deviation and were compared using *t*-test. Furthermore, $p<0.05$ was considered as statistically significant.

RESULTS

Comparison of diagnosis results among MR, dual-source spectral CT, and combined detection

Among the cohort of patients, 80 cases of lumbar disk herniation, 40 cases of prolapse, 33 cases of bulge, 27 cases of sequestration, and 20 cases of nodules were detected by surgical pathologic evaluation. MR detected 172 cases of lumbar disk herniation, with a detection rate of 86.00%. Dual-source spectral CT detected 171 cases of lumbar disk herniation, with a detection rate of 85.50%. MR combined with dual-source spectral CT detected 195 cases of lumbar disk herniation, with a detection rate of 97.50%. There was no apparent difference between MR and dual-source spectral CT in detecting lumbar disk herniation, and the difference was not statistically significant ($p>0.05$). However, there was a statistically significant difference when MR or dual-source spectral CT was compared with the combination of MR and dual-source spectral CT ($p<0.05$) (Table 1).

Comparison of diagnostic signs among MR, dual-source spectral CT, and combined detection

Among the cohort of patients, 102 cases with calcifications, 83 cases with spinal cord deformities, 70 cases with intervertebral disk degeneration, 121 cases with intervertebral disk gas, 85 cases with dural sac compression, and 78 cases with nerve root compression were detected during surgery. The detection rate of spinal cord deformities and intervertebral disk deformation by MR was higher than that by dual-source spectral CT, but the detection rate of calcifications and intervertebral disk gas by MR was lower than that by dual-source spectral CT. The detection rate of diagnostic signs based on imaging by MR or dual-source spectral CT alone was lower than that by combined detection; there was an apparent difference between any two groups, and the difference was statistically significant ($p<0.05$) (Table 2).

DISCUSSION

Lumbar disk herniation primarily occurs due to lumbar disk degeneration and partial or complete rupture of the annulus fibrosus accompanied by the nucleus pulposus protrusion, which stimulates and compresses the nerve roots and cauda equina, thus causing symptoms such as lumbago, lumbar and leg pain, lower limb numbness, or sciatica[6]. Lumbar disk herniation is one of the particularly common spinal degenerative diseases in clinical practice. As the aging trend of the population has

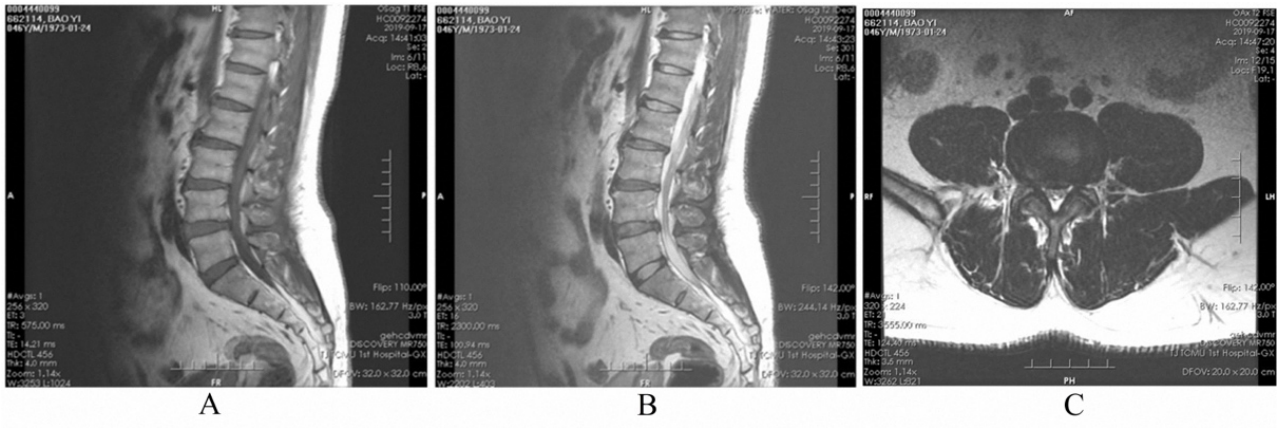

Figure 1. Representative sagittal T1-weighted image: (A) T2-weighted image; (B) and representative transverse T2-weighted image; (C) of the lumbar region by using magnetic resonance scanning obtained from a 46-year-old patient.

intensified in recent years, the incidence of lumbar disk herniation has gradually increased. Factors such as age, damage accumulation, pregnancy, and heredity are all risk contributors for lumbar disk herniation[7]. Bending, lowering the head, or sitting for a long time, strain accumulation, and exogenic action can cause rupture of the annulus fibrosus and backward protrusion of the endplate[2]. With an increase in age, the intervertebral disks gradually degenerate and the water content of the nucleus pulposus and annulus fibrosus decreases, which causes the loss of elasticity and appearance of fissures in the nucleus pulposus and annulus fibrosus[8]. Patients in the early stage of lumbar disk herniation often present with lumbar and leg pain and numbness of the lower limbs, but these symptoms can progress to intermittent claudication and cauda equina syndrome as the degeneration progresses, causing a serious impact on activities of daily living and work.

Currently, clinical examinations utilize lumbar X-ray plain films, CT, MR, and other imaging modes, but X-ray plain films have low specificity and sensitivity in the detection of lumbar disk herniation and thus have limited application in the clinical setting[9]. The MR diagnostic technique can show spinal nerve lesions, contour, and nerve root morphology, which demonstrates lesions in the lumbar disk and identifies other space-occupying lesions in the spinal canal[10]. The CT diagnostic mode can help physicians identify bulges, prolapse, protrusion, and other conditions indicative of lumbar disk herniation. In some cases, facet joint hyperostosis, vertebral hyperplasia, calcifications, and thickening of ligamentum flavum can be demonstrated; however, nerve root compression is more difficult to demonstrate by CT[11]. Clinical studies have reported that the routine CT has a lower detection rate for far lateral lumbar disk herniation, so the dual-source spectral CT based on the progress and development of routine CT has been widely used. Dual-source spectral CT can fully show different matters by adjusting the keV and, compared with the routine CT mode, optimize the signal-to-noise ratio, thus clearly demonstrating nerve root compression and intervertebral facet joint compression[12].

In this study, all patients had MR or dual-source spectral CT examinations alone or in combination. There was no significant difference between MR and dual-source spectral CT in the detection rate of lumbar disk herniation and clinical imaging signs, respectively, but their combination significantly improved the detection rate and showed no significant difference with surgical findings. It is concluded that CT scan, as an important method for clinical auxiliary diagnosis of lumbar

Table 1. Comparison of diagnosis results among magnetic resonance, dual-source spectral computed tomography, and combined detection.

Diagnostic mode	MR	Dual-source spectral CT	Combined detection
Case number (n)	200	200	200
Prolapse [n(%)]	34(17.00)*	33(16.50)*	38(19.00)
Bulge [n(%)]	28(14.00)*	27(13.50)*	32(16.00)
Protrusion [n(%)]	71(35.50)*	72(36.00)*	78(39.00)
Sequestration [n(%)]	23(11.50)*	22(11.00)*	27(13.50)
Nodules [n(%)]	16(8.00)*	17(8.50)*	20(10.00)

*p<0.05 compared with combined detection. MR: magnetic resonance; CT: computed tomography.

Table 2. Comparison of diagnostic signs among magnetic resonance, dual-source spectral computed tomography, and combined detection.

Diagnostic mode	MR	Dual-source spectral CT	Combined detection
Case number (n)	200	200	200
Calcification [n(%)]	85 (42.00)*	93 (46.50)*[a]	100 (50.00)
Spinal cord deformity [n(%)]	76 (38.00)*	72 (36.00)*[a]	81 (40.50)
Intervertebral disk deformation [n(%)]	63 (31.50)*	57 (28.50)*[a]	70 (35.00)
Intervertebral disk gas [n(%)]	101 (50.50)*	113 (56.50)*[a]	120 (60.00)
Dural sac compression [n(%)]	76 (38.00)*	77 (38.50)*	84 (42.00)
Nerve root compression [n(%)]	66 (33.00)*	65 (32.50)*	76 (38.00)

*p<0.05 compared with combined detection; [a]p<0.05 compared with magnetic resonance. MR: magnetic resonance; CT: computed tomography.

disk herniation, has a fast scanning speed, and the dual-source CT further scans the different lumbar flexion and extension activities in a four-dimensional (4D) mode to improve the diagnostic rate. Of note, there is a relatively small amount of radiation exposure with the dual-source CT scan[13]. MR is helpful to determine the specific site and severity of the lesion in all directions and in multiple sequences, with high resolution and safety (i.e., no radiation exposure), but MR shows lower sensitivity in the detection of hyperostosis, ligament calcification, and other conditions[14]. The combination of MR and dual-source spectral CT has full advantage of the synergistic effect to visually and clearly depict lumbar disk herniation from a dynamic perspective, thus providing a more objective and reasonable reference for clinical treatment strategies.

CONCLUSIONS

MR combined with dual-source spectral CT can improve the diagnosis and treatment efficiency and effectiveness of lumbar disk herniation, and it is worth popularizing and application in clinical practice. This study still has some limitations. The sample size of this study is relatively small. Larger sample will make the results more convincing. More subjects should be enrolled in the future studies for obtaining more satisfactory results.

AUTHORS' CONTRIBUTIONS

JW: Conceptualization, Writing – review & editing. **LW:** Data curation, Formal Analysis. **CC:** Data curation, Formal Analysis. **YL:** Writing – original draft. **HL:** Writing – original draft.

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Lead-DBS: an additional tool for stereotactic surgery

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SUMMARY

OBJECTIVE: Use Lead-DBS software to analyze stereotactical surgical outcome of an operated population and demonstrate that small target deviations do not compromise the stimulation of desired structures, even with small amperages.

METHODS: Image exams of patients submitted to deep brain stimulation for movement disorders treatment were processed in Lead-DBS software. Electrode stereotactic coordinates were subtracted from the planned target and those deviations, compared among different anatomical targets and sides operated firstly and secondly. We also quantified the frequency of relation between the activated tissue volume and the planned target through computer simulations.

RESULTS: None of the 16 electrodes were exactly implanted at the planned coordinates. A stimulation of 3 mA reached 62.5% of the times the planned coordinates, rising to 68.75% with a 3,5 mA. No statistical significance was demonstrated in any comparison of laterality and anatomical sites.

CONCLUSIONS: The simulation of small amperage fields could reach the intended target even when electrode placement is suboptimal. Furthermore, such a goal can be achieved without overlapping the volume of activated tissue with undesired structures. Software Lead-DBS proved to be a valuable complementary asset for surgical stereotactical result assessment.

KEYWORDS: Deep brain stimulation. Software. Neurosurgery. Movement disorders. Parkinson disease.

INTRODUCTION

Movement disorders refer to a group of neurological conditions that cause abnormal voluntary or involuntary movements. This spectrum of disorders includes Parkinson's disease (PD), dystonia, tremor, ataxia, as well as other less prevalent diseases[1-3]. Even though the clinical presentation of these disorders varies, they share similarities, such as a rising prevalence and incidence over the years[4]. Taking into account the aging of populations and the increase in life expectancy, the World Health Organization (WHO) estimates that 1% of the global population over 65 years old is affected by PD and predicts that the number of individuals affected in 2030 will be of 8 million[4]. To improve the management of motor symptoms, surgical treatment with deep brain stimulation (DBS) is a longing alternative that can be associated with classical pharmacological treatment, thus reducing the dosage and side effects of dopaminergic drugs and improving motor clinical outcome and life quality[5,6].

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The correct electrode positioning has been deemed of crucial importance because accurate electrode placement ensures stimulation of desired structures (such as subthalamic nucleus and internal globus pallidus), at the same time preventing excitation of areas whose stimulation could cause adverse motor and behavioral effects (red nucleus, internal capsule, substantia nigra, and medial lemniscus)[7,8]. Precise implantation of the electrodes by the surgeon is a challenging task, and it is exemplified by the fact that large trials showed a substantial variation of final electrode position in patients[7,8].

Those variations and errors can be due to technical or anatomy-related factors. Technical factors can be the precise determination of the stereotactic coordinates because of image distortions, pixels size, and the thickness of image slices. Brain-related factors involve the human heterogeneity of brain tissue and the intracranial relocation of the brain as a result of dura mater perforation with the subsequent inflow of air in the subdural space, which occurs during the surgical procedure[9].

However, misplacement of the electrode often does not affect clinical outcomes[10,11]. As previously mentioned, the further away the electrode is from its intended trajectory, the higher are the chances of poor clinical outcome and emergence of side effects[7,8]. Even so, the setup of the device remains a crucial step in these patients' follow-up. Performed by a specialist, selection of poles, amplitude, frequency, and pulse width can be optimized for better clinical outcomes[12]. The volume of activated tissue (VAT) can attenuate motor and non-motor (such as verbal fluency) symptoms and minimize the risk of collateral effects[13,14].

Lead-DBS (lead-dbs.org; Horn & Kühn.; RRID:SCR_002915)[15] is a free online software based on MATLAB language and functions, used to process, and combine different image modalities. It can also remove artifacts and enhance image quality[16]. Importantly, it also allows to localize (either automatically or manually) the placement of intracerebral electrodes and recreate them on 3D interactive atlases.

Despite not being a licensed software for clinical use (therefore, not licensed for intraoperative use) it can recreate electromagnetic activity, revealing the overlap between electrodes activity and cerebral parenchyma[15]. Our experience with this software seems to confirm medical literature on the aspect of the positive contribution of the VAT set up for DBS outcome[13,14,17].

We aimed with this study, firstly, to demonstrate the valuable use of technology (specifically, Lead-DBS) as a complementary tool for surgical outcome evaluation. Secondly, we intended to show that electromagnetic activity can relate to the desired cerebral areas, even when electrode placement is suboptimal.

METHODS

Study participants

Eight patients with movement disorders, previously evaluated by the Federal Fluminense University hospital (University Hospital Antonio Pedro, HUAP) neurosurgery team, were submitted to DBS surgery for treatment of motor symptoms between the years 2017–2020. Their surgeries were prescribed following National Health Surveillance Agency (ANVISA) recommendations, and the procedure was always performed by the same team of surgeons. Five of the patients had idiopathic PD, two had primary dystonia, and one had rubral tremor secondary to multiple sclerosis exacerbation. There were four male and four female patients, and their ages varied between 10–79 years (48.6±18.7).

Imaging exams

All patients were submitted to a pre-operatory 3T cranial magnetic resonance imaging (MRI) six months before the procedure. Those exams had at least 60 coronal slices, starting at the upper point of the skull, with a slice thickness of 1.4 mm, and no inter-slice gaps. The sequences acquired on this protocol were T1, T2, and flair. A post-operative high-resolution CT scan with at least the same number and thickness of slices was performed 30 days after the surgery. Only one patient had a post-operative MRI. Those exams were already part of the routine medical evaluation followed by the neurosurgery team. One of the neurosurgeons responsible for this trial evaluated image quality and the absence of artifacts before image processing. Exams were also approved by an image quality filter function on Lead-DBS.

Surgical procedure

Surgeries were performed following national regulatory agency and medical literature recommendations[18]. The patients were subjected to a pre-operatory CT with an isocentric system linked to their skull. This image was used to plan surgical trajectory and target, using intra-operative computer software recommended by the electrode manufacturer. The obtained stereotactic coordinates were plotted at the isocentric system to guide the trajectory and final target.

After bone exposure, a 15 mm opening was made using a surgical drill, followed by the opening of the dura mater. A micro-electrode system was placed to verify localization during the surgery. After reaching the desired target, electrode (Medtronic model 3397) macrostimulations with the patient awake were performed. If a significant improvement of motor function was observed with no side effects, the surgery was deemed complete. If not, a trajectory or target correction was performed.

Software acquirement and utilization

Lead-DBS (version 2.3) and SPM12 were used within the Matlab 2018a platform[14,19].

Data generation

All image inputs on Digital Imaging and Communications in Medicine (DICOM, a standard format for radiological images visualization in medicine) format were converted to Neuroimaging Informatics Technology Initiative (NIfTI, an open file format usually used for neuroimaging manipulation) files using SPM 12 software conversive function. The electrode model implanted for each patient was obtained by consulting patient medical records and was introduced at the program. The protocols used for co-registration and normalization of images were the ones recommended at the Lead-DBS official walkthrough for each imaging modality. Next, a brain-shift function was also performed[20], followed by electrode trajectory automatic pre-reconstruction[21]. Manual electrode trajectory correction was the last step before tridimensional reconstruction.

Montreal Neurological Institute (MNI) coordinates were obtained for electrode limits, and each pole was converted to Anterior commissure/Posterior commissure related coordinates (AC/PC) using Lead-DBS[22]. Optimal target coordinates were the same as standard coordinates defined by Schrader (2002) and were marked on the 3D reconstruction image[8]. We subtracted the coordinates from the centroid of the contact visually closest to the optimal target to obtain optimal target distancing (Table 1). On pre-operative planning, stereotactic optimal coordinates are defined not only by standard coordinates but also with an individual MRI evaluation and stereotactic atlases observation. Even though, we chose to use the above-mentioned standard coordinates because of their closeness to our patients' planned targets (all patients had no difference of planned targets larger than 1 mm on each axis from such coordinates) and, therefore, a way to promptly mark an optimal target on each reconstruction and facilitate our data analysis.

The volume of activated tissue (VATs) was then simulated using 2–3,5 mA monopolar settings[23], at the pole visually closest to the optimal target. These simulations were always conducted by the same researcher and were raised until the minimum voltage that led to an overlap of VAT, and the optimal target was reached. Screenshots were archived for each patient.

Statistical analysis

All data were processed using IBM SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A Kruskal-Wallis test was used to identify statistical significance between two comparisons:

Table 1. Optimal target stereotactic coordinates considered for this respective study.

	Right			Left[a]		
	x	y	z	x	y	z
Gpi	20	3	5	-20	3	5
STN	13	-3	5	-13	-3	5

[a]The difference between laterality in the same anatomical targets is only the module of the x-axis. Gpi: Internal globus pallidus; STN: Subthalamic nucleus.

1) Distance from an ideal target between firstly operated side and secondly operated side;
2) Distance from an ideal target between GPi and STN.

The significance threshold used was $p<0.05$.

RESULTS

Electrode localization

The average values of:

1) electrode inferior limit and
2) deviation from the optimal target, together with standard deviation, are listed in Table 2.

The x and y axes had smaller deviations compared to the z-axis. The differences of electrode localization between different anatomical sites were not significant with a threshold of $p<0.05$ (p-values of 0.67, 0.75, 0.9, respectively for each axis). Similarly, differences of electrode placement between sides operated firstly and secondly (the left side and the right side were operated first on four times each) showed no statistical significance with a threshold of $p<0.05$ (Figure 1).

VATs simulations

We found an overlap of the VAT and the optimal target in 10 electrodes placed (62.5%), using a limit of 3 mA for amperage. This overlap was observed in 11 (68.75%) electrodes when the limit for amperage was raised to 3.5 mA.

Clinical outcome

This study did not evaluate clinical improvement from surgeries or conducted a clinical follow-up. However, the medical records of patients undergoing surgery in the period from June 2017 to June 2020 indicate that no secondary surgery was performed because of post-surgical complications or for the purposes of electrode placement correction.

Table 2. Stereotactic surgical outcomes by subgroups.

Anatomical Target	Stereotactic surgical outcome						Optimal target deviations[a]					
	Left			Right			Left			Right		
	x	Y	z	x	y	z	x	y	z	x	y	z
Gpi	-20.91 ±0.5	2.5 ±1.52	7.92 ±1.68	19.53 ±2.68	3.06 ±1.44	6.58 ±3.12	-0.91	-0.49	2.92	-0.47	0.06	1.58
STN	-13.07 ±1.44	-3.41 ±2.21	6.22 ±0.67	8.74 ±2.11	-3 ±1.07	7.36 ±1.81	-0.075	-0.41	1.22	-4.26	-0.0075	2.36

The values anticipated by a plus or minus sign are standard deviation while the others refer to average. Gpi: Internal globus pallidus; STN: Subthalamic nucleus. [a]The values of standard deviation plotted on the surgical outcome group are the same for their respective correspondent on optimal target deviations group, since those values were obtained by a subtraction from a fixed optimal value for each anatomical target.

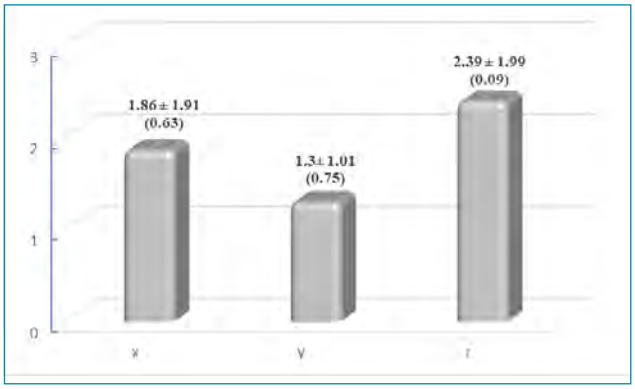

Figure 1. Differences between axes of sides operated firstly and secondly in millimeters. On top of each bar mean and standard deviation values were placed for each axe. p-values placed between parenthesis were obtained by a Kruskal-Wallis test between the two groups.

DISCUSSION

Despite conducting a study with a limited number of heterogeneous patients, we had consistent observations regarding the stereotactic localization of the electrodes. When observing the x and y axes, it was notable the closeness of electrode placement values (no more than 2–2.5 mm) with the established optimal targets. The z-axis had larger deviations, but this fact is already expected because of brain shift influence (brain shift effect is larger on cranial-caudal axis because intracranial air entry has a larger effect on this same axis)[7,8]. As previously mentioned, small deviations are acceptable in clinical practice and do not usually compromise the clinical outcome of DBS surgery[24,25].

Even though this study could not quantify if there was a statistical difference in clinical outcome between different anatomical targets or sides operated consecutively (larger influence from brain shift on the second side), we can affirm that we do not consistently make deviations due to those variables (no statistical significance found).

We aimed to reaffirm (with the use of Lead-DBS software), as previously reported, the capacity of the VAT to reach the desired structures, even when small deviations occur during electrode placement[13,14,17]. The scientific consensus is that stronger stimulations bring higher risks of side effects such as sexual perversion, language impairment, emotional disturbances, extrapyramidal symptoms, and others[13,14,17]. Even so, VATs generated with 2–3.5 mA (the initial voltage utilized when DBS is activated) showed a satisfactory area of stimulation, which overlapped with the optimal targets in 68,75% of electrodes implanted. Yet, despite such reach, the VATs did not stimulate areas that could generate adverse effects (substantia nigra, rubral nucleus, or internal capsule). Other parameters, such as pulse amplitude and frequency, which were not considered in this study, could modify the area of stimulation.

Another important point is the complementary use of Lead-DBS. Although manufacturers of DBS platforms provide a demonstration of the magnetic field on their software, none of them can show the nuclei stimulated according to the values set on the DBS itself (amperage, voltage, and others). Having a multimodal imaging software, such as Lead-DBS, that provides such information accompanied by the stereotactic surgical outcome, may provide surgeons a more accurate analysis of their work.

Lastly, it is important to mention that Lead-DBS use is widely accepted as a complementary tool. Its role for research and other goals are already validated and reviewed in the medical literature[15]. The impact of the VAT role on therapeutic effects for many disorders is also another issue substantially addressed and consolidated on medical literature[13,14,17].

Therefore, this study corroborates the fact that Lead-DBS is a valuable complementary tool for surgical stereotactical outcome evaluation and that VAT amperage can optimize the area of stimulation without co-stimulate unwanted structures.

CONCLUSIONS

This study corroborated Lead-DBS quality as a complementary tool for surgical stereotactical outcome assessment. Simulations showed that small amperage VATs can stimulate the desired structures without reaching potentially originators of adverse effects.

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AUTHORS' CONTRIBUTIONS

RBR: Conceptualization, Formal analysis, Software, Investigation, Writing – original draft. **VLA:** Software, Investigation, Writing – original draft. PYO: Formal analysis, Investigation, Writing – original draft. **NSMN:** Formal analysis, Investigation, Writing – original draft. **MAON:** Investigation, Supervision, Validation. **RRTC:** Investigation, Supervision, Validation. **BLP:** Conceptualization, Investigation, Supervision, Validation, Writing – original draft.

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Study on the changes of blood glucose in hemodialysis patients with diabetes

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SUMMARY

OBJECTIVE: The aims of this study were to observe the regularity of blood glucose changes in hemodialysis patients with diabetes, time of onset of hypoglycemia and blood glucose level during dialysis, and to explore the sensitive early warning indicators of hypoglycemia in dialysis patients.

BACKGROUND: Diabetes patients have a high incidence of hypoglycemia during hemodialysis.

METHODS: A total of 124 maintenance hemodialysis patients with diabetes were selected for this study. Before dialysis, one, two, and three h after dialysis, and when hypoglycemia symptoms occurred, the blood glucose changes were monitored, the blood glucose drop range was observed when hypoglycemia symptoms occurred, and the correlation between the two was analyzed.

RESULTS: After the start of the dialysis, the patient's blood glucose showed a downward trend. The symptoms of hypoglycemia were most obvious within one–two hours, with an incidence rate of 57.9%. When the blood glucose drop percentage reached 37.7%, the specificity and sensitivity of early warning hypoglycemia symptoms were 84.6 and 73%, respectively.

CONCLUSIONS: For hemodialysis patients with diabetes, attention should be paid to the symptoms of hypoglycemia during dialysis, and blood glucose should be monitored before dialysis and after 1–2 h of dialysis. If the blood glucose drop percentage is greater than 37.7%, the timely measures should be taken.

KEYWORDS: Diabetes mellitus. Hemodialysis. Blood glucose.

INTRODUCTION

In maintenance hemodialysis patients with diabetes, the incidence of hypoglycemia during dialysis is as high as 16.9–47.6%, which may cause heart and cerebrovascular accidents in severe cases[1,2]. Hypoglycemia can be diagnosed in diabetic patients with a blood glucose value of ≤3.9 mmol/L. However, since the blood glucose of patients in dialysis is in a state of non-physiological decline, some patients will have symptoms of hypoglycemia earlier before the blood glucose value reaches 3.9 mmol/L, and some patients have unperceived hypoglycemia. More experienced nursing staff should not only pay attention to low blood glucose levels but also combine the observation of the symptoms of hypoglycemia and the blood glucose drop range to achieve early detection and early prevention.

The focus of this study was to find the impact of the blood glucose drop range during hemodialysis on the clinical symptoms of hypoglycemia in patients with diabetic nephropathy and to use the blood glucose drop percentage as a reminder to carry out nursing interventions for patients in advance, so as to reduce the occurrence of hypoglycemia in patients with

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diabetic nephropathy during hemodialysis and ensure the safety and comfort of patients during dialysis.

METHODS

Clinical data

A total of 124 maintenance hemodialysis patients with diabetes who were treated in Renji Hospital Affiliated to Medical College of Shanghai Jiaotong University, Shanghai Sixth People's Hospital, and Punan Hospital in Pudong New Area, Shanghai from October 2018–July 2019 were selected as research groups.

The inclusion criteria were as follows:

a) patients who were clinically diagnosed as end-stage diabetic nephropathy or end-stage nephropathy with diabetes, wherein diabetes meets the WHO diagnostic criteria, and nephropathy meets the diagnostic criteria of the Nephrology Branch of Chinese Medical Association;
b) patients with informed consent to participate in the investigation and research;
c) patients with regular hemodialysis duration longer than 3 months–i.e., hemodialysis was performed three times a week four hours each time;
d) patients with complete cognitive ability and who cooperated with the research and investigation;
e) patients who were above 18 years old.

The exclusion criteria were as follows:

a) patients with severe consumptive diseases such as malignant tumor;
b) patients with severe complications such as hypertension and heart failure;
c) patients who did not cooperate with the investigation and research;
d) patients who took drugs that affect blood glucose during dialysis, such as glucocorticoids (prednisone, dexamethasone, etc.), contraceptives, anti-asthmatic drugs, antituberculosis drugs, diuretics, adrenaline, antipsychotics, and immunosuppressive drugs;
e) patients who suffered from mental and neurological diseases; and
f) patients who did not follow the physician's advice for dialysis.

Research methods

This study is an investigative study, focusing on the observation of blood glucose changes, hypoglycemia symptoms, and time of onset of hypoglycemia in hemodialysis patients with diabetes.

Blood glucose monitoring tools

Johnson & Johnson blood glucose meter and the supporting test papers were used. The blood glucose meter was calibrated once a day by the professional staff of Johnson & Johnson using a special simulated blood glucose solution (quality control solution), and the error value was within ±10%. During the entire research process, the brands of blood glucose meters and test papers were not changed. The blood glucose meter and blood glucose test paper were checked for the validity period of the quality inspection, and there was no damp and mildew.

Observation indicators

Blood glucose level: The blood glucose level was noted before dialysis, one, two, and three h after dialysis, and when hypoglycemia symptoms occurred. When the blood glucose value is <3.9 mmol/L, the patient is diagnosed as hypoglycemia.

Hypoglycemia symptoms: according to the "Expert Consensus on the Management of Hypoglycemia in Diabetic Patients in China," hypoglycemia symptoms are divided into autonomic symptoms and neurological hypoglycemia symptoms. Symptoms of the autonomic nervous system include hunger, sweating, anxiety, paresthesia, palpitations, tremors, pale complexion, tachycardia, and pulse pressure. And symptoms of the neurological hypoglycemia include weakness, dizziness and headache, confusion, abnormal behavior, cognitive impairment, blurred vision, diplopia, central blindness, hypothermia, epilepsy, and coma. During the research and observation process, the patients were given health education about the symptoms of hypoglycemia in advance, and they were instructed to inform the nurses of their feelings when any of the above symptoms of hypoglycemia occurred. At the same time, researchers should also pay close attention to the patient's physical signs.

Time of onset of hypoglycemia: when the patient complains of any of the above symptoms of hypoglycemia or the researcher observes that the patient has symptoms of hypoglycemia, the accurate time of the appearance of the hypoglycemia symptoms is recorded immediately, with the unit of time accurate to the minute. During the entire dialysis process, if the patient has neither the symptoms of hypoglycemia nor the measured blood glucose value per hour that is ≥3.9 mmol/L, it means that the patient has not had a hypoglycemia event during the four hours dialysis process.

Research implementation process

The experiment was introduced to the patient, the patient's consent was received, and the informed consent form was signed.

The general information of the patient were recorded.

Interpretation and education: patients were guided to understand hypoglycemia symptoms correctly and to timely inform researchers when any hypoglycemic symptoms appear.

If the patient has no complaints of hypoglycemic symptoms during the entire hemodialysis process, he/she should be monitored at 1-h intervals (before dialysis, and one, two, and three h during dialysis), and if the blood glucose value of the four measurements is not <3.9 mmol/L, it means that the patient does not have hypoglycemia during hemodialysis.

If the patient does not complain of hypoglycemia symptoms during hemodialysis, but the blood glucose value measured during hourly monitoring is ≤3.9 mmol/L, it means that the patient has hypoglycemia during hemodialysis and the time should be recorded.

If the patient complains of any symptoms of hypoglycemia during hemodialysis, immediately measure the blood glucose value at that time and the time should be recorded.

Taking into account the safety of the patient: After the patient has symptoms of hypoglycemia and/or blood glucose value <3.9 mmol/L, it is recommended that the patient is allowed to eat or be given glucose treatment. Then, the patient's symptoms should be closely observed, and the blood glucose level should be monitored 15 min later to ensure the safety of patients during hemodialysis.

Statistical methods

Double entry of patient data was checked and eliminated, and the data were analyzed by SPSS23.0 statistical software. The χ^2 test was used for the comparison of count data, and $p<0.05$ indicates that the difference was statistically significant. The χ^2 test was used to compare the incidence of hypoglycemia in different time periods, and $p<0.05$ was considered statistically significant. The receiver operating characteristic (ROC) curve was used to evaluate the specificity and sensitivity of blood glucose level, blood glucose drop range, and blood glucose drop percentage to the occurrence of hypoglycemia symptoms, with $\alpha=0.05$ as the test level.

RESULTS

General information

As shown in Table 1, there is no significant difference between the basic data and the clinical information of patients in the hypoglycemia group and the nonoccurring group.

Comparison of the occurrence of hypoglycemia symptoms in each time period

There are differences in the incidence of hypoglycemia in the four time periods, and the differences are statistically significant. The incidence of hypoglycemia in 60–120 min is the highest, with an incidence of 69.4%. The test level is α:0.05/6=0.0083. After pairwise comparison, it can be found that the incidence of hypoglycemia at 60–120 min is the highest, and the difference is statistically significant.

Table 1. Comparison of patient's basic information.

Basic information		Hypoglycemia group	Non-hypoglycemic group (n)	t/χ^2	p-value
Gender	Male	62	6	0.440	0.506
	Female	49	7		
Age		58.40±2.41	60.17±0.60	-0.911	0.364
Years of hemodialysis		5.45±0.67	5.15±0.19	0.511	0.611
Primary disease	Diabetic nephropathy	75	5	0.980	0.323
	End-stage nephropathy with diabetes	43	1		
Years of diabetes		6.92±0.49	7.89±0.16	-1.784	0.077
Medication or not	No	63	8	0.110	0.742
	Yes	48	5		
Type of hypoglycemic drugs before current dialysis	Oral	17	3	0.550	0.458
	Insulin injection	23	2		

The ROC analysis of blood glucose level, blood glucose drop range, blood glucose drop percentage, and the occurrence of hypoglycemia

As shown in Figure 1 and Table 2, it can be found that the area under the ROC curve (AUC) of blood glucose when symptoms occur is 0.183, p=0.000.

The AUC of the blood glucose drop range is 0.686, p=0.028, the critical value is 4.05, the sensitivity is 67.6%, and the specificity is 69.2%.

The AUC of the blood glucose drop percentage is 0.834. When the AUC is between 0.7–0.9, the experimental accuracy is high, p=0.000. The critical value of the blood glucose drop percentage is 37.7%, the sensitivity is 73%, and the specificity is 84.6%. When the blood glucose drop percentage is 37.7%, it is prone to symptoms of hypoglycemia, which is worthy of clinical vigilance.

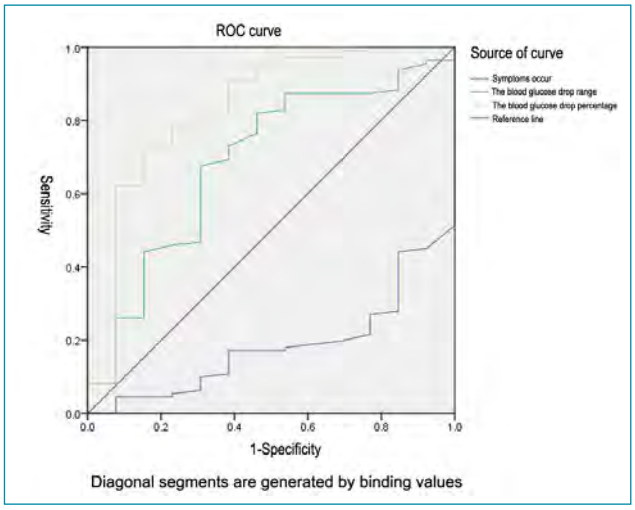

Figure 1. Area under the receiver operating characteristic curve.

Comparing the areas under the three curves, it can be seen that the AUC of the blood glucose drop percentage is 0.834, indicating that the blood glucose drop percentage is more accurate in diagnosing the occurrence of hypoglycemia symptoms than the blood glucose level and the blood glucose drop range.

DISCUSSION

Hemodialysis patients with diabetes have many reasons for frequent hypoglycemia during dialysis. First, the patient's own kidney failure, the kidney's inactivation and excretion of insulin, or hypoglycemic drugs are reduced, resulting in the accumulation of insulin in the body[3-4]. Second, during hemodialysis, insulin is a macromolecular substance and cannot be easily removed by dialysis treatment, while glucose, as a small molecular substance, can freely pass through the filter membrane of the dialyzer. Third, due to the difficulty in storage of glucose-containing dialysate and the occurrence of nosocomial events, sugar-free dialysate is widely used in hospitals in China. Guo Jianzhong et al.[5] found that with the sugar-free dialysate, about 5.5–6.0 g glucose can be lost per hour. Once serious hypoglycemia occurs and the treatment is not timely, it will not only affect the quality and comfort of the dialysis patients but also cause cardiovascular and cerebrovascular accidents[6,7]. The ratio of complication and mortality of hemodialysis patients with diabetic nephropathy to that of patients with nondiabetic nephropathy is 2:1[1]. Nursing staff should pay close attention to the changes in blood glucose in patients with diabetic nephropathy during dialysis.

In previous studies, many scholars have proposed the importance of monitoring blood glucose and observing the symptoms of hypoglycemia during dialysis. Domestic researcher Zhang Ronghua[8] proposed that during dialysis for diabetic nephropathy, blood glucose should be monitored before dialysis and one, two, and three h after dialysis, and timely measures should be taken to control the occurrence of hypoglycemia. Although diabetic

Table 2. Receiver operating characteristic analysis of blood glucose level, blood glucose drop range, blood glucose drop percentage, and the occurrence of hypoglycemia.

Area under the curve					
Test result variable	Area	Standard error[a]	p-value	Asymptotically 95%(CI)	
				Lower limit	Upper limit
Blood glucose at symptom onset	0.183	0.047	0.000	0.090	0.276
Blood glucose drop range	0.686	0.080	0.028	0.530	0.843
Blood glucose drop percentage	0.834	0.070	0.000	0.696	0.972

[a]Under the nonparametric assumption.

patients are diagnosed with hypoglycemia only when their blood glucose value is <3.9 mmol/L, domestic scholar Wang Jianhua[9-13] proposed that hypoglycemia can also occur if blood glucose is not low. In most cases, the severity of hypoglycemia symptoms such as hunger, palpitation, and sweating is basically consistent with the blood glucose level of patients, but there are also exceptions. Clinically, when some diabetic patients have symptoms of hypoglycemia such as palpitation and hunger, the results of immediate blood glucose test are not low. This phenomenon is called "hypoglycemia reaction." Although the blood glucose in "hypoglycemic response" is not low, it should not be overlooked or ignored. In principle, it should be treated the same as hypoglycemia, and appropriate amount of carbohydrates must be supplemented in time before the blood glucose level drops to 3.9 mmol/L to quickly relieve the symptoms of hypoglycemia and prevent cardiovascular and cerebrovascular accidents.

During this study, the blood glucose level showed a downward trend in the process of hemodialysis, and the main symptom of hypoglycemia was hunger. During this experiment, there was no case of severe hypoglycemia (endangering the patient's heart and cerebral vessels and even life, and blood glucose value <2.8 mmol/L). After the patient developed symptoms of hypoglycemia, he/she was treated immediately, instead of using the blood glucose value of 3.9 mmol/L as the judgment standard, so as to effectively reduce the occurrence of severe hypoglycemia. It can be seen that although the incidence of hypoglycemia in patients with diabetic nephropathy is high in hemodialysis, as long as the nursing staff pay close attention to the changes of blood glucose and the symptoms and signs of hypoglycemia and intervene in advance before the blood glucose value reaches 3.9 mmol/L, it can effectively reduce the occurrence of malignant hypoglycemia.

As shown in Figure 1 and Table 2, the ROC curve analysis shows that the critical value of the blood glucose drop percentage is 37.7% with AUC=0.834 (p=0.00). A curve is drawn with sensitivity as the ordinate and 1-specificity as the abscissa. The larger the AUC, that is, the closer the curve is to the upper left, the higher the sensitivity and specificity that this method can achieve at the same time, and the greater the diagnostic value. When the AUC>0.7, it indicates that the blood glucose drop percentage has certain specificity and sensitivity for the prediction of hypoglycemia symptoms. This study changed the previous medical staff's cognition of hypoglycemia in patients with diabetic nephropathy during hemodialysis that 3.9 mmol/L is not the only and accurate standard for the diagnosis of hypoglycemia. Since the symptoms of hypoglycemia in patients with diabetic nephropathy during hemodialysis are earlier than the blood glucose value of 3.9 mmol/L, the blood glucose drop percentage can be used to indicate the occurrence of hypoglycemia more in advance and more accurately. In future clinical practice, blood glucose management process in dialysis can be formulated according to the blood glucose drop percentage.

CONCLUSION

Through this study, during hemodialysis, it is proved that the percentage of blood glucose drop reaching 37.7% is more accurate for predicting the symptoms of hypoglycemia in patients with diabetic nephropathy.

AUTHORS' CONTRIBUTIONS

LSHL: Conceptualization. **YY:** Data Curation, Formal Analysis. **PC:** Writing – original draft, Writing – review & editing. **SYZ:** Writing – original draft, Writing – review & editing. **HFQ:** Data Curation, Formal Analysis. **CYY:** Writing – review & editing. **HFZ:** Writing – review & editing.

ETHICS APPROVAL

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University. Written informed consent was obtained from all participants.

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Association between hyperuricemia and hypertension: a case–control study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the association between hyperuricemia and systemic arterial hypertension.

METHODS: This was a case–control study where individuals aged >18 years were included, who were divided into hypertensive and non-hypertensive groups, excluding those with incomplete information in medical records or with the chronic kidney disease epidemiology collaboration <60 mL/min/1.73 m³. Systemic arterial hypertension was categorized as a dependent variable, while the independent variables were hyperuricemia (i.e., primary variable), sex, education, the practice of physical activity, alcoholism, smoking, diabetes mellitus, chronic kidney disease, a family history of systemic arterial hypertension, age, isolated hyperlipidemia, and mixed hyperlipidemia. Statistical analysis included the univariate and multivariate data analysis, performed by adjusting the logistic regression models using the software R (R Core Team [2018]).

RESULTS: Out of 103 patients evaluated, 75 patients were included in this study. In hypertensive patients, hyperuricemia was more frequent (p=0.029), being present in 18.9% individuals. In the univariate analysis, a statistically significant association was found between hyperuricemia and systemic arterial hypertension (OR 10.9; 95%CI 1.29–1420.0; p=0.023); however, in the multivariate analysis, when adjustment was made for age, the only control variable that persisted in the model, this association ceased to be significant (OR 8.5; 95%CI 0.87–1157.0; p=0.070).

CONCLUSIONS: There was no independent association between hyperuricemia and systemic arterial hypertension. The latter was associated with diabetes mellitus, chronic kidney disease, and age.

KEYWORDS: Hypertension. Uric acid. Hyperuricemia.

INTRODUCTION

Cardiovascular diseases (CVDs) represent the leading cause of death today, causing approximately 17.3 million deaths annually, which corresponds to about 31.5% of all causes and 45% of noncommunicable causes[1]. In Brazil, the rates are quite similar to those detected worldwide, with a mortality rate for CVD corresponding to 31% of all causes of death and 42% of the non-communicable causes[2].

Among the primary causes, systemic arterial hypertension (SAH) accounts for 45% of the cardiac deaths, while 51% of deaths are caused by stroke, affecting 36 million adults in Brazil and costing more than 15 million dollars annually to the public health system[2,3]. In Brazil, Chor et al. in a study with 15,103 public servers in six capitals verified a prevalence of 35.8% SAH, with a predominance among men (40.1 *versus* 32.2%)[4]. SAH is a multifactorial condition and is associated with several other pathologies, such as diabetes mellitus (DM), chronic kidney disease (CKD), and obesity[3].

Hyperuricemia is defined as the presence of serum uric acid levels >7 mg/dL for men and >6 mg/dL for women[5]. High consumption of meat, alcohol, and fructose and use of diuretics are risk factors for its presentation[5-7].

Several epidemiological studies have pointed out the association between high levels of uric acid and CVD, such as

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hypertension, CKD, vascular dementia, metabolic syndrome, preeclampsia[8,9], and type one DM[10]. Nevertheless, establishing a causal relationship between hyperuricemia and hypertension, mainly due to the coexistence of other risk factors, has always been challenging[9,11].

Some experimental models seek to explain this relation based on the inhibition of uricase (or urate oxidase), an enzyme responsible for degrading uric acid into allantoin[8,11,12]. In these studies, rats with uricase inhibited due to oxalic acid administration developed severe hyperuricemia and hypertension[8]. Moreover, other hypotheses are mainly based on the mechanisms of induction of renal vasoconstriction mediated by endothelial dysfunction and the renin-angiotensin-aldosterone system[11-13], as detailed in Figure 1.

This study aims to evaluate the association between hyperuricemia and SAH, controlled by the other classic risk factors for SAH.

METHODS

A total of 103 patients from a Federal Teaching Hospital were evaluated from November 2017 to September 2018.

In this case-control study, the case group comprised patients with SAH and the control group was composed of non-hypertensive patients.

Patients who were aged above 18 years, who were diagnosed with SAH, who did not have CKD (CKD Epidemiology Collaboration [CKD-EPI] <60 mL/min/1.73 m^3), and who had documented uric acid levels in the past three years were included in this study. Regarding the diagnosis of SAH, 68 patients with systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg who were measured and confirmed in an outpatient clinic were included. For the control group, 35 patients without a diagnosis of SAH and CKD, who had documented uric acid levels, were included. Patients whose medical records did not contain complete information regarding the variables studied and normotensive patients taking medication with the potential to raise the serum uric acid level were excluded.

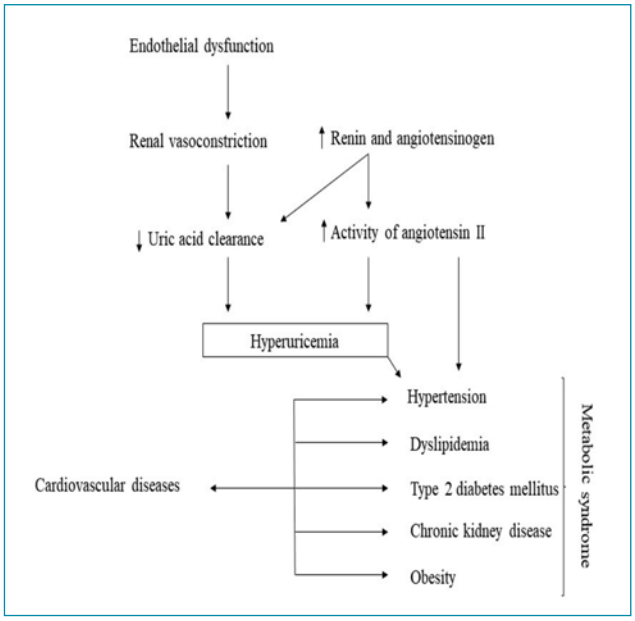

Figure 1. Theoretical rationale for the possible mechanisms of association between hypertension and hyperuricemia, and of these with cardiovascular risk factors. Adapted from Indraratna et al.[13].

To assess the possible association between hyperuricemia and SAH, the statistical analysis was unfolded in two stages. In the first stage, simple logistic regression models were adjusted to check whether not only hyperuricemia but also other sociodemographic and clinical characteristics showed a statistically significant association with SAH. In the second stage, after verifying that hyperuricemia and SAH showed a statistically significant association, multiple logistic regression models were adjusted to assess the independent effect of hyperuricemia on SAH, after controlling for other clinical and sociodemographic characteristics that could be confounding factors.

The sample size calculation considered the earlier data from Nossent et al.[6], which showed an OR 7.7 for the risk of SAH in patients with hyperuricemia and a prevalence of asymptomatic hyperuricemia of 9%. Thus, the minimum sample size to obtain a power of 90% with 95%CI in the 1:1 cases/control ratio and margin loss of 5% was 74.

The statistical significance of the OR tests was evaluated using the likelihood ratio test, and their 95%CI were obtained by a method based on the likelihood function. In all tests, a significance level of 5% was adopted. The statistical analysis was performed using the R software (R Core Team [2018]).

The research protocol entitled "Uric acid as predictor of systemic hypertension" was approved according to the opinion number 2,383,186, with CAAE number 77473717.3.0000.5208.

The data were collected from medical records; therefore, there was no contact with the selected patients, and the requirement for informed consent was waived by the Ethics Research Committee.

RESULTS

During the study period, 103 patients were evaluated. Of these, only 75 patients presented data regarding uric acid levels and were included in this study.

Table 1 shows the results of the univariate analysis of the association between SAH and the sociodemographic and clinical variables of the sample studied.

Table 1. Univariate analysis of the association between systemic arterial hypertension (SAH) and sociodemographic and clinical variables.

	SAH		OR (95%CI)	p*
	Yes	No		
	n (%)	n (%)		
Hyperuricemia				0.023
Yes	10 (100.0)	0 (0.0)	10.9 (1.29–1420.0)†	
No	43 (66.2)	22 (33.8)	1.0	
Sex				0.489
Male	24 (70.6)	10 (29.4)	1.4 (0.56–3.31)	
Female	44 (63.8)	25 (36.2)		
Schooling				0.354
Up to first degree (incomplete/complete)	12 (63.2)	7 (36.8)	2.1 (0.43–10.74)	
Second or third degree (incomplete/complete)	4 (44.4)	5 (55.6)	1.0	
Physical activity practice				0.506
More than 150 min/week	4 (100.0)	0 (0.0)	0.4 (0.003–4.84)†	
Less than or up to 150 min/week	15 (78.9)	4 (21.1)	1.0	
Alcoholism				0.177
Yes	9 (52.9)	8 (47.1)	0.5 (0.15–1.41)	
No	39 (70.9)	16 (29.1)	1.0	
Smoking				0.075
Yes	1 (25.0)	3 (75.0)	0.1 (0.01–1.48)	
No	48 (69.6)	21 (30.4)	1.0	
Diabetes				0.028
Yes	23 (82.1)	5 (17.9)	3.1 (1.05–8.96)	
No	45 (60.0)	3 (40.0)	1.0	
Chronic kidney disease				0.026
Yes	11 (91.7)	1 (8.3)	6.7 (1.22–124.8)	
No	56 (62.2)	34 (37.8)	1.0	
Family history of SAH				0.692
Yes	27 (60.0)	18 (40.0)	1.3 (0.37–4.46)	
No	7 (53.8)	6 (46.2)		
Age (years)				<0.001
≤60	22 (44.9)	27 (55.1)	7.1 (2.76–18.04)	
>60	46 (85.2)	8 (14.8)	1.0	
Isolated hyperlipidemia				0.658
Yes	11 (61.1)	7 (38.9)	0.8 (0.27–2.28)	
No	48 (66.7)	24 (33.3)	1.0	
Mixed hyperlipidemia				0.453
Yes	4 (80.0)	1 (20.0)	2.2 (0.24–20.91)	
No	52 (64.2)	29 (35.8)	1.0	

*Verisimilitude ratio test; †OR and 95%CI estimated using the Firth method.

In the univariate analysis of the association between hyperuricemia and SAH, hyperuricemia was more frequent among cases than controls (18.9% *versus* 0%, p=0.023). The OR of SAH was approximately 11 times higher in patients with hyperuricemia compared with those without hyperuricemia.

To control the possible confounding effect of these variables on the association between hyperuricemia and SAH, the multivariate logistic regression model was adjusted, in which the explanatory variables chosen were those with p<0.20 in the univariate analysis (Table 1); however, alcoholism and smoking were excluded, considering that the absence of information about the levels of uric acid among smokers and drinkers would lead to a considerable reduction in the sample size.

Table 2 presents the results of the adjustments of the initial multivariate logistic model and the final multivariate logistic model, the latter obtained from the initial model through the "backward" selection process, where in each step, the variable with the highest p>0.05 was removed from the resulting model. Thus, the variables DM and CKD were excluded in the process.

The results of the final model showed that after adjustment in the variable age, hyperuricemia was not significantly associated with SAH, although the OR of SAH in patients with hyperuricemia was 8.5 times higher than the corresponding OR in those without hyperuricemia.

Table 2. Initial and final multivariate models to assess the effect of hyperuricemia as a possible factor associated with the occurrence of systemic arterial hypertension.

	Initial model		Final model	
	OR (95%CI)	p	OR (95%CI)	p*
Hyperuricemia	6.8 (0.67–92.8)	0.112	8.5 (0.87–1157.0)	0.070
Age >60 years	6.3 (2.07–22.12)	0.001	7.1 (2.37–24.22)	<0.001
Diabetes	2.1 (0.60–8.88)	0.249		
Chronic kidney disease	1.6 (0.24–17.49)	0.653		

*Verisimilitude ratio test; OR and 95%CI estimated using the Firth method.

DISCUSSION

The difficulty in establishing a causal relationship between hyperuricemia and SAH has been frequently reported in the literature, since it is difficult to separate hyperuricemia as an isolated risk factor for SAH, considering that it usually coexists with several other cardiovascular risk factors[9]. Nevertheless, several recent studies have indicated hyperuricemia as an independent risk factor for the development of SAH, besides being a marker of CVDs[7].

In a Brazilian study developed with 204 patients, a significant association of hyperuricemia with stroke (OR 2.38; 95%CI 1.2–7.24), SAH (OR 7.76; 95%CI 2.72–15.76), hyperlipidemia (OR 5.05; 95%CI 1.59–11.32), peripheral neuropathy (OR 3.49; 95%CI 1.52–12.23), and arterial thrombosis (OR 4.95; 95%CI 1.98–15.34) was observed[14].

In a 5-year follow-up cohort study of 5,889 Japanese individuals aged between 30–85 years, on comparing a group with elevated uric acid levels and another with normal levels, an association was found between hyperuricemia and increased incidence of SAH (14.9 *versus* 6.1%; p<0.001), dyslipidemia (23.1 *versus* 15.5%; p<0.001), CKD (19.0 *versus* 10.7%; p<0.001), and obesity (8.9 *versus* 3.0%; p<0.001)[15].

In Brazil, Ferreira et al.[16] evaluated the association between levels of uric acid and cardiometabolic risk factors in 149 adults aged between 20–55 years. The authors suggested that higher levels of uricemia would be associated with greater fat mass and lipid alterations[16]. The association between hyperuricemia, cardiometabolic risk factors, and metabolic syndrome was also evaluated in a study by Silva et al. with 80 patients, who showed hyperuricemia in individuals with metabolic syndrome (5.1±1.6 mg/dL), in men with abdominal obesity, women with obesity, patients with lower HDL levels, and hypertensive individuals (p<0.05)[17].

Although more prevalent in older individuals, a relationship between hyperuricemia and primary hypertension in children has been pointed out[11]. In a group of 125 children and adolescents aged 6–16 years, a serum uric acid concentration >5.5 mg/dL was found in 89% of participants with primary hypertension, 30% of those with secondary hypertension, and 0% of those with white coat hypertension and the control group[18].

Palmer et al.[19] evaluated the levels of uric acid in a cohort study of 58,072 Danish individuals, seeking to establish an association between hyperuricemia, SAH, and ischemic events. No association was found between hyperuricemia and SAH, even when systolic and diastolic arterial pressures were evaluated separately.

Thus, the independent association between hyperuricemia and SAH is still not well established, mainly due to the

presence of comorbidities in the participants evaluated in clinical studies[7,19,20].

The main limitation of our study was the absence of information in medical records, which reduced our sample size. We have verified studies in the literature that evaluated the association between hyperuricemia and SAH in samples smaller than ours[17]. We emphasized that this is a case-control study whose design and sample are adequate to answer the clinical question raised. The study used the logistic regression techniques to control the effect of other variables that could influence the analysis of the association between hyperuricemia and hypertension.

CONCLUSIONS

No independent association was found between hyperuricemia and SAH. The latter was associated with the variables such as DM, CKD, and age.

AUTHORS' CONTRIBUTIONS

TTDB: Conceptualization, Methodology, Project administration, Writing – original draft. **LSB:** Writing – review & editing. **MAOSV:** Writing – review & editing. **ABMSL:** Methodology, Project administration. **SGL:** Conceptualization, Methodology, Project administration, Writing – review & editing.

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The effects of Coronavirus disease-2019 (COVID-19) pandemic on routine antenatal care visits and complications of pregnancy

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SUMMARY

OBJECTIVE: Routine follow-up of pregnancy is a comprehensive care process starting from planning of pregnancy that involves rational and careful use of medical, psychological, and social support. In this study, our objective was to compare the adherence rate to routine antenatal follow-up program during the COVID-19 pandemic with that of previous years among pregnant women, in an effort to shed light on health policies to be developed similar events in the future.

METHODS: This retrospective cross-sectional study was carried out between March 11, 2019, when isolation measures were initiated in the context of precautionary steps taken in Turkey against the COVID-19 pandemic, and June 1, 2020, when the "normalization" was initiated.

RESULTS: During the study period in 2020, the proportion of cesarean sections were higher, 61.1%, as compared to previous years (p=0.27). The stillbirths were numerically lower (1.2%, p=0.77), but the rate of spontaneous abortions was significantly higher (19.6%, p=0.009). The number of follow-up visits per pregnancy was lower than in previous years (3.8, p=0.02), although the proportion of patients visiting the outpatient units for regular controls to the overall patient group increased as compared to previous years (52.0%).

CONCLUSION: During the flare-up of the COVID-19 pandemic (i.e. between March and June 2020), the rate of obstetric/neonatal morbidity and mortality except spontaneous abortion was not significantly higher as compared to the corresponding period in previous years. However, considering the potential increase in the risk of obstetric complications during a pandemic, specialized management programs targeting basic pregnancy follow-up services should be developed.

KEYWORDS: COVID-19. Pregnancy. Newborn.

INTRODUCTION

Routine follow-up of pregnancy is a comprehensive care process starting from the planning stage of pregnancy that involves rational and careful use of medical, psychological, and social support for the pregnant women[1,2]. The objectives of the pregnancy follow-up include the protection and improvement of maternal and neonatal health, and to reduce maternal, fetal, and neonatal morbidity and mortality through early recognition and management of the health problems that occur before or during pregnancy[3,4].

Each year, approximately 600 pregnant women and 2.5 million newborns die in the first month of life[4-6]. The fact that most of these deaths are due to preventable causes arising during pregnancy and labor is a clear indication of the importance of maternal and fetal follow-up at every level of healthcare.

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While the World Health Organization (WHO) recommends a minimum of four follow-up visits during pregnancy, in our country and most of the developed world, the follow-up visits are periodically performed every four weeks in the first 32 weeks, every two weeks up to week 36, and then once weekly[7]. However, under unexpected conditions such as a pandemic affecting most parts of the society, it has been observed that the regular follow-up assessments of pregnant women may be hampered due to the combined effect of preventive measures taken by the authorities, specific relocation of health resources, and the anxiety and fears experienced with individuals. In countries highly affected by the Ebola pandemic in the past, an 80% reduction in routine pregnancy care together with a decline in vaccination rates were reported[8].

Following the origin of the deadly pandemic referred to as the "coronavirus disease-2019" (COVID-19), countries and health authorities, and particularly the WHO initiated a series of preventive measures[9,10]. In this line of activities, the preventive measures implemented in our country included also "provision of prioritized outpatient care to patients with an appointment, while patients without an appointment were asked to re-apply for an appointment unless they require emergency care based on triage results"[10-12]. It may be assumed that such measures implemented in our country as well as globally may have an impact on maternal and fetal morbidity and mortality.

The objective of our study was to compare the COVID-19 pandemic era and previous years in terms of the number of pregnant women attending hospital visits as well as the most frequent complications associated with pregnancy.

METHODS

This retrospective cross-sectional study was carried out at the Departments of Gynecology and Obstetrics, Rize Research and Training Hospital and Gynecology and Obstetrics, Rize State Hospital. The study protocol was approved by the Ethics Committee for Non-Interventional Research, Recep Tayyip Erdogan University (permission no: 2020/171). The study was carried out between 11 March 2019, when isolation measures were initiated in the context of precautionary steps taken in Turkey against the COVID-19 pandemic, and 1 June 2020, when the "normalization" was initiated. Data on the total number of pregnancies, number of pregnancy follow-up visits, outcomes of pregnancy, the total number of births, and postnatal clinical course were retrieved from the hospital medical records for pregnant women of all age categories. The data obtained through this method were compared with the corresponding data from 2018 and 2019.

Fetal loss before 20 weeks of gestation was referred to as "spontaneous abortion", while those occurring after that time were referred to as "stillbirth".

Statistical analysis

Compliance of numerical variables in the study with normal values was examined by visual and analytical methods, and non-normal distribution parameters were defined by specifying the median and interquartile distribution, and categorical variables by specifying the percentage and number. Kruskal-Wallis test was used to compare variables that were not normally distributed, and chi-square test was used to compare categorical variables. IBM SPSS 21.0 (Chicago, USA) software was used while evaluating the study data. p-value less than 0.05 was considered statistically significant.

RESULTS

In two study centers, a total of 501 births, of which 306 were cesarean sections, were recorded between 11 March and 1 June in 2020. The mean gestational age at birth was 38.0±2.7 weeks [27–41] with a mean birth weight of 3038±627 (835–4450) grams. The female to male ratio was 237:264. No maternal deaths occurred *versus* six stillbirths. Of the overall group of newborns, 115 (23.0%) were admitted to the Newborn Intensive Care Unit (NICU) due to a variety of indications. The mean maternal duration of hospital stay was 1.5±0.6 days (1–3) postnatally. Table 1 shows the outcomes of the pregnancies according to study years.

During the study period in 2020, a total of 1051 pregnant women were identified in Rize province, with a total of 7645 visits to antenatal outpatient units, 3975 of which involved antenatal follow up (visits occurring within 10 days of an antenatal visit were considered control examinations, and thus were excluded from these numbers). The number of follow-up visits per pregnancy was 3.8, which was lower compared to two previous years (8.3 and 8.1, respectively) (p=0.02). On the other hand, the proportion of pregnancy follow-up visits to the overall patient group during the study period (52.0%) was higher (37.2 and 39%, respectively) (p=0.02). The numerical data for the three-year period regarding the pregnancies and outpatient visits are shown in Table 2.

When the outcomes of pregnancies were examined, the rate of spontaneous abortions in 2020 (19.6%) was significantly higher compared to other years (p=0.009). The number of stillbirths was reduced (1.2%), although this reduction was not statistically significant (p=0.77). Similarly, the proportion of cesarean sections and infant mortality was higher compared to previous years, but again the differences were insignificant (p=0.27 and p=0.63). When hospitalizations after birth were

Table 1. Pregnancy results of the cases included in the study by years (March–June period).

	2018		2019		2020	
Total number of births (n)	606		698		501	
Normal birth number (n)	287		383		195	
Number of cesarean delivery (n)	319		315		306	
Hospitalization duration (day)*	1.7±0.4 (1–3)		1.8±0.6 (1–5)		1.5±0.6 (1–3)	
Birth time (week)*	38.3±2.6 (25–41)		38.1±2.5 (27–41)		38.0±2.7 (27–41)	
Sex of the newborn (n)	Girl	Boy	Girl	Boy	Girl	Boy
	311	295	333	365	237	264
Average body weight of the newborn (g)*	3117±664 (875–4200)		3139±684 (870–4450)		3038±627 (835–4450)	
Maternal deaths (n)	0		0		0	
Number of stillbirths (n)	7		10		6	
Number of NICU hospitalizations (n)	149		156		115	
Number of infant deaths (n)	8		4		7	

*Mean±standard deviation (min–max). NICU: neonatal intensive care unit.

considered, NICU admissions occurred at a higher rate in 2020 (23%), compared to previous years, with the difference being statistically insignificant (p=0.74). Although infant deaths were also higher (1.4%), the difference again was not statistically significant (p=0.63). The statistical data regarding the outcomes of pregnancy are shown in Table 3.

DISCUSSION

During disease outbreaks, health resources are primarily allocated to disease groups that are associated with severe complications in case of delayed diagnosis and treatment[13,14]. Under such circumstances, usual healthcare may be hampered due to the increased demand for health services, alterations in health management policies, as well as due to the fear/risk of contracting the disease from infected individuals in health facilities. In this study examining the antenatal follow-up and complications of pregnancy during the first three months of the COVID-19 pandemic in our country, although there was a significant reduction in the number of follow-up visits among pregnant women, rate of feto-maternal complications (excluding spontaneous abortion) and cesarean section did not appear to be significantly different.

A special category that should not be overlooked during a pandemic includes pregnant women. Adequate and timely provision of maternal care not only reduces the occurrence of important obstetric complications but also allows early

Table 2. Numerical data of antenatal polyclinic follow-ups by years (March-June period).

	2018	2019	2020	p
Number of Pregnant*	935	1102	1051	0.68
Total number of applications to Antenatal Polyclinic	20875	22861	7645	0.01
Number of controls	7775	8927	3975	0.02
Number of controls per Pregnancy	8.3	8.1	3.8	0.02
Number of controls/ total number of Polyclinic Rate (%)	37.2	39.0	52.0	0.06

*Number of pregnancies detected in whole Rize province.

Table 3. Statistical data on the results of pregnancies by years (March-June period).

	2018	2019	2020	p
Abortion rate (%)	17.9	14.1	19.6	0.009
Stillbirth rate (%)	1.2	1.4	1.2	0.77
Cesarian section ratio (%)	52.6	45.1	61.1	0.27
NICU hospitalization rate (%)	24.6	22.3	23.0	0.74
Infant mortality rate (%)	1.3	0.7	1.4	0.63

NICU: neonatal intensive care unit.

identification of congenital malformations[15,16]. In our study, the attendance rate to outpatient units for antenatal care was lower during the pandemic as compared to the corresponding periods in 2018 and 2019. This lower attendance rate despite the absence of an interruption in outpatient care may be explained by the preference of the study population for not visiting a healthcare facility due to a variety of reasons. Despite the reduced number of follow-up visits per pregnancy, the minimum requirement set forth by the WHO, i.e. four visits, was approached (3.8 follow-up visits per pregnancy in the current study). Also when the patients attending to outpatient units were grouped as those attending for antenatal follow-up and those for other reasons, there was a noticeable increase in the proportion of patients attending for control (52%), suggesting adequate use and proper management of resources during the pandemic. When one considers the fact that pregnant women were asked to attend follow-up visits, particularly during the third trimester or due to increased risk level, it can be assumed that adequate information on the importance of follow-up visits could be conveyed to these pregnant women.

In our study, independent of the COVID-19 infection on maternal and neonatal mortality, there was an increase in the proportion of spontaneous abortions (19.6%) during the pandemic in comparison with the corresponding periods in 2018 and 2019. The participants of this study were under routine follow-up with no COVID-19 diagnosis. This increase in spontaneous abortions may be related to the increased incidence of asymptomatic infections. In addition, the decrease in the number of pregnancy follow-ups may cause an increase in the rate of spontaneous abortion. However, although the link between COVID-19 infection and spontaneous abortions is an interesting research subject, we are unable to reach a definitive conclusion regarding this association as no antibody screening for COVID-19 was done in our patient group.

Previously, a 24% increase in stillbirths was reported during pandemics, due to the limited access to healthcare. Similarly, an increase in maternal mortality was found in that same study[15]. On the other hand, no significant differences between the pandemic period and previous years could be detected in terms of maternal and neonatal mortality in our study. We believe that this latter finding may be due to early recognition of high-risk patients during antenatal outpatient visits, rational choice of visit intervals (although they were longer), and presence of adequate healthcare understructure.

In our country, almost all pregnant women opt to deliver in a healthcare facility rather than having home delivery. However, this may be different during a pandemic. Due to the high patient load in larger healthcare centers, patients may be more inclined to receive primary healthcare. Furthermore, physicians have a general disposition to carry out more cesarean sections to reduce the duration of hospital stay, and may even prefer shorter hospital stay for patients after the delivery[12,13]. In our study, an insignificant increase in the rate of cesarean deliveries was observed during the pandemic as compared to previous years (61.1%, p=0.27). Although the data for cesarean indications have not been presented, factors that may help explain this increase include the willingness for rapid discharge to home, and the urge to stay away from situations with a high risk of virus transmission. The reduction in the postnatal hospitalization time also appears to support this hypothesis. Although the postnatal complication data for mothers is unavailable, the decline in the duration of hospitalization points out the importance of appropriate education and patient management regarding the post-discharge period.

In the current study, there was an insignificant increase in NICU admission rates (23%, p=0.74) and infant mortality (1.4%, p=0.63) during the pandemic. This association of COVID-19 pandemics with increased NICU admission and infant mortality is obscure. Furthermore, some studies showed a significant decrease in rates of prematurity, with a small increase in stillbirths following the implementation of preventive health policies aimed at alleviating the effects of the COVID-19 pandemic[17,18]. Possible cited reasons include the preventive measures against the pandemic as well as the personal and physical isolation measures implemented. Similarly, the reluctance of the pregnant women in following regular prenatal visits due to "fear from infection transmission" may represent one of the potential reasons for the very slight increase observed in newborn intensive care unit admissions and deaths in our study.

Although the extent of the effects of the COVID-19 pandemic on healthcare services is yet to be fully defined, media news and published studies suggest that the pandemic may have a significant impact on the health of mothers and babies in the future[19-21]. No maternal deaths have been observed in our study, and no significant increase in neonatal morbidity and mortality was recorded; however, there was a significant decrease in the number of patients attending outpatient units. On the other hand, the fact that routine follow-up of pregnant women and newborns may be interrupted during periods of the pandemic. Routine follow-up is essential, which may require activation of appointment systems specifically suited for certain patient groups, infrastructure for telemedicine, home care for pregnant women, or reduced queue time in hospitals in an effort to protect women representing a risk group. Also, online or media-based educational activities may be organized to inform pregnant women about emergency conditions.

Limitations of our study include the use of data restricted to two centers only in the Rize province of Turkey, as well as

the fact that comparisons were based on the first three-month period during the pandemic. Another limitation relates to the lack of the examination of the socio-cultural reasons for the reduced rates of hospital attendance since the study had a retrospective design. In addition, SARS-CoV-2 PCR analysis was not performed in pregnant women, so a direct relationship cannot be shown between spontaneous abortion and feto-maternal complications and COVID-19 disease. If we knew the SARS-CoV-2 PCR results of cases with spontaneous abortion, we could express more precisely whether there was a relationship between abortion and COVID-19.

In conclusion, this retrospective cross-sectional study showed that the frequency of obstetric/neonatal morbidity and mortality in the first three months of the COVID-19 pandemic were not significantly different as compared to the corresponding periods in 2018 and 2019 except for spontaneous abortion. During the pandemic period, spontaneous abortion rates increased compared to previous years. Although the number of attending to outpatient units and antenatal follow-up visits were reduced, the recommended number of antenatal controls were carried out, which may be explained based on the quality of the healthcare services provided as well as the presence of adequate health infrastructure. However, large-scale prospective studies examining the short and long-term effects of the interruption of antenatal follow-up visits are required during prolonged periods of outbreaks such as corona that have the potential to transform into a pandemic.

AUTHORS' CONTRIBUTION

YY: Conceptualization. **AYY:** Data curation. **IEY:** Formal analysis. **TA:** Data curation, Formal analysis. **MKK:** Data curation, Formal analysis. **BG:** Writing – original draft, Writing – review & editing. **BY:** Validation.

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Validity and reference values for the 3-minute shuttle run test in spanish preschoolers

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SUMMARY

OBJECTIVE: The purpose of this study was to analyze the validity and provide normative values for the three-min shuttle run test in Spanish preschoolers.

METHODS: A total of 497 children (mean age 4.83±0.57 years; 47.8% girls) performed the three-min shuttle run test. Posttest body mass index and heart rate values were taken as internal validity indicators.

RESULTS: Age- and sex-specific percentiles for cardiorespiratory fitness were provided. Boys performed better than girls in the test. A significant association was observed between the total distance covered and heart rate (p=0.002). No correlation was found between body mass index and the test score, although the total distance covered by normal weight and obese children was significantly different (296.9 *versus*. 271.3 m; p=0.013).

CONCLUSIONS: This study provides age- and sex-specific cardiorespiratory fitness normative values for the three-min shuttle run test when performed by Spanish preschoolers. This test is an interesting option when the lack of resources limits the measurement of cardiorespiratory fitness in the preschool setting.

KEYWORDS: Reference values. Cardiorespiratory fitness. Children. Spain.

INTRODUCTION

Cardiorespiratory fitness (CRF) is the most important marker for health and disease during childhood[1,2]. Thus, it seems important to track CRF during the early years and, consequently, include its assessment in health and educational monitoring systems.

To accurately fulfill this aim, meaningful, reliable, and sensitive outcome measures are required. In this regard, laboratory-based direct measures of this physiological variable are considered the gold standard for this purpose. However, the accuracy and utility of these tests for preschoolers have been questioned, given the smaller body size relative to the testing equipment, the reduced motivation, and the potentially shorter attention span[3].

In this context, field-based tests represent a practical and feasible option, due to their low cost and ease administration. However, as field-based tests are indirect, they must show adequate psychometric properties (i.e., reliability and validity) before they can be used for gathering valuable data. There are a reduced number of CRF field-based tests whose psychometric properties have been identified when performed by preschoolers. In their thorough revision of health-related physical fitness test for preschoolers, Ortega et al.[4] found five CRF tests whose reliability had been previously informed. However, their validity was unknown. To the authors' knowledge, up to date, the preschool-adapted 20-m shuttle-run test (from the PREFIT battery) is the only CRF test whose validity (convergent) was identified by comparing its results against the original 20-m shuttle run test[1].

However, there are two important facts that should be taken into account when administering this test to preschoolers.

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First, the utility for accurately identifying CRF through the estimation of maximal oxygen consumption in these shuttle-run tests has recently been seriously questioned[5]. Second, this test requires materials as well as human resources for its development. An area of more than 20 m length and audio system are required. Besides, it has been suggested that at least two adults must accompany children while running for an accurate performance[6]. These resource requirements and practical implementation issues that seem to appear when this test is carried out in the preschool setting negatively influence its scalability[7].

Contrary to this background, the three-min shuttle run test (3MSRT)[8] stands out as an interesting alternative option, since it requires minimal equipment, and it can be performed by the children themselves. Previous study has confirmed that this test is reliable in preschoolers[2,8,9]. In addition, the test has shown a significant association with the original 20-m shuttle run test, and it has also been identified as a more feasible option for assessing CRF in preschoolers[2]. In spite of the fact that the 3MSRT is still considered by researchers working in the field of preschoolers and health[10], it is not as widely used as the 20-m shuttle-run versions. This could be tied to the fact that no study has provided evidence regarding its validity and also to the lack of reference values that allow the categorization of children according to CRF levels.

Under these circumstances, this study had a twofold objective. First, it was aimed at providing sex-and-age-reference standards by gender and age for the 3MSRT when performed by Spanish preschool children. Second, the aim was to inform about its content validity when administered in this population.

METHODS

This study was performed using the data gathered by physical education students from February 2014 to March 2019, while doing their internship curriculum.

Participants

The participants were normal healthy Spanish urban children who were recruited from 12 different kindergartens in Northern Spain. Those who were between four and five years old and who did not show any medical problem that could affect the completion of the proposed measurement tests were deemed eligible for the study. Parental permission and child assent were obtained after stakeholders were informed that they could decide whether or not to take part in the study, what the objectives were, and the possible risks and benefits. The protocol of this study was approved by the Local Ethics Committee.

Measurements

- *Anthropometrics:* The weight (kg) and height (cm) of children were measured by means of a digital scale and a portable statimeter. The body mass index (BMI) was calculated dividing the body weight in kilograms by the height in meters squared (kg/m^2).
- *Cardiorespiratory Fitness:* For the 3MSRT, two poles (1.5 m in height) were placed 10 m apart to form a straight 10-m long running track. Children had to run from one side to the other, go around the pole, and then return to the starting point. They were encouraged to run as fast as possible and to stop as little as possible for three min. A tape measure was placed between the poles, to register the total distance covered, which is the test score.
- *Heart Rate:* Heart rate (HR) was registered two min before the test began (HR basal) and just after the test was finished (peak HR) by means of a HR monitor (Polar RS400, Kempele, Finland) connected *via* Bluetooth to an iPad Air 2.

Procedure

All tests were carried out on groups of 10–12 children during the psychomotricity sessions and daily break times in the kindergartens' facilities (gymnasium or school playground). Two evaluation sessions were carried out on alternate days of the same week. During the first session, BMI was measured, and the protocol of the test was explained and performed by the evaluator. Several trials were carried out by the children after observing the correct execution, in order for them to familiarize with the test protocol. The second session was devoted to perform the 3MSRT.

All the measurements were performed in each of the kindergarten, which were included in this study, by a preschool teacher and a physical education student who were previously trained in the performance of the test.

Statistical analysis

The data are expressed as mean±standard deviation for quantitative variables or as n (%) for qualitative variables. With the SPSS program, we compared categorical variables with the chi-square test and continuous variables with independent data Student's *t*-test or ANOVA (with Bonferroni correction for multiple comparisons), after assessing normality of the data using the Kolmogorov–Smirnov test. To estimate percentiles of the population results in the 3MSRT (stratified for age and sex), we used a subgroup size weighting to account for heterogeneity among subgroups of children from the different kindergartens included in this study. Additionally, to study internal validity of the 3MSRT, we used BMI and HR as the main comparison variables. A two-sided $p<0.05$ indicated statistical significance.

RESULTS

The final sample for this study included 497 children (mean age 4.83±0.57 years; 47.8% girls). The anthropometric and CRF values obtained by them (whole sample and separated by sex and age) are shown in Table 1. The prevalence of obesity and overweight reached around 30% values on the analyzed sample.

Boys significantly outperformed girls in the total distance covered in the 3MSRT, regardless of age. CRF was significantly higher in the five-year-old group in comparison with the four-year-old children, regardless of sex.

Table 2 shows the specific sex and age reference values according to 10th, 20th, 30th, 40th, 50th, 60th, 70th, 80th, and 90th percentiles. The total distance covered increased with age both in boys and girls, but significant differences ($p<0.001$) were only found between four and five years for boys and between boys and girls of both four–five-year olds (Figure 1).

A significant association was observed between the total distance covered and the heart rate registered in the children after finishing the test ($p=0.002$), as shown in Figure 2A. No correlation was found between BMI and the CRF of children, although a significant difference was observed when comparing the total distance covered by normal weight and obese children (296.9 m *versus* 271.3 m; $p=0.013$) as it can be observed in Figure 2B.

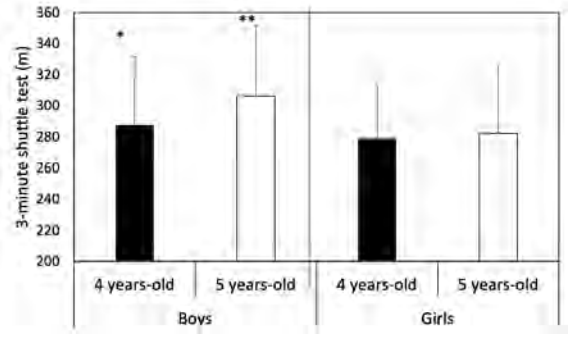
Table 1. General characteristics of the sample.

	Total sample (n=497)	Boys (52.2%)		Girls (47.8%)		Significant differences
		4 years old (38.4%)	5 years old (61.6%)	4 years old (44.2%)	5 years old (55.8%)	
Weight (kg)	20.42 (3.26)	19.1 (2.84)	21.42 (3.09)	18.95 (2.64)	21.53 (3.49)	Age**
Height (cm)	111.12 (6.64)	107.69 (4.79)	113.86 (6.54)	107.31 (4.73)	113.85 (6.64)	Age**
BMI (kg/m^2)	16.49 (1.70)	16.42 (1.72)	16.51 (1.71)	16.42 (1.55)	16.59 (1.9)	–
BMI categories (IOTF)						
Normal weight (%)	355 (71.4)	76 (80.9)	105 (69.5)	70 (70.7)	83 (66.4)	–
Overweight (%)	112 (22.5)	12 (12.8)	38 (25.2)	23 (23.2)	32 (25.6)	–
Obese (%)	30 (6)	6 (6.4)	8 (5.3)	6 (6.1)	10 (8)	–
Weighted 3MSRT (m)	289.38 (43.42)	287.41 (43.97)	306.14 (45.57)	278.67 (35.70)	281.99 (44.13)	Age** and sex**
Basal HR (bpm)	110.43 (10.46)	107.74 (11.36)	113.35 (10.89)	105.92 (8.49)	113.04 (8.99)	Age**
Maximum HR (bpm)	193.29 (10.16)	192.95 (9.32)	191.48 (10.71)	195.23 (10.24)	194.24 (10.0)	Sex*

Values are mean (standard deviation) or n (%). 3MWT: 3-min shuttle run test; BMI: body mass index; BPM: beats per minute; HR: heart rate; IOTF: international obesity task force. Differences by age and sex were analyzed with χ^2 test, Student's *t* test, or ANOVA, as appropriate. *p<0.05; **p<0.001.

Table 2. Meters completed in the 3-min shuttle run test by sex and age-weighted percentiles.

	Percentiles									
	n	10th	20th	30th	40th	50th	60th	70th	80th	90th
Total sample	497	240	260	270	280	288	296	310	320	344
Boys										
4 years old	94	230	255	270	280	285	296	310	320	340
5 years old	151	250	275	285	295	310	320	330	340	360
Girls										
4 years old	99	230	255	268	270	275	285	295	304	320
5 years old	125	224	250	270	275	285	290	300	315	340



*p<0.001 *versus* 5 years old; **p<0.001 *versus* girls. Bars represent mean, and error bars represent standard error.

Figure 1. Meters completed in the three-min shuttle run test by sex and age groups.

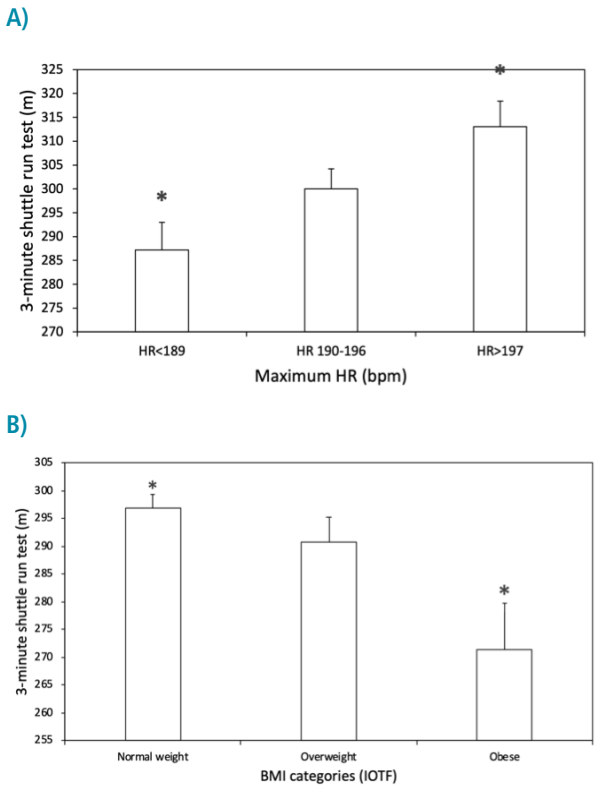


Figure 2. Distance covered in the three-min shuttle run test (m) according to **(A)** maximum HR achieved (*p=0.002 between children with HR<189 and HR>197) and **(B)** IOTF BMI categories (*p=0.013 between normal weight and obese children). Differences analyzed with ANOVA with Bonferroni correction. Bars represent mean, and error bars represent standard error. HR: heart rate in beats per min; BMI: body mass index; IOTF: International Obesity Task Force.

DISCUSSION

This study aimed at establishing reference values for the 3MSRT, as well at providing information regarding its content validity. Given the necessity to assess CRF in preschoolers, the data showed in this study can be of interest for physical education teachers and health practitioners.

Cardiorespiratory fitness reference values are necessary for detecting and monitoring the health of preschoolers, as well as to classify them based on their performance on field-based tests. In addition, normative data can help to set the bases for carrying out interventions aimed at developing the fitness level and the health status of children from an early age. To the authors' knowledge, only two very recent studies have provided reference values for CRF in preschoolers, as assessed by means of the adapted 20-m shuttle-run test[11,12]. Therefore, the present results add valuable information to the existing scientific body of knowledge.

The findings showed in this study are in line with previous observations regarding the significant impact that age and sex has on the preschoolers' CRF[1], which speak in favor of the 3MSRT discriminatory power.

We analyzed the relationship between the total distance covered in the test and the HR registered after its performance, as an indication of its content validity. The obtained results showed the existence of a significant association between both variables. In spite of the fact that this procedure for assessing the content validity of a CRF field-based test has been used in adult population[13], its accuracy could be criticized, on the basis that HR response to a maximal effort differs between children and adults. Nevertheless, when our statistical analysis was designed, we followed previous observations suggesting that those preschoolers with greater running ability would possess a more efficient cardiac function[14]. Our findings are in line with those obtained by Cadenas-Sánchez et al.[6], who after administering the adapted 20-m shuttle run test in preschoolers, it was observed that the greater the distance covered, the higher the HR. In this regard, we should acknowledge that peak HR values obtained in this study were lower than those observed in the original (4 bpm) and adapted versions (6–9 bpm) of the 20-m shuttle run test[1,6]. These differences, slightly higher for the adapted version than for the original one, could be due to adults running alongside the children, as suggested in the modified 20-m shuttle run protocol. Nevertheless, the mean HR peak values observed in our sample were much higher than those found by Mimura et al.[14] and Tuan et al.[3] in a sample of preschoolers who performed a submaximal cardiorespiratory laboratory test. These findings imply that the protocol of the 3MSRT demands maximal effort from the participant.

Body mass index has shown to significantly impact CRF in preschoolers[15,16]. Therefore, as a secondary indication of content

validity, we opted for analyzing the degree of association established between BMI values and the 3MSRT score. Contrary to what could be initially expected, no significant correlation was observed between both variables. Although we found that those children with lower BMI performed better in the test, the significant differences in the total distance covered were only registered between normal weight and obese preschoolers. A possible explanation for these results relies on previous observations suggesting that BMI might not be a good indicator of adiposity in preschoolers and that fat free mass index (FFMI) should be used instead[3]. In support of this assumption, Latorre-Román et al.[17] did not found any significant association between BMI and CRF fitness in preschoolers, while several studies have confirmed that preschoolers with higher FFMI show greater CRF[3,18]. Hence, the data on the accuracy of using BMI as an indicator of CRF field-based tests' content validity remain inconclusive.

There are some limitations that should be acknowledged. First, our sample was made up of Spanish urban preschoolers, which limits the generalization of the obtained findings. Second, we used BMI values for identifying the content validity of the test, instead of using FFMI, which seems a more accurate factor. Finally, although the data was obtained by different researchers previously familiarized with the study procedure, it should be acknowledged that inter-rater reliability was not assessed.

CONCLUSIONS

This research provides age- and sex-specific CRF normative values for the 3MSRT when performed by Spanish preschoolers. The obtained findings indicate that this test becomes an interesting option when the lack of resources limits the measurement of CRF in the preschool setting.

AUTHORS' CONTRIBUTIONS

JCD: Conceptualization, Formal Analysis, Writing – original draft. **MASL:**Writing – original draft. **RIML:** Data curation. **CA:** Conceptualization, Writing – original draft.

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Factors affecting pathological complete response after neoadjuvant chemotherapy in breast cancer: a single-center experience

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SUMMARY

OBJECTIVE: The aim of this study was to examine the characteristics of patients admitted to our hospital with a diagnosis of breast cancer who reached pathological complete response after being operated following eight cycles of neoadjuvant chemotherapy.

METHODS: Between 2015–2020, patients with pathological complete response who were operated on after neoadjuvant chemotherapy and sent to our clinic for radiotherapy were evaluated.

RESULTS: The median age of the patients was 51 years. The most common histological type was invasive ductal cancer. The number of pathological complete response patients was 74 (28%), and the number of non-pathological complete response patients was 188 (72%). Patients with pathological complete response had a smaller tumor diameter than the non-pathological complete response group (p=0.001). For pathological complete response, T1 stage, N1 stage, NG 3, Ki-67 >20%, negative estrogen receptor, negative progesterone receptor, positive Cerb-B2, and adding trastuzumab to chemotherapy were statistically significant (p<0.05). Before neoadjuvant chemotherapy, stage T1–T2 (p=0.036), LN0–1 (p=0.026), Cerb-B2 positivity (p=0.025), and an initial nuclear grade of three (p=0.001) were found to be the factors affecting pathological complete response.

CONCLUSIONS: With neoadjuvant chemotherapy, the size of locally advanced tumors decreases, allowing breast conserving surgery. The neoadjuvant chemotherapy response can be used as an early indicator of the prognosis of patients with breast cancer. Today, neoadjuvant chemotherapy is also used for patients with early-stage, operable breast cancer because it has been shown in many studies that reaching pathological complete response is associated with positive long-term results. If we can identify patients who have reached pathological complete response before neoadjuvant chemotherapy, we think we can also determine a patient-specific treatment plan at the beginning of treatment.

KEYWORDS: Breast cancer. Neoadjuvant chemotherapy. Treatment.

INTRODUCTION

Of all cancers, breast cancer has the second highest death rate in women[1]. Neoadjuvant chemotherapy (NAC) first began to be used for locally advanced, inoperable breast cancers. Then, it was used to reduce the tumor size and achieve good cosmetic outcomes. NAC treats systemic micrometastatic disease from the beginning and reduces the tumor burden within the breast and axillary lymph nodes[2]. Currently, it is also used for patients

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with small tumors. Since an intermediate assessment is performed during NAC, it provides early awareness of a nonresponsive tumor and provides an opportunity to terminate non-useful treatment and/or switch to an alternative treatment[3]. Tumors with high proliferation rates and negative hormone receptors are more sensitive to chemotherapy and are more likely to be within the pathological complete response (pCR) group[4,5]. It is believed that tumors with Her2-positive and triple-negative (TN) subtypes have higher (60–80%) pCR values; whereas luminal A subtype tumors are the least likely to achieve pCR[4-6]. This study aimed to evaluate patients who reached PCR at the end of the NAC and to illustrate the clinical and pathological factors affecting pCR.

METHODS

Between 2015–2020, patients with pCR who were operated on after NAC and sent to our clinic for radiotherapy were evaluated. The exclusion criteria for this study were as follows: bilateral breast cancer, male breast cancer, other malignancies, and metastatic breast cancer. This study was approved by the Ethics Committee (2614/2020) of our hospital. Disease-free survival (DFS) was assessed at the time before metastasis or local recurrence, while the overall survival (OS) was assessed at the final follow-up or the time before death.

Clinical assessment

Breast masses were diagnosed with a tru-cut biopsy. Patients who were radiologically and/or clinically positive for lymph nodes were administered a fine needle aspiration biopsy. We used Black's nuclear grade system. When there was no evidence of a residual invasive tumor in the breast or axillary lymph nodes (ypT0N0/ypTisN0) using the Miller–Payne classification, the histological response to NAC was considered to be pCR[7]. A categorization of Miller–Payne grade five was made when no malignant cells from the tumor were present and only vascular fibroelastotic stroma persisted. Nevertheless, ductal carcinoma *in situ* may be present, and estrogen receptor (ER) and progesterone receptor (PgR) statuses were assessed by immunohistochemical analysis; tumor cells ≥1% were counted as positive. Tumors were deemed Her2 (human epidermal growth factor)-positive with a Cerb-B2 score of 3+(powerful homogeneous staining). For the 2+score (medium homogeneous staining), amplification was described by the chromogenic *in situ* hybridization approach. After the fourth and the eighth chemotherapy treatments, clinical and radiological response diligence was done. Anthracycline-based agents were preferred in the first four cycles, and taxane-based agents (±trastuzumab) were preferred in the next four cycles. Initial 18-fluorodeoxyglucose positron emission tomography for staging was performed on 80% of patients. Tumors were evaluated by the staged tumor node metastases method (7th edition).

Statistical analysis

Statistical analyses were carried out with the help of the SPSS version 26.0 program. The compatibility of variables with normal distribution was studied using the Kolmogorov–Smirnov test. Mean, SD, and median values were used when presenting descriptive analyses. Categorical variables were compared with the Pearson's chi-squared test. The Mann-Whitney U test was used when evaluating nonparametric groups. The survival analysis of pCR was studied with the Kaplan–Meier estimator. The factors affecting the complete response were studied with the binary logistic regression. Cases where the p-value was below 0.05 were evaluated as statistically significant results.

RESULTS

The median age of the patients was 51 years (range: 25–76 years). The number of pCR patients was 74 (28%), and the number of non-pCR patients was 188 (72%). The most common histological types were invasive ductal cancer (IDC, n=213), invasive lobular carcinoma (ILC, n=14), apocrine carcinoma (n=13), mixed type (IDC+ILC, n=8), invasive micropapillary carcinoma (n=6), metaplastic carcinoma (n=5), and mucinous cancer (n=3). Patients with pCR had a smaller tumor diameter than non-pCR group (p=0.001). For pCR T1 stage, N1 stage, nuclear grade (NG) 3, Ki-67>20%, negative ER, negative PgR, positive Cerb-B2, adding trastuzumab to chemotherapy was statistically significant (p<0.05). But, there was no difference between the groups in terms of radiation dose and menopausal status (p>0.05). Mastectomy patients received 50 Gy of radiation (62% pCR and 57% non-pCR group); 60–66 Gy of radiation (38 pCR and 43% non-pCR group) was given to patients with breast conserving surgery (BCS). All patients received RT. Distant metastasis was observed more frequently in those who did not achieve pCR (p=0.011). The most common location of metastasis was bone (n=8), and the second most common location was the brain (n=7) and lymph nodes (n=7), followed by the liver (n=4), the lung (n=3), and local recurrence (n=3). Our pCR rate was 28%. The general characteristics of patients are shown in Table 1.

The 5-year DFS was 87% in the pCR group and 65% in the non-pCR group (p=0.023). The 5-year OS rate was 98% in the pCR group and 48% in the non-pCR group (p=0.033) (Figure 1). The factors affecting pCR were examined with the binary logistic regression. Before NAC, stage T1–T2 (p=0.036), LN0–1 (p=0.026), Cerb-B2 positivity (p=0.025), and an initial nuclear grade of three (p=0.001) were found to be the factors affecting pCR (Table 2).

Table 1. General characteristics for pathological complete response pathological complete response and non-pathological complete response groups.

	Complete response (present) n (%)	Complete response (absent) n (%)	p-value
Age	49±10.2	51±9.5	0.792
Tumor diameter	3.0±3.7	4.0±4.4	0.001
Histology			
Invasive ductal cancer	63 (85)	150 (80)	0.318
Others	11 (15)	38 (20)	
T stages			
T1	15 (20)	10 (5)	0.002
T2	45 (61)	121 (64)	
T3	6 (8)	24 (13)	
T4	8 (11)	33 (18)	
Lymph node stages			
N0	4 (5)	8 (4)	0.015
N1	30 (41)	49 (26)	
N2	36 (49)	95 (51)	
N3	4 (5)	36 (19)	
Nuclear grade			
1	0 (0)	7 (4)	<0.001
2	16 (22)	96 (51)	
3	58 (78)	85 (45)	
Ki-67 ratio			
Unknown	6 (8)	25 (13)	0.014
≤20	6 (8)	39 (21)	
>20	62 (84)	124 (66)	
Estrogen receptor			
Positive	43 (58)	149 (79)	<0.001
Negative	31 (42)	39 (21)	
Progesterone receptor			
Positive	40 (54)	129 (69)	0.027
Negative	34 (46)	59 (31)	
Cerb-B2 status			
Positive	39 (53)	44 (23)	<0.001
Negative	35 (47)	144 (77)	
Chemotherapy			
4 AC+4 docetaxel	30 (40)	137 (73)	<0.001
4 AC+12 paclitaxel	5 (7)	9 (5)	
Chemo+trastuzumab	39 (53)	42 (22)	
Radiotherapy			
50 Gray	46 (62)	107 (57)	0.438
60–66 Gray	28 (38)	81 (43)	
Menopausal status			
Premenopause	37 (50)	93 (49)	0.938
Postmenopause	37 (50)	95 (51)	

Statistically significant p-values are marked in bold. AC: antracycline and cyclophosphamide.

DISCUSSION

In the treatment of breast cancer, the use of NAC is common to decrease the size of the breast mass and permit BCS[8]. The determination of biomarkers before NAC among pCR and non-pCR groups may support the decision to perform BCS at the beginning of treatment[9]. In our study, about 41% of patients underwent BCS in both groups.

In the study by Goorts et al. of 2,046 patients, the most important predictor of pCR was the cT stage[10]. Of the cT1 patients, 31% reached pCR, and among the cT4 patients, 16.5% reached pCR. In this study, positive Cerb-B2, negative ER, and negative PgR were also pCR predictors[10]. For most hormone receptor-positive breast cancers, the pCR rate is low, and chemotherapy does not seem to be helpful[11]. The study by Ohara et al. determined that the luminal A subtype was correlated

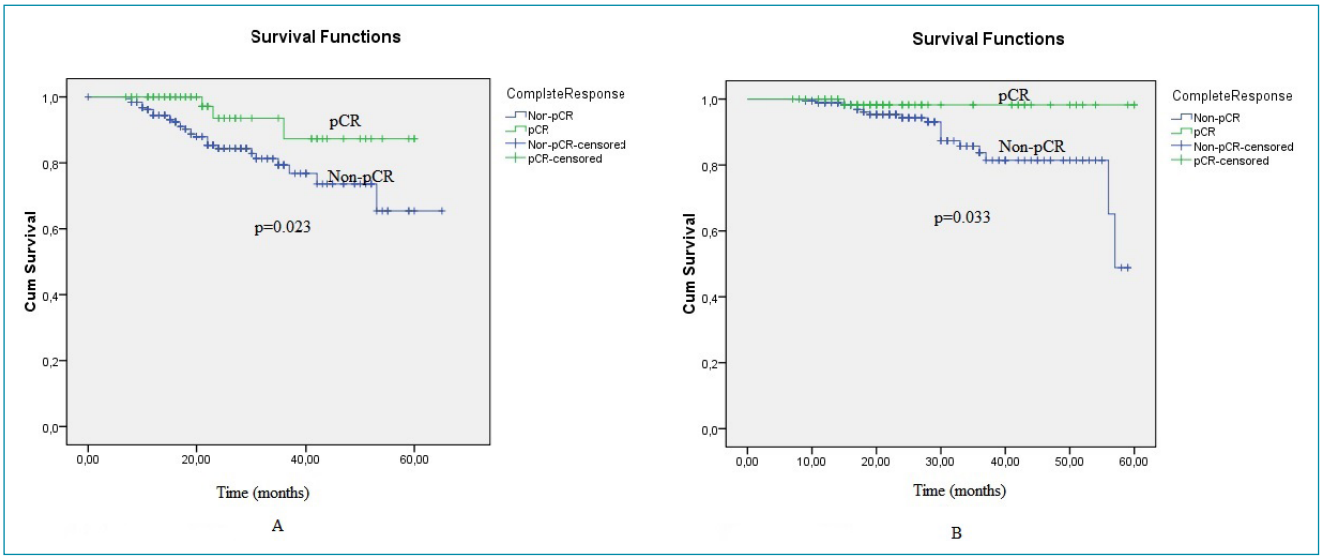

Figure 1. For pathological complete response and non- pathological complete response groups. (A) Disease-free survival. (B) Overall survival.

Table 2. Binary logistic regression analysis for pathological complete response.

	HR	95%CI	p-value
T stages			
T3–4 *versus* T1–2	2.201	1.053–4.602	0.036
LN stages			
LN2–3 *versus* LN0–1	2.074	1.092–3.938	0.026
Estrogen receptor			
Negative *versus* positive	2.012	0.657–6.165	0.221
Progesterone receptor			
Negative *versus* positive	0.629	0.215–1.840	0.398
Cerb-B2 status			
Negative *versus* positive	0.223	0.060–0.825	0.025
Nuclear grade			
Nuclear grade1–2 *versus* NG3	0.314	0.157–0.628	0.001
Ki-67 ratio			
≤20 *versus* >20	0.455	0.173–1.201	0.112
Chemotherapy			
Taxanes+trastuzumab *versus* taxanes	1.361	0.359–5.164	0.651

Statistically significant p-values are marked in bold. LN: lymph nodes.

with the lowest pCR levels[11]. In this study, the logistic regression analysis showed that a low initial clinical stage (T1–T2) and positive Cerb-B2 were statistically significant. Although, ER negativity and PgR negativity are statistically significant for pCR in the univariate analysis, they were not found to be associated with pCR in logistic regression analysis.

In the study by Jarząb et al. of 353 patients treated with NAC, higher rates of pCR were observed in grade three tumors and in patients with Ki67≥20%[12]. In the study by Song et al., tumor localization, nuclear grade, first clinical stage, and number of lymph nodes in the initial diagnosis were identified as important factors affecting OS in the multivariate analysis[13]. In a study by Jain et al., a Ki-67 index >35 and Cerb-B2 positivity were found to be independent predictive factors of pCR[14]. In our study, NG3 positivity and Cerb-B2 positivity before NAC were significant factors affecting pCR in patients, but the Ki-67 ratio was not statistically significant in the logistic regression analysis.

It is known that involved lymph nodes play an important role in the prognosis of patients with breast cancer. Fayanju et al. found that patients who were clinically node-positive at the time of the first diagnosis and who reached pCR had a good prognosis comparable to those who were clinically node-negative at the time of the first diagnosis[15]. The study by Lv et al. showed that before NAC, negative axillary lymph nodes were a positive predictive factor for pCR[16]. OS after NAC is higher with breast-only residual disease compared to residual disease only in the lymph nodes. OS is lowest in both residual diseases. In our study, LN0–1 patients achieved pCR, and OS and DFS were statistically significant.

Achieving pCR is very important for improving OS in patients with nodal involvement in breast cancer. In the study by Silva et al. of 243 patients, the presence of negative hormone receptors was found to be a predictive factor of pCR and associated with shorter OS and DFS. pCR was found to be associated with longer DFS and OS[17]. In several studies where pCR was achieved after NAC, it has been shown that the risk of death decreases and OS increases[9,15,17,18]. In our patients, OS and DFS were statistically significant in the pCR group compared with the non-pCR group.

In some studies, the chemotherapy agents in the NAC protocol have been shown to help achieve pCR[17,19]. In terms of chemotherapy protocols, the addition of trastuzumab to the treatment was not significant in the logistic regression analysis, even if it was significant in the univariate analysis in this study.

The limitations of our study include its small sample size and retrospective design as well as the fact that subgroups such as luminal-A, luminal-B, luminal-B Her-2 positive, triple-negative, and pure her-2 were not included because Ki-67 was unknown in about 11% of patients.

CONCLUSIONS

The NAC response can be used as an early indicator of the prognosis of patients with breast cancer. Today, NAC is also used for patients with early-stage, operable breast cancer because it has been shown in many studies that reaching pCR is associated with positive long-term results. Before NAC, stage T1–T2, LN0–1, Cerb-B2 positivity, and an initial nuclear grade of three were found to be the factors affecting pCR in this study. If we can identify patients who have reached pCR before NAC, we think we can also determine a patient-specific treatment plan at the beginning of treatment.

AUTHORS' CONTRIBUTIONS

OM: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **BI:** Conceptualization, Formal Analysis, Writing – review & editing. **RUG:** Conceptualization, Data curation. **DCT:** Conceptualization, Data curation, Formal Analysis, Investigation. **EA:** Conceptualization, Writing – review & editing. **SBH:** Conceptualization, Data curation, Writing – review & editing. **MBU**: Data curation, Investigation, Writing – review & editing.

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Pelvic floor muscle training program for women in the puerperal period: clinical progress after intervention

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SUMMARY

OBJECTIVE: To evaluate the sexual function of women in the puerperal period after a postpartum pelvic floor musculature training program. We also sought to evaluate correlations between sexual dysfunction in the women and their delivery type and compare the frequency of sexual dysfunction and the quality of resumed sexual function following vaginal and cesarean deliveries.

METHODS: This clinical study included an intervention, carried out between July and December 2019, in which data were collected about 28 rooming-in women at a Maternity School. Data were divided into vaginal delivery and cesarean delivery. Sexual function was evaluated by the Female Sexual Function Index and the International Consultation on Incontinence Questionnaire-Short Form to assess the Incontinence Urinary and qualifies urinary loss. The intervention consisted of a muscle training exercise program. ANOVA tests were used to establish differences between groups.

RESULTS: There was an improvement in all outcomes, but there was no time *versus* group interaction. Improvement in sexual function was observed ($p<0.001$), the impact of urinary incontinence on quality of life ($p<0.001$), and pressure of the muscles of pelvic floor muscles ($p<0.001$) over time. There was no time *versus* group interaction for sexual function ($p=0.87$), the impact of urinary incontinence on quality of life ($p=0.88$), and pressure of the pelvic floor muscles ($p=0.66$).

CONCLUSIONS: Pelvic floor muscle exercise programs seem to be a very promising strategy concerning improving sexual activity among puerperal patients.

Keywords: Sexual behavior. Postpartum period. Sexuality. Urinary incontinence.

INTRODUCTION

Pregnancy is a critical phase in a woman's life, and her experience is influenced by some factors, including hormonal, physical, and psychological changes. During this period, these transformations significantly impact her concept of sexuality, generally leading to problems in life for two[1,2].

Many uncertainties and anxieties permeate and sometimes impact women's daily lives, and consequently their sexual partners, especially about the pregnancy-puerperium period[2,3]. Some studies[1-4] indicate that both pregnancy and the puerperium constitute a crucial phase for the appearance of sexual problems and urinary incontinence (UI), and some women may show decreased sexual interest in general at this stage of life[5,6].

The pelvis is considered the lower part of the trunk and starts from the pelvic bones' upper edge. It is divided into a smaller pelvis and a broader pelvis. The pelvic floor (PF) is the

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most overloaded structure during pregnancy[3,7,8]. It is responsible for supporting the pelvic organs and maintaining urinary, fecal, and sexual functions and includes the pelvic and urogenital diaphragms. Both form a muscle group that closes the lower opening of the pelvis[7,9].

The levator ani and coccygeal muscles form the pelvic diaphragm. The urogenital diaphragm (or membrane of the perineum) is a more superficial layer formed by the ischiocavernosus, bulbocavernosus, transverse superficial, and deep muscles of the perineum, and striated anal sphincter[7].

The PF muscles made up of 70% slow-twitch (type 1) fibers and 30% fast-twitch (type 2) muscle fibers, are considered the only transverse muscles that support a load of the human body[7,10]. Like all skeletal striated muscles, the PF muscles have four properties that are excitability, which is the ability to respond to stimuli with contractility. The latter is the ability to contract when receiving a stimulus; extensibility, which is the ability to passively or actively stretch; elasticity, which is the ability to return to resting length after being subjected to stretching or shortening[3,7].

Respecting the PF dysfunction, the correct assessment is critical, consisting of a complete medical history and physical examination, including examining the PF[10,11].

A fundamental aspect of the evaluation includes researching an unfavorable obstetric history (difficult deliveries, use of forceps, prolonged labor, and traumatic ruptures or episiotomies) without forgetting to address the patient's intestinal patterns, including diarrhea, constipation, or both[8,12].

Regarding sexuality, the couple may have decreased desire and frequency of sexual activity, but the desire is increased in some cases. Couples tend to abstain from vaginal penetration, and the frequency of sexual activity may decrease for fear of harming the fetus, cause a miscarriage or premature birth[3,8,13]. There may be changes in the choice of sexual positions, particularly when discomfort/pain is felt[11].

The most common female sexual complaint during pregnancy and after childbirth is dyspareunia, or pain during vaginal penetration, especially after the first pregnancy. When the couple cannot adapt to changes in sexual activity during pregnancy[8,14], and after childbirth, this may cause critical emotional issues that negatively affect the welfare of both parties[15].

The presence of sexual dysfunction may be a factor resulting from a sum of factors, which promote total or partial barriers in the woman's sexual response, related to desire, excitement, and orgasm[8,16], negatively impacting her quality of life.

This study aimed to evaluate the sexual function of puerperal women after a postpartum pelvic floor musculature training program, as well as to evaluate some correlation between sexual dysfunction in puerperal women and the way of delivery, and to compare the frequency of sexual dysfunction and the quality of the resumption of sexual function in puerperal women of vaginal and cesarean delivery.

METHODS

We conducted a prospective pilot study at rooming-in of a public university hospital. The first participant was recruited on July 01, 2019, and the last on December 31, 2019.

As inclusion criteria, we looked for apparently healthy postpartum women. Women under the age of 18 were excluded from our study, as well as those suffering from psychiatric disorders and/or taking any drugs known to interfere with sexuality (antidepressants, anxiolytics, and neuroleptics).

Eligible women who were rooming-in were randomly selected and invited to participate. After having discussed the study's objectives, responsibilities, and the procedures involved, the volunteers who chose to participate signed the Informed Consent Form (ICF) and were asked to complete a questionnaire on sociodemographic, clinical, and behavioral characteristics. They were asked about age, ethnicity, marital status, education, origin, general history, family, obstetric history, and data on the previous pregnancy, smoking, and use of illicit drugs and alcohol.

The intervention consisted of a muscle training exercise program, including PF exercises with manual awareness, exercises with adductor dissociation, exercises with the sitting patient, and standing exercises. In addition, the FSFI questionnaires (Female Sexual Function Index)[17], were applied to assess the female sexual response in the postpartum period and the ICIQ-SF (International Consultation on Incontinence Questionnaire-Short Form)[18], to assess the impact of Incontinence Urinary quality of life and qualifies urinary loss. The volunteers signed the Free and Informed Consent Form (ICF) and were evaluated during the 48 hours after delivery (still hospitalized), and in the second and third months postpartum, this monitoring was carried out at rooming-in of the referred maternity.

Data collection took place in four stages: the application of the evaluation form, questionnaires, and physical examination to women in labor; assistance during the immediate puerperium period, consisting of four physiotherapy sessions in the first 48 hours after delivery and delivery of a booklet with exercises for the PF and postpartum care; a two-month reevaluation: reevaluation of the puerperal woman 60 days after the delivery date, with the delivery of a booklet with other exercises for the PF; a three-month revaluation: reevaluation of the puerperal woman 90 days after the date of delivery.

The database was built using the Statistical Package for Social Sciences (SPSS) software version 22.0. We first performed

exploratory data analysis describing the sample according to the sociodemographic, clinical, and behavioral aspects of the women studied. Next, a univariate analysis of the sample was performed, and we compared the averages of each domain according to the risk of sexual dysfunction (FSFI≤26.5) using the Student's *t*-test for independent samples.

Descriptive statistics were performed to present the socio epidemiological characteristics of the research volunteers. Inferential statistics were used to establish the possible differences between the groups and analyze the primary outcome (sexual function) and the secondary outcomes (UI and vaginal manometry). ANOVA tests were used to establish differences between groups, except for vaginal manometry, since only two evaluations were possible.

Ethics

This study was approved by the Ethics Committee of Universidade Federal do Rio Grande do Norte (UFRN), number 30951413.7.0000.5292. The study was conducted following the Declaration of Helsinki and its modifications[19].

RESULTS

In general, the observed result was that over time, there was an improvement in all outcomes, but there was no time-*versus*-group interaction. Table 1 shows the general characteristics of the sample submitted to the physical therapy intervention. There was a balance between the results of studied patients in the CD and VD groups concerning age, gestational age at the time of delivery, and APGAR values in the first and fifth minutes in the studied patients.

Improvement was observed in sexual function (p<0.001), impact of urinary incontinence on quality of life (p<0.001), and pressure of the muscles of PF muscles (p<0.001) over time (Figure 1). On the other hand, there was no time-*versus*-group interaction for sexual function (p=0.87), impact of urinary incontinence on quality of life (p=0.88), and PF muscles' pressure (p=0.66).

Table 1. Socio-demographic, behavioral, and clinical of the study population (n =28).

	CD	VD
Age (years)	30.36±6.52	29.07±5.38
Schooling (%) up to High School	61.35	98.22
College	39.65	1.88
Marital Status (%) living with a partner	78.57	92.86
living without a partner	21.43	7.14
Gestational Age	38.43±0.98	37.29±1.80
Apgar 1st minute	8.57±0.53	8.71±0.76
Apgar 5th minute	8.86±0.38	9.00±0.00

CD: cesarean delivery; VD: vaginal delivery; Apgar: Activity/muscle tone.

Table 2 shows the comparison of values between groups, highlighting that there was no significant difference in each assessment. There was no relationship between the mode of delivery (vaginal and cesarean), and the report of impaired sexual function in the patients studied. Therefore, there does not seem to be a difference in the return to sexuality when comparing postpartum women with normal and cesarean delivery after performing the PF exercise program proposed by the study in question. Over the three months of evaluation, regardless of the type of delivery, sexual function remained the same.

DISCUSSION

The assessment of women's degree of sexual satisfaction is a current and constant problem since numerous variables, such as social, human, biological, psychological, physiological, and cultural taboos, can influence the degree of final sexual satisfaction[1,8].

The sexual complaint is one of the most frequent problems patients regularly share with obstetricians, and, unfortunately, it continues to be approached in a very simplistic way most of the time. Considering that sexual dysfunction may be associated with an increased risk of conflicts between the couple during pregnancy[8,12], the etiological diagnosis of this condition is important. Therefore, appropriate treatment can be instituted when necessary to avoid the many affective problems–the non-acceptance of sexual relations during pregnancy, the fear of resuming this activity, and others–and assess the correlation between delivery type and sexual dysfunction in the puerperium[20-22]. During pregnancy, the relative hypo-estrogenism, similar to climacterics, influences these patients' sexual intercourse and sexual dysfunction. Additionally, the muscles have estrogen and testosterone receptors that decrease with aging and reduction of ovarian function[23-25]. Besides that, the progressive increase in uterine volume increases intra-abdominal pressure and overload in the PF. These increases added to the excessive gain in body mass and the action of hormones such as relaxin, progesterone, and estrogen that generate more excellent elasticity of the PF tissues[7,26] can cause urinary and fecal incontinence, pain, and sexual dysfunction if the musculature is not prepared. Progesterone is responsible for decreasing the pressure of urethral closure and also for the hypotonicity of the PF, and relaxin and estrogen increase the amount of water in the tissues of the pelvic region[7,27], which directly relates to decreases in the strength of PF muscles and, consequently,

to the emergence of urinary incontinence, as mentioned by several study authors[1,8,10,28]. They are also essential during labor, as this region must have sufficient extensibility to allow the fetus to pass through the vaginal canal without lacerations. The lack of stretching and awareness of this musculature can generate important perineal[26].

Some studies show that the stretching of perineal structures is extreme during the fetus's passage through the vaginal canal. They showed that the perineal body is subjected to an elongation of up to 65% of its resting state and concluded that PF muscles have their extensibility increased by up to 177% during the passage of the fetus[1,7,26]. Thus, awareness

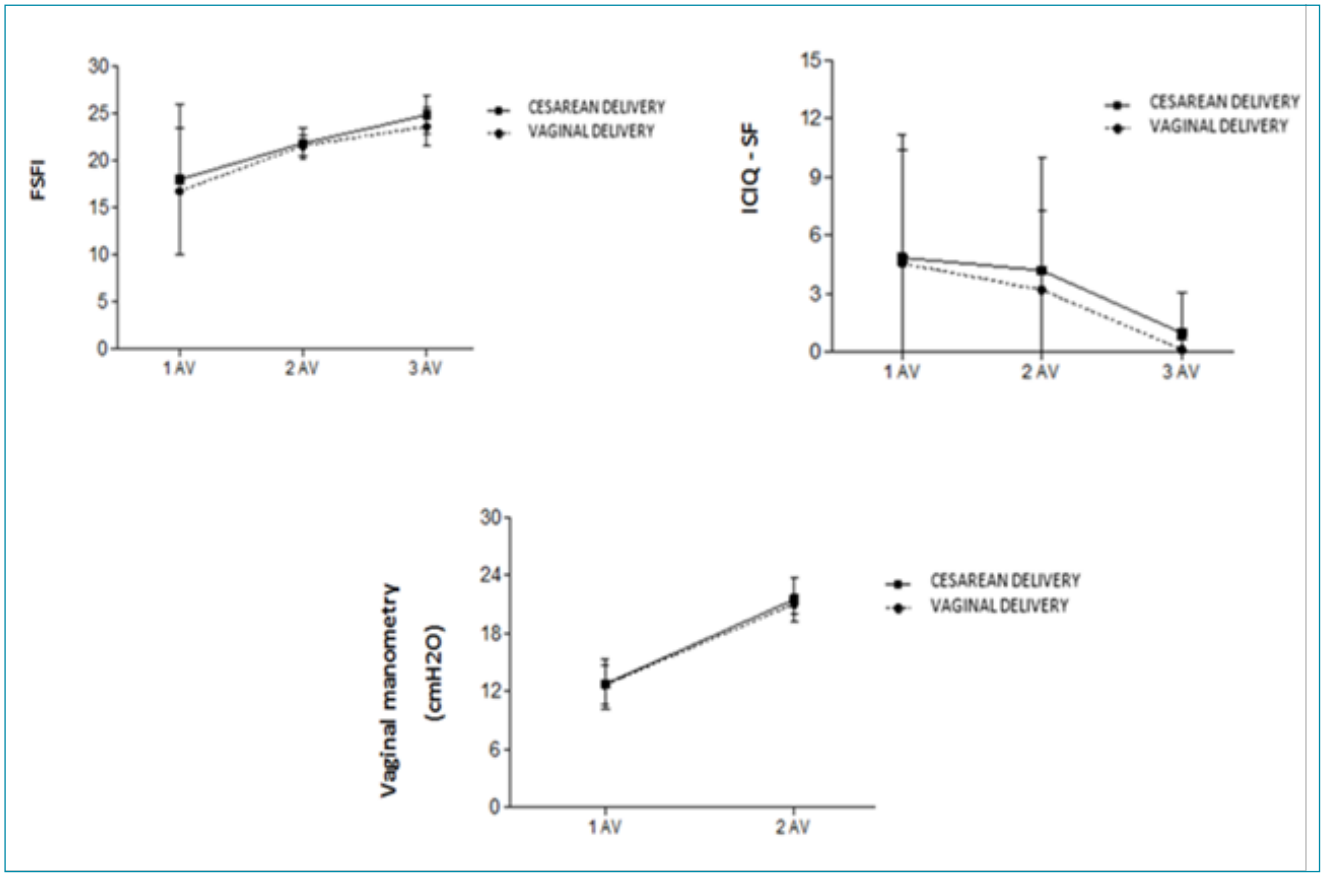

Figure 1. Evaluation of sexual function, the impact of urinary incontinence on quality of life, and vaginal manometry over three months.

Table 2. Comparative values between volunteers for cesarean delivery and vaginal delivery (n=28).

		CD	VD	p-value
		(n=14)	(n=14)	0.66
FSFI	1st AV	17.97±2.58	16.75±2.03	0.61
	2nd AV	21.60±1.43	21.75±1.33	0.11
	3rd AV	24.82±1.98	23.59±1.98	0.66
ICIQ-SF	1st AV	4.86±6.35	4.57±5.81	0.90
	2nd AV	4.21±5.75	3.21±4.08	0.60
	3rd AV	1.08±2.14	0.13±0.52	0.14
VM (cmH_2O)	1st AV	12.80±2.69	12.69±1.96	0.90
	2nd AV	21.50±2.29	21.03±1.06	0.49

CD: cesarean delivery; VD: vaginal delivery; FSFI: female sexual function index; ICIQ-SF: international consultation on incontinence questionnaire-short form; VM: vaginal manometry; cmH_2O: centimeters of water.

and gaining extensibility of PF muscles are essential for the woman to experience the gestational period with greater safety and prepare for possible vaginal delivery[8,11]. During the expulsive phase, the perineum tissues and muscles are subject to spontaneous laceration due to the passage of the fetus through the vaginal canal or provoked (instrumentalization of childbirth)[26]. It is known that there are several risk factors for perineal laceration[8,20], and we can mention some such as the fetus with great weight at birth, the second stage of prolonged labor, primiparity, the position adopted during the expulsive phase, the directed pull, the white race, among others[1,8]. PF muscles training has little to do with childbirth outcomes; it is more useful for preventing urinary, fecal, and sexual dysfunctions. Some studies, however, analyzed the effects of training on some aspects, such as the duration of the second stage of delivery and the prevalence of laceration, but no significant results were found to prove the influence of PF muscle training on positive delivery outcomes[26,27].

The great motivation and benefit of this study were to investigate physiotherapy as a facilitating agent in the puerperium, progressively improving sexual function. The study results show that the training of the PF muscles can emerge as an important alternative for the prevention and treatment of this type of woman's condition, reducing possible physical and emotional complications. Women who underwent the study's exercise program improved sexual function and muscle pressure measured by vaginal manometry. As a limitation of the study, we can mention the sample size and the difficulty in assessing PF muscles' extensibility. Unlike other muscle groups, stretching the PF does not involve the range of motion of joints.

This study's principal limitation includes the relatively small number of participants enrolled, but the latter is justified by the COVID-19 pandemic we are facing. However, there are no other publications related to this subject, and the results presented in this study can improve sexuality and, consequently, the quality of life in women in the postpartum period.

CONCLUSIONS

The prescription of PF muscle exercise programs for the improvement of sexual function of women in the puerperal period seems to be a very promising strategy concerning improving the resumption of sexual activity in women in the postpartum period.

AUTHORS' CONTRIBUTIONS

MNM: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MTABCM:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **VTC:** Data curation, Formal Analysis. **MCO:** Data curation, Formal Analysis. KSM: Conceptualization, Writing – original draft, Writing – review & editing. **ACAS:** Writing – original draft, Writing – review & editing. **AKG:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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Correlation between tactile acuity, pain intensity, and functional capacity in individuals with chronic neck pain

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SUMMARY

OBJECTIVE: The aim of this study was to verify the correlation between tactile acuity, intensity of pain at rest, and movement and functional capacity in individuals with chronic neck pain.

METHODS: This was a cross-sectional study composed of two groups: individuals with chronic neck pain and individuals without neck pain. Evaluations were performed using the Numerical Rating Pain Scale at rest and movement, Neck Disability Index, and two-point discrimination test.

RESULTS: The final sample consisted of 100 volunteers, 50 in each group. The groups did not show significant differences (p>0.05) in personal characteristics. It was observed that volunteers with cervical pain presented alterations in tactile care, with a significant and clinical increase in the perceived distance (Median 6.66; 95%CI 6.29–7.02; Cohen's d 7.22; 95%CI 6.15–8.30), and yet, positive, moderate, and significant correlation between two-point discrimination test, intensity of pain at rest and movement, and neck disability index (r=0.778–0.789, p<0.05).

CONCLUSION: Tactile acuity is associated with pain intensity at rest and movement and functional capacity in individuals with chronic neck pain.

KEYWORDS: Chronic pain. Neck pain. Musculoskeletal pain.

INTRODUCTION

Understanding the necessary diversified composition of assessment methods and, even more, preliminary findings indicating cortical changes followed by a decrease in local tactile acuity in individuals diagnosed with chronic neck pain[1,2], it is essential to include the assessment tools of the somatosensory system in these individuals.

The two-point discrimination test (TPDT) is a valid evaluation tool to detect changes in the functional organization of the somatosensory system[1], because it has a good reliability when used in the cervical region[3]. Described as the ability to discriminate between two tactile stimuli, TPDT is performed with a rigid, double-ended instrument positioned at different distances over the region to be evaluated. The shorter the distance detected between two ends, the greater the innervation density of slow-adapting fibers and cutaneous receptors functionally present in the skin. Thus, the greater the perceived distance, the worse the tactile acuity and, consequently, the worse the functional impairment of the somatosensory system[4].

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In this context, deficits in functional tactile sensitivity are related to changes in the functional organization of the somatosensory cortex[1]. For this aspect and also because we understood that neck pain is a complex and globally prevalent clinical condition, it is important to investigate the correlation between tactile acuity, other dimensions of chronic pain, and the functional capacity related to the cervical spine in volunteers with chronic neck pain, demonstrating that tactile acuity, which reflects changes in the somatosensory cortex, is related to the sensory, cognitive-behavioral, and functional dimension of chronic pain; one can support the need for the applicability of all these assessments in the clinical environment, favoring better and more complete intervention strategies[1,2].

The aim of this study was to verify the correlation between tactile acuity, intensity of pain at rest and movement, and functional capacity in volunteers diagnosed with chronic neck pain.

METHODS

Study design

A cross-sectional study was carried out. In this way, a physical therapist was in charge of recruiting, diagnosing, and allocating volunteers in two groups: a cervical pain group and a control group. Another physical therapist was in charge of administering the assessments, and a third researcher processed and analyzed the data. All researchers were familiar with the assessment procedures, having an average of five years of training in Physiotherapy. All participants signed an informed consent form, which was approved by the institution's Human Research Ethics Committee under process number 66425417.2.00005511.

Participants

Considering the correlation as the main objective of the study, a previous sample calculation was performed based on the detection of a slight correlation between the variables, considering a confidence coefficient of 0.95 and an amplitude of the confidence interval for the intraclass correlation coefficient (ICC) of 0.30. In addition, the calculation was performed to detect moderate reliability (ICC=0.75)[5], and therefore a sample size of 24 volunteers was estimated. To supply possible sample losses, 30 volunteers per group were defined to carry out this study.

For this, volunteers of both genders should have had neck pain for more than 90 days and be aged between 18–59 years. To identify neck pain, the following diagnostic criteria were used: score on the Neck Disability Index (NDI) ≥5 points and score on the Numerical Rating Pain Scale (NRPS) ≥3 points at rest or during active cervical movement, considering the last seven days as reference; these volunteers were allocated to the cervical pain group[6]. For comparison, volunteers of both genders were recruited without a diagnosis of chronic neck pain, without pain in the neck, aged between 18 and 59 years, and with the following diagnostic criteria being adopted: NDI score ≤5 points and NRPS score ≤3 points at rest or during active cervical movement, considering the last seven days as reference; these volunteers were allocated to the control group[6].

Volunteers with a history of cervical trauma; head, face, or cervical surgery; having undergone physiotherapeutic treatment for neck pain in the last three months; use of analgesics, anti-inflammatories, or muscle relaxants on the day of the evaluation and/or in the last week; presence of systemic and autonomic diseases; and medical diagnosis of fibromyalgia and neurological diseases were excluded.

Assessments

NRPS was used to assess the intensity of pain in the cervical, at rest, and on movement. Validated for the Portuguese language, simple and easy to measure, it consists of a sequence of numbers from 0–10, in which the number 0 represents "no pain" and the number 10 represents "the worst pain imaginable"[7]. The intensity of pain at rest was assessed based on the seven days prior to the assessment. To check the intensity of pain after movement, pain intensity was taken as a reference after performing the active movement sequence: flexion/extension, right/left inclination, right/left lateral rotation, all performed once for each movement.

To assess functional capacity, the NDI was used. The instrument was adapted and validated for the Brazilian population, with a high degree of internal consistency (r=0.74) and test–retest reliability characterized as acceptable[8]. Thus, the NDI consists of 10 sections that investigate disability related to cervical pain. For each section, it is possible to mark one in six answers, corresponding to the scores from 0–5. Therefore, the score for the classification of disability through pain varies between 0–50 points: with 0–4 points, without disability; 5–14 points, mild disability; 15–24 points, moderate disability; 25–34 points, severe disability; and 35–50 points, complete disability[8].

To determine tactile acuity in the cervical region, TPDT was performed using a digital caliper Starrett Brasil[a]. The points established with measurements ranging from 2–25 mm were used as a measurement reference. A caliper was positioned perpendicularly over the region to be analyzed so that the two tips touched the skin of the cervical region at the same time, only using the weight of the caliper itself, in an anteroposterior direction with the volunteer in sedestation (Figure 1)[4]. The analyzed region was chosen according to the report of the highest pain intensity reported by the volunteer, and for those who did not report local pain, the point between the C2 and C3 vertebrae was previously

established much because it was pointed out as the most symptomatic level, common when neck pain is involved[9,10]. Each distance between the tips was tested three times, in random order, and the response with the least perceived distance between the two points was considered to be the one that presented, at least, two repeated responses every three attempts[4].

Figure 1. Two-point discrimination test.

Statistical analysis

Histograms were created to determine the normality of the data. When non-normal distribution of variables was demonstrated, Spearman's correlation coefficients (rs) were calculated to determine the strength of associations between variables. The magnitude of the correlations was determined based on the classification proposed by Zou et al.[11]: 0=no correlation; 0≥0.20=weak correlation; 0.20≥0.50=moderate correlation; 0.50≥0.80=strong correlation; and 0.80≥1.00=perfect correlation. Statistical analysis was performed using the Statistical Package for Social Sciences, version 17.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

This study was composed of two distinct groups: individuals with chronic neck pain (n=50) and individuals without neck pain (n=50). The groups did not show significant differences (p>0.05) in demographic characteristics, as shown in Table 1. With regard to TPDT, it was observed that individuals with pain presented alterations in tactile discrimination, with a significant and clinical increase in perceived distance [Median (MD) 6.66; 95%CI 6.29–7.02; Cohen's d 7.22; 95%CI 6.15–8.30] when compared with the control group.

There was a positive, moderate, and significant correlation between TPDT, pain intensity at rest and movement, and NDI (r=0.778–0.789, p<0.05), as shown in Table 2, so that the greater the intensity of pain and disability, the greater the perceived distance in TPDT.

Table 1. Comparison between the groups of demographic and clinical variables in the study.

	Cervical pain group	Control group	MD (95%CI)	Cohen d (95%CI)
Age (years)[a]	23.64 (2.70)	23.76 (2.31)	-0.12 (-0.88–1.12)	–
Gender (Female %)[b]	46 (92)	42 (84)	–	–
Weight (kg)[a]	73.84 (7.46)	73.24 (7.12)	0.60 (-3.49–2.29)	–
Height (m)[a]	1.72 (0.09)	1.70 (0.08)	0.02 (-0.05–0.01)	–
BMI (kg/m^2)[a]	24.84 (2.71)	25.12 (2.35)	-0.28 (-0.73–1.28)	–
NRPS (escore)[a]				
at rest	4.76 (0.82)	0.10 (0.30)	4.66 (4.41–4.90)[c]	7.40 (6.30–8.50)[d]
after movement	5.44 (0.76)	0.06 (0.23)	5.38 (5.15–5.60)[c]	9.58 (8.19–10.96)[d]
NDI (escore)[a]	16.20 (2.04)	2.18 (1.45)	14.02 (13.31–14.72)[c]	7.92 (6.75–9.08)[d]
TPDT (mm)[a]	10.02 (0.97)	3.36 (0.87)	6.66 (6.29–7.02)[c]	7.22 (6.15–8.30)[d]

BMI: body mass index; NRPS: numerical rating pain scale; NDI: neck disability index; TPDT: two-point discrimination test; MD: mean difference; CI: confidence interval. [a]Values shown as mean (standard deviation); [b]Values presented in absolute number (percentage); [c]Significant difference (p<0.05, independent *t*-test); [d]Clinical relevance.

Table 2. Correlation between tactile acuity and pain measurement variables in patients with chronic neck pain (n=50).

	TPDT (mm)
NRPS at rest (escore)	rs 0.785, p<0,001[a]
NRPS after moviment (escore)	rs 0.789, p<0,001[a]
NDI (escore)	rs 0.778, p<0,001[a]

NRPS: numerical rating pain scale; NDI: neck disability index; TPDT: two-point discrimination test; [a]Significant correlation (p<0.05, Spearman's correlation coefficient).

DISCUSSION

The current level of evidence suggests that deficits in tactile acuity are present in several chronic pain conditions including neck pain[3]. At least seven studies have been involved in the direct analysis of tactile acuity using TPDT in chronic neck pain. Our study differs from the others by trying to relate and expand the analysis of tactile acuity in the different dimensions of chronic pain.

The first dated study on the relationship between tactile acuity and chronic pain was carried out with a group of individuals characterized with chronic polyarticular pain, with only five individuals having pain exclusively in the cervical region; of these, one had pain in other regions of the body[12]. Even with this great difference, we found results similar to Seltzer et al.[12], attesting to the reduction in tactile acuity in the presence of chronic pain. However, we presented more clearly defined and specific criteria for the diagnosis of chronic neck pain, obtaining a more reliable and homogeneous sample to analyze this relationship.

Thus, our results reinforce previous findings regarding the presence of reduced tactile sensitivity in individuals with chronic neck pain when compared with individuals without a diagnosis of chronic neck pain[1,13]. The greater the presence of pain intensity, the greater the interruption of sensory feedback, manifesting itself in the reduction of tactile acuity. We believed this to be a real clinical trend in patients with chronic neck pain, even when the intensity of the pain is related to movement, as performed in our study.

It is quite true that the relationship between musculoskeletal pain intensity and tactile acuity has not been shown to be consistent in the literature[3]. Heerkens et al.[13] attested that this relationship is incipient. However, the criteria used to characterize the sample are totally different from those used in our study and in the study by Harvie et al.[1] as we actually included individuals diagnosed with chronic neck pain with pain intensity ≥3 points on a scale of 10.

There is much to understand regarding how the imprecision or interruption in the processing of information is related to various areas of the body in individuals with chronic pain[14]; however, we hypothesized that the state of chronicity and intensity of pain impacts the somatosensory reorganization with a notable impairment of tactile acuity. We further reinforced our hypothesis when we observed the results obtained from the studies by Adamczyk et al.[15] and López-de-Uralde-Villaneuva et al.[16], who found that acute experimental neck pain did not promote changes in tactile acuity. López-de-Uralde-Villaneuva et al.[16] continued further showing greater somatosensory impairment, through TPDT, in individuals with chronic neck pain, especially when neuropathic features are present.

This study has its limitations and opens opportunities for future research mainly because it was a cross-sectional study and the results were descriptive, had no predictive character, and could not be used to establish direct causal relationships.

CONCLUSIONS

Our data suggest that tactile acuity is associated with pain intensity at rest and with movement and functional capacity in individuals with chronic neck pain.

AUTHORS' CONTRIBUTIONS

AVDF: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **CAFPG:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **DBG:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **CSBF:** Conceptualization, Data curation, Formal Analysis, Methodology, and writing and editing the review. **FP:** Conceptualization, data curation, formal analysis, methodology, Writing – review & editing. **CAFPG:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing. **AVDF:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing. **CSS:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing.

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Sleep analysis in emergency nurses' department

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SUMMARY

Shift work increases the risk of suffering physiological and psychological alterations, due to the sleep disorders that it usually produces in the staff with this type of workday.

OBJECTIVE: Analyze the influence of shift work on sleep quality in the nursing staff of the emergency department of the University Hospital of Leon.

METHODS: A total of 70 emergency department nurses aged between 24–56 years were divided into two groups (rotating shift and fixed morning or afternoon shift). The Pittsburgh sleep quality index was used for this purpose. In order to establish differences between the two groups, a bivariate analysis was performed using the χ^2 test.

RESULTS: The results showed that both groups had "rather poor" subjective sleep quality, with scores of 8.5 for fixed shift *versus*. 6.3 for a rotating shift. The group of nurses' rotating shifts slept an average of 5.39 hours compared to 7.47 hours for a fixed shift. Significant differences were found in sleep latency, sleep disturbances, and the use of sleep medication, with more negative results for the rotating shift.

CONCLUSIONS: Rotating shift produces a poor quality of sleep compared to a fixed morning or afternoon shift, and it would be interesting for the center itself to establish sleep improvement and sleep hygiene programs.

KEYWORDS: Sleep wake disorders. Nursing. Emergencies. Health.

INTRODUCTION

Human beings live in constant change, experiencing variations in both psychological and physiological functions daily, with sleep quality being an essential element in this. The concept of sleep quality is a complex construct to define, made up of quantitative and qualitative factors[1].

Chronobiology is the science that deals with the study of biological phenomena expressed in a rhythmic pattern[2]. Three variants of chronotypes have been established based on preferences in the performance of daily tasks, in this sense, we distinguish between morning (refers to people who prefer to sleep early and get up early without difficulty, being already at that time perfectly fit for work and showing a good level of alertness, physical and mental performance in the morning)[3]; evening (people who prefer to sleep and wake up late, with better mood and performance in the afternoon and early evening); and indifferent (people who prefer to sleep and wake up late, with better mood and performance in the afternoon and early evening). Finally, the indifferent, typical of individuals with greater flexibility, who choose intermediate schedules according to the needs of their routine and the undifferentiated[4].

If we focus on the work performed by the nursing staff, we can observe how it is carried out continuously, without interruptions, being able to affirm that the work schedule is twenty-four hours throughout the year[5]. This leads to a fragmented schedule in different shifts within the specialized care centers.

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The rotating shift, developed by the nursing profession, alters the natural rhythms of the organism, which leads to a series of negative consequences for the health of professionals. It is in this sense where the alteration of the natural sleep pattern, family reconciliation problems, stress, and anxiety can be appreciated[6].

The National Institute of Safety and Hygiene at Work reflects that rotating shift has negative effects on the quality and/or quantity of sleep for workers, causing, among others, feelings of drowsiness, tiredness and can affect work performance, increasing the risk of accidents due to fatigue[7].

It has been described how the quality perceived by nurses is poor, where the average number of hours of sleep is between 5.5–7[8]. There are various tools for assessing the quality and perception of sleep, the Pittsburgh Sleep Quality Index Questionnaire being the most widely used worldwide (PSQI)[9]. It is a questionnaire of 19 items that allows the assessment of sleep quality. On the other hand, after obtaining the total score, each subject is given a score ranging from 21 points, with scores above five being considered as poor sleep quality.

The work carried out in the hospital emergency department requires continuous patient care 24 hours a day. For this reason, there is a staff working on rotating shifts, fixed morning shifts and night shifts. It is an area of continuous entry and exit of patients. In this sense, it is important to point out that the work role developed in this service implies a continuous alertness[10].

The workload of this staff is higher than in other services, where workers refer to "the amount of work I have", they receive a greater "burden of responsibility", "rushing and being overwhelmed due to lack of time to do my job" and "stress" according to the perceived quality assessment[11]. Another aspect that may lead to reflection is the perception that their work has moderate negative consequences for their health[12].

All professionals often have to face complicated decisions, which have ethical implications in the practice of care. In this sense, nursing has become a special type of staff, a risk team because it involves personal, professional, and institutional factors that are potential causes of sleep disturbances[13].

According to all of the information presented, this study aims to analyze the quality and pattern of nurses' sleep in the emergency department and to determine whether there are significant differences between the pressures, depending on the shift they work.

METHODS

A descriptive, observational and cross-sectional study was carried out. The data extracted in this study were obtained from February–September 2020. A total of 70 nurses from the emergency department of the University Hospital of Leon (CAULE), aged between 24 and 56 years, participated in the study. The sample was divided into two groups: fixed mornings or afternoons (28 nurses) and rotating (42 nurses).

The inclusion criteria established were: to be active in the emergency department during the time established for data collection, not to have been on sick leave in the last month and to have been in the department for at least 15 days before the study.

All participants gave written informed consent. On the other hand, the study followed the guidelines for observational studies in epidemiology (STROBE), and the project was approved by the Clinical Research Ethics Committee of the Hospital of León, receiving the favorable opinion of this Committee with the number 19181: Chronobiology and sleep disorders concerning shift work in the nursing staff of the University Hospital of Leon.

The instrument used to assess the sleep quality of the nurses was the Pittsburgh Sleep Quality Index[8], Spanish version[14]. It is a questionnaire of 24 questions that allows the assessment of seven components (efficacy of regular sleep, sleep latency, total sleep duration, sleep quality, use of sleep medication, daytime dysfunction, and sleep disturbance), 19 of them provide the final score[13]. On the other hand, the morning and evening sleepiness of the participants was analyzed using the Adam and Almirall questionnaire[15].

Data collection was carried out by a single responsible researcher to provide all participants with the same instructions for completing the questionnaires. First of all, we had the approval of the nursing management of the CAULE, and then we informed the supervisor's unit on the aim and purpose of the study.

Statistical analyses were analyzed using the SPSS v 22.0 statistical package (Inc., Chicago, IL, USA) for Windows, setting the level of significance at $p<0.05$.

Descriptive data were presented as mean values, quantitative variables of standard deviation (SD) and qualitative variables of percentages, and frequencies. To establish the differences between the different work shifts, the χ^2 (chi-square) test was performed, setting the significance level at $p<0.05$.

When analyzing the reasons for having had problems sleeping in the last month and based on the fact that it was an open-ended question, the ATLAS ti v.9 program was used, allowing us to analyze large volumes of text by segmenting the different quotes.

RESULTS

If we consider the sex of the sample, we can see that 57 (81.4%) of the sample were women compa red to 13 (18.6%) men. With an average age of 35±2.31 years and an experience of 9.9±3.64 years in the emergency department.

As for the Pittsburg sleep quality index, it was 6.3±1.82 for the fixed morning or afternoon shift and 8.5±2.36 for the rotating shifts, showing this as both groups perceive poor sleep quality by showing values above five as established by the index used (scores ≥5 are considered poor sleepers as established by the index).

When assessing the different components of the Pittsburg sleep quality index, significant differences were observed between the two groups in different components such as sleep quality (χ^2=28.1; p=0.006; R^2=0.12), duration of sleep (χ^2=31.2; p=0.032; R^2=0.16), the efficacy of regular sleep (χ^2=11.3; p=0.048; R^2=0.21) and medication use (χ^2=10.8; p=0.021; R^2=0.13) (Table 1), showing these values as the perception of sleep is of worse quality in rotating shift nurses.

If we analyze the different factors that make it difficult for staff to sleep, we can see that there are significant differences in four of the items evaluated, with the most negative results for the rotating shifts, with the following data: not sleeping in the first half-hour (χ^2=6.32; p=0.045; R^2=0.78); waking up during the night or early morning (χ^2=5.36; p=0.034; R^2=0.23) and sleep disturbances (χ^2=4.23; p=0.031; R^2=0.36) (Table 2).

Table 1. Descriptive data of the PSQI according to the components analyzed.

	Very good (%)	Good (%)	Bad (%)	Quite bad (%)	χ^2	gL	p	Effect size R2
Subjective sleep quality								
Rotating shift	12.4	16.3	42.6	28.7	28.1	4	0.006	0.12
Fixed shift	29.6	38.3	18.9	13.2				
Sleep latency								
Rotating shift	7.9	32.1	14.6	22.6	11.5	4	0.531	0.02
Fixed shift	22.6	62.9	7.1	7.4				
Sleeping duration								
	>7 hours	6–7 hours	5–6 hours	<5 hours				
Rotating shift	11.2	23	63.2	2.6	31.2	4	0.032	0.16
Fixed shift	15.9	42.1	35.2	6.8				
Efficacy of regular sleep								
	>85	75–84	65–74	+65				
Rotating shift	2.2	26.3	2.3	51.2	11.3	4	0.048	0.21
Fixed shift	60.9	18.1	16.2	4.8				
	Never	Less than once a week	Once or twice a week	Three or more times a week	χ^2	gL	p	Effect size: R2
Sleep disturbances								
Rotating shift	9.4	46.2	18.2	26.2	9.3	4	0.571	0.16
Fixed shift	12.3	51.2	10.3	26.2				
Use of sleep medications								
Rotating shift	18.1	37.1	36.2	8.6	10.8	4	0.021	0.13
Fixed shift	26.7	53.8	16.1	3.4				
Daytime dysfunction								
Rotating shift	15.2	46.2	21.4	17.2	29.5	4	0.054	0.31
Fixed shift	26.5	56.8	9.6	7.1				
	Rotating shift				Fixed shift			
Total PSQI	6.3				8.5			

χ^2: chi-square; gL: degrees of freedom; p: signification; PSQI: Pittsburgh sleep quality index.

Table 2. Sleeping problems.

	Rotating shift				Fixed shift				χ^2	gL	p	Effect size: R2
	None in the last month (%)	Less than once a week (%)	Once or twice a week (%)	Three or more times a week (%)	None in the last month (%)	Less than once a week (%)	Once or twice a week (%)	Three or more times a week (%)				
Causes of sleep problems												
Not sleeping in the first half hour	17.1	30.5	36.2	16.2	36.2	37.2	18.5	8.1	6.32	4	0.045	0.78
Waking up during the night or in the early morning hours	24	18.9	42.1	14.9	22.8	36.1	26.1	15	5.36	4	0.034	0.23
Getting up to go to the toilet	26.7	6.3	65.8	1.2	35.1	11.3	52.3	1.3	3.26	4	0.564	0.57
Sleep disturbances	16.4	4.6	78.4	0.6	22.1	6.8	69.7	1.4	4.23	4	0.031	0.36
Unable to breathe properly	98.1	1.9	–	–	99.3	0.7	–	–	6.12	4	0.654	0.65
Coughing or snoring noisily	1.5	26.9	26.4	45.2	2.4	10.4	36.2	51	5.21	4	0.647	0.87
Feeling cold	3.2	78.6	18.2	–	55.2	16.4	26.1	2.3	4.32	4	0.612	0.81
Feeling too warm	25.5	26.2	48.3	–	24.3	22.3	53.4	–	6.21	4	0.712	0.78
Having nightmares	78.3	12.3	6.4	3	81.2	16.2	2.6	–	4.23	4	0.654	0.64
Suffering pain	89.5	9.3	1.2	–	72.4	27.6	–	–	6.2	4	0.611	0.54
Medication use in the last month												
Drowsiness while driving in the last month	23.9	36.4	26.3	13.4	64.3	28.2	7.5	–	3.4	4	0.036	0.32

χ^2: Chi-square; gL: degrees of freedom; p: signification.

As for the most common open-ended responses expressed by the study participants when it comes to being able to sleep, we found the following: "worry about the work situation", "increased workload", "tachycardia", and "chest tightness".

When analyzing the morning and evening routine of the nurses in the service through the Adam and Almirall questionnaire, 78.4% of the sample is "very tired" during the first half-hour after getting up in the morning. As for the time of night when they are most tired and feel the need to sleep, the rotating shift shows that it is after one am when they have this need, compared to the group of workers on fixed shifts who express this need at 11 pm. There are also differences in the time at which the staff feel better during the day, with 9 am being the time for the fixed shift workers and midnight for the rotating shift.

Finally, when asked whether they consider themselves to be morning or afternoon commuters, both groups consider themselves to be "more morning than afternoon".

DISCUSSION

Sleep problems among shift nurses have been increasingly recognized as an important problem at both individual and organizational levels. The results obtained show that nurses have a poor perception of sleep quality regardless of the shift they work. Both the groups, rotating shift and fixed shift workers obtained total scores in the Pittsburg sleep quality index of more than five, a value that shows that both groups are considered to be poor sleepers. Data very similar to those obtained in the work developed by Galera and Lopez[16] where they analyzed a sample of nurses and nursing assistants who work 8-hour shifts versus others who work 12-hour shifts, showing how the values obtained in the total score of the Pittsburg sleep quality index were 8.3 hours vs. 6.3 hours. In this same sense, our data are in line with what was analyzed in the work of Medina and Sierra[17] where they show how rotating shifts have a poorer perception of sleep quality regardless of the work performed. On the contrary, those who work with fixed and conventional shifts have total scores below five[17].

If we focus on the service, we can see that the total score obtained by the rotating shift is 8.5, a number higher than what was found by Rodriguez and colleagues[18], who obtained a score of 7.8 where most of the sample belonged to the emergency department, intensive care unit and internal medicine. Despite these results, it is important to point out that few studies deal exclusively with the quality of sleep of emergency staff, since most of the existing studies analyze nursing staff as a whole.

Regarding the components of the Pittsburg sleep quality index, significant differences were found in the quality of sleep, duration of sleep, use of sleep medication, and frequent sleep efficacy. These components coincide with those found in the study by Galera and López[16], where the same was found, except for habitual efficacy where no significant difference was found. It has also been pointed out in several studies that sleep quality, duration of sleep, and use of medication are the most altered components in rotating shifts[11,19,20].

One of the aspects, where we found significant differences between both groups, is in the difficulty that rotating shifts have in falling asleep in the first half-hour (χ^2=6.32; p=0.045; R^2=0.78), an aspect that was analyzed in the work of Sun and collaborators[20], where they analyzed various effective interventions to improve the sleep patterns of shift nurses and the quality of sleep in order to improve their health (15–30 minute nap breaks, social support and an adequate working environment).

Finally, it is important to point out that the sample indicates to be more alert in the evening, being this a factor that influences sleep disturbances when working shifts, so it would be of great interest to establish measures to improve the quality of sleep[21].

CONCLUSIONS

The nursing staff perceives a poor quality of sleep, a factor that is aggravated in workers who have a rotating shift, where it is appreciated how the hours of rest and problems and/or difficulties in falling asleep are greater. This may be due to the fact that the human being usually follows a routine operation, which in shift nurses is altered, resulting in a constant change of schedules of daily life, and consequently in the habits and schedules of rest.

For all these reasons, it is essential for health care managers to consider improvements in shifts, as well as the development of programs to improve the sleep of their health care staff.

AUTHORS' CONTRIBUTION

CJG: Conceptualization, Data curation, Formal Analysis.
MPC: Conceptualization, Data curation, Formal Analysis.
NFM: Conceptualization, Data curation, Formal Analysis.

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Fibrinogen-to-albumin ratio may be a predictor for ascending aortic aneurysm

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SUMMARY

OBJECTIVE: The predictive value of the fibrinogen-to-albumin ratio has been evidenced in coronary artery disease. Available data demonstrated that inflammation and oxidative stress are the relevant mechanisms of ascending aortic aneurysm formation and dilatation. The fibrinogen-to-albumin ratio reflects oxidative stress and inflammation. This study investigated the correlation between fibrinogen-to-albumin ratio and ascending aortic aneurysm.

METHODS: A total of 250 consecutive patients with ascending aortic aneurysm and 250 consecutive patients with normal ascending aortic diameter were included in the study using comprehensive transthoracic echocardiography. All data and fibrinogen-to-albumin ratio were compared between two groups.

RESULTS: The fibrinogen-to-albumin ratio levels were significantly higher in ascending aortic aneurysm group compared with normal ascending aortic diameter group ($p<0.001$). Also, there was significantly positive correlation between the diameter of the ascending aorta and the fibrinogen-to-albumin ratio ($p<0.001$).

CONCLUSION: Fibrinogen-to-albumin ratio is associated with ascending aortic aneurysm and may serve as blood marker for identifying high-risk patients.

KEYWORDS: Fibrinogen. Albumin. Ascending aortic aneurysm. Inflammation.

INTRODUCTION

The normal diameter of the ascending aorta depends on the age, sex, and body size of the patient. Aneurysm is a weakening or expansion of the aorta by more than 50% of predicted diameter[1,2]. The most frequent cause of ascending aortic aneurysm (AAA) is cystic medial degeneration, in which the flexible fibers present in the wall of the aorta deteriorate and thin out the wall of the aorta and cause it to dilate and form an aneurysm. This process usually occurs in later decades, at about the age of 60 or 70 years. Smoking and hypertension are also associated with aneurysm development[3]. Inflammatory diseases of the aorta can be classified as a spectrum of diseases with different clinical and histopathological definitions. The most common of these diseases is atherosclerosis, a disease that primarily influences the aortic intima[4,5].

Fibrinogen is a human serum glycoprotein consisting of three pairs of non-superposable polypeptide series[6]. It is the major plasma protein clotting factor. It is also a standard positive acute-phase reactant protein and an independent predictor of coronary artery disease[7]. It has been reported that the fibrinogen-to-albumin ratio (FAR) may be associated with acute coronary syndrome[8], end-stage renal disease[9], hypertension[10], and recurrent stroke[11].

According to the reviews found in literature, the pathogenesis of degenerative AAA could be caused by fibrinogen. Based on this information, the aim of this study was to determine whether the diameter of the ascending aorta or AAA is associated with FAR.

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METHODS

For the purpose of this study, the newly diagnosed AAA patients were examined in a series from June 2014 to June 2018. Out of 421 patients in total, those who had acute and chronic hepatitis (n=6), Marfan syndrome (n=3), cardiomyopathies (n=16), arrhythmias (n=12), renal dysfunction (creatinine >1.5 mg/dL; n=21), severe aortic regurgitation (n=10), active infectious disease (n=1), malignancy (n=24), chronic obstructive pulmonary disease (n=41), chronic inflammatory disease (n=3), and dilation solely in the aortic root (n=34) were excluded from our study. So, the remaining AAA patients (n=250) were included. In this study, the control group comprised an equal number of freshly diagnosed high blood pressure patients with normal aortic sizes to the group of freshly diagnosed AAA patients with hypertension, after age and sex matching. This study was approved by the Ethics Committee of the University.

A total of 500 patients were included in this study. Throughout the study, all patients underwent full transthoracic echocardiographic investigation, and dimensions of the aorta were recorded for each patient. AAA was diagnosed when the diameter of the singular abdominal aorta was ≥40 mm. Before carrying out the physical examination, the history of each patient was thoroughly evaluated, and the medical decision utilized 12-channel ECG results. Based on the blood pressure levels, corporally calculated by a mercury sphygmomanometer favorable with the guidelines, when the average value of three records (in two or four visits) for a systolic and a diastolic blood pressure was not less than 140 and 90 mmHg, respectively, this calculated value was clinically defined as hypertension. A glucose level of 126 mg/dL or higher, despite continuing antidiabetic treatment or following a diabetic diet, was evaluated as diabetes mellitus, and as diabetic predisposition when the glucose level reached 100 mg/dL. The classification of active smokers was achieved during diagnosis, independent of the counts of cigarettes smoked. Hyperlipidemia was defined in patients whose total cholesterol (TC) and triglyceride (TG) values were higher than 200 and 150 mg/dL, respectively. The body mass index formula used was [weight (kg)/height (m^2)].

For the main analyses, blood samples were obtained after 12 h of fasting to calculate the plasma glucose, high-density lipoprotein (HDL)-cholesterol, TGs, TC, and low-density lipoprotein cholesterol in all patients. A Horiba hematology analyzer was utilized for complete blood count analysis for the samples in ethylenediaminetetra acetic acid anticoagulated tubes. An analysis was conducted to designate monocyte counts to calculate the monocyte/HDL ratio for each patient. The hospital noted 1–8% as the reference measure for minimum heart rate. The formula of the Chronic Kidney Disease Epidemiology Collaboration was used to estimate the glomerular filtration rate. The nephelometric method was used to determine the high-sensitivity C-reactive protein (hsCRP) levels recognized as baseline, using a Horiba analyzer.

For all the patients, the complete transthoracic assessment was directed based on the aortic size measured through an ACUSON SC2000 PRIME Ultrasound System with a 2.5–3.5 MHz transducer. After collected from the electronic patient registry system, the echocardiography sheets showed at least three sequential beats, and all the view analyses were evaluated by a specialized cardiologist. The highest intra-observer variability coefficient was 5%. Computed tomography was requested for patients scheduled for surgery.

To define left ventricular ejection fraction, the modified Simpson method was performed on an apical four-chambered echocardiogram.

The structural investigation of the aortic valve was carried out on both the parasternal long-axis and short-axis images. The inner diameter of the aortic wall was evaluated. The aortic size was calculated from both the sinotubular junction and the sinus of Valsalva level. The American Society of Echocardiography recommended to measure the size of the proximal ascending aorta using M-mode echocardiography on the parasternal long-axis image in which the largest aortic size can be examined via a leading technique in a vertical plane to the parasternal long axis of the aorta. AAA was determined as an ascending aortic size of higher than 40 mm.

Statistical analysis

The results were statistically analyzed using the SPSS Statistics Version 22.0 Software Package (SPSS Inc., Chicago, USA). The number of patients in each group was adjusted to 250. We calculated the minimum number of individuals who should be sampled with 90% power and 0.05 Type I error as at least 46 (R 3.0.1. open source program). The primary effect variable was determined as the FAR. The 0.1 change FAR was accepted as clinically relevant. Standard deviation of the primary effect variable was calculated as ±0.21. The Kolmogorov–Smirnov test was used to determine the statistical distribution patterns. Mean±standard deviation or percentages were used as the descriptive statistics. Intergroup comparison was accomplished using Mann-Whitney U test for the nonparametric data and Student's *t*-test for the normally distributed or parametric data. The χ^2 test was used for testing the relationships between the categorical variables. The Pearson's or Spearman's correlation test was used to evaluate the linear relationship between two continuous variables when suitable. Stepwise multivariate linear regression analysis and univariate linear regression analysis were used to determine the relationships between potential risk factors and AAA size. The precondition for the multivariate linear regression model was $p<0.10$. The significance level was determined as $p<0.05$ for the statistical analyses.

RESULTS

The demographic, echocardiographic, and drug use characteristics of the patients are shown in Table 1. There was no significant difference between the groups, except for hypertension (p=0.015). The echocardiographic features of the patients are shown in Table 2. AAA significantly enlarged the diameters of vena contracta of aortic regurgitation, the sinus of Valsalva, aortic annulus diameter, sinotubular junction, arcus aorta, and ascending aorta (for all, p<0.001).

The laboratory parameters of the groups are shown in Table 3. The AAA patients had significantly higher levels of hsCRP (p<0.001), uric acid (p=0.027), and fibrinogen (p=0.004). The albumin levels were lower (p=0.041) and the FAR was significantly higher in the patient group.

Table 1. Clinical and demographic characteristics of the study population.

	Control group (n=250)	Case group (n=250)	p-value
LVEF (%)	63.1±2.2	61.0±2.2	0.523
ARVC (mm)	0.8±1.0	2.4±1.0	<0.001
Aortic annulus diameter (mm)	2.19±0.21	2.30±0.37	<0.001
Sinus Valsalva diameter (mm)	3.47±0.71	4.07±0.78	<0.001
Ascending aorta diameter (mm)	3.27±0.24	4.60±1.47	<0.001
Bicuspid aortic valve, n (%)	45 (18.0)	8 (3.2)	<0.001

Data are given as mean±SD, n or median (interquartile range). ARVC: vena contracta width of aortic regurgitation; LVEF: left ventricular ejection fraction.

Table 2. Echocardiographic characteristics of the study population.

	Control group (n=250)	Case group (n=250)	p-value
LVEF (%)	63.1±2.2	61.0±2.2	0.523
ARVC (mm)	0.8±1.0	2.4±1.0	<0.001
Aortic annulus diameter (mm)	2.19±0.21	2.30±0.37	<0.001
Sinus Valsalva diameter (mm)	3.47±0.71	4.07±0.78	<0.001
Ascending aorta diameter (mm)	3.27±0.24	4.60±1.47	<0.001
Bicuspid aortic valve, n (%)	45 (18.0)	8 (3.2)	<0.001

Data are given as mean±SD, n or median (interquartile range). LVEF: left ventricular ejection fraction; ARVC: vena contracta width of aortic regurgitation.

Table 3. Blood parameters of the study population.

	Control group (n=250)	Case group (n=250)	p-value
Glucose, mg/dL	113.9±42.3	109.3±37.1	0.481
Creatinine, mg/dL	1.07±0.25	1.07±0.32	0.749
Uric Acid, mg/dl	5.51±2.37	6.71±2.67	0.027
Hemoglobin, g/dL	13.8±1.4	14.0±1.7	0.410
WBC, $10^3/mm^3$	7.8±2.4	8.1±2.4	0.343
Hs-CRP, mg/L	4.5±2.5	8.4±3.7	<0.001
Total cholesterol, mg/dL	188.9±42.8	181.2±45.3	0.056
LDL-C, mg/dL	118.8±33.8	112.7±45.3	0.291
HDL-C, mg/dL	47.3±10.7	47.7±12.7	0.847
Albumin (g/dL)	3.83±0.09	3.68±0.14	0.041
Fibrinogen (µg/ml)	364±36	467±73	0.004
Fibrinogen-to-albumin ratio	95±10	127±24	<0.001

Data are given as mean±SD, n or median (interquartile range). WBC: white blood cell; Hs-CRP: high-sensitivity C-reactive protein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MHR: monocyte – high-density lipoprotein ratio.

The predictors (Tables 1 and 3) of AAA therapy were determined through univariate and multiple linear regression analyses, and the results are shown in Table 4. In the univariate regression analysis, higher hypertension rate (OR 1.518; 95%CI 1.351–1.706; p=0.014), higher hsCRP levels (OR 1.041; 95%CI 1.022–1.061; p<0.001), lower albumin levels (OR 1.051; 95%CI 1.008–1.087; p=0.015), higher fibrinogen levels (OR 1.048; 95%CI 1.030–1.073; p=0.010), and higher FAR (OR 1.201; 95%CI 1.158–1.246; p<0.001) were related to AAA. The multiple linear regression analysis demonstrated that higher hsCRP levels (OR 1.032; 95%CI 1.013–1.1052; p=0.002) and higher FAR (OR 1.224; 95%CI 1.165–1.281; p<0.001) were independent predictors of AAA.

FAR was significantly and positively correlated with the diameter of the ascending aorta (p<0.001, r 0.928; Figure 1).

DISCUSSION

This study determined that increased FAR was associated with the maximum diameter of the ascending aorta. Aortic aneurysm is considered as a separate degenerative process involving all layers of the vessel wall. A wide variety of inflammatory and infective disorders may lead to AAA. *Mycobacterium tuberculosis* is associated with AAA.

Fibrinogen acts a part in blood clotting, fibrinolysis, and inflammatory response[12]. Kannel et al.[13] and Stone et al.[14] identified that fibrinogen is a risk factor for cardiovascular disease. Wilhelmsen et al.[15] reported that fibrinogen is a risk factor for the development of stroke and myocardial infarction. Increased fibrinogen levels are associated with early signs of coronary artery disease in patients[16]. Zhao et al.[17] stated that fibrinogen is associated with coronary collateral circulation in stable coronary artery disease patients.

Serum albumin has been proven to have antioxidant activity and anti-inflammatory effects[2,18,19]. Low serum albumin levels are associated with ischemic heart disease, stroke, and venous thromboembolism[20]. A higher FAR has been found useful in predicting the risk of atrial fibrillation[21]. Özdemir et al.[10] reported that the FAR is associated with hypertensive patients who have inflammation in the pathogenesis of the disease. Biomarkers associated with inflammation have been identified in patients with AAA and dissection[22]. Inflammatory markers, such as fibrinogen, albumin, and CRP, have been used to predict cardiovascular risk[23].

Microvascular dysfunction and inflammation are associated with both fibrinogen elevation and AAA. In the literature, we did not find any study investigating the relationship between the FAR and AAA. Both AAA and FAR are associated with inflammation.

In our study, we determined that FAR was significantly different between the groups, and higher FAR was an independent risk factor for AAA progression. Also in the present study, the FAR was a highly sensitive and specific indicator for predicting the clinical class and disease severity of AAA. AAA is a simple and easily available parameter, which does not necessitate an additional expense. This costless and useful parameter may provide the clinicians to predict patients with AAA, which may cause mortality.

Our study had some limitations. This study is a retrospective cohort study with a comparatively small sample size. We don't

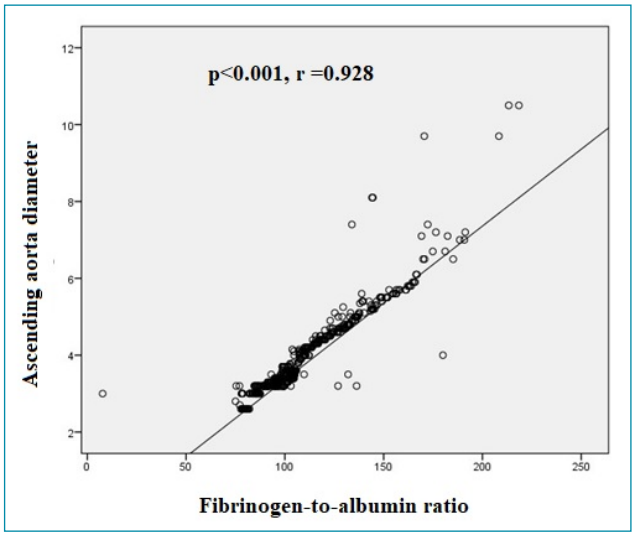

Figure 1. The correlation between fibrinogen-to-albumin ratio and ascending aorta diameter.

Table 4. Multivariate linear regression analysis showing the predictors for the ascending aortic dilatation.

	Univariable Beta (95%CI)	p-value	Multivariable Beta (95%CI)	p-value
Hypertension	1.518 (1.351–1.706)	0.014	1.477 (0.998–2.187)	0.057
Uric Acid	1.045 (0.996–1.099)	0.086		
Hs-CRP	1.041 (1.022–1.061)	<0.001	1.032 (1.013–1.052)	0.002
Albumin	1.051 (1.008–1.087)	0.015	1.066 (1.020–1.123)	0.076
Fibrinogen	1.048 (1.030–1.073)	0.010	1.051 (1.033–1.074)	0.055
Fibrinogen-to-albumin ratio	1.201 (1.158–1.246)	<0.001	1.224 (1.165–1.281)	0.001

Hs-CRP: high-sensitivity C-reactive protein.

have the follow-up major adverse cardiac events data. So, our results should be confirmed by future multicenter prospective longitudinal studies with larger sample size. Then, we gathered only the baseline characteristics of the patients. Therefore, the connection between the dynamic variance in the FAR and outcomes could not be examined. Finally, this study is not a randomized controlled study. Large-scale randomized controlled studies are still needed to further evaluate the predictive value of FAR on the severity of AAA.

AUTHORS' CONTRIBUTIONS

OA: Data curation, Investigation, Writing – original draft. **MSK:** was involved in Methodology, Supervision, Writing – original draft.

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Can various complete blood count parameters helpful in preoperative diagnosis of adnexal torsion?

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SUMMARY

OBJECTIVE: Adnexal torsion is an important gynecological emergency due to nonfrequent but possible adverse reproductive outcomes. There is no specific laboratory marker to support the preoperative diagnosis or that can be used clinically. The aim of this study was to investigate the diagnostic values of platelet, neutrophil, lymphocyte, and red cell markers as an early indicator of ovarian torsion.

METHODS: This retrospective study included 28 female patients who were treated surgically for adnexal torsion between August 2010 and July 2020, and 29 control group women. The demographic data and routine hematological values of patients were compared for adnexal torsion prediction.

RESULTS: There were no differences between the groups in terms of the platelet count, platelet distribution width, red cell distribution width, and mean platelet volume values, and there were no differences in the demographic data. Statistical differences were found among white blood cell, hemoglobin, hematocrit, neutrophil and lymphocyte counts, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio, and 81.5% sensitivity and 82.1% specificity were identified for neutrophil/lymphocyte ratio 2.45 (area under the curve AUC 0.892; 95%CI 0.808–0.975; p<0.001). Odds ratio for neutrophil/lymphocyte ratio was 2.62 (95%CI 0.861–7.940, p=0.029).

CONCLUSION: According to the regression analysis, neutrophil/lymphocyte ratio was found to be the most beneficial among all blood count parameters for the pre-diagnosis of AT.

KEYWORDS: Adnexal torsion. Hemogram parameters, Prediction

INTRODUCTION

Adnexal torsion (AT) is defined as the complete or partial twisting of the suspensory ligament that provides vascular support to the ovary and extends from the pelvic side wall. In case of torsion, low-pressure venous and lymphatic flow is disturbed, initially causing growth and edema in the ovary. As torsion continues, it affects the arterial flow leading to thrombosis, ischemia, and hemorrhagic infarction.

Adnexal torsion is a rare condition, and it can be observed at any age and ranks fifth among all the emergency surgical indications with a rate of 2.7%[1,2]. In contrast, 15% of surgically treated adnexal masses are caused by torsion[3]. AT is diagnosed clinically, and its diagnosis can be supported by imaging methods. Its final preoperative diagnosis is challenging due to the lack of specific symptoms. Various laboratory markers have been used for the preoperative diagnosis; however, a specific marker has yet to be found[4]. Since it is a gynecological emergency showing various levels of inflammatory response and thrombosis due to vascular stasis, increased nonspecific inflammatory markers in local and systemic circulation can be identified which have been used for preoperative AT diagnosis in many studies[4,5]. The first and the simplest test requested for patients who presented with acute abdomen is a complete blood count (CBC). This test can provide us with numerous inflammatory

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markers. The most important ones are the mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), platelet distribution width (PDW), and platelet/lymphocyte ratio (PLR)[6-8].

In our study, whether CBC parameters can be used to predict AT, which is a pathology-inducing inflammatory response, is investigated.

METHODS

Hospital information management systems and surgery records were analyzed retrospectively, and 28 women, who were diagnosed with AT and whose diagnosis was confirmed surgically between August 2010 and July 2020, were included in this study. A total of 29 women who were admitted to the hospital during the same period without any condition formed the control group. Ethical approval for the study was received from the Ethics Committee of Adiyaman University.

Inclusion criteria

Women aged between 18–45, who were presented with lower abdominal pain with adnexal mass detected during assessment, who were operated on with a pre-diagnosis of AT, and who had an intraoperative diagnosis, were included.

Exclusion criteria

Women with a history of inflammatory disease, such as systemic lupus erythematosus, familial Mediterranean fever, and rheumatoid arthritis; a positive pregnancy test; renal or hepatic failure; diabetes mellitus; hypertensive disease; hemoglobinopathy; a history of myocardial infarction or thrombosis; detection of acute appendicitis during radiological assessment; or other possible causes, such as urinary tract infection, during laboratory assessment were excluded.

Factors, such as age, patient complaints, parity, body mass index (BMI), CBC parameters (hemoglobin [Hgb] and hematocrit [Hct]), leukocyte count (%), lymphocyte count, platelet count, MPV, PDW, RDW, NLR, and PLR, were taken into consideration for assessment. Surgical consent was taken from all patients before the procedure.

Early diagnosis of AT was based on the findings of a physical examination, and ultrasonography (USG) was used as a supportive evaluation. In ultrasound imaging, isolated ovarian growth, a cyst or solid ovarian mass, presence of fluid in pouch of Douglas, or lack of blood flow in ovarian parenchyma were interpreted as possible AT. Following the early diagnosis, diagnostic laparoscopy was performed on patients depending on their medical condition and the technical equipment of the operating room. Patients with ovarian torsion were evaluated for this study. All pathological materials collected from patients were sent for examination.

Blood samples

All assessments were initiated 1 h after blood collection. Venous blood samples taken from the antecubital region with the vacutainer system (BD, Becton, Dickinson and Co., Franklin Lakes, NJ, USA) and placed into ethylenediaminetetraacetic acid (EDTA) anticoagulant-containing tubes (BD Vacutainer®, K2E 5.4 mg; BD, Plymouth, UK) were analyzed using the Cell-Dyn Ruby (Abbott Park, IL, USA) hematology analyzer.

Statistical analysis

Statistical analysis of data was performed using SPSS for Windows 23.0 (IBM Corp., Chicago, IL, USA). The Mann-Whitney U test was performed to compare the continuous variables of the two groups. The χ^2 test was performed to compare categorical data. Data were presented as mean±standard deviation. $p<0.05$ was considered statistically significant.

RESULTS

When 28 women in the AT group were compared with 29 women in the control group, no difference was identified in terms of age, BMI, and parity. Preoperative color Doppler ultrasound revealed loss of ovarian parenchyma blood flow in 18 patients (75%). In terms of CBC, platelet count, MCV, RDW, PDW, and MPV were similar in both the groups ($p>0.05$; Table 1). Compared with the control group, white blood cell, neutrophil count (%), NLR, and PLR of the AT group were higher. However, Hgb, Hct, lymphocyte count, eosinophil count, and basophil count were lower in the AT group.

In the logistic regression analysis performed to predict AT, only NLR was able to predict AT ($p<0.001$, Nagelkerke R square: 0.637). Odds ratio for NLR was 2.62 (95%CI 0.861–7.940, $p=0.029$). In the receiver operator characteristics (ROC) curve analysis performed (Figure 1), it was identified that NLR could be used to predict AT with 81.5% sensitivity and 82.1% specificity when the cutoff value is 2.45 (AUC 0.892; 95%CI 0.808–0.975, $p<0.001$).

DISCUSSION

Adnexal torsion is a very rare cause of acute pelvic pain when compared with other gynecological emergencies such as pelvic inflammatory disease and hemorrhagic ovarian cyst, and there are many contradictions to its diagnosis[2,9]. Diagnosis is often made with detailed medical history, physical examination followed by suspicion, and ultrasound findings that support the

diagnosis. It is most commonly seen in the reproductive age group but it can also occur during prepubertal and postmenopausal periods. Clinical findings are nonspecific. In 85% of the cases, pelvic pain is accompanied by nausea, vomiting, low-grade pyrexia, and sinus tachycardia[10,11]. However, in rupture cases accompanied by torsion, intra-abdominal hemorrhage may occur with severe clinical findings. AT mostly presents itself as an acute event on top of a chronic condition (dermoid tumor or ovarian hypertrophy like in polycystic ovary syndrome [PCOS])[12]. In this study, to support the diagnosis and to identify risk groups, a strong correlation was identified with an ovarian cyst larger than 5 cm, which was included in the scoring system[13]. The other four parameters are based on clinical findings.

The traditional approach to AT is surgery. The most common surgical approach is partial or complete oophorectomy or salpingo-oophorectomy, but in some cases, detorsion or oophoropexy can also be performed. A very rare procedure is the shortening of the utero-ovarian ligament[14,15]. It is quite a rare procedure due to expectant management and possible dangers due to a conservative approach. Especially in intermittent torsion, delayed diagnosis or misdiagnosis can lead to a decrease in or the loss of the reproductive capacity of the ovary[10].

Adnexal torsion may present different images in the ultrasound. Ovarian growth (the most common finding), mass,

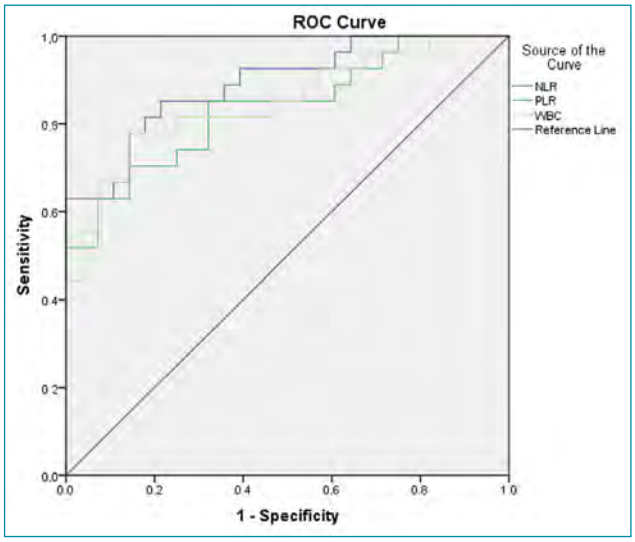

Figure 1. The receiver operator characteristics (ROC) curve analysis.

Table 1. Demographic data and laboratory results of the groups.

	Torsion	Control	p-value
	n=28	n=29	
Age (year; mean±SD)	30.2±11.7	33.1±11.2	0.295
BMI (kg/m^2; mean±SD)	26.2±6.1	25.7±4.1	0.911
Parity (mean±SD)	3.9±2.5	2.8±1.5	0.094
WBC (×10^3/μL; mean±SD)	12.7±8.9	7.4±1.6	<0.001
Hemoglobin (g/L; mean±SD)	11.9±2.1	13.5±1.4	0.002
Hematocrit (%; mean±SD)	35.8±6.1	40.6±4.1	0.002
Platelet count (×10^3/μL; mean±SD)	249.4±62.5	277.3±57.3	0.057
MCV (fL; mean±SD)	82.5±7.9	86.7±6.4	0.122
MCHC (g/L; mean±SD)	33.8±5.1	32.5±1.4	0.219
RDW (%; mean±SD)	12.8±2.0	12.6±1.3	0.861
MPV (fL; mean±SD)	8.5±1.5	8.4±1.4	0.955
PDW (fL; mean±SD)	19.6±1.9	19.4±1.6	0.350
Neutrophil (%; mean±SD)	76.5±12.1	58.4±7.5	<0.001
Lymphocyte (%; mean±SD)	17.4±9.6	33.2±7.2	<0.001
Eosinophil (%; mean±SD)	0.44±0.65	0.86±0.89	0.004
Basophil (%; mean±SD)	0.70±0.49	0.97±0.33	0.001
NLR (mean±SD)	7.13±5.89	1.91±0.69	<0.001
PLR (mean±SD)	19.8±13.0	8.8±2.6	<0.001

n: number of patients; BMI: body mass index; WBC: white blood cells; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; MPV: mean platelet volume; PDW: platelet distribution width; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio.

free fluid in the pouch of Douglas, peripheral follicles in the enlarged ovary, and curling in the vascular pedicle in gray-scale ultrasound, a solid mass with hypo–hyperechoic areas are the findings that suggest torsion[16,17]. Ovarian growth can be defined as the diameter of the ovary being >4 cm (or >20 cm^3)[16]. The vortex-like appearance of blood flow in the curled ovarian vascular pedicle in color Doppler ultrasound is called the "whirlpool sign." Even though its presence is almost pathognomonic for AT, it occurs in 13–80% of cases[18]. Another important color Doppler ultrasound finding is blood flow loss in the ovarian parenchyma; various studies detected this condition in 60–100% of cases[5,17]. Computed tomography (CT) and magnetic resonance imaging (MRI) can also offer useful information of AT[19]. However, their use has been limited due to high costs and because they do not offer any additional information compared with USG. For this reason, we did not use CT or MRI for diagnosis in any patient.

A CBC is performed on all patients admitted to the emergency room with acute pelvic pain for infection, inflammation, and anemia diagnosis. In addition, there is no single or combined marker that can be used for preoperative diagnosis in cases suspected of AT. The most commonly used markers are C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α). However, they have low sensitivity and specificity for use by themselves in diagnosis[4,5,20].

Adnexal torsion causes various degrees of inflammation and inflammatory responses, and the idea that these would be reflected in laboratory assessments is the basis of our study. Routine CBC has caused interest due to easy obtainability of inflammatory markers that require no additional cost. No significant difference was found between AT and control groups in terms of MPV, PDW, and RDW values. This result is in parallel with some studies in the literature while contradicting with others[21,22]. This contradiction may be caused by three issues:

I. lack of laboratory standardization,
II. natural changes to parameters investigated during torsion/detorsion, and
III. normal morphological changes to existing cells during the period between torsion and diagnosis.

Conversely, in line with the literature, leukocyte count was found to be high in the AT group as it is an inflammatory condition. Low counts of Hgb and Hct in the patients in our study were caused by intra-abdominal hemorrhage, which are identified during surgery in the majority of patients, as evidenced from patient files.

The ratios such as NLR and PLR are important inflammatory markers[23]. Our study investigated possible changes to these parameters as AT causes various levels of inflammatory processes. Study data reveal that both NLR and PLR increase significantly in torsion cases. In the inflammatory process, there is an increase in neutrophil and platelet levels in the blood which serve as mediators in the cellular battle and recovery; lymphocytes gather on the ischemic tissue surface, and their levels decrease in the blood to limit inflammation and improve recovery, leading to relative lymphopenia. We considered that these cellular changes are the reasons why NLR and PLR increase. Detailed assessment describes us that for AT cases, the critical level is 2.45, and the risk of AT increased by 2.6-fold above 2.45. At the same time, 81.5% sensitivity and 82.2% specificity were identified for values above 2.45 (Figure 1). We considered that these values can be used by a clinician to support the pre-diagnosis of AT in suspected cases following physical examination and imaging.

As a result, it has been shown in our study that NLR can be used as inflammatory markers for routine AT assessment in laboratories. Studies involving more cases will be able to offer more information.

AUTHORS' CONTRIBUTIONS

DK: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **MB:** Data curation, Investigation, Methodology, Writing – review & editing. **GO:** Data curation. **MK:** Methodology, Project Administration, Resources, Writing – original draft.

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Relationship between obstructive sleep apnea syndrome and functional capacity in patients with diabetes mellitus type 2: an observational transversal study

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SUMMARY

OBJECTIVE: The aim of this study was to verify the association among obstructive sleep apnea, functional capacity, and metabolic control.

METHODS: This was a cross-sectional study involving individuals of both sexes with clinical diagnosis of diabetes mellitus type 2 who were above 18 years of age. The assessment consisted of a volunteer identification form, a 2-minute step test, and the Stop-Bang questionnaire. In order to assess metabolic control, HbA1c and fasting glucose data were collected from medical records.

RESULTS: A total of 100 individuals with diabetes mellitus type 2, of whom 61% were women, were included in this study. According to the Stop-Bang instrument, 26, 57, and 17% of patients had low, intermediate, and high risk of developing OSA, respectively. There was no association between the 2-minute step test and metabolic variables and diabetes mellitus type 2 chronicity with Stop-Bang.

CONCLUSIONS: We concluded that there is no association among obstructive sleep apnea measured by means of Stop-Bang instrument, functional capacity measured by means of 2-minute step test, and metabolic variables in individuals with diabetes mellitus type 2.

KEYWORDS: Sleep apnea. Diabetes mellitus. Exercise test. Metabolic disease.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a chronic disorder of multifactorial etiology that affects about 2–4% of the adult population, and it is characterized by partial or total airway occlusion during sleep, related to anatomical changes of the respiratory tract, neuromuscular factors, and genetic predisposition, with consequent reduction or cessation of airflow, thus causing respiratory arrest for 10 s or more[1-2].

Among the associated pathologies, diabetes mellitus (DM) often presents itself as a disorder that coexists with OSA, and this coexistence is justified with the risk factors shared with other disorders, such as obesity. In addition, studies indicate that short sleep duration is associated with decreased glucose tolerance, insulin sensitivity, and a consequently increased risk of developing diabetes[3-6]. Furthermore, research suggests that diabetic patients are more likely to sleep during the day than

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nondiabetic patients and are more likely to be involved in traffic accidents due to daytime sleepiness[7].

Polysomnography, although considered the gold standard for diagnosing this syndrome, is of high cost and is difficult to access. In this sense, low-cost instruments, easy applicability, and availability have been used, as is the case with questionnaires. Thus, the Stop-Bang questionnaire demonstrated good sensitivity and specificity in screening for this syndrome[2,8].

Functional capacity may be negatively affected in individuals with OSA associated with fatigue, excessive sleepiness, excess weight, and low energy, which characterize the clinical presentation of the pathology[9]. Therefore, the 2-minute step test (2MST) appears as an alternative way to assess the functional capacity of an individual, considering that the ability to walk reflects the ability to maintain a series of activities of daily living in addition to enabling knowledge of the functional profile and the ability to guide decision-making in strategies aimed at preventing disabilities[10,11].

Given the above, the hypothesis of this study was that there is an association among OSA, functional capacity, and metabolic variables in individuals with DM. Therefore, the objective of this study was to verify the association among OSA, functional capacity, and metabolic control variables.

METHODS

This was a cross-sectional, observational, and analytical study developed at the Ceuma University (Street Josué Montello, 1, Jardim Renascença, CEP 65075-120, São Luís, MA, Brazil), with a recruitment period from August 2018 to August 2019 after the study procedures were approved by the Research Ethics Committee of the said institution by means of opinion number 2.469.206. All volunteers included in this study validated their participation by signing the informed consent form.

The inclusion criteria adopted were as follows: individuals of both sexes, with a clinical diagnosis of diabetes mellitus type 2 (T2DM) according to the Brazilian Diabetes Society, and aged ≥18 years. All volunteers were sedentary according to self-report. The exclusion criteria in the present study were as follows: patients with uncontrolled systemic arterial hypertension, amputated diabetes and unable to perform the 2MST, cardiovascular and respiratory diseases limiting their ability to participate in the proposed tests, a clinical diagnosis of neurological diseases, the inability to understand the tests and questionnaires, and any type of medication to sleep.

The assessment consisted of a volunteer identification form, the 2MST, and the Stop-Bang questionnaire[8]. In order to assess metabolic control, HbA1c and fasting glucose data were collected from medical records.

The 2MST is calculated by measuring the number of elevations using a knee as a reference. For this study, the number of right knee elevations for 2 min without running was counted and standardized. The minimum knee height, appropriate for the stride, was leveled at a midpoint between the patella and the anterosuperior iliac spine[11].

During the test, the patient was accompanied by a team member and received support if there was a chance of imbalance. The vital signs were monitored before the start and at the end of the test. The blood pressure (BP) measurement was evaluated using a sphygmomanometer and stethoscope (Premium brand), and the peripheral oxygen saturation (SpO_2) and heart rate were measured using an oximeter (MeasuPro model OX150, USA) with a sensor positioned on the index finger and the reading determined after signal stabilization. The chronometer was triggered and interrupted only if the patient requested suspension of test; if indicated by chest pain, intolerable dyspnea, excessive sweating, pallor, dizziness, or cramps; if his/her BP needed to be checked; or if the stipulated time was over. If the patient suddenly interrupted the walk simply to take rest, the timer continued to run. Patients were instructed to wear comfortable clothes and shoes at the time of the test and to take their medications normally.

The Stop-Bang questionnaire consists of a series of eight questions related to snoring, tiredness/fatigue/drowsiness, interrupted breathing during sleep, BP, body mass index, age, neck circumference, and gender, with a total score ranging from 0–8 and answers of only yes or no (scores 1 and 0, respectively). The presence of three or more affirmative responses indicates a high risk for OSA[8].

Statistical analysis

Descriptive analysis was performed and presented with the minimum, maximum, average, and standard deviation values. In addition, to verify the association between the risk of developing OSA with the other variables evaluated, logistic regression was used with the following independent variables: 2MST, HbA1c, blood glucose, and chronicity of T2DM. The association values were presented through the odds ratio (OR) and 95% confidence interval (CI). The risk of developing OSA, assessed using the Stop-Bang questionnaire, was categorized as follows: patients with intermediate and high risk were grouped in the high risk group (n=74) and patients with low risk were grouped in the low risk group (n=26). All data were analyzed using SPSS software (version 17.0; Chicago, IL, USA) at a significance level of 5%.

RESULTS

A total of 160 patients with T2DM were initially recruited at a secondary health care center for patients with T2DM. However, after applying the eligibility criteria, 60 patients were excluded,

leaving a final sample containing 100 individuals with T2DM, of whom 61% were women.

According to the Stop-Bang instrument, 26, 57, and 17% of patients had low, intermediate, and high risk of developing OSA, respectively. Other clinical data of the study participants are described in Table 1.

When verifying the association between the risk of developing OSA and the other variables, it was observed that the logistic regression model that used the Stop-Bang questionnaire presented adequate modeling (overall=72.7%; Hosmer and Lemeshow test, p=0.867; Nagelkerke R^2=0.050). Table 2 presents the OR values, and no significance was identified (p>0.05).

Table 1. Characteristics of the participants with diabetes mellitus type 2.

	Mean	Standard deviation
Age (years)	59.26	9.86
DM2 time (years)	10.07	7.25
Blood glucose (mg/dL)	214.42	100.24
HbA1c (%)	8.31	2.50
Height (m)	1.56	0.08
Weight (kg)	70.38	15.05
BMI (kg/m^2)	28.72	5.41
NC (cm)	37.64	3.73
AC (cm)	97.93	11.87
2MST (score)	68.09	20.21

HbA1c: glycated hemoglobin; BMI: body mass index; NC: neck circumference; AC: abdominal circumference; 2MST: Two-minute step test.

Table 2. Association between the risk of developing obstructive sleep apnea according to the Stop-Bang and the metabolic control and functional capacity of patients with diabetes mellitus type 2.

	β	SE	OR (95%CI)	p-value
Constant	2.632	1.21	–	0.030
2MST	-0.018	0.01	0.98 (0.95–1.00)	0.136
HbA1c (%)	-0.073	0.11	0.93 (0.74–1.15)	0.510
Blood glucose	-0.001	0.01	1.00 (0.99–1.01)	0.629
DM2 chronicity	-0.002	0.03	0.99 (0.93–1.06)	0.924

SE: standard error; OR: odds ratio; CI: confidence interval; HbA1c: glycated hemoglobin; 2MST: two-minute step test.

DISCUSSION

The main findings of this study were as follows:

a) there was no association between OSA and functional capacity measured by means of 2MST and
b) there was no association between OSA and metabolic variables.

Although different methodologies, in agreement with a study by Nisar et al. evaluated on 1,533 individuals, assessed the presence of OSA by polysomnography and the functional capacity by exercise stress echocardiogram, only 404 showed impaired functional capacity. In addition, another recent study highlights the impact of OSA on cardiorespiratory fitness[12].

Recently, a study conducted by Nogueira et al. with the objective of evaluating the reliability of 2MST in healthy individuals concluded that it is a reliable test and still has slight precision in differentiating active and sedentary individuals. The assessment of functional capacity by rapid, simple, and low-cost tests in this population is relevant in view of the need to identify functional limitations due to the disease. In addition, this assessment using this test can and should be used as a method to assess the effectiveness of the proposed treatments[13].

Although OSA was not associated with metabolic variables, it is known that patients affected with this disorder have higher fasting blood glucose levels and high plasma insulin levels, regardless of obesity[14]. In addition, there is an evidence that sleep deprivation is associated with higher glucose levels, development of insulin resistance, and pancreatic beta cell dysfunction, which is justified despite chronic hypoxemia, increased sympathetic nervous system activity, and increased circulating cortisol intermittent observed in individuals with OSA, culminating in a change in the homeostasis of this variable[15-17]. The non-association between OSA and the metabolic variables found in this study may be possibly justified by the discrepancy in the time of diagnosis of DM, as well as by the control and/or lack of metabolic control found in the population in question.

Regarding the possible clinical implications, based on the previous literature and the results of the present study, OSA should be considered as a secondary factor that implies the functional capacity in diabetic patients along with other factors such as diabetic neuropathy and/or cardiovascular autonomic neuropathy. However, longitudinal studies on this topic are needed to support this clinical implication.

This study has some limitations that should be mentioned. There was an important variation in the time since a diagnosis of T2DM; however, it is worth mentioning that although the medical diagnosis was made within this period of time, it is believed that the metabolic disorder existed for a longer time. Furthermore, peripheral neuropathy was not assessed according

to the gold standard[18], but all patients were asked about any difficulty in walking or lack of sensitivity in the metatarsals and feet as a whole.

CONCLUSIONS

We concluded that there is no association among OSA measured by means of Stop-Bang instrument, functional capacity measured by means of 2MST, and metabolic variables in individuals with T2DM.

AUTHORS' CONTRIBUTIONS

MAF: Funding acquisition. **AKSM:** Funding acquisition. **RBSL:** Funding acquisition. **MAO:** Funding acquisition. **ADSA:** Writing-original draft, Writing – review & editing. **ASR:** Supervision. **LRLNP:** Funding acquisition. **PRF:** Conceptualization, Methodology, Formal analysis, Investigation, Writing-original draft. **MCG:** Methodology, Supervision. **DBD:** Conceptualization, Formal Analysis, Methodology, Resources, Funding Acquisition, Investigation, Supervision, Writing-original draft, Writing – review & editing.

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Turkish validity and reliability of the COVERS pain scale

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SUMMARY

OBJECTIVE: The objective of this study is to determine the Turkish validity and reliability of COVERS.

METHODS: This study was conducted on 41 newborns as methodological design. The scales, such as newborn information form, COVERS, preterm infant pain profile (PIPP), and neonatal infant pain scale (NIPS), were used in the study. Validity (e.g., language, content concurrent, and construct) and internal consistency and inter-rater reliability of the scale were conducted.

RESULTS: It was found that COVERS showed a high correlation with PIPP and NIPS, and the item-total correlation of COVERS was above 0.30 during and after heel lance procedure. The Cronbach's α values were 0.77 and 0.83 during and after heel lance procedure, respectively. The kappa values of the items of COVERS were between 0.38 and 0.78 during heel lance procedure.

CONCLUSIONS: It was concluded in this study that there was a moderate correlation in intraclass correlation coefficients for scores of COVERS during both diaper change and heel lance procedures. It has been concluded that the scale is valid and reliable in 27-week-old and older newborns.

KEYWORDS: Neonatal intensive care unit. Newborn. Pain. Reliability. Validity.

INTRODUCTION

Preterm and term newborns experience pain and stress due to numerous and very different reasons such as intubation, venipuncture, and nasogastric/orogastric tube insertion in Neonatal Intensive Care Units (NICUs)[1]. Newborns experience approximately 70 stressful procedures[2] or 51 painful stimuli per day in the NICU[3]. Newborns may respond to pain in an exaggerated or attenuated manner as a result of frequent painful and invasive procedures[4]. The pain experienced by the newborns can not only prevent his/her behaviors, family infant interaction, and infant's adaptation to the outside world, but also cause changes in the development of brain and senses and affect the growth negatively[1].

Failure to appropriately assess the pain of newborns may result in delayed treatment and negative consequences[5]. Emotional status that cannot be expressed verbally by infants is involved in pain assessment, thus resulting in problems about the definition and treatment of pain. Newborns are dependent on others for the definition and treatment of pain[1]. Since newborns cannot express themselves, they show pain in behavioral and physiological ways[6]. Physiological changes related to pain in newborns include the changes in heart rate, respiratory rate, blood pressure, and oxygen and carbon dioxide levels in the blood. Behavioral changes related to pain include crying, facial expressions, motor movements, and behavioral status changes[7].

For the objective assessment of pain, the American Academy of Pediatrics recommends the use of validated and reliable scales[8]. Many scales have been developed for the measurement and evaluation of pain in newborns[5,9]. It has been reported that pain scales that are not suitable for the unsuitable population are used,

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so it is important to use appropriate pain scales for newborns[9]. Hand et al.[10] developed COVERS and reported that it is a valid scale for both preterm and term newborns. O'Sullivan et al.[11] proved that the scale is valid and reliable. Considering the negative consequences of acute pain in newborns, it is very important to evaluate the pain of the newborn with a valid and reliable scale in daily clinical practice in the NICU[12]. This study was conducted to determine the reliability and validity of COVERS, which has not been used yet in newborns in Turkey.

METHODS

Setting, design, and sample

This study was conducted using a methodological design in a 16-bed NICU of a public hospital between January and June 2018. The case number was determined for a moderate effect size [(Δ: 0.50), β: 0.20 (80% power: 1–β) and α: 0.05] was found as 28 newborns. Forty-one newborns who met the criteria were included in this study. The inclusion criteria for the infants were determined as follows: being 24 weeks old and older[11], receiving no analgesic treatment within the last 12 h, and having no congenital anomaly.

Newborn information form

The form included questions about gestational week, weight, length of hospital stay (in days), gender, diagnosis, respiratory support, and the type of receiving respiratory support.

Neonatal infant pain scale

The scale consisting of behavioral parameters was developed by Lawrence et al.[13]. It consists of six subscales such as facial expression, crying, breathing patterns, arm movement, leg movement, and state of arousal. The scores of the scale range between 0 and 7, and the score higher than 4 points signifies pain. The Cronbach's α value of neonatal infant pain scale (NIPS) was reported as 0.95, 0.87, and 0.88 before, during, and after the procedure, respectively[13]. Akdovan[14] adapted the scale into Turkish, and the Cronbach's α value of the scale was found to be between 0.83 and 0.86. In this study, the Cronbach's α values were 0.79 and 0.87 during and after heel lance procedure, respectively.

Preterm infant pain profile

The scale was developed for 28- to 36-week preterm infants by Stevens et al.[15]. It evaluates behavioral (e.g., eyebrows, eyes, nasolabial furrow, and facial movement) and physiological (e.g., heart rate and oxygen saturation) parameters of the infant. The score of the scale ranges between 0 and 21. While a score of <5 indicates no pain, a score of >10 indicates moderate to severe pain. The Cronbach's α value of preterm infant pain profile (PIPP) was found to be between 0.59 and 0.76[15]. The reliability and validity study of the scale was conducted by Akcan and Yiğit[16] in Turkey. The Cronbach's α value of the scale was between 0.68 and 0.78[16]. In this study, the Cronbach's α values were 0.72 and 0.32 during and after heel lance procedure, respectively.

COVERS pain scale

The scale, which was developed by Hand et al.[10], consists of six subscales and depends on physiological (e.g., oxygen requirement and vital signs) and behavioral (e.g., crying, expression, resting, and signaling distress) measurements (Table 1). The subscales of the COVERS scale are scored with 0, 1, and 2 points, and the scale score ranges between 0 and 12. The validity of the scale in 27- to 40-week infants was analyzed[10]. The scale was valid and reliable in newborns older than 24 weeks, and it can be applied in the clinic[11].

Forward and backward translation

The researchers translated COVERS scale into Turkish, and the translated scale was checked by 10 pediatric nursing academicians. The scale translated into Turkish was translated back into English by a linguist. The original scale and the translated English scale were checked and found similar by another linguist. The language validity was performed in this way.

Content validity

The scale was evaluated by 10 pediatric nursing academicians. Each expert was asked to evaluate the relevance level of each item about the purpose of the questionnaire with a 4-point Likert scale as "completely appropriate" to "not appropriate." The content validity index of the scale was calculated as 0.91.

Study protocol

This study was conducted in supine position during both diaper change and heel lance procedures between 10:00 a.m. and 11:00 a.m. during weekdays while the infants were awake, and the process was recorded on video. Both diaper change and heel lance procedures were applied to each infant. The scales were applied 1 min before, during, 1 min after the diaper change, and during heel lance procedure (i.e., at the first time when manual lancet penetrated) and 1 min after heel lance procedure (i.e., applying cotton). The application lasted for an average of 5 min.

Concurrent validity and construct validity

For concurrent validity, the infants were evaluated with the scales such as COVERS, PIPP, and NIPS. For construct validity, they

Table 1. Original COVERS scale.

	0	1	2
Crying	No	High pitched or visibly crying	Inconsolable or difficult to soothe
Oxygen requirement	None	<30%	>30%
	At baseline O_2	<20%	>20%
	Breathing comfortably	Change in breathing pattern	Significant change in breathing pattern
Vital signs	HR and/or BP WNL for age or at baseline	HR and/or BP <20% of baseline	HR and/or BP >20% of baseline
	No apnea or bradycardia or at baseline	in frequency of apnea and bradycardia	in frequency and severity of apnea and bradycardia
Expression	None/facial muscles relaxed	Grimace, min-mod brow bulge, eye squeeze, nasolabial furrow	Grimace/grunt, mod-max brow bulge, eye squeeze, and nasolabial furrow
Resting	Sleeping most of the time	Wakes at frequent intervals – fussy	Constantly awake (even when not disturbed)
Signaling distress	Relaxed	Arms/legs flexed or extended "time-out signals"	Flailing and arching

HR: heart rate; BP: blood pressure; WNL: within normal limit.

were assessed using the scales in painful and nonpainful procedures. According to the literature[10], nonpainful procedure was determined as the diaper change, and the painful procedure was determined as heel lance procedure.

Inter-rater reliability

The diaper change and heel lance procedures were performed by a nurse included in this study. Another nurse involved in this study recorded the application process and the monitor showing heart rate and oxygen saturation of the infant via a video recorder. The nurse making the video recording in this study and the academician nurse included in this study watched the videos of the infants independently and evaluated the infants according to COVERS, PIPP, and NIPS.

Ethics statement

Ethics committee approval permission (IRB: 2017,12,4,05,021) was obtained from the hospital. Permissions to use scales were obtained by authors via e-mail. The written informed consent was obtained from the parents.

Statistical analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) was used for the statistical analyses. Normality assessment of the variables was made by using the Shapiro-Wilk test. The statistical significance level was set at 0.05. The internal consistency of COVERS at each time point was established using mean inter-item correlations, corrected item-total correlations, and the Cronbach's α reliability coefficients. Inter-rater reliability was established using kappa measure of agreement for categorical data and intraclass correlation coefficients (ICCs) for the continuous data. While the Spearman's rho correlation coefficient was used for concurrent validity, the Wilcoxon signed rank test was used for construct validity.

RESULTS

The characteristics of the infants were shown in Table 2.

Concurrent validity

In <37 weeks (n=28), a statistically significant correlation was determined between COVERS and PIPP scores during ($p=0.768$, $p<0.001$) and after ($p=0.617$, $p<0.001$) heel lance procedure, and between COVERS and NIPS scores during ($p=0.785$, $p<0.001$) and after ($p=0.800$, $p<0.001$) heel lance procedure.

In >37 weeks (n=13), a statistically significant correlation was determined between COVERS and PIPP scores during ($p=0.854$, $p<0.001$) and after ($p=0.869$, $p<0.001$) heel lance procedure,

Table 2. Characteristics of newborns (n=41).

Identify		Min–max	M±SD
Gestation weeks		27–41	33.98±4.05
Weight (g)		780–4,200	2,368.41±922.14
Number of days		1–75	9.34±15.62
		n	%
Gender	Female	18	43.9
	Male	23	56.1
Diagnose	Premature	26	63.4
	Respiratory distress syndrome	8	19.5
	Sepsis	4	9.8
	Hyperbilirubinemia	2	4.9
	Hypoglycemia	1	2.4
Receiving respiration support	Yes	12	29.3
	No	29	70.7
If yes	CPAP	5	41.7
	Incubator inside oxygen	4	33.3
	Hood oxygen	3	25

M: mean; SD: standard deviation; CPAP: continuous positive airway pressure.

and between COVERS and NIPS scores during (p=0.823, p<0.001) and after (p=0.951, p<0.001) heel lance procedure.

Construct validity

Table 3 shows the distribution of the COVERS mean scores of the newborns before, during, and after the diaper change and heel lance procedures.

Internal consistency

The item-total correlation values of COVERS were 0.32–0.82 and 0.39–0.86 during and after heel lance procedure. The Cronbach's α values of COVERS were 0.77 and 0.83 during and after heel lance procedure.

Inter-rater reliability

Table 4 shows the kappa results during diaper change and heel lance procedures. ICC values obtained for COVERS total score were 0.741 (95%CI, 0.514–0.862) during diaper change procedure and 0.579 (95%CI, 0.211–0.776) during heel lance procedure.

DISCUSSION

In a systematic review, it was stated that the validity and reliability of a scale must necessarily have construct validity, internal consistency, and inter-rater reliability[17]. In this study, content validity, concurrent validity, and construct validity were tested for the validity of the COVERS scale. For the reliability of the scale, internal consistency and inter-rater reliability were tested.

For correlation values, it was reported that values between 0.70 and 0.89 showed a high correlation and values between 0.90 and 1.00 showed a very high correlation[18]. It was determined in a study conducted by Hand et al.[10] that while COVERS showed a high degree of correlation with PIPP (r=0.84) in preterm infants, it showed a very high degree of correlation with NIPS (r=0.95) in full-term infants. In this study, COVERS was found to be highly correlated with PIPP and NIPS. According to the results of this study, COVERS was found to have concurrent validity. Construct validity is defined as the degree to which a test measures what it is supposed to measure[19]. It was found in this study that there was a significant difference between the mean scores of COVERS in nonpainful and painful procedures. The results of this study are consistent with the literature[10]. In this study, it was determined that COVERS, which was adapted to Turkish, had construct validity.

In the literature, it has been reported that 0.30 and above is accepted as the optimum for corrected item-total correlation, and it becomes perfect as it approaches to 1[20]. In this study,

Table 3. Distribution of COVERS pain mean scores before, during, and after the diaper change and heel lance procedure (n=41) determined by using Wilcoxon signed rank test.

COVERS	Before	During	After
Diaper change	0.636	3.415	1.439
Heel lance	1.341	5.122	1.829
p	<0.001	0.003	0.439

Table 4. COVERS kappa measure of agreement analysis results of two observers during diaper change and heel lance procedure (n=41).

COVERS	During diaper change				During heel lance procedure			
	Kappa	SE	95%CI		Kappa	SE	95%CI	
			Lower	Upper			Lower	Upper
Crying	0.681	0.134	0.418	0.943	0.789	0.115	0.564	1.000
Oxygen requirement	0.448	0.152	0.151	0.746	0.522	0.132	0.264	0.779
Vital signs	0.394	0.139	0.122	0.666	0.414	0.142	0.135	0.693
Expression	0.561	0.121	0.324	0.798	0.474	0.114	0.251	0.698
Resting	0.345	10.150	0.051	0.639	0.433	0.117	0.204	0.661
Signaling distress	0.473	0.155	0.169	0.777	0.381	0.176	0.037	0.726

SE: standard error; CI: confidence interval.

since item-total correlation of COVERS was above 0.30 during and after heel lance procedure and showed that the items were appropriate, no item was excluded from the scale. It was reported in the study by O'Sullivan et al.[11] that corrected item-total correlation of COVERS was 0.19–0.68 during heel lance procedure and only the score of the item "oxygen requirement" was below 0.30. In contrast to the literature[11], the score of this item was found to be above 0.30 in this study.

The Cronbach's α value between 0.70 and 0.95 is reported to be an acceptable value[21,22]. In the literature[11], the internal consistency of COVERS was 0.78. The results of this study were found to be compatible with the literature. For kappa statistic values, it is reported that <0.20 is weak agreement, 0.20–0.40 is acceptable agreement, 0.40–0.60 is moderate agreement, 0.60–0.80 is good agreement, and 0.80–1.00 is perfect agreement[23]. In the literature, the kappa values of COVERS are reported to be between 0.29 and 0.78 at baseline and between 0.22 and 0.67 at heel lance. Acceptable agreement of COVERS was seen in "vital signs, expression, and signaling distress" items at baseline and in "vital signs, expression, resting, and signaling distress" items at heel lance[11]. In this study, acceptable agreement of COVERS was found in "vital signs and resting" items during diaper change and in "signaling distress" item during heel lance procedure. For ICC, it is reported that <0.5 is weak, 0.5–0.75 is moderate, 0.75–0.90 is good, and >0.90 is perfect[24]. In the study by O'Sullivan et al.[11], ICCs for scores of COVERS were 0.82 (95%CI, 0.72–0.88) at baseline and 0.80 (95%CI, 0.69–0.87) during heel lance. In this study, it was found that there was a moderate correlation in ICCs for scores of COVERS during both diaper change and heel lance procedures.

It has been reported in the literature that PIPP and NIPS are frequently used to evaluate acute pain of preterm and term newborns[9]. The COVERS scale includes the parameters of both the NIPS and PIPP scale. However, the criteria used for scoring on the COVERS scale include newborns with a wider week[10]. Although crying is a parameter of behavioral responses to pain, it is unlikely that an intubated infant will have a high-pitched crying[10]. Compared with NIPS[13], the COVERS scale included visible crying within the behavioral parameter[10]. Compared with the PIPP scale, the COVERS scale has brought a new perspective to oxygen requirements. Since the oxygen requirement of the infant is not always an indicator of pain, the COVERS scale focuses on the change of oxygen demand rather than its value[10].

CONCLUSIONS

It was concluded that based on content validity, concurrent validity, and construct validity analyses of COVERS adapted into Turkish, it is a valid scale, and based on internal consistency and inter-rater reliability analyses, it is a reliable scale. COVERS can be used in all newborns with a gestational age of ≥27 weeks. In future studies, it may be suggested to adapt the COVERS scale to different cultures and to investigate the validity and reliability of the COVERS scale on infants in the postneonatal period.

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AUTHORS' CONTRIBUTIONS

MCI: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **NUÖ:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Validation, Writing – original draft. **BM:** Conceptualization, Funding acquisition, Methodology, Validation, Writing – original draft, Writing – review & editing. **EÇ:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Software, Validation, Writing – original draft. **EC:** Conceptualization, Data curation, Funding acquisition, Writing – original draft.

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REVIEW ARTICLE
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Management of gastrointestinal complications of enteral nutritional therapy in the ICU

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INTRODUCTION

Enteral nutrition therapy (ENT) is a common nutritional strategy for inpatients, playing a role in the nutritional needs of the disabled that is normally provided through an oral diet[1]. Although several benefits have been reported, ENT can cause harm by its interruption in 85% of patients, with gastrointestinal occurrences as a major cause often occurring in critical patients[1-3].

Since critical illness causes several changes in gastrointestinal motility, the most frequently mentioned diseases in the literature include diarrhea, high gastric residual volume, and constipation, affecting approximately 92% of intensive care unit (ICU) patients, who may experience more than one of these complications[2].

The treatment of gastrointestinal complications in critically ill patients is fundamentally important for the adequate ENT supply and, consequently, for better patient clinical evolution[2].

There have been few studies on this issue that provide evidence and appropriate recommendations for clinical practice. Even the main clinical guidelines provide little information regarding the management of gastrointestinal complications.

Thus, the purpose of this integrative review was to collect data on the best approaches to gastrointestinal complications with the greatest impact in the ICU during ENT.

METHODS

This paper is an integrative literature review, an approach that allows the combination of several methodologies, both experimental and non-experimental, and the content of an empirical or theoretical nature[4].

This was conducted in the PubMed, Lilacs, and Cochrane Library databases, with the following indexed terms and their respective synonyms of the Medical Subject Headings (MeSH), as well as the following Boolean connectors: # 1 Enteral Nutrition AND # 2 Intensive Care AND # 3 Food intolerance OR Diarrhea OR Constipation OR Vomiting OR Gastric Residual Volume NOT # 4 Pediatric. The term "gastric residual volume" and its synonyms are not part of the indexed terms in MeSH, but they were included to increase the number of studies that addressed the topic. Additionally, the references of the selected articles were analyzed to select other unidentified studies when searching the databases.

Specifically, articles that were published in the last five years, written in English, Spanish, or Portuguese, that addressed the management of high gastric residual volume (GRV), vomiting, diarrhea, and constipation in the ICU during ENT in adult patients were included. On the other hand, literature reviews, letters, editorials, and comments were excluded.

RESULTS

In the database search, 305 studies were found, of which 37 were included in this review following the steps described in Figure 1. The main characteristics of the included studies, except for the results described below, are presented in Table 1.

Initially, regarding high GRV and vomiting, ENT characteristics that were associated with its occurrence were those with lipid and protein compositions. Thus, a decrease in such complications was observed in patients who received ENT with medium-chain triglycerides (MCT), omega-3 polyunsaturated fatty acids, and peptide-based formulas[5-8].

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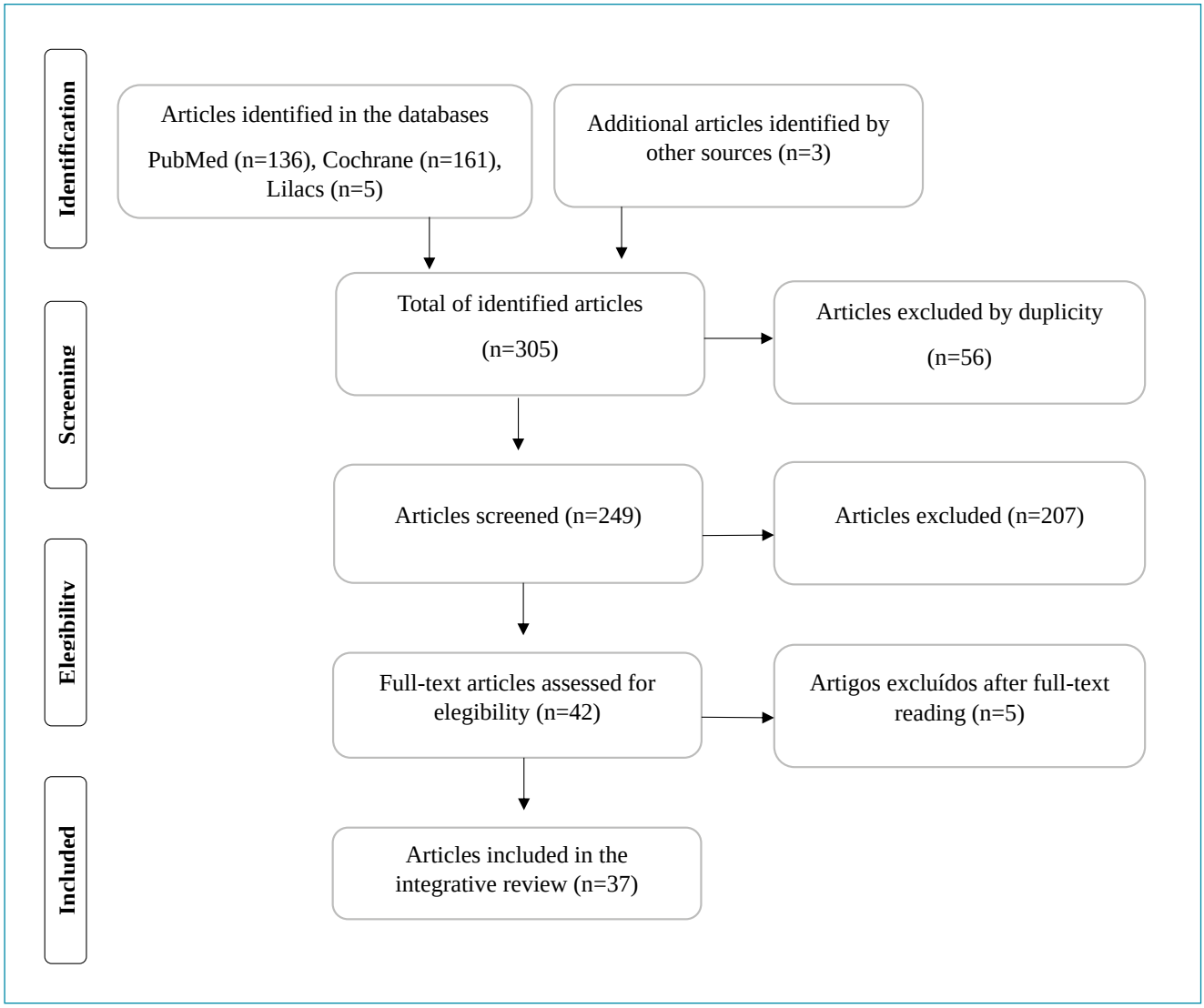

Figure 1. Flowchart of eligibility.

Many studies still aim to evaluate GRV monitoring, even though it has been largely abandoned in the ICUs, as already established and recommended by several guidelines.

Therefore, a significant reduction in elevated GRV, abdominal distension, diarrhea, and prescribed prokinetic agents was found in studies that removed GRV monitoring[9,10]. Another benefit observed with this removal was the better achievement of nutritional goals, which were achieved more quickly without increasing complications[5,11,12].

Furthermore, it is emphasized that elevated GRV is not equivalent to gastrointestinal intolerance, does not always reflect aspiration risk, and that a single episode should not require reduction or immediate interruption of the ENT rate, but should lead to a careful examination of secondary causes[13].

In contrast, only one study found favorable results for frequent GRV monitoring, showing lower vomiting and diarrhea incidences in the group that was monitored with shorter gaps; however, this group also had a smaller hourly infusion rate increase than the intervention group[14].

Alternatively, the use of ultrasound imaging to evaluate GRV has proved to be beneficial, despite the need for standardization. This practice is based on data that point to a correlation between measurements of parts of the antrum and the aspirated volume, showing that gastric ultrasound can accurately estimate GRV in critically ill patients[15].

Moreover, other advantages were found, proving that gastric aspiration did not provide an accurate GRV estimate compared to ultrasound[16] and that ultrasound can reduce reflux occurrence and increase ENT supply[17].

Table 1. Characteristics of the studies.

Author, country	Methodology	Sample size
Heinonen et al.[2], Australia	Observational retrospective	100 patients
Qiu C et al.[5], China	Randomized controlled trial	144 patients
Tihista et al.[6], Uruguay	Randomized controlled trial	92 patients
Liu et al.[7], Taiwan	Observational retrospective	72 patients
Seres et al.[8], United States	Pilot, prospective randomized	49 patients
Wiese et al.[9], Australia	Observational retrospective	181 patients
Wang et al.[10], China	Systematic review and meta-analysis	5 articles. 998 patients
Ozen et al.[11], Turkey	Randomized controlled trial	51 patients
Bruen et al.[12], United States	Retrospective historical cohort	61 patients
Pham et al.[13], United States	Systematic review	26 articles
Büyükçoba et al.[14], Turkey	Randomized controlled trial	60 patients
Sharma et al.[15], United States	Pilot, prospective cohort	19 patients
Bouvet et al.[16], France	Prospective cohort	61 patients
Chen et al.[17], China	Randomized controlled trial	72 patients
Zhu et al.[18], China	Randomized controlled trial	141 patients
Ge et al.[19], China	Randomized controlled trial	70 patients
Taylor et al.[20], United Kingdom	Randomized controlled trial	50 patients
Li et al.[21], China	Systematic review	8 articles. 835 patients
Wang et al.[22], China	Systematic review and meta-analysis	5 articles. 325 patients
Friedman et al.[23], Brazil	Randomized controlled trial	115 patients
Nasiri et al.[24], Iran	Randomized controlled trial	60 patients
Reis et al.[25], Brazil	Systematic review	8 articles. 639 patients
Yagmurdur et al.[26], Turkey	Randomized controlled trial	120 patients
Tuncay et al.[27], Turkey	Randomized controlled trial	46 patients
Kamarul et al.[28], Malaysia	Systematic review and meta-analysis	14 articles. 1414 patients
Alberda et al.[29], Canada	Pilot, case-control	32 patients
Mahmoodpoor et al.[30], Iran	Randomized controlled trial	100 patients
Shimizu et al.[31], Japan	Randomized controlled trial	72 patients
Manzanares et al.[32], United States	Systematic review and meta-analysis	30 articles. 2972 patients
Jakob et al.[33], Switzerland	Randomized controlled trial	90 patients
Vieira et al.[34], Brazil	Prospective cohort	23 patients
Chen et al.[35], China	Observational prospective	533 patients
Wesselink et al.[36], Netherlands	Retrospective cohort	433 patients
Lewis et al.[37], Canada	Systematic review and meta-analysis	13 articles. 1341 patients
Pérez-Sánchez et al.[38], Spain	Observational prospective	139 patients
Fukuda et al.[39], Japan	Observational retrospective	282 patients
Prat et al.[40], France	Observational prospective	189 patients

Concerning the place of ENT administration, data are still controversial. Favorable results have been demonstrated for post-pyloric administration, with a reduction in the rate of vomiting, ventilator-associated pneumonia (VAP), abdominal distention, diarrhea, regurgitation, and aspiration[18-20]. In contrast, other studies, despite confirming a significant VAP reduction, found no reduction in the incidence of vomiting and diarrhea with post-pyloric feeding[21-23].

Regarding the administration method, no differences were found between bolus and intermittent administration related to vomiting, high GRV, constipation, diarrhea, and bloating[24].

Finally, concerning the risk factors observed, the patient's positioning with a bed angle <30º had a significant influence on the GRV increase[2].

Concerning diarrhea, improvements have been demonstrated with the use of fibers, as well as better nutritional offers, recommending specifically soluble fibers as safe for critically ill patients who are hemodynamically stable[25-27].

Only one study found results that were not favorable to the use of fibers in critically ill patients, noting that fiber reduces diarrhea in ENT patients, but not in critically ill patients[28].

Regarding probiotics, two studies were favorable for their use, but the results were not statistically significant. The first study tested the use of two bottles per day of a drink containing 10 billion *Lactobacillus casei*, resulting in a lower rate of diarrhea associated with antibiotics[29]. Similarly, in another study, *Lactobacillus (casei, acidophilus, rhamnosus, bulgaricus), Bifidobacterium (breve, longum*), and *Streptococcus spp.*, were used as probiotics, which also resulted in a decrease in diarrhea[30].

In this perspective, a study evaluated the effect of symbiotics, using probiotics *B. Breve* and *L. casei*, and prebiotic galactooligosaccharides on the intestinal microbiota of critically ill patients. As a result, a decrease in diarrhea incidence was observed, suggesting its prophylactic use in modulating the intestinal microbiota[31].

However, a meta-analysis including only studies with critically ill patients which evaluated both probiotics and symbiotics found benefits, such as reducing infections, including VAP; however, no improvement in diarrhea was found[32].

Although these studies show evidence that probiotic use favors diarrhea prevention and treatment, there was no statistical significance in the results presented, and further research in critical patients is necessary, especially because of the existence of different strains and dosages to be tested.

Another characteristic of ENT was addressed in a study that reported decreased diarrhea in the group that received ENT with MCT[5]. In contrast, another study failed to show this relationship with fat (MCT and fish oil) and protein content (hydrolyzed) modifications[33].

Finally, regarding risk factors, it was observed that antibiotic use, prokinetic therapy, high Acute Physiology And Chronic Health Evaluation II (APACHE II), post-pyloric ENT, and post-pyloric hyperosmolar drug administration were associated with increased diarrhea[2,34-36]. Only one study found no relationship between prokinetic therapy and a significant increase in the rate of diarrhea[37].

In the case of constipation, few studies have addressed the ENT management for its treatment, all of which use an observational methodology. In this context, a higher constipation occurrence was observed in patients receiving a fiber-free diet[38]. In addition, late ENT is considered a risk factor for constipation[39].

Drugs reported as risk factors for constipation were sedatives, muscle relaxants, iron and calcium supplements, antihypertensives, and vasopressors[2,33,38-40]. Finally, another risk factor found for constipation was surgery performance[39].

Constipation causes many detriments to ENT, such as increases in the mechanical ventilation time, length of ICU stay, and VAP incidence and mortality, influencing the achievement of nutritional goals[40]; however, this may receive less importance in clinical practice as reflected in the studies found.

CONCLUSIONS

It stands out from this review that in the management of gastrointestinal complications in ICU patients, such as high GRV, vomiting, and diarrhea, ENT formulas with fat content (such as MCT) modification are possibly more effective. Furthermore, it has been shown how fibers, particularly soluble fibers, can be used to treat diarrhea. However, constipation is poorly discussed in the literature.

This work demonstrates the importance of knowing the formula compositions used in ICUs. There is a need for more publications addressing ICU gastrointestinal complications when ENT is indicated, especially for constipation.

AUTHORS' CONTRIBUTIONS

CPC: Conceptualization, Data Curation, Formal Analysis, Methodology. **DLG:** Conceptualization, Methodology, Project Administration, Writing – Review & Editing. **MCAF:** Conceptualization, Methodology, Project Administration, Writing – Review & Editing.

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REVIEW ARTICLE
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The relationship between smoking and brain aneurysms: from formation to rupture

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INTRODUCTION

Cerebral aneurysms occur in 3–5% of the general population and are characterized by localized structural deterioration of the arterial wall, with loss of the internal elastic lamina and disruption of the media layer[1]. The most dreaded complication of a cerebral aneurysm is its rupture, which is likely related to several modifiable and nonmodifiable risk factors[2]. Subarachnoid hemorrhage (SAH), secondary to intracranial aneurysm (IA) rupture, has a high mortality, which approaches 50% in some studies[3].

Aneurysms deemed at low risk of rupture are typically kept under image surveillance, while endovascular embolization or surgical clipping is commonly offered to patients deemed to be at a higher risk of aneurysm rupture[4]. Although the exact underlying etiology that causes IA rupture is not clearly understood, cigarette smoking is considered to be the most significant modifiable risk factor[5].

Cigarette smoking is a major health hazard, with 5.4 million premature deaths worldwide every year and an average loss of 13–15 years of life expectancy[6]. Understanding how nicotine exposure impacts IA may have important implications for screening and counseling of patients. Therefore, the aim of this study is to evaluate the effects of smoking on the formation, growth, rupture, and even recurrence of IAs, by incorporating the data obtained from a review of the literature available.

METHODS

This is a descriptive study based on the literature available in the MEDLINE/PubMed database. The terms searched, all in English, were as follows: "smoking" AND "intracranial aneurysms," "pathophysiology," "aneurysms formation," "aneurysm growth," "aneurysms rupture," "subarachnoid hemorrhage," and "residual aneurysms." All articles that were considered relevant were included in this review, as were the studies referenced therein, to raise awareness about the method. Duplicate items were discarded.

DISCUSSION

The prevalence of intracranial saccular aneurysms is estimated to be 3.2–4% in a population without comorbidity, with a mean age of 50 years and with a 1:1 gender ratio[7]. Most IAs (approximately 85%) are located in the anterior circulation, predominantly on the circle of Willis arteries[8].

Aneurysmal SAH occurs at an estimated rate of 6–16 per 100,000 population, and its high morbidity and mortality rates are attributed mainly to brain damage that is caused by a severe initial hemorrhage, early rebleeding, and delayed cerebral ischemia[9]. As IAs are the major etiology of SAH, risk factors can be considered the same for both situations, which are mainly associated with hypertension, cigarette smoking, and alcohol consumption[10].

The pathogenesis of the formation of intracranial saccular aneurysms is multifactorial[11]. Usually, there is an endothelial dysfunction in response to turbulent flow and hemodynamic stress, which leads to compensatory responses that alter the endothelium. This results in functional and morphological changes that activate an inflammatory response in the vessel wall, leading to a proinflammatory local environment and an extracellular matrix remodeling by matrix metalloproteinases (MMPs)[12,13].

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When it comes to analyzing cigarette smokers, they have a significantly increased risk of SAH compared with the nonsmoker population. In the case–control study carried out by Bonita[14], the relative risk values of SAH for men and women were 3.0 and 4.7, respectively, and according to the number of cigarettes smoked, the risk increased. Those who smoked and those who had hypertension had a risk of SAH that is 15 times higher when compared with normotensive nonsmokers[14].

There are multiple hypotheses about the mechanisms through which smoking can lead to vascular inflammation, hemodynamic stress, endothelial dysfunction, and, ultimately, wall weakening and rupture[15] (Table 1). Cigarettes are composed of a mixture of chemical substances that release a bunch of harmful toxins when burnt, which can enter into the bloodstream and lead to many vascular adverse effects[16]. To understand it more clearly, we can analyze the impact of cigarette smoking on each stage of the development of aneurysms, such as its formation, growth, rupture, and, eventually, its recurrence (Figure 1).

Smoking and aneurysm formation

Hemodynamic forces play a key role in the development of the cerebral aneurysm, as they are highly associated with rapid degradation of the internal elastic lamina, followed by thinning of the media and outward bulging of the vessel wall[17]. Cigarette smoking contributes to this situation as it significantly increases the wall shear stress by raising the blood viscosity and the blood volume and also through the induction of cerebral vasoconstriction[18]. Similarly, nicotine may also raise wall shear stress as it inhibits nitric oxide synthase, which impairs the nitric oxide signaling pathway that is responsible for cerebral vasodilation[19].

Conjointly, smoking has shown to directly upregulate endothelin type B receptors in the cerebral arteries through the activation of key intracellular inflammatory signal molecules, such as mitogen-activated protein kinases and the NF-κB signal pathway, which plays a critical role in the pathogenesis of cerebral aneurysms[20].

Cigarette smoking also decreases the effectiveness of α1-antitrypsin, an inhibitor of proteases such as elastase (i.e., proteolytic enzyme), resulting in the vessel wall injury that can be associated with the hypoxemia-induced inflammation due to the smoke-related increased levels of carbon monoxide, proinflammatory cytokine tumor necrosis factor-α (TNF-α), and reactive oxygen species from cigarette combustion, which potentiates the possibility of development of the aneurysm[8,21].

Smoking and aneurysm growth

The persistence of a proinflammatory environment is the main factor that contributes to the development of aneurysms as studies have shown that smokers have higher levels of interleukin-1β (IL-1β), TNF-α, and interleukin-6 (IL-6)[22], which are, respectively, associated with reducing the biosynthesis of collagen[23], activating MMP that remodels the extracellular matrix on the injured endothelium[24], and induction of gene polymorphisms[25].

Besides the proinflammatory status, Juvela et al.[26] observed that smoking habits and the number of cigarettes smoked daily seem to be more important in terms of aneurysm growth than the duration of smoking or age at which one began smoking, and those who gave up smoking did not present an increased risk for aneurysm expansion, as their growth rates were the same as in nonsmokers[26]. This suggests the importance of smoking control, even after the diagnosis of a cerebral aneurysm, as the risks appear to diminish rapidly within a few years of quitting[27].

Smoking and aneurysm rupture

Many studies have shown that cigarette smoking is a significant risk factor for the development of SAH. Anderson et al.[27] analyzed 432 incident cases of SAH that are compared with 473 controls, and the results showed that cigarette smokers have five times the risk of SAH compared with nonsmokers, and about one-third of all cases of SAH could be attributed to current smoking.

The risk of aneurysm rupture also seems to be higher in the initial three hours after smoking, due to the release of catecholamines stimulated by nicotine, with a greater risk ratio in women than in men[14,28]. Hence, synergistic mechanisms that increase the hemodynamic stress present a higher risk for its rupture when associated with smoking, such as hypertension, alcohol consumption, stimulant drugs (i.e., cocaine), and other factors associated with elevated blood pressure, uncompensated blood flow, or increased blood viscosity[29].

It is also known that inhalation of smoke from cigarettes irritates the lung tissue and causes an inflammatory reaction characterized by the elevated levels of white blood cells, which can secrete free radicals, elastase, and collagenase that may contribute to the injury of the endothelial cells[30].

There is also an association between cigarette smoking and thrombosis that can predispose aneurysm rupture, as nicotine increases plasminogen activator inhibitor-1 in human brain–derived endothelial cells, and it increases the levels of tissue factor, which is a key factor in thrombogenesis[31].

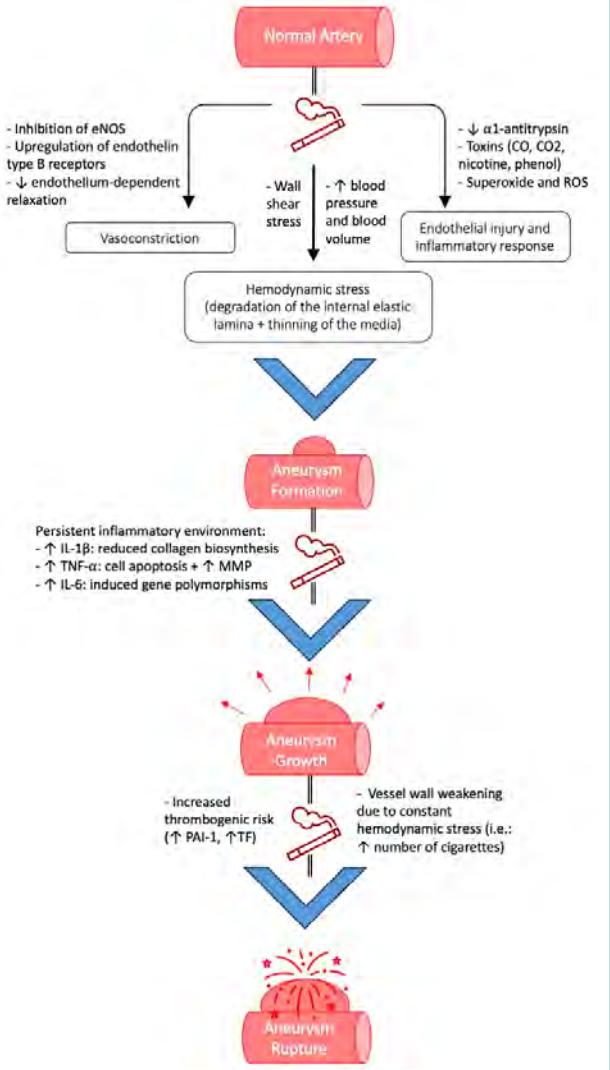
Smoking and aneurysm recurrence or residual

Patients who are smokers and who have undergone endovascular repair of cerebral aneurysms have shown an increased

Table 1. Smoking-induced mechanism described for the pathogenesis of aneurysms.

Author	Smoking-induced mechanism described for the pathogenesis of aneurysms	Related outcome
Schievink WI et al.[8]	Decreased effectiveness of α1-antitrypsin and increased levels of proteolytic enzymes (i.e., elastase) contribute to the degeneration of the vessel wall, for example, through increased elastin degradation	Aneurysm formation
Price JF et al.[18]	Increased blood viscosity and blood volume and induction of cerebral vasoconstriction contribute to intensify the wall shear stress	
Gerzanich V et al.[19]	Inhibition of eNOS and impairment of the NO vasodilating pathway contribute to promote vasoconstriction of the cerebral arteries, which increases the pressure of blood against the walls of the vessel (increased wall shear stress)	
Hashimoto T et al.[17]	Hemodynamic forces cause rapid degeneration of the internal elastic lamina, followed by thinning of the media and outward bulging of the vessel wall	
Jayaraman T et al.[21]	Increased levels of TNF-α, CO, and ROS associated with hypoxemia-induced inflammation contribute to the inflammatory status that contributes to the injury of the vessel wall	
Xu CB et al.[20]	Upregulation of endothelin type B receptors in cerebral arteries induces cerebral vasoconstriction, which increases the pressure of blood against the walls of the vessel (increased wall shear stress)	
Juvela S et al.[26]	The greater the number of cigarettes smoked daily, the higher the risk of aneurysm growth due to constant inflammatory stimulus and progressive vessel wall weakening	Aneurysm growth
Jayaraman T et al.[24]	Higher levels of TNF-α can activate MMP that remodels the extracellular matrix on the injured endothelium and lead to the irreversible degradation of the vessel wall	
Aoki T et al.[23]	Higher levels of IL-1β can reduce the biosynthesis of collagen and promote apoptotic cell death, which contributes to vessel wall weakening	
McColgan P et al.[25]	Higher levels of IL-6 can act on the induction of gene polymorphisms, which suggests being relevant as some gene bases have recently been related to intracranial aneurysms development	
Juvela S et al.[28]	Nicotine stimulates the release of systemic catecholamines that can cause a transiently elevated blood pressure 2–3 h after smoking and can increase the risk of aneurysm rupture	Aneurysm rupture
Zidovetzki R et al.[31]	Nicotine can increase the levels of PAI-1 and TF, the key factors in thrombogenesis that can lead to thrombus formation, which can contribute to the proinflammatory environment and increase the hemodynamic stress against the walls of the aneurysms	
Kumar V et al.[30]	Elevated levels of white blood cells (i.e., neutrophils and monocytes) due to inflammatory reaction and consequent release of free radicals, elastase, and collagenases can contribute to endothelial cells injury and vessel wall weakening and increase in the risk of aneurysm rupture	
Tulamo R et al.[13]	Smoking-induced endothelial injury and de-endothelization with consequent hyperactivation of the coagulation cascade can contribute to the proinflammatory environment and further breakdown of the cerebral aneurysm wall	
Andreasen TH et al.[29]	Synergistic mechanisms (i.e., hypertensions, alcohol consumption, stimulant drugs, and hypercolestemia) can increase the risk of rupture as they can amplify the hemodynamic stress against the walls of the aneurysms	

CO: carbon monoxide; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; PAI-I: plasminogen activator inhibitor-1; ROS: reactive oxygen species; SAH: subarachnoid hemorrhage; TF: tissue factor; TNF-α: tumor necrosis factor-α; MMP: matrix metalloproteinase; IL-1β: interleukin-1β; IL-6: interleukin-6.



eNOS: endothelial nitric oxide synthase; ROS: reactive oxygen species; IL-1: interleukin-1; TNF-: tumor necrosis factor-; MMP: matrix metalloproteinases; TF: tissue factor.

Figure 1. The impact of smoking on aneurysms development.

risk of aneurysm recurrence as it was analyzed in the study conducted by Futchko et al.[32], in which the odds ratios (ORs) for aneurysm recurrence for current and former smokers were 2.739 and 2.698, respectively, compared with never smokers. In the same way, Aguiar et al.[33] also investigated this relationship based on the results obtained from 167 IAs treated by microsurgical clipping, from which 38 patients developed residual lesions, as 27 of them were current smokers compared with only 11 nonsmokers. Thus, it revealed an increased risk of residual aneurysms for current smokers (OR 3.38, 95%CI), possibly due to the effects of cigarette substances on the vessel well and on the blood flow of the brain as already described on the above mechanisms.

CONCLUSIONS

Cigarette smoking is still a very frequent habit among the general population, despite how much is known about its many harmful attributes, such as various ways that tobacco exposure can influence the pathogenesis of the cerebrovascular aneurysm as explored in this study. Therefore, it is of great importance to better understand the biological mechanisms of how it can lead to vascular inflammation, hemodynamic stress, endothelial dysfunction, and consequent vessel wall weakening to prevent the occurrence of IAs and to avoid further complications such as aneurysms ruptures and consequent SAH.

AUTHOR'S CONTRIBUTIONS

PB: Data Curation, Writing – original draft. **GBA:** Conceptualization, Writing – original draft. **RCS:** Conceptualization, Writing – review & editing.

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REVIEW ARTICLE
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Asymptomatic microscopic hematuria in women

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INTRODUCTION

Asymptomatic microscopic hematuria (AMH) is an important clinical sign of urinary tract malignancy. AMH has been variably defined over the years. It could be defined as three or more red blood cells per high-power field in the absence of infection as indicated in the American Urological Association (AUA) guidelines[1]. The evidence is primarily based on the data related to male patients. However, whether the patient is a man or a woman influences the differential diagnosis of AMH, and the risk of urinary tract malignancy (e.g. bladder, ureter, and kidney) is significantly less in women than in men[1,2].

Among women, being older than 60 years, having a history of smoking, and having gross hematuria are the strongest predictors of urological cancer. In low-risk, never-smoking women younger than 50 years without gross hematuria and with fewer than 25 red blood cells per high-power field, the risk of urinary tract malignancy is £0.5%[1-3].

Although AMH has a clinical importance, the research on women in this area has been limited. It is incumbent on the experts in the field of female pelvic medicine to advance the science and develop management algorithms for AMH in women[4].

Faced with this situation, the objective of this study was to review the literature to identify the recommended guidelines about how to approach AMH in women.

METHODS

Search strategy

This study was performed by a qualitative review.

Selection criteria

All of the publications indexed in Medline (PubMed), LILACS, and BIREME databases in August 2020 were searched using the key words "hematuria," "guideline(s)," and "women."

Data collection and analysis

Following this search strategy, a total of 14 articles were included in this study. Out of 14 studies, 11 commented on recommendations and best strategies to approach this sign in women. Three studies were excluded because of their different objectives (i.e. two of them have studied urinary tract infection in women and the other interstitial cystitis/painful bladder syndrome). Another study has been included in a quote of teaching form for the citation of causes of AMH.

RESULTS AND DISCUSSION

It is estimated that about two-third of the women with hematuria in one examination will not present in another during the lifetime, since menstruation, fever, infection, injury of the urinary tract, and physical exercise are the main causes for this contamination[5].

According to Richter et al., the risk factors for AMH in women are smoking, a history of pelvic radiation, and a history of nephrolithiasis[6]. When stratifying the quantity of AMH, women with increased red blood cells per high-power field were more likely to have significant findings on their imaging results[6].

Medical history followed by the physical examination is the initial step to assess hematuria. Subsequently, a distinction should be made between glomerular and non-glomerular hematuria. This can be achieved by a search of red blood

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cell casts or dysmorphic cells. The main causes of glomerular hematuria in women are as follows: immunoglobulin A (IgA) nephropathy, thin glomerular membrane disease, and hereditary glomerulonephritis[5].

Malignant neoplasia, nephrolithiasis, cystitis, urethritis, and other causes of non-glomerular bleeding can be diagnosed by imaging examination. To evaluate lithiasis, the computed tomography (CT) should be utilized with or without radiocontrast, respectively. Patients with risk factors for bladder cancer should be performed a urinary cytology test or undergo a cystoscopy. Other less frequent causes of hematuria can be investigated depending on the clinical indications[5].

A practical guideline for general practice for imaging of the urinary tract in adults has suggested that ultrasound should be chosen in patients with microscopic hematuria (MH) and nonspecific abdominal pain. The CT should be used in cases with nonspecific findings using urography and ultrasound[7].

In 2012, the AUA released a revision of the AMH guidelines for postmenopausal women. That study population included 237 women with a mean±SD age of 67.1±8.3 years. In postmenopausal women evaluated for AMH, the overall prevalence of urinary tract malignancy was low at 1.4%[8].

The AUA cited that future directions should include continued research into the confounding risk factors for AMH in postmenopausal women such as vaginal atrophy, pelvic organ prolapse, and recurrent urinary tract infection. Investigation on the exact correlation of urinary dipstick to microscopic urinalysis may also be a way to decrease the number of unnecessary and costly evaluations if definitive evidence shows that trace blood is not associated with AMH[8].

On the contrary, the prevalence of AMH is greater in postmenopausal women (i.e., about 20%) than that in the general population, presumably due to the same risk factors such as pelvic organ prolapse or vaginal atrophy[8,9]. Cystoscopy, renal function testing, and CT urography are now recommended after one positive urinalysis, regardless of gender or the presence of prolapse. Due to the low incidence of urological malignancy detected as well as the increased prevalence of MH found in women with prolapse, specific guidelines for the management of MH in this population are needed[9].

Limitations may difficult the analysis of AMH in women. The proper evaluation and treatment options are understudied in females[4,10,11]. While urinalysis remains a common diagnostic tool, most cases of both MH and gross hematuria are not fully evaluated according to the guidelines. The use of cystoscopy, cytology, and upper tract imaging is limited[10]. Besides, the guidelines recently updated by the AUA for the evaluation of AMH are based on the data derived predominantly from men. AMH in women requires separate guidelines[4,10,11].

In addition, although gross hematuria is a relatively uncommon condition in general obstetrics and gynecology practice, MH is a common incidental finding during routine antepartum or other gynecological visits[10]. Pregnancy, menstruation, and vaginal atrophy increase the number of potential false diagnoses[10]. Probably, due to these factors, unfortunately women are less likely to be referred to urology or urogynecology, and also women wait longer than men for review and diagnosis of bladder cancer[12].

CONCLUSIONS AND RECOMMENDATIONS

The American College of Obstetricians and Gynecologists and the American Urogynecologic Society encourage organizations producing future guidelines on the evaluation of MH to perform sex-specific analysis of the data and produce practical sex-specific recommendations[1].

In the meantime, the American College of Obstetricians and Gynecologists and the American Urogynecologic Society recommend that asymptomatic, low-risk, never-smoking women aged 35–50 years undergo evaluation only if they have more than 25 red blood cells per high-power field[1].

Among women, being older than 60 years, having a history of smoking, and having gross hematuria are the strongest predictors of urological cancer[1]. Faced with this scenario, this review may encourage and provide evidence for future guidelines on AMH in women.

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AUTHORS' CONTRIBUTIONS

GVM: Data curation, Writing – review & editing. **SBM:** Data curation, Writing – review & editing. **LMO:** Data curation, Writing – review & editing. **MMD:** Data curation, Writing – review & editing. **CCT:** Data curation, Writing – review & editing. **MGFS:** Conceptualization, Formal Analysis, Writing – review & editing.

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COMMENTARY
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Comment on "Seasonal variation of clinical characteristics and prognostic of adult patients admitted to an intensive care unit"

Xuegao Zheng[1], Jiya Zhou[2]*

Dear Editor,

We read with great interest the study by Galvao, G[1] and colleagues in which they demonstrated that summer months presented a higher proportion of clinical and emergency surgery patients with higher mortality rates and sepsis at intensive care unit admission did not show seasonal behavior. A seasonal pattern was found for the mortality rate. the negative cholesterol profile was mainly related to antiretroviral treatment time and was especially associated with time for HIV infection in those with lipodystrophy self-reported. This study offers a new strategy for improving antiretroviral treatment in adults living with and without virus infection. However, some concerns should be raised in my opinion.

To begin with, there are many reasons for the higher mortality rates of adult patients admitted to an intensive care unit. Thus, the author should explore the reason why summer months presented a higher proportion of clinical and emergency surgery patients, with higher mortality rates. A reasonable explanation is also recommended to explain this phenomenon.

Secondly, Figure 4 shows that the death rate is higher from 2014 to 2015, and then the death rate is decreasing with years. We speculate that the death rate may be associated with the medical technology of the intensive care unit (ICU) for adult patients of the University Hospital of the State University of Londrina.

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COMMENTARY
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Comment on "Homeobox B2 is a potential prognostic glioblastoma biomarker"

Renwen Xing[1], Lianping He[2], Yuanlong Gu[3], Yonghua Mou[1]*

Dear Editor,

We read the study by Ming Li[1] and colleagues with great interest, in which They revealed the impact of HOXB2 on the prognosis of glioma and its possible role through the PI3K/AKT signaling pathway. This work has a certain degree of guiding significance for the further exploration of disease mechanisms and clinical prognosis evaluation. But there are still a few questions. I want to discuss this with the author and colleagues.

Firstly, Although the current research displays that all types of tumors may have the same basic driving and evolution mechanism, different types of tumors are still considered to have different pathological characteristics during the occurrence and development process, which has also led to the clinical evolution of different tumors. The prognosis is different. The author points out that the Homeobox B2 gene has a prognostic function in lung cancer research, and further deduces that the Homeobox B2 gene has a similar function in glioma. There is no direct connection between them, and the scientific hypothesis is not rigorous enough.

Secondarily, the role of the homeobox B2 gene in the PI3K/Akt signaling pathway is not explained clearly in this paper. All the molecular biology experiments in vitro are to demonstrate the role of the homeobox B2 gene in the PI3K/Akt signaling pathway. We suggest that the author should show the PI3K/Akt signaling pathway graphically and explain the role of the PI3K/Akt signaling pathway in the evolution of glioma. In this way, readers can better understand the significance of the author's scientific research, and enlighten relevant scholars for further research work.

AUTHORS' CONTRIBUTION

RX: Data curation, Formal Analysis, Writing – original draft. **LH:** Investigation, Visualization. **YG:** Resources, Investigation. **YM:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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COMMENTARY
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The relationship between physical performance and vision may be an accompanying relationship

Yibin Ma[1], Ping Liu, Ronghui Nie[1], Dawei Song[1]*

Dear Editor,

We were pleased to read the study by Wu K[1], and colleagues in which they found that physical exercise might help improve visual acuity. University students should practice strength exercises to improve physical performance. I think this view needs to be discussed further. We will add some of our points.

First, the relationship between physical performance and vision may be an accompanying relationship, not a cause–effect relationship. Indeed, eye exercises can effectively prevent myopia. But we can't say that there is a causal relationship between sports performance and vision. There are many reasons for good physical performance, such as long-term exercise, personal physical fitness, and so on. Good eyesight may be caused by less usage of eyes, or it may be due to better preventive measures. The causal relationship between physical activity and vision needs to be further confirmed by a queue study.

Additionally, the authors studied the correlation between physical performance and vision, but did not take into account the confounding factor. Age and gender tend to modify the correlation between physical performance and vision. The authors also did not give the general demographic characteristics of the subjects, such as age, gender, education level and economic level. Only by presenting more baseline data can we better explore the relationship between physical performance and vision.

AUTHORS'CONTRIBUTION

Yibin Ma and Ping Liu contributed equally to this work. Both the authors drafted, reviewed, and approved this paper.

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COMMENTARY
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Comment on "Ankle-brachial Index and associated factors in individuals with coronary artery disease"

Guanqing Chen[1], Lianping He[1]*

Dear Editor,

We were pleased to read the high-level study by the research team of Saulo Henrique Salgueiro de Aquino et al.[1]. They found that the independent risk factors for peripheral arterial occlusive disease were age, history of diabetes, and history of systemic arterial hypertension. Although this study is significant for the prevention and treatment of cardiovascular disease, we still believe that there are also some issues to be explored further.

First of all, the author intended to investigate the relationship between ankle-pleural index and the major risk factors for coronary heart disease, however, the conclusions of this study failed to support the purpose of the study. In other words, the title of the article does not accurately reflect what is being studied.

Furthermore, when studying the relationship between different risk factors and ankle-pleural index, it is not clarified that why did the author use the rank sum test rather than the student's *t* test. The possible reason may be that ankle-pleural index is a non-normal distribution. It would have been better that the author would have explained the possible reason. Age is a risk factor for both diabetes and hypertension, there is no definitive association between ankle-pleural index and diabetes or hypertension. If ankle-pleural index is associated with age, then ankle-pleural index is not a good predictor for diabetes and hypertension.

AUTHORS' CONTRIBUTION

GC: Writing – original draft, Writing – review & editing.
LH: Writing – original draft, Writing – review & editing.

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COMMENTARY
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Comment on "Depression, anxiety and spirituality in oncology patients"

Yi Lin[1], Yuanlong Gu[2]*

Dear Editor,

We were glad to read the paper by Turk et al.[1] and his research group. They found that spirituality can be a complementary tool in the treatment of patients with cancer. The results indicated that improving spirituality may be more important for the treatment and prevention of cancer. However, in my point, there are some problems should be further discussed in this study.

First of all, the aim of this study was to relate anxiety and depression levels to the spirituality levels of oncology patients. Obviously, it is well known that spirituality was negatively associated with anxiety and depression. Generally speaking, there are less prevalence of anxiety and depression among cancer patients with higher spirituality. Besides, their conclusion drawn from the results failed to answer the purpose of the study. It can be seen that the author's research purpose and research conclusions were not strongly correlated.

Secondly, the software used in those study should be mentioned in the statistics analysis section. Additionally, the criteria of statistical significance should also be offered, for example, $p<0.05$ was considered as statistics significance. Do mental scores, depression scores, and anxiety scores follow normal distributions? Since the distribution type of the data has an important basis for the selection of statistical methods, the author did not give the normality test of the above score. In Table 2, the authors analyzed the correlation between mental scores, depression scores, anxiety scores, and age and income. What statistical methods are used for these scores among patients with different levels of education: analysis of variance (ANOVA) or non-parameter testing? If ANOVA was used in their study, the average and standard deviations should have been provided to the readers.

Finally, the limitation of cross-sectional study is that causal inference cannot be made. Spirituality, depression, and anxiety are all associated with tumor development. Thus, why do the authors think that mentality is only a complementary option for tumor therapy? If the depression and anxiety of patients have been intervened, spirituality of the patient could be improved. Of course, in order to obtain the relationship between spirituality and tumor development, further follow-up studies of large samples are necessary.

AUTHORS' CONTRIBUTION

YL: Writing – original draft, Writing – review & editing. **YG:** Writing – original draft, Writing – review & editing.

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COMMENTARY
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Comment on "Nutritional and hematological factors associated with the progression of Alzheimer's disease: a cohort study"

Chenchen Pan[1,2], Ying Chen[1]*

Dear Editor,

We were pleased to read the high-level paper published by the research group of E. de Gregorio[1]. Their findings revealed that overweight or obese may promote the development of Alzheimer's disease (AD) and may also be the risk factors of dementia. Although this study was of great significance for the prevention and treatment of AD, we believe that there are some problems should be addressed.

First of all, since this prospective cohort study intended to explore the relationship between obesity and the risk of AD, obviously, the subjects should have been divided into two groups: obesity group and healthy group; and then, calculating the frequency of AD between two groups in the following-up. It was clear that the failure of the study was not to set up a control group.

In addition, the sample size of this study was small. There were no detail descriptions of the inclusion and exclusion criteria of AD in the methods section. The authors only compared the biochemistry of the subjects between two years (2011 and 2014). What causes the changes of biochemical? The biochemical index might have been changed with age.

Finally, the general demographic characteristics of the subjects, such as age, gender and occupation should be described. The study aimed to evaluate the relationship between dietary habit and cognitive function; however, intervention trial was not offered in the present study. The measurement of the vitamins intake should have been included in methods section.

AUTHORS' CONTRIBUTIONS

CP: Writing – original draft, Writing – review & editing.
YC: Writing – original draft, Writing – review & editing.

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COMMENTARY
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Comment on "Response to direct-acting antiviral agents in chronic hepatitis C patients with end-stage renal disease: a clinical experience"

Xiaofei Li[1]*, Lianqing Lou[1]

Dear Editor,

We read with great interest the study by Tatar et al.[1] in which they demonstrated that treatment with OBV/PTV/r and DSV with or without RBV resulted in high rates of sustained virologic response in HCV GT1-infected patients with end-stage renal disease. Although this article is interesting, in our opinion, some issues should be addressed.

The authors enrolled 36 patients for investigating in this study, 3 patients were excluded due to death, missed visits, and abandoning treatment. Thirteen patients were infected with genotype 1b, and 15 with genotype 1a. However, in five patients, the subtype of genotype 1 could not be analyzed, so it was considered as genotype 1a. It is not reasonable to define these five people as genotype 1a. It is better to increase the number of enrolling cases or to exclude the data of these 5 patients.

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COMMENTARY
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Comment on"Association between changes in body fat distribution, biochemical profile, time of HIV diagnosis, and antiretroviral treatment in adults living with and without virus infection"

Shuang Wu[1], Xiaofei Li[1]*

Dear Editor,

We read with great interest the study by Soares[1] et al. in which they demonstrated that the negative cholesterol profile was mainly related to antiretroviral treatment time, and was especially associated with time for HIV infection in those with self-reported lipodystrophy. This study offers a new strategy for improving antiretroviral treatment in adults living with and without virus infection. However, some concerns should be raised in my opinion.

To begin with, "Anova" in the statistical analysis section should be "ANOVA", ANOVA is the abbreviation of analysis of variance. Additionally, when ANOVA is used, a post hoc test also is needed. Thus, the author should give a more detailed analysis process, especially which method for post hoc test.

Secondly, this study found that excess weight seems to be directly correlated to higher risks due to the accumulation of fat in the abdominal region. We speculate that gender may be a confounding factor in the present study. Due to gender may affect the association between body fat distribution and antiretroviral treatment in adults, sub-group analysis (men and female) is necessary for Table 2 and Table 3.

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