RAMB

Journal of The Brazilian Medical Association

Volume 67, Number 8
August, 2021

AMB Associação Médica Brasileira

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RAMB
Journal of The Brazilian Medical Association
Volume 67, Number 8, August, 2021
ISSN 0104-4320
ISSN 1806-9282 (On-line)

SECTIONS

LETTERS TO THE EDITOR

POINT OF VIEW

ARTICLES

ORIGINAL ARTICLES

REVIEW ARTICLES

COMMENTARY

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The RAMB, Journal of The Brazilian Medical Association, is an official publication of the Associacao Medica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B1 Capes databases, and licensed by Creative CommonsR.
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LETTER TO THE EDITOR
https://doi.org/10.1590/1806-9282.20210581

COVID-19 in patients treated with intravesical Bacillus Calmette Guerin

Rujittika Mungmunpuntipantip[1]*, Viroj Wiwanitkit[2]

Dear Editor,

We would like to share ideas on the publication "Investigation of the frequency of COVID-19 in patients treated with intravesical BCG". Karabay et al. concluded that "Intravesical BCG administration does not decrease the frequency of COVID-19 infection[1]." Indeed, effect of BCG on COVID-19 is an interesting issue. While some authors show that BCG might be useful, others present totally discordant ideas. A common consideration on any report of the BCG effect on COVID-19 is the confounding factor. Theoretically, by molecular mechanism via tertiary lymphoid structure (TLS) organogenesis[2,3], BCG might be useful. Trained immunity might occur after BCG vaccination. However, it is necessary to allow a period for immune training. From the observation by Karabay et al.[1], it might be interesting to assess time effect. Additionally, many confounding factors can affect the observed frequency of COVID-19[4]. In the report by Karabay et al.[1], the number of subjects are also few. A larger study might give different results.

AUTHORS' CONTRIBUTIONS

RM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **VW:** 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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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 11, 2021. Accepted on July 14, 2021.

LETTER TO THE EDITOR
https://doi.org/10.1590/1806-9282.20210599

Predictors of mortality in patients with abdominal aortic aneurysm

Tamer Turk[1], Muhammed Savran[2], Mesut Engin[1]*

Dear Editor;

We have read with great interest the article by Aksoy and Uysal[1] entitled "A simple risk scoring systems to evaluate the presence of aneurysm and one-year mortality in patients with abdominal aortic aneurysm using CHA2DS2-VASc and ATRIA". First of all, we congratulate the authors for their invaluable contribution to the literature. However, we would like to add some very important factors affecting mortality in patients with abdominal aortic aneurysm (AAA).

In their article, the authors aimed to investigate the effect of two scoring systems on the diagnosis of AAA and mortality in patients diagnosed with AAA. A total of 120 patients were included in the study. Firstly, patients were divided into two groups as those with AAA (n=60) and those without AAA (n=60), and then mortality analysis was performed on patients diagnosed with AAA. Mortality was observed in 20 (33.3%) patients diagnosed with AAA as a result of one-year follow-up. In the multivariate analysis, in addition to a scoring system that was the subject of the study, and high blood glucose levels were determined as an independent predictors of mortality[1]. However, we could not obtain clear data on whether surgical or endovascular treatment was applied to patients with AAA. In the method part, we determined an exclusion criterion such as "need for preoperative resuscitation". Have surgical or endovascular procedures been applied to patients with diagnosis of AAA? If they were operated, how many patients have you performed endovascular procedures?

We agree with the authors about the usability of these scoring systems in diagnosing AAA. Studies have shown that they play a role in the prognosis of cardiovascular diseases[2]. However, we think that the case of whether surgical or endovascular procedures were applied to the patients should be added to the multivariate analysis when performing the mortality analysis. Otherwise, the data obtained may be misleading.

In a recent study involving a large number of patients (38,008 patients), in-hospital mortality was found to be 1.07% in patients who underwent elective endovascular procedures. Also in this study, the overall survival rates were 96.2% at 6 months, 93.5% at 1 year, 88.3% at 2 years, 82.8% at 3 years, 76.2% at 4 years, 69.4% at 5 years, 63.7% at 6 years, 54.4% at 7 years, and 38.8% at 8 years. In addition, approximately 70% of the patients included in the study had an AAA diameter of 50 mm and more[3]. In the study of Aksoy and Uysal, AAA diameters were given as 53.8±7.5 mm versus 53.2±6.8 in patients with a diagnosis of AAA with and without mortality, respectively, and the mortality rate was found to be 33.3% in one-year follow-up[1]. In a meta-analysis including 15,475 patients, the annual rupture rate was found to be a maximum of 8.2% in AAA patients with a diameter of 3–5.4 cm[4].

As a result, it would be useful to discuss whether any intervention was applied while revealing the predictors of one-year mortality in patients with a diagnosis of infrarenal AAA. Knowing the causes of death in patients with a diagnosis of AAA who did not undergo any intervention would be useful in terms of revealing the effects of the risk factors investigated in the article.

AUTHORS' CONTRIBUTIONS

TT: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **MS:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **ME:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 18, 2021. Accepted on June 27, 2021.

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POINT OF VIEW
https://doi.org/10.1590/1806-9282.20210359

Would the STRASS study be an "unbroken" paradigm for retroperitoneal sarcomas?

Samir Abdallah Hanna[1]*, Alice Roxo Nobre de Souza e Silva[1], Tomás Yokoo Teodoro de Souza[1], Felipe Cicci Farinha Restini[1], David Rodrigues Ferreira Neto[1], Letícia Hernandes de Brito[1], Ana Paula Alves Pereira[1], João Luis Fernandes da Silva[2], Maria Thereza Mansur Starling[1,3]

The authors of the study that was recently published in the journal Lancet Oncology[1] deserve praise and compliments for the difficulty in conducting a phase III, open, multicenter, randomized study, particularly in the case of retroperitoneal sarcomas (an uncommon and heterogeneous entity). Since 30 years ago, from a small randomized series[2] exploring the role of intraoperative radiotherapy in retroperitoneal sarcomas, no strong evidence for radiotherapy as a suitable treatment for this disease has been observed. In the medical field, our decisions are usually based on Level I Evidence. As radio-oncologists, however, the following important aspects could be pointed out from this study:

1. The construction of a "composite" primary end point, including local and distant failures, as well as anesthetic and surgical issues (ASA 3 intraoperatively, peritoneal sarcomatosis, incomplete resection and exclusion of patients from the study, early imaging assessment for surgical adequacy) seemed to be audacious and innovative. However, the study was designed to demonstrate a 20% "superiority" in the neoadjuvant radiotherapy arm of this purpose, which may seem too radical, taking into consideration "only" 260 cumulative patients. The achievement of statistical significance was further hampered by the low compliance with the recommended protocol, in which only 65% of patients adequately completed the therapeutic plan. In addition, there was great heterogeneity among the treatment methods, as 26% of patients deviated in their protocols.

Reductions in recurrence can generate benefits in the survival of these patients. With due respect to comparisons between prospective randomized studies and retrospective publications, Nussbaum et al.[3] demonstrated the benefits in survival for neoadjuvant radiotherapy "skipping" recurrence evaluations in patients with retroperitoneal sarcomas by means of National Cancer Database analyses. This required a sample of 563 patients. Perhaps, the authors of STRASS could have kept local recurrence as an end point more directly and clearly related to the objective of the study (locoregional treatments). Moreover, even if the analysis of local recurrences was not envisaged, the local recurrence rate observed by the authors was almost half of that in irradiated patients, thus the need to separate local recurrences as a single end point.

2. The early response evaluation (by means of images at 2 weeks postradiotherapy) for resectability purposes and verification of the RECIST criteria is unclear. As there was no time for a therapeutic response to radiotherapy treatment, the evaluation of resectability should not have been performed at this moment. Moreover, cases presenting lesion enlargement based on RECIST criteria were already characterized as disease progression, not being initially referred to surgery. The response rate is best stipulated by pathological characteristics plus RECIST criteria. This aspect has been previously studied[4,5] particularly in extremity sarcomas (among other neoplasms), where the clinical and pathological response rates are directly correlated with the time between neoadjuvant treatments and surgery, although radiological alterations mentioned above are not sufficient to confirm disease progression in this scenario. After radiotherapy, particularly in the earlier period, significant vasodilatation and inflammation of the irradiated tissue occurs, leading to a possible increase in its volume, thus being

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 30, 2021. Accepted on April 26, 2021.

equivocal to veto the surgical possibility—the curative pillar of the retroperitoneal sarcoma. How did the authors evaluate some patients (15/19) who presented "disease progression," but had been successfully operated on with free margins? Why were these patients excluded from the analysis?

3. Even though it was not planned within the same study (analysis in STRASS 2[6]), it would be worth knowing the effects of systemic therapies in the neoadjuvant setting, including their interactions with radiotherapy. Some drugs have interesting response rates depending on the histological subtype, and exploring this strategy could change the current treatment patterns.

4. The dose of 50 Gy over 5 weeks has been the standard "generic" radiotherapy dose in the neoadjuvant setting, including its adoption in the study by O'Sullivan et al.[7], involving patients with soft-tissue sarcomas of the extremities, primarily analyzed as outcomes of scar complications—not oncological outcomes. Thus, the neoplastic dose employed by the STRASS researchers may be questionable if considered in comparison with this Canadian study. Sarcomas are radioresistant tumors. Would it be possible, when using intensity-modulated radiation therapy (used in 95% of STRASS patients), to use higher doses applied to the tumor? Would it not be worthwhile to apply dose escalation in areas with supposedly greater difficulty of resection, preferably after a multidisciplinary discussion with the surgeons?

5. In view of the difficulty in obtaining a homogeneous sample of various histological subtypes, why did the authors not reduce the range of inclusion of the histological subtype in the study? For example, they could have considered only liposarcomas and leiomyosarcomas. Perhaps, the study design could have been modified according to the less heterogeneous sample (even taking into consideration that most patients were liposarcoma cases). It is important to remember that the main benefit of radiotherapy for patients with retroperitoneal sarcoma is the improvement in the local control of the disease. Such a role becomes even more relevant in patients whose surgical outcome is not ideal, as in cases of resections with compromised margins (R1) or macroscopic residual disease (R2). Thus, the analysis of the results of the subgroups of this study according to the degree of resection is fundamental, and to understand that the selection of the best candidates for surgery may result in the exclusion of those who benefit the most from the local control resulting from radiotherapy. In an interim analysis performed for sensitivity assessment of the study, early local progression was not considered a primary end point for patients who subsequently achieved complete surgical resection. Most patients (75%) had liposarcoma (well-differentiated 33.1%, dedifferentiated 39.5%), whereas leiomyosarcoma accounted for 14.3% of cases. After a median 43-month follow-up, local recurrence-free survival was 60.4% versus 58.7% for the irradiated versus nonirradiated group (p=0.95). After the interim analysis, this end point could be considered only in the liposarcoma subgroup[8].

6. From the methodological point of view, one can question the degree of radiotherapy treatment described in the procedures of the publication. Retroperitoneal sarcomas are usually diagnosed with large volumes, and, in fact, the mean size identified in the study was 16 cm. However, a clinical treatment volume (CTV) of 5–6 cm was stipulated, to which a planning margin (PTV) of 9–12 cm was added, depending on the axis in question. It is important to note that the study does not specify whether there was editing of CTVs according to the risk organs, as well as whether there were dose limits recommended for them. This issue becomes even more relevant when we face high rates of toxicities, especially gastrointestinal and hematological, which may indicate excessive irradiation of the abdominal cavity and bone marrow, respectively. Another important methodological flaw is the fact that the histological grade was not reported in about 25% of the patients.

The search for the best treatment for retroperitoneal sarcomas still keeps us finding the balance based on the best evidence. In our career, we take into consideration the value and reference of the STRASS study, while believing in the benefits of irradiative treatments in retroperitoneal sarcomas. At least in the weekly multidisciplinary sarcoma tumor boards at our institution, we maintain this strategy to treat the patients who come to us. This debate is not over yet.

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SAH: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ARNSS:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **TYTS:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **FCFR:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **DRFN:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original

draft. **LHB:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **APAP:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **JLFS:** Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **MTMS:** 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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POINT OF VIEW
https://doi.org/10.1590/1806-9282.20210606

A comment on psychological distress and women's hair loss related to the COVID-19 pandemic

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The COVID-19 pandemic has brought many uncertainties as to its origins and future directions[1]. While scientists of different specialties focus on new strategies on how to minimize physical sequels related to COVID-19 infection, many patients remain vulnerable to having their psychological state neglected.

In 2020, inevitable doubts have emerged, as the pandemic developed, impacting the patients' quality-of-life not just by the restrictions imposed by the governmental efforts to halt virus spread worldwide, but also by the unpredictable behaviour of COVID-19, such as its infectivity, pathogenicity, virulence, lethality, and immunogenicity[2].

From that timepoint onwards, as social contacts reduced and due to the patients' mourning for their family members death, health practitioners were invited to look at their patients from a more comprehensive perspective, caring for both physical and psychological aspects.

The study of early psychological aspects during the pandemic, especially for women, has been published by many authors, generating interesting data. The first paper reporting the psychological impact of the COVID-19 outbreak came from Spain, where González-Sanguino and colleagues conducted a survey with 3,480 people and found that female patients were more likely to show greater depressive symptoms and anxiety[3]. Accordingly, Choi et al. evaluated the level of depression and anxiety in 500 patients from Hong Kong, where 25.4% of the respondents reported that their mental health had deteriorated since the COVID-19 pandemic began[4], reinforcing the importance of González-Sanguino's work.

It is true that long before the pandemic, hair loss was already considered a major source of suffering for female patients requiring dermatological assistance. In accordance with Trüeb, as stated in his book "The difficult hair loss patient", hair loss pictures one of the most genuine concerns presented by women of several ages in dermatology, irrespective of other concomitant skin conditions[5]. Nonetheless, hair-loss related complaints are still prone to be neglected in clinical practice.

The importance of hair for women's psychological status is gradually attracting attention from different specialties, and patients under extremely stressful situations have shown concern for their hair, even when facing life-threatening conditions. For instance, in 2017, Villar et al. prospectively evaluated 339 patients at the Breast Cancer Unit of the University Hospital Complex of A Coruña (Spain) who had been undergoing treatment for breast cancer from December 2013 to February 2015[6]. Hair loss was cited by the patients as one of the most disturbing consequences of chemotherapy during the whole process[6].

Although it is not known yet the impact of associated hair-loss related stress and pandemic-related anxiety on women's quality-of-life, the number of patients complaining of hair problems has recently increased, since several types of alopecia can be worsened by physical and psychological distress[1,7,8]. Accordingly, the number of reports on alopecia areata and telogen effluvium, either aggravated or induced by COVID-19 infection, constantly rises in the literature[7,8].

It is possible that the severity of the hair shed correlates with the severity of COVID-19 infection[1]. Patients with high fever

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 22, 2021. Accepted on June 27, 2021.

seem to experience more hair loss than asymptomatic ones[1]. It is interesting to notice that post COVID-19 telogen effluvium develops earlier than expected for general febrile conditions and can be rather intense, bringing extra source of anxiety for the affected women[1]. Also, alopecia areata, a common dermatological source of distress for many patients worldwide, seem to have increased during the pandemic too, though it is not clear whether the virus itself is implicated in the pathogenesis or if the recent cases only reflect the new levels of psychological stress peculiarly seen during the pandemic.

In fact, it is not only because COVID-19 infection has eventually been proven that every hair problem can be regarded as a mere consequence. It is likely to think that patients who were receiving regular treatment for any given alopecia might have gotten worse, since lack of accessibility to hospitals and restrictions to medications has built barriers to proper assistance.

Finally, as the pandemic develops and COVID-19 complications appear, it becomes difficult for the attending physician to wisely deal with every patient's need. As previously exposed, the new scenario favours the appearance of mental and physical illness, urging health practitioners to look for a multidisciplinary approach. As for many other medical areas, specialized care is also needed when evaluating patients complaining of hair loss.

AUTHORS' CONTRIBUTIONS

HDR: Conceptualization, Formal analysis, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **GAI:** Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **BPBDL:** Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **RVAM:** Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SLMD:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MFRGD:** Data curation, Formal analysis, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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POINT OF VIEW
https://doi.org/10.1590/1806-9282.20200974

Autonomy versus paternalism: will of the person or will of the collective?

Trajano Sardenberg[1]*, Reinaldo Ayer de Oliveira[2]

Spanish doctors Diego Gracia[1] and Diego Capilla[2] state, in separate texts, the gradual collapse of paternalism within doctor-patient relationships, which is, nowadays, called clinical relationships, involving several health professionals and the patient. In the 1960s, when values related to private management of the body, sexuality, life, and death begin to assume a fundamental role in people´s life who demand respect for their wills and wishes, the autonomy or better, the respect to autonomy emerges from books and theory into a clinical relationship. Slow transformations, putting paternalism outside making autonomy the center of a clinical relationship, suffer an expressive increase in speed. The book by Beauchamp and Childress "Principles of biomedical ethics"[3], 1979, establishes the principles of respect for autonomy, of non-maleficence, of beneficence and justice as marks for the practice and resolution of ethical conflicts and dilemmas within a clinical relationship, despite stating that there is no hierarchy among them, it reinforces denial of paternalism[4].

In the real world, theory and practice are different. A patient with terminal and severe cancer who refuses surgery which causes more suffering and requests pain and well-being care represents a distressful situation yet easy to do so and which respects the patient´s will. But, on the other hand, what about a patient with breast cancer who refuses conventional treatment and requires only homeopathy and acupuncture? Doubtlessly, the doctor´s respect to a patient´s autonomy, in such a case, is almost impossible, unless the doctor stops being human and acts only as an insensitive machine. When cases involve children, doctor´s confusion and suffering are even worse. How to face parents who refuse treatments, with good curing chances, for their children? In such cases, society must act, within the law as well as in a convincing way.

Respect for people´s autonomy in society cannot be total. If this were to be, it would be the chaos of a society without the limits of the law. The free will of Stuart Mill[5], in the 19th century, can only be practiced in a democratic and mainly responsible society. Within this context, several countries enact laws that obliges people to be careful. Seat belts in cars, as well as helmets for motorcycles, are classical examples. In countries where health services attend all people with no individual charge, such aspect is even more important. It´s easy to understand. A person exercises his/her free will and does not wear a helmet on the motorcycle; suffers an accident with severe skull trauma and has all the treatment and support is paid by society. It is free will with no responsibility and lots of selfishness, followed by the thought that "I do whatever I want and if there is a problem the State takes care of everything including my family". Another situation of free will without responsibility and with lots of selfishness and opportunism is observed in people who live in large urban societies who do not take vaccines and do not vaccinate their children and rely on herd immunity, thinking that "others are at risk of vaccines, even if it´s minimal, and my family and I are immunized. According to Battin et. al. in "The patient as victim and vector – ethics and infectious disease"[6], 2009, therefore a decade before the beginning of the COVID-19 pandemic, discuss the limits of bioethics mainly concerning the principle of autonomy in severe infectious disease with rapid and wide dissemination.

Respecting the will of patients, of people, not only people but also social and group cultures within a democratic society, is not an easy task (within a totalitarian society people´s autonomy does not exist), especially when such individual wills or even partially collective, conflict with rights and wills of the majority. Considering people´s autonomy and collective interests is

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on November 08, 2020. Accepted on January 12, 2021.

a gigantic goodwill task as well as negotiation. One of the difficulties is to establish who is going to speak up for the collective interest. Laws, a special kind of collective, isolated and unconvinced are ineffective in a democratic society. The guidelines and rules from government officials forcing the use of masks and prohibiting agglomerations during the current pandemic of the new coronavirus have not been followed by a large part of the population and the State is unable to apply punitive actions provided by law.

Kwame A. Appiah in his book "*O Código de honra: como ocorrem as revoluções morais*"[7] (The honor code – how moral revolutions happen) explains the role of active intellectuals in the moral debate for promoting changes in customs, analyzing the end of duel practices in Europe, the aesthetic of small feet in Chinese women as well as African slavery in Americas. Appiah mentions that in China the small and deformed women's feet turned from aesthetic beauty and pride to shame and ugliness. Recently, intense action by international organizations, associated with intellectuals as the writer Mia Couto and local activists such as Theresa Kachindamoto, Mozambique proclaimed a law prohibiting marriage between girls and adults[8,9]. Due to the strength of the arguments, exhaustively explained, those behaviors considered normal and of high moral and aesthetic value are now considered by the majority of society as incorrect, coarse, and immoral. In Brazil, the campaign against smoking is an example of success, combining extensive scientific persuasion about the harmful effects of tobacco, laws which restrict its use, bans on advertising and strong economic tightening through high taxes. Perhaps the most important thing has been the emphatic message that smoking is no longer glamourous, making up a moral and aesthetic victory.

The ethics of paternalism, having someone determining what has to be done by patients and all people, disrespecting autonomy has no place in free democratic societies. Social experiences of such practice in recent human history when a group of people on behalf of the majority established what was right and wrong only succeded in totalitarian societies thus causing loss of freedom and enormous human suffering. The flexibility of autonomy should be the exception and the prevalence of collective interest must be sought through explicit arguments in society with scientific and especially moral, ethics, and spiritual approaches. The laws which may arise from this democratic process will certainly be closer to the wills of the people in our society.

AUTHORS' CONTRIBUTIONS

TS: Conceptualization, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **RAO:** Conceptualization, Formal Analysis, Investigation, Writing – original draft.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210087

Structural validity of the Japanese Orthopedic Association back pain evaluation questionnaire in individuals with chronic low back pain

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SUMMARY

OBJECTIVE: The main aim of this study was to evaluate the structural validity of the Brazilian version of the Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ).

METHODS: Individuals with chronic low back pain were included. The data collection of the study occurred by means of online platform. Confirmatory factor analysis was performed. The theoretical version proposed for the JOABPEQ with five domains was tested. The following indices were considered to verify the fit of the model: comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and chi-square/degrees of freedom (DF).

RESULTS: The final sample consisted of 175 volunteers, mostly women (68%), adults (mean age of 28.98 years), lean (mean body mass index of 25 kg/m^2), with incomplete higher education, single, with mean of pain chronicity of 61.50 months and mean of pain intensity of 6.78 points on the Numeric Pain Scale. Regarding the structure of the JOABPEQ, the original version with five domains was adequate: chi-square/DF=1.52, CFI=0.954, TLI=0.948, and RMSEA=0.055. The factorial load ranges from 0.41 to 0.90.

CONCLUSIONS: This study confirms the structure of JOABPEQ with 5 domains (low back pain, lumbar function, walking ability, social life function, and mental health) and 25 items in individuals with chronic low back pain.

KEYWORDS: Chronic low back pain. Questionnaire. Reproducibility of results.

INTRODUCTION

Chronic low back pain is one of the main causes of musculoskeletal disability presented by the world population, affecting mainly the adult population, with clinical diagnosis centered on patient reports, and the majority being nonspecific and with a multifactorial etiology[1]. According to the study by Carregaro et al.,[2] in the Brazilian population, health cost and loss of productivity due to low back pain are substantial, with men having higher levels of disability compared to women.

Therefore, it is extremely important to have accessible and low-cost instruments to measure the disability of these individuals, such as questionnaires, which must have adequate psychometric properties and precise statistical values to be used[3-5]. Usually, the most evaluated psychometric properties are reliability, content

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: this work was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; finance code 001).
Received on May 01, 2021. Accepted on July 13, 2021.

validity, responsiveness, and cross-cultural adaptation[3]. For the Brazilian population, previous studies support the clinical use of the Roland–Morris Disability Questionnaire (RMDQ)[6], Bournemouth Questionnaire[7], STarT Back Screening Tool[8], and Oswestry Disability Index[9]. Another interesting tool is the Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ), developed by Fukui et al.[10]. It is a questionnaire centered on the patient's self-report and encompasses five domains: low back pain, lumbar function, walking ability, social life function, and mental health.

The original version of the JOABPEQ has adequate reliability (kappa ≥0.48)[11,12]. In addition, this questionnaire has already been adapted and validated for Chinese[13], Turkish[14], Korean[15], Thai[16], Iranian[17], and Arabic[18] languages. In Brazil, the questionnaire was translated and cross-culturally adapted for the Brazilian population by Poletto et at.,[19] with good reliability (Cronbach's alpha ≥0.90) and construct validity (magnitude of the significant correlations with domains of the Medical Outcomes Study 36-Item Short Form Survey and Oswestry Disability Index, r=0.22–0.79).

However, there is no study in the literature that proposed to evaluate the structural validity of the JOABPEQ. This psychometric property is a specific statistical procedure with the objective of verifying whether the domains and items originally proposed in the creation of the questionnaire are supported statistically[3].

The objective of this study was to evaluate the structural validity of the Brazilian version of the JOABPEQ in individuals with chronic low back pain. The hypothesis of this study is that the originally proposed structure of JOABPEQ with five domains is supported by factor analysis, according to the previous study[12]. In the scientific literature, only the study conducted by Fukui et al.[12] analyzed the internal structure of JOABPEQ. The clinical relevance of the present study is to ensure that the JOABPEQ measures what it proposes to measure, giving a clinimetric basis for the use of this questionnaire by clinical professionals and researchers.

METHODS

Study design

This study of structural validity of a questionnaire was carried out according to the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN)[3]. The data collection of the study occurred by means of online platform.

The study procedures were approved by the Research Ethics Committee of the Universidade Federal do Maranhão (opinion number 14783219.2.0000.5087). The volunteer recruitment took place in the university community, by means of dissemination, with physiotherapists and physical education professionals working in the rehabilitation of patients with chronic low back pain, and dissemination on social media. All volunteers included in the study validated their participation by signing informed consent forms.

Participants

The sample size calculation was based on COSMIN: seven times the number of items of the questionnaire[3]. In these terms, considering the JOABPEQ with 25 items, the present study was composed of 175 individuals with chronic low back pain.

We included participants of both sexes between the ages of 18 and 60 years, with pain report at least 3 months and with minimum pain intensity of 3 points on the Numeric Pain Scale (NPS)[20]. The following exclusion criteria were adopted: unlettered; history of trauma, fractures, or acute spinal injuries; spine surgery; use of painkillers in the past 7 days; physiotherapeutic treatment for low back pain in the previous months; or the presence of other chronic pain.

Assessments

The online form featured an anamnesis with questions related to personal, sociodemographic, and anthropometric aspects to characterize the sample. In addition, the NPS, RMDQ, and JOABPEQ were answered.

The NPS is a simple and easy-to-measure scale that consists of a sequence of numbers, ranging from 0 to 10, in which a value of 0 represents "no pain" and a value of 10 represents "worst pain imaginable." The volunteers graduated their pain based on these parameters. Pain intensity was assessed with the individual at rest and after active movements (flexion, extension, inclinations, and rotations) of the lumbar spine. This scale was adapted and validated for Portuguese by Ferreira-Valente et al.[21]

The RMDQ is a questionnaire that has been validated and adapted by Nusbaum et al.[6] for the Brazilian population. This is an instrument that assesses disability related to low back pain and consists of 24 items that describe daily activities, in which each response is quantified from 0 to 1 (total score varying 0–24 points). The higher the total score, the greater the level of disability.

The JOABPEQ has been translated, adapted to Brazilian Portuguese, and validated by Poletto et al.[19] The questionnaire consists of 25 items covering issues related to low back pain, lumbar function, walking ability, social life function, and mental health. The subscale scores range from 0 to 100, and the higher the score, the better the individual's condition. Based on the study by Fukui et al.,[12] formulas were defined to calculate the score for each domain, as described in Table 1.

Table 1. Formulas for calculating the score for each Japanese Orthopedic Association Back Pain Evaluation Questionnaire domain.

Domain	Formula
Low back pain	('Q1–1'×20+'Q1–2'×20+'Q1–3'×20+'Q1–4'×10–70)×100÷70
Lumbar function	('Q2–1'×10+'Q2–2'×10+'Q2–3'×20+'Q2–4'×10+'Q2–5'×30+'Q2–6'×20–100)×100÷120
Walking ability	('Q3–1'×30+'Q3–2'×20+'Q3–3'×10+'Q3–4'×10+'Q3–5'×30–100)×100÷140
Social life function	('Q4–1'×2+'Q4–2'×4+'Q4–3'×6–22)×100÷74
Mental health	('Q5–1'×3+'Q–2'×4+'Q5–3'×6+'Q5–4'×6+'Q5–5'×3+'Q5–6'×3+'Q5–7'×3–28)×100÷103

Q1: Questions (1–4) related to the low back pain domain; Q2: Questions (1–6) related to the lumbar function domain; Q3: Questions (1–5) related to the walking ability domain; Q4: Questions (1–3) related to the social life function domain; Q5: Questions (1–7) related to the mental health domain.

Statistical analysis

Confirmatory factor analysis (CFA) was performed using R Studio software (Boston, MA, USA), using the lavaan and semPlot packages. The analysis was performed based on a polychoric covariance matrix and a robust diagonally weighted least squares (RDWLS) extraction method, given that the JOABPEQ score has an ordinal categorical nature. The theoretical version proposed for JOABPEQ with five domains was tested[19]. The following indices were considered to verify the fit of the model: comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and chi-square/degrees of freedom (DF). As an acceptability parameter of the model, CFI and TLI >0.90, RMSEA <0.08, and chi-square/DF <3 were considered[22].

RESULTS

In this study, 205 individuals with chronic low back pain participated. Of these, 22 were excluded for having a score below 3 on the NPS, 4 for having a traumatic injury to the spine, and 1 for having undergone a surgical procedure. Thus, the final sample consisted of 175 volunteers, mostly women (68%), adults (mean age of 28.98 years), lean (mean body mass index of 25 kg/m^2) with incomplete higher education, single, with mean chronicity of 61.50 months and mean of pain intensity of 6.78 points on the NPS. Table 2 presents the other personal characteristics of the study sample.

Regarding the structure of the JOABPEQ, the original version with five domains was adequate based on the analysis of the fit indices generated from the CFA, as provided in Table 3. In addition, Table 4 indicates the covariance between the domains of the JOABPEQ, ranging from 0.471 to 0.826, and Figure 1 shows the factorial loads of each item in their respective domains, ranging from 0.41 to 0.90.

Table 2. Characterization of the study sample with presentation of values in mean and standard deviation or number and percentage.

Variables	Participants (n=175)
Sex	
Female	119 (68%)
Male	56 (32%)
Marital status	
Single	111 (63.42%)
Married	57 (32.57%)
Widower	2 (1.14%)
Divorced	5 (2.85%)
Educational level	
Complete primary education	1 (0.57%)
Incomplete primary education	2 (1.14%)
Complete secondary education	27 (15.42%)
Incomplete secondary education	4 (2.28%)
Complete higher education	34 (19.42%)
Incomplete higher education	56 (32%)
Complete postgraduate	39 (22.28%)
Incomplete postgraduate	12 (6.85%)
Age (years)	28.98 (9.32)
Weight (kg)	69.89 (15.82)
Height (cm)	1.66 (0.09)
BMI (kg/m^2)	25 (4.55)
Chronicity (months)	61.50 (54.53)
NPS (score, 0–10)	6.78 (1.93)
RMDQ (score, 0–24)	4.80 (4.99)
JOABPEQ (score, 0–100)	
Low back pain	30.50 (24.20)
Lumbar function	69.30 (27.90)
Walking ability	75.90 (29.10)
Social life function	20.80 (13.07)
Mental health	54.40 (19.17)

BMI: Body Mass Index; NPS: Numerical Pain Scale; RMDQ: Roland-Morris Disability Questionnaire; JOABPEQ: Japanese Orthopedic Association Back Pain Evaluation Questionnaire.

Table 3. Fit indexes of the model of the Japanese Orthopedic Association Back Pain Evaluation Questionnaire with five domains in the studied sample (n=175).

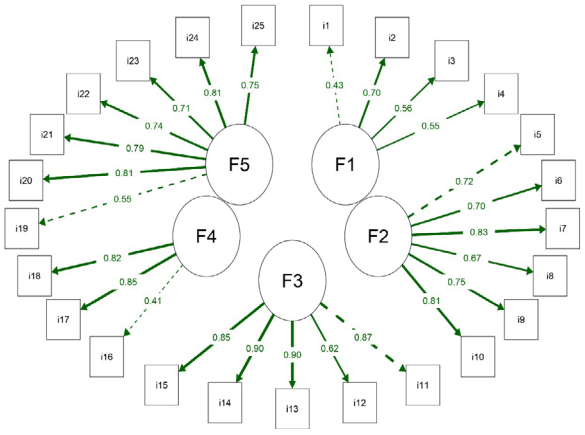
Chi-square	DF	Chi-square/DF	CFI	TLI	RMSEA (90%CI)
404.269	265	1.52	0.954	0.948	0.055 (0.044–0.066)

DF: degrees of freedom; CFI: comparative fit index; TLI: Tucker-Lewis Index; RMSEA: root mean square error of approximation.

Table 4. Covariance between Japanese Orthopedic Association Back Pain Evaluation Questionnaire domains.

Domains	F1	F2	F3	F4	F5
F1	1	-	-	-	-
F2	0.665	1	-	-	-
F3	0.730	0.826	1	-	-
F4	0.764	0.823	0.756	1	-
F5	0.719	0.471	0.604	0.596	1

F1: Low back pain; F2: Lumbar function; F3: Walking ability; F4: Social life function; F5: Mental health.



F1: Low back pain; F2: Lumbar function; F3: Walking ability; F4: Social life function; F5: Mental health.

Figure 1. Path diagram with the factorial loads for each Japanese Orthopedic Association Back Pain Evaluation Questionnaire domain.

DISCUSSION

The results of the present study show that the JOABPEQ is a questionnaire that has a structure of five domains and 25 items. Only the study conducted by Fukui et al.[12] analyzed the internal structure of JOABPEQ by means of exploratory factor analysis using the maximum likelihood extraction method. The factor load varied from 0.26 to 0.81 and five domains were identified.

Despite the statistical differences between the studies (our study used CFA with the RDWLS extraction method because it is more suitable for ordinal categorical variables), the structure we found is the same as the structure with five domains proposed by Fukui et al.[12]. The factorial loads of our study were relatively higher, varying between 0.41 and 0.90.

When comparing the characteristics of the sample, our study was composed mostly women, with mean age of 28.98 years, mean chronicity of 61.50 months, and mean of pain intensity of 6.78 points on the NPS. The sample of the study conducted by Fukui et al.[12] was composed mostly men, with mean age of 50.7 years. This previous study did not assess the pain intensity, but classified the majority of patients with moderate severity of low back pain by means of qualitative analysis. Despite the differences between the studies, we considered our sample representative due to the eligibility criteria used here and the difference presented can be justified by the use of an online platform for data collection (the diffusion of technology is greater among younger people).

In the Brazilian Portuguese language, the study by Poletto et al.[19] performed translation and cross-cultural adaptation and evaluated the reliability and construct validity of the JOABPEQ. Despite this scientific initiative, it should be noted that no study has verified the structural validity of the JOABPEQ in the Brazilian population, an analysis that is a way of ensuring that the internal structure of the questionnaires (items and domains) is adequately based on rigorous statistical procedures, such as factor analysis[3,23].

In relation to other validations of the JOABPEQ, the Arabic version[18] assessed the instrument's internal consistency with a Cronbach's alpha value of 0.87, and, in addition, convergent validity was performed, which was confirmed with a correlation coefficient >0.4 for each item. Furthermore, an Iranian study[24] identified satisfactory results for internal consistency (Cronbach's alpha ≥0.71) and, as in the Arab study, convergent validity (r≥0.48) was also achieved, obtaining satisfactory results, suggesting that the items had a substantial correlation with the subscale it represents.

Our study differs from the methodology used in the validation of the JOABPEQ for the Arab and Iranian populations, given that our study used CFA, a more robust and refined method[25] than the simple correlation between the score of the items and the subscales.

In addition, cross-cultural adaptation of the JOABPEQ in other languages investigated the reliability and construct validity, as in the case of the versions in Thai[16], Korean[15], Chinese,[13] and Turkish[26]. We emphasized again that none of these studies

analyzed the internal structure of the questionnaire, as recommended by a robust international guideline[3,23].

The present study has some limitations. Data collection was carried out online due to the COVID-19 pandemic. In this way, we did not conduct a face-to-face clinical evaluation with the participants, and the eligibility criteria were applied based only on the participant's self-report.

CONCLUSION

This study confirms the structure of the JOABPEQ with five domains (low back pain, low back function, walking, social life function, and mental health) and 25 items in individuals with chronic low back pain.

AUTHORS' CONTRIBUTIONS

JSP: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **APS:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **GGCA:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **LPM:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **FOP:** 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.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210243

Association between SYNTAX II Score and late saphenous vein graft failure in patients undergoing isolated coronary artery bypass graft surgery

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SUMMARY

OBJECTIVE: Coronary artery bypass graft (CABG) surgery is a well-established treatment modality for patients with multivessel coronary artery disease (CAD). Syntax II Score has been established as novel scoring system with better prediction of postprocedural outcomes. This study aimed to investigate the prognostic value of SYNTAX II Score for predicting late saphenous vein graft (SVG) failure in patients undergoing isolated CABG.

METHODS: The records of 1,875 consecutive patients who underwent isolated CABG with at least one SVG were investigated. Those who underwent coronary angiography and SVGs angiography at least 1 year after the CABG were included. Patients were divided into two groups based on the presence or absence of SVG failure. For each group, predictors of late SVG failure and subsequent clinical outcomes were analyzed.

RESULTS: According to this study, the presence of hypertension, higher rates of repeat revascularization, and higher SYNTAX II Scores were found to be independent predictors of late SVG failure. In addition, the prognostic value of SYNTAX II Score was found to be significantly higher than anatomical SYNTAX Score in terms of predicting late SVG failure and major adverse cardiovascular and cerebrovascular event.

CONCLUSIONS: There was a strong association between SYNTAX II Score and late SVG failure in patients undergoing isolated CABG.

KEYWORDS: Late saphenous vein graft failure. SYNTAX II Score.

INTRODUCTION

Saphenous vein grafts (SVGs) are widely used venous conduits for coronary artery bypass graft (CABG) surgery. However, long-term surgical success and subsequent clinical benefits following CABG largely depend on graft patency[1-4]. The rates of SVG failure during the first 12 to 18 months following CABG have been reported to reach approximately 25% and the patency of grafts progressively decreased following years[5,6]. Due to adverse cardiac events associated with SVG failure, preventing graft failure is of utmost importance[7].

SYNTAX scoring system was established with the intent of determining whether the percutaneous coronary intervention (PCI) or CABG was preferable in patients with coronary artery disease (CAD) requiring revascularization[8]. Thereafter, SYNTAX II scoring system has been established by integrating anatomical features and clinical characteristics of patients with the intent of achieving better prediction of postprocedural outcomes[9].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 22, 2021. Accepted on July 18, 2021.

Although SYNTAX II provides a more accurate and individualized estimate of postprocedural outcomes, its predictive value for the occurrence of late SVG failure is inconclusive.

In this study, we aimed to investigate the prognostic value of SYNTAX II Score for predicting late SVG failure and its association with subsequent clinical outcomes in patients undergoing isolated CABG.

METHODS

Study design

In this retrospective study, subjects were selected from the 1,875 patients with multivessel CAD who underwent isolated CABG with at least one SVG between 2009 and 2011. Those who later underwent subsequent coronary angiography and SVG angiography between January 2010 and January 2020 due to stable ischemic findings detected by noninvasive imaging modalities including positive cardiovascular exercise stress testing or myocardial perfusion defects were included in the study. Demographic and clinical characteristics of patients and the indication for the procedure were retrospectively analyzed. Patients who underwent coronary angiography and SVG angiography at least 1 year after the CABG were included and those who did not meet this criterion were excluded. In addition, patients undergoing emergent CABG or concomitant valve surgery, patients with a prior history of severe valvular disease, congenital heart disease, severe organ dysfunction including liver or kidney failure, malignancy, lack of regular follow-up, and those nonadherent to their medical treatment following surgery were excluded. After exclusion criteria had been applied, a total of 280 patients were enrolled in the present study (Figure 1). According to our study, patients were divided into two groups based on the presence or absence of late SVG failure. The obtained data pool was statistically analyzed. Informed consent was obtained from all patients in accordance with a protocol approved by the Ethics Committee of Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (approval number: 2020/57, dated August 18, 2020).

Data collection

The demographic data, baseline cardiovascular risk factors, clinical features, and laboratory values were obtained from patient files and hospital records. Routine blood tests were performed to assess complete blood count, liver and kidney functions, and lipid profile. Regarding follow-up parameters, major adverse cardiovascular and cerebrovascular events (MACCEs) were recorded. In addition, anatomical-based SYNTAX Score and novel SYNTAX Score II were recorded using the online calculator (www.syntaxscore.com)[9].

Assessment of coronary angiograms

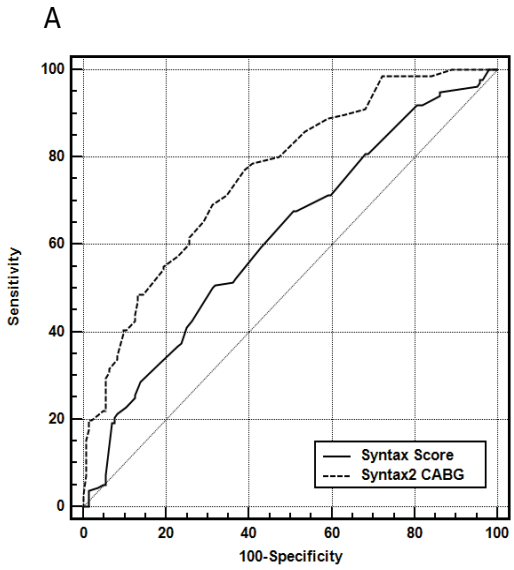
All angiograms and interventions were performed by experienced operators using standard methods and through either femoral or radial access. The left internal mammary artery (LIMA) and each aortic anastomosis were selectively injected. An aortic root angiogram was performed if the status of the SVG could not be determined by graft or stump injection. All angiograms were interpreted by the consensus of two interventional cardiologists blinded to the patients' clinical and laboratory data. A graft was described as failed if it had 70% or more stenosis or was completely occluded. If a graft had less than 70% stenosis and the whole course of the graft was visualized, it was described as patent. In sequential vein grafts, each segment was analyzed as a separate graft. Intraobserver and interobserver coefficients of variation [standard deviation (SD) of the differences between two observations divided by the mean value and expressed as a percent] were found to be 1.1% and 1.9%, respectively.

Statistical analysis

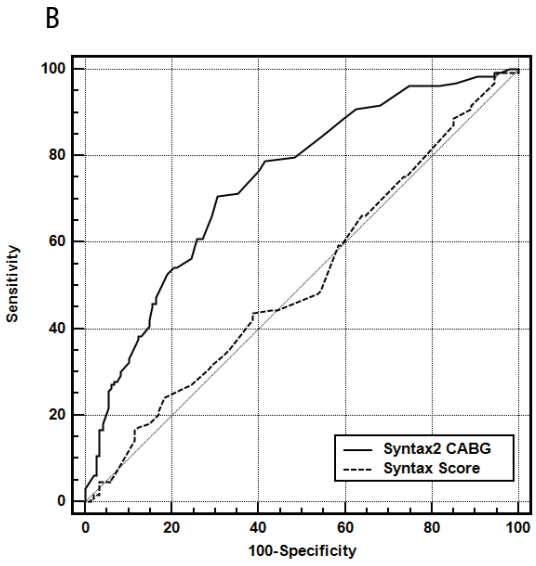
Data were analyzed with the NCSS (Number Cruncher Statistical System) 2007 statistical software (Utah, USA) pocket program. In this study, data are expressed as mean±SD for continuous variables and as counts and percentages for categorical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the distribution of continuous variables. The χ^2 test and Fisher's exact test were used to analyze categorical variables. The Student's *t*-test was used for continuous variables with normal distribution and the values were presented as mean±SD. Comparison of intergroup continuous variables without normal distribution was analyzed using Mann-Whitney *U*-test. A $p<0.05$ was considered to indicate statistical significance. Logistic regression analysis was used to assess the predictors of late graft failure. Variables with $p<0.05$ by univariate analysis were included in the multivariate logistic regression analysis model and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. All statistical tests were two-sided, and the level of significance was set at $p<0.05$.

RESULTS

Of the 1,875 patients initially screened, a total of 280 patients were included in the study. Based on our data, 136 patients had at least one late SVG failure (study group), while 144 patients had patent SVG (control group). The patient characteristics are



Receiver operating characteristic analysis for predicting late saphenous vein graft failure



Receiver operating characteristic analysis for predicting major adverse cardiovascular and cerebrovascular events

681 patients were excluded from the study

102 patients who underwent coronary angiography during the first year following CABG
239 patients who underwent emergent CABG
112 patients who underwent concomitant valve surgery
98 patients with a prior history of severe organ dysfunction
39 patients with a prior history of congenital heart disease
91 patients with a prior history of malignancy

Initially 1,194 patients were enrolled

451 patients with late SVG failure (+)

743 patients with late SVG failure (–)

315 patients excluded from the study

164 patients failed to appear for more than 1 visit
45 patients excluded due to inadequate hospital recordings
106 patients excluded due to treatment discontinuation

599 patients excluded from the study

309 patients failed to appear for more than 1 visit
98 patients excluded due to inadequate hospital recordings
192 patients excluded due to treatment discontinuation

136 patients (SVG failure (+) group)

144 patients (SVG failure (–) group)

CABG: coronary artery bypass grafting; SVG: saphenous vein graft.

Figure 1. 1,875 patients undergoing coronary artery bypass grafting with a diagnosis of multivessel coronary artyery disease.

summarized in Table 1. Both groups were similar in terms of demographic and clinical characteristics. On the other hand, history of hypertension (HT) and diabetes mellitus (DM) was significantly higher in patients with late SVG failure (+) compared to patients with late SVG failure (-), (96.32 versus 73.61%; 61.76 versus 44.44%, p<0.05). Baseline laboratory values were also compared between the two groups. However, serum uric acid level (5.87±1.98 mg/dL versus 5.02±1.52 mg/dL, p<0.05), neutrophil count (5.54±1.39×10^3/mm^3 versus 4.90±1.33×10^3/mm^3, p<0.05), and creatinine level (1.05±0.36 mg/dL versus 0.91±0.23 mg/dL, p<0.05) were significantly higher in patients with late SVGs failure (-) compared to patients with late SVG failure (-). In addition, neutrophil-to-lymphocyte ratio was significantly higher in patients with late SVG failure (+) compared to patients with late SVG failure (-) (2.92±1.38 versus 2.40±1.23, p<0.05). Regarding echocardiographic measurements, patients with late SVG failure (+) had a lower estimated preprocedural left ventricular ejection fraction (LVEF) compared to those with late SVG failure (-), (47.74±11.17 versus 54.9±8.55, p<0.05).

Table 1. Baseline characteristics of patients compared between groups.

		SVG Failure (-) n:144	SVG Failure (+) n:136	p
Age		58.52±8.1	60.24±7.96	0.074
Sex n (%)	Female	25 (17.36)	35 (25.74)	0.088
	Male	119 (82.64)	101 (74.26)	
Smoking history n (%)		74 (51.39)	85 (62.50)	0.061
DM (n/%)		64 (44.44)	84 (61.76)	0.004
HT n (%)		106 (73.61)	131 (96.32)	0.0001
Previous MI n (%)		71 (49.31)	69 (50.74)	0.881
Previous PCI n (%)		64 (44.44)	56 (41.18)	0.581
Syntax II score		25.52±9.62	36.00±10.83	0.0001
Syntax score		27.89±5.74	30.17±5.91	0.001
LVEF (%)		54.9±8.55	47.74±11.17	0.0001
Total cholesterol (mg/dL)		201.06±52.92	207.49±65.26	0.366
HDL (mg/dL)		39.63±12.92	38.26±10.32	0.330
LDL (mg/dL)		130.55±42.48	131.54±42.42	0.846
Triglyceride (mg/dL)		192.87±91.17	209.61±115.35	0.178
Glucose (mg/dL)		137.17±56.44	143.07±64.25	0.415
HbA1c (%)		6.8±1.68	7.18±2.08	0.099
Uric acid (mg/dL)		5.02±1.52	5.87±1.98	0.003
Creatinine (mg/dL)		0.91±0.23	1.05±0.36	0.0001
eGFR (CKD-EPI)		99.73±23.46	82.57±27.71	0.0001
WBC (10^3/mm^3)		9.03±2.69	8.79±2.64	0.452
Hemoglobin (g/dL)		13.58±1.60	13.66±1.74	0.701
Platelet (10^3/mm^3)		242.97±68.21	257.34±66.47	0.079
Neutrophil (10^3/mm^3)		4.90±1.33	5.54±1.39	0.0001
Lymphocyte (10^3/mm^3)		2.26±0.65	2.25±1.74	0.966
NLR		2.40±1.23	2.92±1.38	0.001
Number of grafts		3.19±0.8	3.35±0.8	0.101

SVG: saphenous vein graft; DM: diabetes mellitus; HT: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; EPI: chronic kidney disease epidemiology collaboration; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio.

Results of follow-up parameters are summarized in Table 2. The mean follow-up time for our study was 101.9±8.22 months. The mean length of intensive care unit stay and the mean length of hospital stay following surgery were compared between the two groups (p>0.05). According to our data, incidence of non-fatal myocardial infarction and repeat revascularization were significantly higher in patients with late SVG failure (+) compared to patients with late SVG failure (-) (38.24 versus 9.03%; 41.18 versus 5.56%, p<0.05). Of the whole cohort, MACCEs were significantly higher in patients with late SVG failure (+) compared to patients with late SVG failure (-) (66.91 versus 29.17%, p<0.05).

Regarding assessment of coronary angiograms, both groups had higher rates of LIMA grafts (96.32 versus 95.14%). According to our study, the rate of LAD-LIMA, DL-saphenous, IM-saphenous, CX-OM-saphenous, RCA-saphenous, RCA PDA SVG, and RCA PL SVG were compared between the two groups (p>0.05) (Table 2).

Table 2. Follow-up and angiographical details of patients compared between groups.

	Graft failure (–) n:144	Graft failure (+) n:136	p
Mean ICU stay after CABG (day)	1.09±0.49	1.2±0.82	0.345
Mean hospital stay after CABG (day)	8.86±4.23	8.99±4.82	0.252
Mean follow up time (month)	100.31±8.04	103.49±8.41	0.001
Postprocedural CVA n (%)	7 (4.86)	13 (9.56)	0.127
Postprocedural PAF n (%)	39 (27.08)	45 (33.09)	0.273
Peripheral intervention n (%)	11 (7.64)	16 (11.76)	0.242
Repeat revascularization n (%)	8 (5.56)	56 (41.18)	0.0001
Long-term CVA n (%)	20 (13.89)	26 (19.12)	0.238
Nonfatal MI n (%)	13 (9.03)	52 (38.24)	0.0001
MACCE (+) n (%)	42 (29.17)	91 (66.91)	0.0001
Assessment of coronary angiograms between groups			
LAD LIMA graft n (%)	137 (95.14)	131 (96.32)	0.625
LAD SVG n (%)	9 (6.25)	16 (11.76)	0.106
LAD SVG failure n (%)	-	4 (2.94)	0.001
D1 SVG n (%)	68 (47.22)	69 (50.74)	0.557
D1 SVG failure (n.%)	-	25 (18.38)	0.0001
IM SVG	14 (9.72)	24 (17.65)	0.053
IM SVG failure n (%)	-	12 (8.82)	0.0001
LCX SVG n (%)	32 (22.22)	30 (22.06)	0.974
LCX SVG failure n (%)	-	10 (7.35)	0.001
LCX OM SVG n (%)	87 (60.42)	87 (63.97)	0.540
LCX OM SVG failure n (%)	-	44 (32.35)	0.0001
RCA SVG n (%)	71 (49.31)	68 (50.00)	0.908
RCA SVG failure n (%)	-	34 (25.00)	0.0001
RCA PDA SVG n (%)	40 (27.78)	30 (22.06)	0.269
RCA PDA SVG failure n (%)	-	15 (11.03)	0.0001
RCA PL SVG n (%)	4 (2.78)	5 (3.68)	0.670

ICU: intensive care unit; CABG: coronary artery bypass grafting; CVA: cerebrovascular accident; PAF: paroxysmal atrial fibrillation; MI: myocardial infarction; MACCE: major adverse cardiovascular and cerebrovascular events; LAD: left anterior descending; LIMA: left internal mammary artery; SVG: saphenous vein graft; D1: first diagonal branch; IM: intermediate artery; LCX: left circumflex artery; OM: optus marginalis; RCA: right coronary artery; PDA: posterior descending artery; PL: posterior lateral.

Table 3. Logistic regression analysis of parameters for predictors of late saphenous venous graft failure

Variables	B	p	OR	95%CI for OR	
				Lower	Upper
DM	0.20	0.662	0.82	0.34	1.98
HT	1.48	0.035	0.23	0.06	0.90
MACCE (+)	0.65	0.292	1.91	0.57	6.36
Repeat revascularization	1.92	0.01	0.15	0.03	0.63
Nonfatal MI	1.34	0.068	0.26	0.06	1.11
LVEF (%)	-0.04	0.065	0.96	0.92	1.00
Uric acid (mg/dL)	0.16	0.248	1.17	0.90	1.54
Creatinine (mg/dL)	0.13	0.899	0.88	0.13	6.22
eGFR (CKD-EPI)	-0.02	0.363	0.99	0.96	1.02
NLR	0.14	0.504	1.15	0.76	1.73
Syntax II CABG score	0.08	0.001	1.09	1.03	1.14
Syntax score	0.01	0.897	1.01	0.93	1.08

DM: diabetes mellitus; HT: hypertension; MACCE: major adverse cardiovascular and cerebrovascular events; MI: myocardial infarction; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; EPI: chronic kidney disease epidemiology collaboration; NLR: neutrophil-to-lymphocyte ratio; CABG: coronary artery bypass grafting.

The variables with p<0.05 in univariate logistic regression analysis are listed in Table 3 and were included in multiple logistic regression analysis. After adjusting for confounding factors, prior history of HT and higher rates of repeat revascularization were found to be independent predictors of late SVG failure. In the receiver operating characteristic curve analysis, for anatomical SYNTAX Score, area under curve (AUC) was 0.617 for predicting late SVG failure (SE:0.033; 95%CI 0.558–0.675) and was 0.761 for SYNTAX II CABG Score (SE:0.029; 95%CI 0.706–0.810). The predictive value of SYNTAX II CABG Score was found to be significantly higher than anatomical SYNTAX Score (p=0.001). Moreover, for anatomical SYNTAX Score, AUC was 0.514 for predicting MACCE (SE:0.035; 95%CI 0.454–0.574) and was 0.741 for SYNTAX II CABG Score (SE:0.030; 95%CI 0.685–0.791). The predictive value of SYNTAX II CABG Score was found to be significantly higher than anatomical SYNTAX Score (p=0.001) (Table 4).

Table 4. Receiver operating characteristic analysis for predicting late saphenous vein graft failure and major adverse cardiovascular and cerebrovascular events.

	AUC	SE	95%CI	p
A				
Syntax 2 CABG	0.761	0.029	0.706–0.810	0.001
Syntax Score	0.617	0.033	0.558–0.675	
B				
Syntax 2 CABG	0.741	0,030	0.685–0.791	0.001
Syntax Score	0.514	0,035	0.454–0.574	

AUC: area under curve; SE: standard error; CABG: coronary artery bypass grafting.

DISCUSSION

In the present study, we investigated demographic and clinical features of patients undergoing isolated CABG and evaluated the factors associated with late SVG failure. Our results indicate that Syntax II Score could be a useful predictor for late SVG failure. To our knowledge, this is the first study in literature to demonstrate the strong association between SYNTAX Score II and late SVG failure in patients undergoing isolated CABG.

CABG surgery is a well-established treatment modality for patients with multivessel CAD. On the other hand, SVG failure limits the long-term benefits of the procedure[10,11]. Due to major adverse cardiac events associated with SVG failure, it is mandatory to maintain graft patency. Basically, SVG failure develops in three phases: early (less than 1 month), intermediate (1 month to 1 year), and late (beyond 1 year)[12]. Early SVG failure results from technical issues or thrombosis and usually occurs at the site of graft

anastomosis. Factors associated with early SVG failure are endothelial injury, poor distal runoff, graft kinking, and small target vessel diameter[12,13]. The main pathological process that contributes to the development of intermediate SVG failure is progressive graft intimal hyperplasia. The underlying mechanism causing this pathologic condition is increased arterial pressure through the venous conduits. When saphenous veins are used as arterial conduits, alterations in hemodynamic status trigger intimal damage, fibrosis, platelet aggregation, release of growth factors, and smooth muscle cell proliferation. Progressive smooth muscle cell and fibroblast proliferation result not only in the development of neointimal hyperplasia but also in the luminal loss[14-17].

On the contrary, late SVG failure develops as a result of an atherogenic process and is frequently observed over the damaged endothelium[12]. Previous studies showed that there were several atherosclerotic risk factors including age, race, gender, hypercholesterolemia, DM, HT, and chronic kidney disease associated with the development of late SVG failure[18-20]. In addition, histopathological studies investigating damaged SVG demonstrated the presence of necrotic core, calcification, and negative remodeling, which support the unfavorable effects of accelerated atherosclerosis[21]. According to human autopsy studies, SVG lesions older than 2 years were found to be more concentric and diffuse and more prone to rupture and occlude compared to native lesions[22-24].

In our study, we observed a strong relationship between the prior history of HT, DM, reduced ejection fraction, CAD severity, and late SVG failure. With respect to assessing the severity of CAD, we used anatomical SYNTAX Score and novel SYNTAX II Score. This scoring system combined the clinical features (age, creatinine clearance, LVEF, left main CAD, sex, chronic obstructive pulmonary disease, and peripheral vascular disease) of patients along with anatomical characteristics of the coronary arteries (anatomical SYNTAX Score) replacing the previously used SYNTAX Score[9]. Several studies confirmed this outcome, including Evaluation of the Xience Everolimus Eluting Stent versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial that implemented this scoring system into the clinical practice and demonstrated more precise outcomes compared to former SYNTAX Score[25]. According to a meta-analysis conducted by Chen et al., SYNTAX Score II was superior to SYNTAX Score and played a substantial role in terms of predicting adverse clinical outcomes in patients who underwent coronary revascularization[26]. Outcomes of our study were compared with their result, which revealed Syntax II score was superior to anatomical Syntax Score in terms of predicting SVG failure and MACCE (p=0.001, for both). Regarding real-world practice, the predictive value of SYNTAX Score II was also confirmed by an observational study conducted by Song et al., who analyzed the outcomes of 4,398 consecutive patients following three-vessel and/or unprotected LMCA-PCI by means of dividing their estimated SYNTAX II Scores into the tertiles (with cutoff points at 20 and 26). According to their study, mortality rate was significantly higher in the upper tertile compared to the intermediate or lower tertiles during the 2-year follow-up (2.7 versus 1.7% versus 0.5%; p<0.001). Multivariate analysis also showed that SYNTAX Score II was an independent predictor of 2-year mortality (hazard ratio, 1.66 [95%CI 1.03–2.68]; p=0.04)[27]. However, in another study conducted by Li et al., there was no relationship between SVG failure and calculated SYNTAX II Scores[28]. Although their outcomes are inconsistent with our findings, their study had some limitations due to the nature of their study. According to their study, traditional risk factors, including HT, DM, and smoking, were not found related to SVG failure. Regarding the strong association between well-known atherosclerotic risk factors and higher SYNTAX Score II, it was inconceivable to achieve such an outcome. Therefore, claiming that there was no association between consensual traditional risk factors and SVG failure would create inconsistency and limit the generalizability of their results. According to a post hoc analysis of the Clopidogrel After Surgery for Coronary Artery Disease trial, the presence of HT, SVG diameter, grafting to the right coronary artery, and low quality of the target vessel correlate with the development of SVG hyperplasia or occlusion by 1 year after CABG. In addition, low target vessel quality and female sex were risk factors for SVG occlusion[29]. These parameters correlate with higher SYNTAX II Scores. They also demonstrated that the use of β-blockers and statins was associated with less SVG disease, confirming the importance of strict adherence to post-CABG medical treatment.

Limitation

The main limitation of the present study is that it was a single-center, retrospective experience with a relatively small sample size. Thus, further prospective studies with a larger population are needed to confirm our results. Although we investigated the predictors of late SVG failure, we did not investigate our patients with regard to occurrence of early and intermediate SVG graft failure. Due to exclusion of patients undergoing emergent CABG or concomitant mitral and aortic valve surgery, outcomes of this study cannot be applied to this population.

CONCLUSIONS

Late SVG failure has diverse etiology and is associated with adverse clinical manifestations and often requires repeat revascularization. Despite various known risk factors, estimated SYNTAX Score II was found to be independent predictor of late SVG failure in patients undergoing isolated CABG. Due to its convenience and easy accessibility, this method can be applied to clinical routine.

AUTHORS' CONTRIBUTIONS

MD: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **OT:** Conceptualization, Data curation, Formal analysis, Resources, Software, Writing – review & editing. **YA:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210257

Prediction model to discriminate leptospirosis from hantavirus

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SUMMARY

OBJECTIVE: The aim of this study was to build a prediction model to discriminate precociously hantavirus infection from leptospirosis, identifying the conditions and risk factors associated with these diseases.

METHODS: A logistic regression model in which the response variable was the presence of hantavirus or leptospirosis was adjusted.

RESULTS: As a result, the method selected the following variables that influenced the prediction formula: sociodemographic variables, clinical manifestations, and exposure to environmental risks. All variables considered in the model presented statistical significance with a $p<0.05$ value. The accuracy of the model to differentiate hantavirus from leptospirosis was 88.7%.

CONCLUSIONS: Concluding that the development of statistical tools with high potential to predict the disease, and thus differentiate them precociously, can reduce hospital costs, speed up the patient's care, reduce morbidity and mortality, and assist health professionals and public managers in decision-making.

KEYWORDS: Leptospirosis. Hantaviruses. Differential diagnosis. Public health.

INTRODUCTION

Hantavirus infection and leptospirosis are diseases relevant to public health and have high lethality coefficients. The incidence of hantavirus in Brazil is, on average, 118 cases/year[1], while leptospirosis presents 3,926 cases, with an average of 1.02 cases/100,000 inhabitants/year[2].

Both are infectious diseases that can present remarkably similar clinical conditions, making differential diagnosis exceedingly difficult in clinical practice. Hantavirus and leptospirosis are transmitted by rodents and are most often reported based exclusively on clinical suspicion since specific diagnostic tests are not available in many locations[3].

The main risk factors of both diseases are floods in the rainy period and inappropriate working and housing environmental conditions, among which occupation of inadequate buildings, disordered urban growth, and agricultural activities stand out[4].

Diseases related to inadequate environmental conditions and water transmission have been on the agenda of international meetings, and the sustainable development goal is to ensure a healthy life and promote well-being for all, aiming to end various epidemics and waterborne diseases[5].

According to Russell et al.[6], the rapid increase in the occurrence of emerging and reemerging zoonoses has led to the development of robust strategies, which enables a more accurate assessment of the situation's gravity, allowing for faster decision-making. Moreover, it was also stated that the early development of these prediction models and their immediate use can control and minimize the impact of these diseases.

Given these possibilities, this study aims to build a prediction model to discriminate precociously hantavirus infection from leptospirosis, identifying the conditions and risk factors associated with these diseases.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 15, 2021. Accepted on July 03, 2021.

METHODS

An epidemiological study, with observational, analytical, and cross-sectional nature with a quantitative approach, was carried out from 2001 to 2016.

This research used secondary data from the public domain and exempted from the appreciation of the CEP/CONEP system.

This study consisted of 2,254 confirmed cases of each hantavirus and leptospirosis, thus completing a total of 4,508 balanced observations. Explanatory sociodemographic variables of epidemiological, clinical, care, and laboratory background were used. The database used was composed of non-nominal information from the notification forms for hantavirus and leptospirosis of the Notifiable Diseases Information System (SINAN) and was provided by the Ministry of Health of Brazil through the Electronic Information Service System to the Citizen (e-SIC).

The descriptive statistics of the study variables were obtained through absolute (N) and relative (%) frequencies.

Logistic regression was used to classify hantavirus and leptospirosis cases based on their explanatory variable values. The probability to differentiate one disease from the other, given covariant x_i, was calculated using the following formula:

$$P(Y=1|x_i) = \frac{\exp(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})}{1 + \exp(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})}$$

where $x_i = (x_{i1}, x_{i2}, \ldots, x_{ik})$ are the explanatory variables for i^{th} observation, β_0 is the intercept, and β_j ($j = 1, \ldots, k$) is the corresponding coefficient for the explanatory variable j^{th}[7].

To assess the predictive capacity of the model, the database was divided into two sets, namely, training and testing. The training database was formed through a random selection of 70% of the observations of the original database and was made up of 1,577 cases of hantavirus and leptospirosis with a total of 3,154 cases. In contrast, the test database consisted of the remaining observations (30%) with 677 cases of hantavirus and leptospirosis with a total of 1,354 cases.

The model parameters were estimated using the training set, and the test set was used to validate it. The prediction capacity was evaluated estimating the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the 2×2 confusion matrix, formed by the observed information (columns) and the information predicted by the model (lines).

All statistical analyses were conducted using R version 3.3.0 software.

RESULTS

Sociodemographic conditions

Among the results to be described, only the gender variable was not selected by the prediction model constructed to differentiate hantavirus infection from leptospirosis. Thus, four sociodemographic variables were selected, namely, age, ethnicity, region, and education.

The individuals that fell ill due to hantavirus and leptospirosis were mostly males (79.1 and 78.9%), aged between 20 and 49 years (70.9 and 59.1%), and whites (68.7 and 45.1%), respectively.

Leptospirosis cases occurred mainly in urban areas, 81.4% (1,283) against 14.2% (224) in rural areas, while those with hantavirus were equally distributed among urban 47.7% (752) and rural areas 47.1% (743).

Regarding education, only 1.4% of individuals had complete higher education and more than a quarter (28.9%) had an ignored level of education. Those with incomplete elementary education, plus illiterates, corresponded to approximately 30 times the number of those with complete higher education, corresponding to 44.5%.

Clinical manifestations

Some signs and symptoms capable of helping in the clinical differentiation between hantavirus and leptospirosis were found in the prediction model; the following characteristics presented the greatest effect on the formula: fever, myalgia, headache, vomiting, dyspnea, and abdominal, renal, hemorrhagic, and neurological manifestations.

Fever was the most frequent symptom, occurring in 86.4 and 90.2% of hantavirus and leptospirosis cases, respectively. Followed by myalgia, fever was also frequently observed in both hantavirus (70.1%) and leptospirosis (82.6%).

Another frequent symptom in both diseases was headache, present in approximately three quarters of individuals with 74.4% in hantavirus and 77.7% in leptospirosis cases.

Vomiting was found in more than half of the cases in both diseases, being present in 60.5% of hantavirus cases and 58.1% of leptospirosis cases.

Dyspnea was reported in more than half of hantavirus cases (54.9%) and approximately a quarter (23.4%) of leptospirosis cases, while abdominal manifestations were observed in approximately one-third of the patients, both in hantavirus (35.9%) and leptospirosis (31.6%) cases.

Regarding renal manifestation, analyses showed that its occurrence was one and a half times higher in leptospirosis (21.7%) than in hantavirus (14.3%) cases.

Hemorrhagic manifestations occurred at the same frequency in hantavirus and leptospirosis (10%) cases. However, almost half (47.7%) of the cases of hantavirus disease ignored this information.

Neurological manifestations were less frequent, appearing only in 7.2% of individuals with hantavirus and 4.1% of leptospirosis cases.

Exposure to environmental risks

Regarding the probable site of infection, it shows that hantavirus was presented at work (55.5%), against 24.2% at home and 4.9% at leisure places, while leptospirosis predominated at home (38.7%), 24.3% at work and 6.8% at leisure places. These results showed that hantavirus disease presented a work-related risk twice higher than leptospirosis, while this presented an infection risk at home one and a half times higher in relation to hantavirus disease.

The presence of rodent signs was identified in 42.7% of hantavirus cases and 45.7% of leptospirosis cases. Direct contact with rodents was identified as a lower risk factor than the presence of rodent signs, considering that only 7.1% of leptospirosis cases were exposed to this risk and 29.2% of hantavirus cases.

Leisure in fresh water was a risk factor almost twice as frequent for leptospirosis infection (31.5%) than for hantavirus (17.0%).

Statistical model

In the construction of the predictive model to discriminate between hantavirus and leptospirosis, 16 variables that influenced the prediction formula were identified. Four were sociodemographic variables, eight were related to clinical manifestations, and four were variables related to environmental risk exposition. All variables considered in the model showed statistical significance with a $p<0.05$ value (Table 1).

The confusion matrix (Table 2) shows the absolute number of hantavirus and leptospirosis cases in the database, called observed, which are distributed in the lines. The cases selected using the statistical tool, called predicted, are distributed in the columns.

The predictive performance of the logistic regression to differentiate hantavirus from leptospirosis based on the data from the compulsory notification forms was assessed by means of accuracy, sensitivity, specificity, and positive and negative predictive values.

The test's accuracy was 88.7%, sensitivity was 89.4%, and specificity was 88%, while the positive predictive value of the test was 88.2% and the negative predictive value was 89.2% (Table 3).

DISCUSSION

It was observed in this study that hantavirus was presented in 18 states of the Brazilian Federation with a higher occurrence in the South, followed by the Southeast and Midwest regions, corroborating with the data described by Brazil[8], in which more than 90% of the registered cases were found in that regions, with 39.3%, 30.2%, and 22.3% cases, respectively. In this study, it was also shown that 69.5% of the cases were registered in only five states of those regions.

Regarding leptospirosis, its occurrence was recorded in all Brazilian states, being more frequent in São Paulo, Rio Grande do Sul, Santa Catarina, Paraná, and Acre, making up for more than half of the reported cases. According to Brazil[4], leptospirosis has an endemic distribution throughout Brazil, with occurrences reported throughout the year.

It was observed that the individuals with leptospirosis presented a similar distribution between urban and rural areas like the percentage of the Brazilian population distribution in these regions, as described by Brazilian Institute of Geography and Statistics (IBGE)[9]. This finding agrees with Longo et al.,[10] and Diaz[11], who stated that leptospirosis affects populations uniformly, both in urban and rural areas.

In this study, the increased risk of illness due to hantavirus was noticeable in people from the rural area (47.1%) when compared with the percentage of the Brazilian rural population (15.6%)[9]. According to Pinto Junior et al.[12] and Longo et al.[10], hantavirus affects mainly rural residents, since they usually live in houses that are permeable to rodents or work under risk exposure conditions.

Male individuals predominated the cases of hantavirus (79.1%) and leptospirosis (78.9%). A survey carried out in Brazil on rural workers' health identified that these have worse health conditions and the majority are males (73.2%), whereas 26.8% are females[13].

According to Goeijenbier et al.[14], environmental and occupational factors are associated with hantavirus infection risk, since the presence of rodents or even their excretions close to homes significantly increased the risk of infection. Walks in forests or rural recreational activity, handling of firewood, house cleaning, and occupational exposure were also identified risk factors. These findings corroborate with those of this study, which found that both exposure to rodents and their excreta, as well as work-related illness, are statistically significant to sicken due to hantavirus and leptospirosis.

The results found in this study, referring to exposure to environmental risks such as leisure activity in fresh water, rodent signs, or even having had direct contact with rodents, as well as illness at work, agree with the study by Gressler et al.[15].

Table 1. Estimated coefficients in the logistic regression and respective descriptors.

	Estimate	Standard error	Odds ratio	Z	p	95%CI (odds ratio scale)	
						Lower bound	Upper bound
(Intercept)	2.604	1.183	13.518	2.202	0.028	1.331	137.300
Sociodemographics							
Black race	0.288	0.289	1.333	0.997	0.319	0.757	2.348
Yellow race	-0.085	0.682	0.918	-0.125	0.900	0.241	3.495
Mixed race	0.792	0.167	2.208	4.752	<0001	1.593	3.061
Indigenous race	-2.626	1.249	0.072	-2.102	0.036	0.006	0.837
Ignored race	1.383	0.240	3.985	5.752	<0.001	2.488	6.384
Age							
5–9 years	-0.397	0.822	0.672	-0.483	0.629	0.134	3.368
10–14 years	-0.276	0.661	0.759	-0.417	0.676	0.208	2.772
15–19 years	-0.653	0.593	0.520	-1.101	0.271	0.163	1.665
20–24 years	-0.821	0.579	0.440	-1.419	0.156	0.141	1.368
25–29 years	-0.979	0.575	0.376	-1.703	0.089	0.122	1.159
30–34 years	-1.093	0.578	0.335	-1.893	0.058	0.108	1.039
35–39 years	-1.584	0.582	0.205	-2.724	0.006	0.066	0.641
40–44 years	-1.205	0.577	0.300	-2.087	0.037	0.097	0.929
45–49 years	-0.695	0.585	0.499	-1.188	0.235	0.159	1.571
50–54 years	-0.653	0.590	0.521	-1.105	0.269	0.164	1.656
55–59 years	-0.850	0.629	0.427	-1.352	0.177	0.125	1.466
60–64 years	-0.822	0.637	0.440	-1.290	0.197	0.126	1.532
65 years or above	-0.225	0.628	0.799	-0.358	0.721	0.233	2.736
Regions							
Rural area	-1.719	0.161	0.179	-10.685	<0.001	0.131	0.246
Peri-urban area	-1.625	0.482	0.197	-3.373	<0.001	0.077	0.506
Ignored area	-0.769	0.350	0.464	-2.195	0.028	0.233	0.921
Educational qualification							
1st to 4th incomplete elementary school grade (EF)	-1.690	0.971	0.185	-1.741	0.082	0.028	1.237
4th complete EF grade	-3.013	0.965	0.049	-3.122	0.002	0.007	0.326
5th to 8th incomplete EF grade	-2.634	0.954	0.072	-2.762	0.006	0.011	0.466
Complete EF	-2.863	0.965	0.057	-2.967	0.003	0.009	0.378
Incomplete high school	-2.296	0.987	0.101	-2.325	0.020	0.015	0.697
Complete high school	-1.351	0.981	0.259	-1.377	0.168	0.038	1.771
Incomplete higher education	-2.871	1.355	0.057	-2.119	0.034	0.004	0.806
Complete higher education	-1.788	1.082	0.167	-1.653	0.098	0.020	1.394
Ignored	-2.346	0.951	0.096	-2.466	0.014	0.015	0.618
Not applicable	-1.103	1.415	0.332	-0.780	0.436	0.021	5.313

Continue...

Table 1. Continuation.

	Estimate	Standard error	Odds ratio	Z	p	95%CI (odds ratio scale)	
						Lower bound	Upper bound
Clinical manifestations							
Vomiting absent	0.134	0.148	1.144	0.911	0.362	0.857	1.527
Vomiting ignored	-0.933	0.444	0.393	-2.104	0.035	0.165	0.938
Renal manifestation absent	-1.172	0.195	0.310	-6.009	<0.001	0.211	0.454
Renal manifestation ignored	-0.392	0.349	0.676	-1.122	0.262	0.341	1.340
Dyspnea absent	1.804	0.155	6.073	11.659	<0.001	4.484	8.224
Dyspnea ignored	2.856	0.391	17.391	7.307	<0.001	8.084	37.410
Hemorrhagic manifestations absent	1.752	0.217	5.764	8.086	<0.001	3.770	8.812
Hemorrhagic manifestations ignored	-3.443	0.284	0.032	-12.107	<0.001	0.018	0.056
Fever absent	-0.519	0.220	0.595	-2.360	0.018	0.387	0.916
Fever ignored	0.159	0.526	1.172	0.301	0.763	0.418	3.287
Neurological manifestations absent	0.537	0.292	1.711	1.839	0.066	0.965	3.033
Neurological manifestations ignored	1.849	0.427	6.355	4.328	<0.001	2.751	14.682
Myalgia absent	-1.169	0.178	0.311	-6.583	<0.001	0.219	0.440
Myalgia ignored	-0.395	0.431	0.673	-0.919	0.358	0.290	1.566
Abdominal manifestations absent	0.700	0.149	2.014	4.696	<0.001	1.504	2.697
Abdominal manifestations ignored	1.228	0.398	3.414	3.084	0.002	1.564	7.450
Exposure to environmental risks							
Work	-1.858	0.169	0.156	-11.022	<0.001	0.112	0.217
Leisure	-0.506	0.328	0.603	-1.541	0.123	0.317	1.147
Other	0.912	0.444	2.488	2.054	0.040	1.042	5.940
Exposure ignored	-0.148	0.202	0.862	-0.735	0.462	0.581	1.280
Leisure in fresh water absent	-1.256	0.168	0.285	-7.485	<0.001	0.205	0.396
Leisure in fresh water ignored	-1.531	0.407	0.216	-3.767	<0.001	0.097	0.480
Rodent signs absent	-0.422	0.144	0.655	-2.934	0.003	0.494	0.869
Rodent signs ignored	-1.856	0.282	0.156	-6.573	<0.001	0.090	0.272
Direct contact with rodent absent	0.995	0.177	2.706	5.617	<0.001	1.912	3.829
Direct contact with rodent ignored	4.041	0.260	56.886	15.517	<0.001	34.145	94.774

Source: Research Data, 2018.; Note; TIPO level "lepto" coded as class 1.

Table 2. Confusion matrix.

		Predicted	
		Hanta	Lepto
Observed	Hanta	605	72
	Lepto	81	596

Source: Research data; 2018.

Table 3. Predictive performance of logistic regression.

	Value
Accuracy	0.887
Sensitivity	0.894
Specificity	0.880
Predictive positive value	0.882
Predictive negative value	0.892

Source: Research data; 2018.

These authors consider leptospirosis an occupational disease, as its occurrence is associated with some work activities.

Corroborating with this study, Goeijenbier et al.[14] and Clement et al.[16] identified that the most frequently observed signs and symptoms in hantavirus were abdominal pain, nausea, vomiting, headache, fever, myalgia, and dyspnea, which can progress to severe acute respiratory failure. Hantavirus can also manifest itself as hemorrhagic fever with renal syndrome, which is recognized by fever, renal failure, and hemorrhage, an almost complete overlap of the classic leptospirosis symptoms.

In patients with leptospirosis, symptoms can vary widely, from asymptomatic patients or even with mild disease, to the most severe manifestation, known as Weil's disease, with the classic triad of jaundice, kidney failure, and hemorrhagic manifestations that is rapidly progressive and has a high lethality rate[14].

In a study by Loubet et al.[17], sociodemographic, clinical, and epidemiological variables were thus used to build the prediction model and like the results of this research, and some clinical signs and symptoms that stood out in the prediction formula, such as intense fatigue and gastrointestinal manifestations, but mainly high fever and anorexia, were identified.

Hong et al.[18] built a prediction model from a clinical database to assess the probability of developing advanced colorectal cancer. In this study, the variables that presented an effect on the prediction formula were age, gender, smoking time, alcohol consumption frequency, and aspirin use.

A similarity between the study by Hong et al.[18] and the present one regarding the nature of the variables identified was observed, as both contain sociodemographic variables and exposure to risk factors.

According to Rouquayrol and Almeida Filho[19], even by achieving the recommended quality, no 100% sensitive or specific test exists, with the possibility of always finding false-positive and false-negative results in diagnostic tests.

In addition, it is relevant to highlight that, according to the Pan American Health Organization[20], the validity of a diagnostic test is composed of some parameters, among them, sensitivity, specificity, and, most importantly, accuracy. As observed in this study, the prediction model developed showed a high accuracy of 88.7% to discriminate between hantavirus and leptospirosis.

CONCLUSIONS

The predictive discrimination of hantavirus and leptospirosis based on sociodemographic, clinical, and epidemiological indicators, obtained through the forms of compulsory notification, become possible to target treatment more precociously and thus speeding up assistance to the sick person, in addition to supporting health managers in the design and implementation of public policies related to health promotion as, healthy housing, basic sanitation, sustainable development, work environments, vector control, among others.

These policies can reduce the population's exposure to the main risk factors and thus minimize the impact of these diseases, considered serious and of high lethality, on public health.

AUTHORS' CONTRIBUITIONS

MRGR: Conceptualization, Formal analysis, Investigation, Methodology, Project Administration, Resources, Visualization, Writing – original draft. **NFGA:** Formal analysis, Investigation, Supervision, Visualization, Writing – review & editing. **SBR:** Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210264

Care protocol for acute traumatic tissue injuries in prehospital mobile service

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SUMMARY

OBJECTIVE: The aim of this study is to elaborate a protocol for the care of acute traumatic tissue injuries in the prehospital mobile service.

METHODS: An extensive search of anteriority that did not reveal the existence of such protocol in other services across the globe was carried out. Subsequently, the literature review was executed on Medline and Lilacs. Related and referenced scientific literature served as the basis for the elaboration and creation of the protocol and its flowchart. The complete protocol was then measured for expert judges with the Delphi methodology. A questionnaire (using the Likert scale) and the initial version protocol were sent by electronic means to 13 medical and nurse coordinators of all SAMU from Paraná. RESULTS: Seven experts returned completed questionnaires in the first round and five in the second round. Average required global content validation index was obtained for the validation requirements of the protocol and its flowchart.

CONCLUSIONS: A protocol for the care of acute traumatic tissue injuries in the prehospital mobile service was developed and authenticated with the viability of routine professional use by the health professional.

KEYWORDS: Emergency medical services. Wounds and injuries. Clinical protocols.

INTRODUCTION

The advent of the industrial era, advanced technology, increased vehicle speed, socioeconomic conditions, poverty, and human nature itself are the factors that have contributed to the progressive increase in different types of trauma[1]. This rise is a public health problem due to the high associated mortality, morbidity, costs, years of potential life lost, and impact on the individual, their family, and society[2].

Appropriate first care to trauma victims, right at the event, with the proper approach to injuries, directly affects morbidity and mortality of patients. Moreover, the costs and quality improvement of the initial approach are related to the level of prehospital care (PHC). All these factors together have a major impact on the progress of severe traumatic injury.

Updated intra-hospital protocols that standardize and organize care have previously been published, and they should be used as routine by all health professionals. However, there is no such protocol for PHC in Brazil or any other country to be used outside of hospitals.

METHODS

This is a primary, descriptive, single-center study. There was no sponsorship from any public or private entity for the development of this study. Possible conflicts of interest may have arisen from the primary author's employment relationship with the Londrina Northern Macro-Regional SAMU.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 30, 2021. Accepted on May 30, 2021.

This project was approved by CEP/UNIFESP under No. CAAE 05053218,1,0000,5505 and was conducted according to the ethical standards of the Declaration of Helsinki and its amendments. All participants provided informed consent to take part in this study, and their anonymity was ensured.

This study was divided into the following three stages:

1. Prior article search, bibliographic survey, content selection, and information treatment;
2. Protocol development, drafting, and creation of the flowchart with layout resources;
3. Protocol validation by urgency and emergency professionals working in PHC (SAMU).

A search of previous studies was first conducted in non-scientific research platforms and websites (i.e., Google Scholar and Yahoo) to reinforce the need for the proposed protocol. Subsequently, a literature search was performed in the Medline, Scielo, and Lilacs databases using the descriptors' emergency medical services, SAMU, protocols, injuries, and wounds, over the past 10 years.

The original content for the protocol was obtained from the fractional scientific literature references provided at the end of the document. All the information found on injuries and traumatic wounds was selected, compiled, summarized, critically analyzed, and used in the final formatting.

The protocol was written in technical language for the use of health professionals, specifically physicians and nurses.

The AGREE II instrument (AGREE Next Steps Consortium, 2009) was used as a tool to model the construction of the protocol body text. Its initial objectives were as follows:

1. To analyze the quality of clinical guidelines;
2. To provide a methodological strategy for the development of clinical guidelines;
3. To report what and how information should be reported in clinical guidelines;
4. To confirm the strength of evidence of the sources used in the development of clinical guidelines.

The evaluation of the protocol content and layout was performed by 13 expert judges using the Delphi method.

The specialists received an invitation letter by e-mail explaining the objective of the study, along with the informed consent form (ICF) and a questionnaire (via Google forms) developed for protocol evaluation.

The questionnaire items presented five responses as follows:

1. Inadequate;
2. Partially adequate;
3. Adequate;
4. Very adequate; and
5. N/A = not applicable.

The content validity index (CVI) was used to measure the percentage of judges who agreed with several aspects of the manual. Thus, the CVI was estimated considering the number of adequate or very adequate responses (3 and 4) for each item, divided by the total number of answers.

The questionnaire evaluated three main topics as follows:

1. Objective (6 items), evaluating the importance of the subject;
2. Structure and presentation (11 items), analyzing the overall presentation, general organization, structure, presentation strategy, coherence, and formatting; and
3. Relevance (4 items).

The selection of experts was conducted by non-probability sampling from a sample the researcher had access to, considering that the sample was properly representative[3].

The inclusion criteria for experts were active positions as medical and nursing coordinators of the SAMU in the state of Paraná and agreement to participate by signing the ICF. There were no exclusion criteria, except for not meeting the inclusion criteria. In case of participant dropout, another member was chosen from the invited group.

RESULTS

The final result of this study was a clinical protocol validated by health professionals who work directly in PHC. This study was analyzed by the medical and nursing coordinators of the SAMU in the state of Paraná who develop activities related to research (Delphi method).

To start the protocol validation, an invitation, a questionnaire, a copy of the protocol, and the ICF were sent via e-mail to each selected professional. Of the 13 experts invited, 7 returned the completed questionnaire in the first round of Delphi and 5 in the second round, performed 2 months after the first round.

A limit of three rounds was previously stipulated by the researcher for the submissions and corrections of the material being elaborated. The consensus was already reached in the first round, and the second round was repeated to confirm the methodology. This rapid positive result is due to the fact that most of the protocol items were based on the PHC professionals' daily practice and common sense. The final overall CVI of the protocol was 0.95 in the first round and 0.98 in the second round, resulting in a final mean CVI of 0.96.

At the end of the document, an algorithm of the care procedures to be performed by the health professional was presented in a simplified and easy-to-follow flowchart. The final protocol has a total of seven pages.

Annex 1 shows the complete protocol for viewing and use. The final flowchart is focused, which was carefully developed with every detail. Simple colors were used for didactic purposes and for better visualization of the sources of information. The objective was to gradually draw attention to specific parts of the flowchart text. Its design is unique and simple, with an artistic, aesthetic, and creative look, giving the document its own identity.

DISCUSSION

The motivation for this study originates from the "pain" related to the difficulty of prehospital mobile care. These difficulties start during the assistance process and continue during the patients' arrival at their destination hospitals for therapeutic follow-up. This lack of flow within the SAMU service in the state of Paraná highlights the need for a care protocol to allow standardization, formatting, and prioritization when assisting victims with acute traumatic tissue injuries.

An article by Jones et al.[4], reporting the lack of protocols for PHC in the United Kingdom, corroborates this study. The teams reported in that article had disorganized and non-standardized behaviors, with no guides or protocols. In a new study, Jones et al.[5] showed this same reality in the emergency departments of hospitals in the same country. This knowledge further motivated the search for models and flowcharts to assist the work of health professionals.

Dantas et al.[6] showed the reality of a town in the state of Bahia, Brazil. The discussion of this local epidemiological profile can be generalized to the entire Brazilian reality. The statistical data found were similar to those in all other studies in the past 10 years in Brazil, confirming the need for improving assistance to traffic accidents in PHC.

The AGREE II (2009) instrument was chosen as the basis for the development of the protocol due to its free access, ease of application, and wide use in health services. The Delphi method, with Likert scale scores, was chosen for the validation of the final product. This methodology was selected for its ease of use and quick applicability in the field throughout validation. The Delphi method, used for validation, can be used to obtain opinions and criteria from a group of specialists on a given topic. It uses questionnaires, and in each phase, information from previous phases is used in the search for consensus among experts[7].

Cunha et al.[8] wrote the scientific article that methodologically motivated and guided the preparation of this study, with a similar structure and methodology. The studies by Rezende et al.[9] and Brown et al.[10] also served as a basis for the development of a flowchart with potential use throughout the Brazilian SAMU, respecting local and general needs. A flowchart associated with an organized protocol has considerable applicability potential.

After construction of the protocol with the final version of the flowchart and complete validation by the expert judges, the next step was its dissemination among potential users. The protocol was submitted to the Brazilian ISBN Agency and received its numerical cataloging and the barcode for future references. It was also presented to other services of prehospital mobile care of SAMU in the state of Paraná and was very well accepted. Several requests for the use of the full protocol by other services have already been sent via e-mail.

A subsequent potential analysis of the implementation of the document in the various micro-regional realities of Paraná in its regional SAMUs could be analyzed in a future study. Furthermore, its use could be applied to many other services in Brazil. Each micro or macro region of the country has a different reality, which could be a limitation. However, in the future, this protocol may be adapted according to the region.

The statistical data generated from the use of this protocol in clinical practice, with tabulation and critical analysis, indicate the availability of further information on this theme. In the researcher's prognostic view, this is a document that will favorably impact the economy and the health of those who suffer traumatic tissue injuries.

AUTHORS' CONTRIBUTIONS

RPB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RSOF:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ASL:** Conceptualization, Data curation, methodology, project management, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CSS:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LMF:** Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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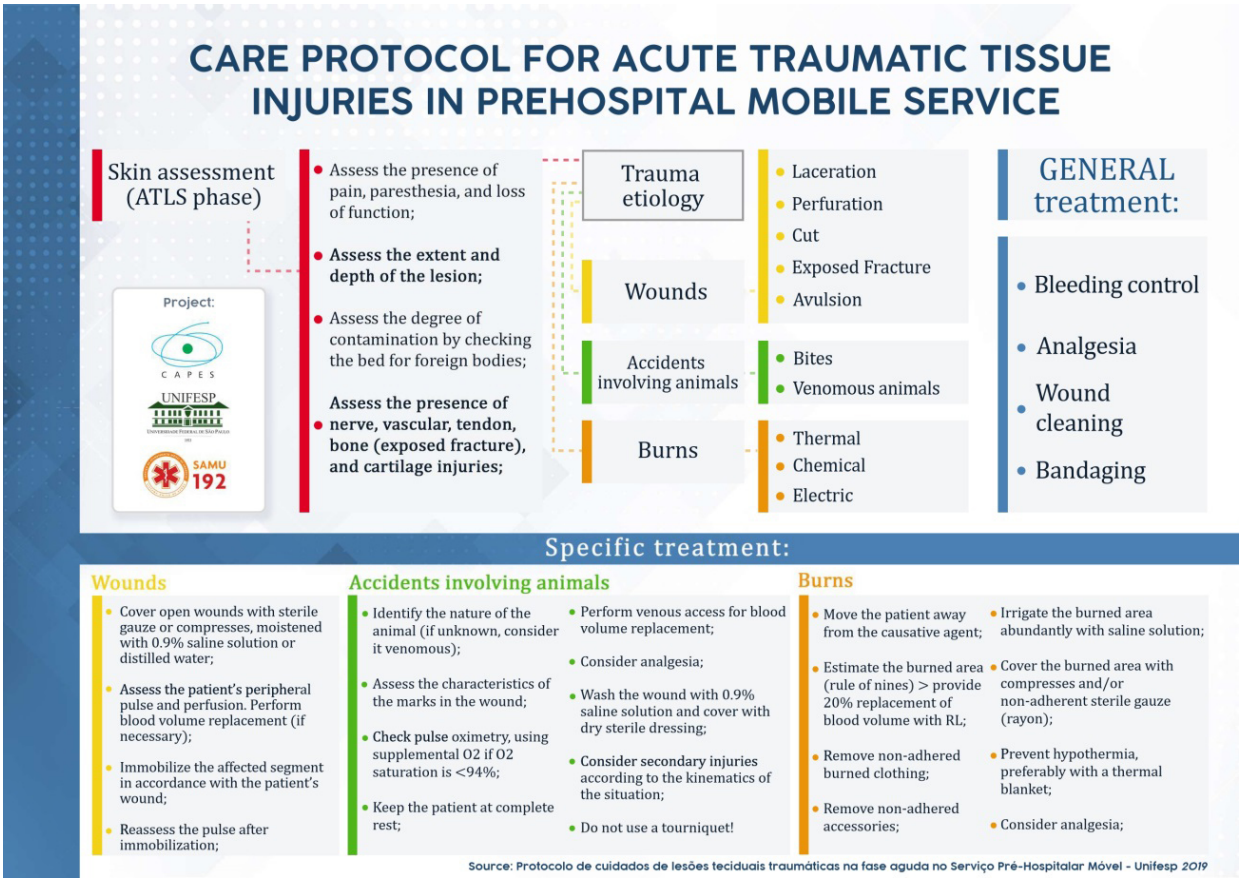
Annex 1. Care protocol for acute traumatic tissue injuries in prehospital mobile service.



ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210451

Exploring the expression profile of vitamin D receptor and its related long non-coding RNAs in patients with acute lymphoblastic leukemia

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SUMMARY

OBJECTIVE: Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer. Previous studies have indicated the involvement of vitamin D receptor (VDR) and related long noncoding RNAs (lncRNAs) signaling in the pathophysiology of several cancers. However, their contribution to ALL remains to be elucidated.

METHODS: In this case-control study, 30 patients with newly diagnosed ALL and 30 age- and sex-matched healthy children were selected. Then, the level of 25(OH) vitamin D and the expression of VDR and four VDR-related lncRNAs were assessed.

RESULTS: No significant difference in serum 25(OH) vitamin D was observed between patients with ALL (20.42±6.5 ng/mL) and healthy subjects (25.45±11 ng/mL). In addition, the expression of MALAT-1, HOTAIR, and P-21 was not statistically significant between the two groups. However, a significant reduction in VDR and H19 expression was observed in patients with ALL ($p<0.05$).

CONCLUSIONS: 25(OH) vitamin D insufficiency was evident in both groups. VDR and H19 signaling might be contributed to the pathogenesis of ALL, which needs further investigations.

KEYWORDS: Acute lymphoblastic leukemia. Vitamin D. Vitamin D receptor. Long non-coding RNA.

INTRODUCTION

Vitamin D deficiency is an important problem worldwide. As a fat-soluble vitamin, it is dominantly produced by human skin in response to solar ultraviolet-B radiation. Vitamin D has an important role in calcium homeostasis and bone metabolism. In addition, its effects on other cellular functions including cell differentiation, proliferation, apoptosis, and immunomodulation have been shown through studying some diseases[1]. Several studies have reported a negative association between serum 25-hydroxyvitamin D levels and risk of cancer[2,3]. Furthermore, vitamin D antitumorigenic effects have been shown in cell culture and animal studies[4].

Cell response to active vitamin D is relied on the level of vitamin D receptor (VDR) expression. VDR is a member of steroid-thyroid-retinoid receptor superfamily of ligand-activated transcription factors[4]. After binding of vitamin D to VDR, this receptor is dimerized with retinoid×receptor and the complex will bind to vitamin D receptor elements (VDREs) throughout the genome. It has been suggested that many VDREs are placed in noncoding regions of DNA. These sequences have no protein coding potential and are transcribed to noncoding RNAs including short and long ncRNA (lncRNAs) based on their size. LncRNAs, which are larger

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was financially supported by Student Research Committee, Kerman University of Medical Sciences (grant no. 98000891).
Received on June 28, 2021. Accepted on July 03, 2021.

than 200 bases in length, have pivotal roles in transcriptional and post-transcriptional regulation of genes. In this regard, some studies have shown the regulatory effects of several lncRNAs on VDR expression[5,6].

As the most common pediatric cancer, leukemia accounts for 30% of all cancers occur in children. About three-quarters of leukemia diagnoses are acute lymphoblastic leukemia (ALL)[7]. ALL appears with defects in lymphoid cells differentiation and abnormal proliferation in bone marrow, peripheral blood, and extramedullary sites[8]. There have been limited studies evaluating vitamin D status in patients with ALL. In this case, a recent investigation has shown low levels of vitamin D in newly diagnosed ALL subjects in Pakistani population[9]. The prevalence of vitamin D deficiency in ALL survivors treated with conventional chemotherapy or hematopoietic cell transplantation was also reported in another study[10]. However, to our knowledge, no study has assessed the level of VDR and VDR-related lncRNAs expression in ALL. Therefore, this study was conducted to assess serum vitamin D level as well as the expression of VDR and four lncRNAs including H19, MALAT-1, P-21, and HOTAIR, which are associated with VDR in patients with newly diagnosed ALL.

METHODS

Human subjects

This case-control study consisted of 30 children with newly diagnosed ALL and 30 healthy volunteers (gender/age matched). All patients were selected from Afzalipour hospital (Kerman, Iran) during 2017 to 2019. They were 17 (56.7%) males and 13 (43.3%) females, with age ranging from 1 to 9 years. In order to be eligible to participate in this study, patients must meet the following criteria:

1. Having informed consent signed by their parents;
2. Having newly diagnosed ALL; and
3. Not having prior treatment (neither chemotherapy nor radiotherapy). Diagnosis was established according to standard morphologic, cytochemical, and cytogenetic criteria by a leukemia hematopathologist. All procedures of this research were approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1399.345).

Collection of blood samples and PBMCs isolation

Five milliliters of blood specimen was withdrawn from patients as well as controls in heparinized tubes. Using Ficoll-Hypaque solution gradient, peripheral blood mononuclear cells (PBMCs) were separated. In brief, blood was diluted and mixed with phosphate-buffered saline and then the mixture was gently added to Ficoll-Hypaque solution. After centrifugation at 800 g for 20 min, PBMCs were found on the upper layer of the separation fluid, while other blood cells including RBCs and granulocytes remained at the bottom.

Serum 25-hydroxy vitamin D measurement

Within 1 h of specimen collection, 2 mL of blood was centrifuged at 2,500 RPM for 20 min. Serum was withdrawn and transferred into tubes. Then, 25(OH) vitamin D concentration was measured using 25(OH) Vitamin D ELISA kit (Monobind Inc., USA) and according to the manufacturer's recommendations.

RNA extraction and quantitative real-time PCR

Total RNA extraction was performed using Trizol reagent (Invitrogen, USA) and complementary DNA (cDNA) was synthesized according to the manufacturer's recommendations (Takara, Japan). Then, RNA concentration and purity were analyzed by a NanoDrop spectrophotometer (Thermo Scientific, USA). Quantitative Real-time polymerase chain reaction (PCR) analysis was performed in a 10-µL final reaction volume using SYBR Green master mix (Amplicon, Denmark). Specific primers were designed using online Primer-Blast tool. Primer sequences and characteristics are provided in Table 1. The amplification was conducted as follows: 95°C for 15 min followed by 35 cycles of 40 s at 95°C, 25 s at 62°C, and 15 s at 72°C. A melting curve from 55°C to 100°C was recorded to detect potential unintended products. All reactions were run in duplicate with MIC Real-time PCR System (Bio Molecular Systems, Australia). RNA relative expression was calculated as fold-change using the comparative threshold cycle method ($2^{-\Delta\Delta CT}$) with beta-2-microglobulin (β2M) serving as the internal control gene.

Statistical analysis

Statistical analysis was carried out using SPSS software version 19.0 (IBM, USA). Descriptive analysis was applied to test demographic variables. Independent t-test was used to compare vitamin D levels between the two groups. Mann-Whitney U test was applied to compare VDR and lncRNAs expression differences between control and ALL groups. The results of VDR and lncRNAs were presented as median with the interquartile range. Other data were expressed as mean±SD. For all tests, $p<0.05$ was considered as the level of significance.

RESULTS

The participants' characteristics are summarized in Table 2. The mean age of control group was 5±4 years and of patient group was 6±4 years. Each group contained 17 boys and 13 girls.

The mean serum level of 25(OH) vitamin D in ALL and control groups were 20.42±6.5 and 25.45±11 ng/mL, respectively, which was not statistically significant (p=0.057). Our data showed that 67% of control group and 92% of patient group had vitamin D insufficiency, which was considered as serum 25(OH) vitamin D level between 10 and 29 ng/mL in this study. Quantification of VDR messenger RNA level in the two groups demonstrated that the expression of VDR was significantly downregulated in patient group (p=0.045). In addition, assessment of relative expression of H19, MALAT-1, P-21, and HOTAIR in the two groups showed downregulation of H19 in ALL group, which was statistically significant (p=0.028). However, no significant difference was observed in other lncRNAs between patient and control groups (p>0.05) (Figure 1).

DISCUSSION

In the present study, we measured the level of serum vitamin D and VDR and some of VDR-related lncRNAs expression in patients with ALL. Our findings demonstrated that the expression of VDR and H19 were markedly reduced in ALL subjects. Although the survival rate of ALL has increased from less than 10% in 1960s to 90% today, it is still the main reason of death from cancer in young people[11]. Unraveling the risk factors that change in ALL may lead to disease prevention and improvement in the treatments. Vitamin D is one of these controversial factors that attracted a lot of attention because of its possible antiproliferative and pro-differentiating effects[12]. Several studies have shown the beneficial effects of vitamin D in some types of solid cancers and also some hematological malignancies[13], but it remains poorly studied with respect to ALL.

Our findings showed a lower mean value of 25(OH) vitamin D in patients with ALL when compared to control group. However, their difference was not statistically significant. Similarly, Naz et al. observed that over 90% of patients with acute leukemia including ALL and acute myeloid leukemia (AML) had insufficient 25(OH) vitamin D levels. They also found that 25(OH) vitamin D insufficiency was more

Table 2. Comparison of general characteristics and laboratory features between control and ALL groups.

Variables	Control group	ALL group
Age (year)	6±4	5±4
Gender (%)	17 males (56.7%) 13 females (43.3%)	17 males (56.7%) 13 females (43.3%)
WBC (×10³/µL)	7180±442	15,980±5331
25(OH) vitamin D (ng/mL)	25.45±11	20.42±6.5

ALL: acute lymphoblastic leukemia; WBC: white blood cell count.

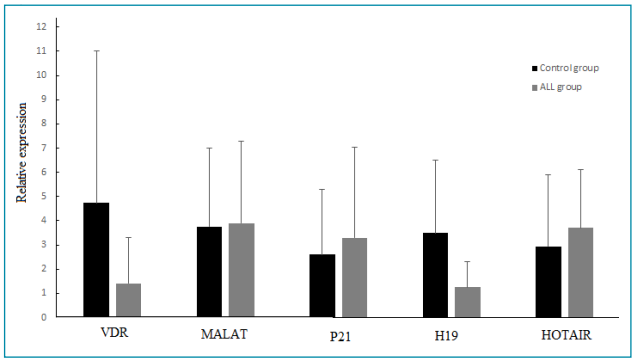

Figure 1. Expression of vitamin D receptor, H19, MALAT-1, P-21, and HOTAIR related long noncoding RNAs levels in the patients with acute lymphoblastic leukemia and healthy control participants. Vitamin D receptor and H19 expression demonstrated significant differences between patient and control group. Data were presented as median with the interquartile range. *p<0.05 compared with healthy control.

Table 1. Nucleotide sequences and characteristics of primers used for expression analysis.

Gene	Forward primer (5′–3′)	T_m	GC%	Reverse primer (5′–3′)	T_m	GC%	Product size (bp)
VDR	TTGCCATACTGCTGGACGC	60.7	58	GGCTCCCTCCACCATCATT	59.1	58	102
β2M	CTCCGTGGCCTTAGCTGTG	60.4	63	TTTGGAGTACGCTGGATAGCCT	61.2	50	69
MALAT-1	GCTCTGTGGTGTGGGATTGA	60.0	55	GTGGCAAAATGGCGGACTTT	60.0	50	179
HOTAIR	GCACCGCTTTTCTAACTGGC	60.1	55	CAGGGTCCCACTGCATAATCA	59.8	52	141
P-21	AGGACCAGAATAACCCGAGC	59.2	55	CTGGGGTCCAGGATGCATAG	59.6	60	109
H19	CACGGCTTTCTCAGGCCTAT	59.8	55	TACAGCGTCACCAAGTCCAC	60.0	55	238

pronounced in patients with ALL as compared to those with AML[9]. Similarly, Bhattacharya et al. reported that 84.95% of children with ALL in North India were deficient in vitamin D and that these children were at a higher risk of developing complications during treatment of ALL[14].

In animal studies, vitamin D has been shown to have antitumor actions in many tissues, which have potentiated this vitamin as an anticancer agent[6]. However, the molecular basis by which this vitamin may be involved in ALL is not understood. Generally, vitamin D exerts its actions through its binding with VDR, which is expressed in most cells in the body. Comprehensive genome-wide in silico and transcriptome screens have reported some VDR activities, including suppression of cells proliferation and migration, enhancement of cells adhesion, and induction of apoptosis in cells[15]. However, few studies have evaluated VDR roles or resistance to its signaling pathway in hematological malignancies[14]. Our results showed that VDR expression was downregulated in ALL samples compared to normal samples. This finding is consistent with similar observations made by several studies[16].

LncRNAs are involved in various cellular processes, including cell proliferation, migration, invasion, and transformation. Accumulating data suggest that dysregulation of lncRNAs is involved in tumorigenesis[17]. A recent study showed that the balance in several oncogenic to tumor-suppressing lncRNAs expression was disturbed in VDR null mice, which resulted in a higher predisposition of these animals to cancer[18]. In another study, Chen et al. showed a reciprocal relation between VDR and H19 expression in colon cancer cells. They reported the regulatory effect of H19 on VDR expression through microRNA 675-5p and also H19 expression inhibition by VDR signaling[19]. Overexpression of MALAT-1 was reported in patients with acute monocytic leukemia by Huang et al. They also observed that MALAT-1 knocking-down inhibited leukemia cell proliferation and induced apoptosis[20]. Hao et al. reported upregulation of HOTAIR in de novo patients with AML and its role in cell proliferation *in vitro*[21]. Downregulation of P-21, a tumor suppressor and post-transcriptional regulator, was observed in patients with chronic lymphocytic leukemia, whereas its low expression was correlated with some clinical outcomes[17]. Based on these reports, we measured the expression of four VDR-related lncRNAs including H19, MALAT-1, P-21, and HOTAIR in patients with ALL. However, we did not find any significant difference in MALAT-1, HOTAIR, and P-21 expression between ALL and healthy group.

According to our data, we observed a significant downregulation of H19 expression in patients with ALL compared to control group. As a paternally imprinted gene, H19 locates in chromosome 11p15.5[22]. It has been reported that H19 plays important roles in embryonic development, growth control, glucose metabolism, and tumor development. Most studies in human have reported upregulation of H19 lncRNA in cancer and considered it an oncogenic lncRNA. However, Hao et al. reported the first evidence of tumor suppressor activity of H19 by transfection of H19 cDNA into G401-transformed kidney cells and observing loss of tumorigenicity of these cells[23]. In another study, Yoshimizu et al. showed the tumor suppressor effect of H19 using *in vivo* murine models of tumorigenesis[24]. Supporting our findings, a study by Schultheiss et al. showed that H19 expression in hepatocellular carcinoma was lower than normal or nontumorous adjacent tissues and concluded that H19 suppressed hepatocarcinogenesis and hepatoma cell growth[25]. Therefore, H19 can be considered both oncogene and tumor suppressor lncRNA.

There are some possible reasons for these discrepancies observed between our results and other data. First, previous studies were performed in different racial groups who differed in genetic factors. Second, we did this study in a small sample size due to low incidence rate of leukemia (3.6/100,000) that might increase the likelihood of a Type II error. Third, cancer type and stage were not the same in all mentioned studies.

CONCLUSIONS

In conclusion, this is the first study showing the downregulation of VDR and H19 expression in patients with ALL. Our results reinforce the potential roles of VDR and H19 as biomarkers in the pathogenesis of ALL. However, the inconsistent results in VDR and H19 expression suggest a necessity for further investigations to explore VDR- and H19-related signaling pathways in the pathogenesis of ALL.

AUTHORS' CONTRIBUTIONS

MNR: Conceptualization, Supervision, Funding acquisition. **AN:** Investigation, Writing – original draft. **MM:** Investigation. **GH:** Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210453

Radiation therapy with elective lymph node irradiation for breast cancer: dosimetric study and impact on cardiovascular risk and second neoplasms

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SUMMARY

OBJECTIVE: The aim of this study was to perform dosimetric analysis of radiotherapy (RT) plans with or without elective nodal irradiation (ENI) and estimate whether the increase in mean doses (MDs) in the heart and lungs with ENI may lead to late side effects that may surpass the benefits of treatment.

METHODS: The dosimetric analysis of 30 treatment plans was done with or without ENI. The planning and dose-volume histograms were analyzed, and the impact on the mortality of cardiovascular and lung cancer was estimated based on the correlation of the dosimetric data with data from population studies.

RESULTS: RT with ENI increased the doses in the lungs and heterogeneity in the plans compared to breast-exclusive RT. When the increase in MDs is correlated with the increase of late side-effect risks, the most important effect of ENI is the increased risk of lung cancer, especially in patients who smoke (average increase in absolute risk=1.38%). The increase in the absolute risk of cardiovascular diseases was below 0.1% in the all the situations analyzed.

CONCLUSIONS: ENI increases the heterogeneity and the doses at the lungs. When recommending ENI, the risks and benefits must be taken into account, considering the oncology factors and the plan of each patient. Special attention must be given to patients who smoke as ENI may lead to a significant increase in MD in the lung and the increased risk of radiation-induced lung cancer may surpass the benefits from this treatment.

KEYWORDS: Radiotherapy. Breast cancer. Lymphatic irradiation. Dosimetry. Smoking.

INTRODUCTION

Breast cancer is the second most common type of cancer in women and represents the fifth most frequent cause of death due to cancer. According to the data from the World Health Organization, 2.1 million new cases had occurred in 2018[1].

The role of radiotherapy (RT) after conservative breast cancer surgery is well established. This treatment leads to overall survival rates similar to those after isolated mastectomy of early-stage tumors[2,3]. Compared with conservative surgery alone, adjuvant RT decreases local and regional relapse rates, incidence of distant metastases, and cancer-specific mortality[3-5].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 01, 2021. Accepted on July 03, 2021.

Axillary lymph node metastases have important prognostic value in patients with breast cancer. It is known that elective nodal irradiation (ENI) can reduce local relapse rates, distant metastases, and cancer-specific mortality[6]. However, this treatment has side effects, and a higher incidence of cardiovascular diseases (CVDs) and secondary neoplasms may occur with increased doses to the heart and lung[7,8]. The risk of CVD is approximately four times higher in women who smoke than in the general population, whereas the risk of lung cancer is up to 20 times higher[9]. The combined effect of tobacco, smoking, and radiation exposure can significantly increase the mortality rate in these patients.

The objective of this study was to perform a dosimetric analysis of RT plans for patients with breast cancer receiving adjuvant treatment with the three-dimensional (3D) conformal RT with and without ENI. Furthermore, it aimed to estimate whether increasing the doses to organs at risk because ENI could lead to an increase in the absolute risk of death due to cardiovascular causes or lung cancer and minimize the potential benefits of this treatment.

METHODS

We performed dosimetric analyses of RT plans involving 3D conformal RT in patients with breast cancer with or without ENI.

Contouring of the target volumes and risk structures was conducted by a single radiation oncologist, according to the recommendations of the Radiation Therapy Oncology Group. Furthermore, 30 plans were prepared for 10 patients in three situations: RT of the breast alone, RT of the breast and the supraclavicular fossa (SCF), and RT of the breast, SCF, and internal mammary chain (IMC). Tangent fields were planned using the field-in-field technique for homogenization; the IMC was treated with a wide tangent field and the SCF with direct fields, with eventual addition of a posterior field for better coverage, if necessary.

The planning and dose-volume histograms were analyzed, and their effects on mortality due to CVD and lung cancer were estimated on a case-by-case basis in the three analyzed situations based on the correlation found between dosimetric and population study data[10]. It was considered that every gray (Gy) of increase in the mean dose (MD) to the lung and heart contributes to 11 and 4% increase in the relative risk of death due to lung cancer and CVDs, respectively. The absolute risks of death from lung cancer in smokers and nonsmokers are 4 and 0.3%, respectively, whereas those in smokers and nonsmokers are 1 and 0.3%, respectively (Table 1).

Statistical analysis was performed using nonparametric Friedman's test, and a significance level less than or equal to 0.05 was considered significant. The MDs to the heart and lungs of the 10 patients in the three situations being studied were used in the calculation to reduce the effect of individual anatomical variations.

Table 1. Cardiovascular and lung cancer risks.

Absolute risk of death (nonsmoking patients)	Lung cancer: 0.3% CVDs: 0.3%
Absolute risk of death (smoking patients)	Lung cancer: 4% CVDs: 1%
Increased relative risk of death for every 1-Gy increment in the mean dose	Lung cancer: 11% CVDs: 4%

CVDs: cardiovascular diseases.

RESULTS

Thirty plans were prepared based on the computed tomography scans of 10 different patients in three situations: only the left breast as the target volume; the SCF and the left breast as the target volumes; and the SCF, IMC, and left breast as the target volumes. The effect on planning target volume (PTV) coverage, heterogeneity, and doses to organs at risk were analyzed in all the plans.

Irradiation of the SCF, IMC, or both did not compromise breast PTV coverage because 95% of this volume received at least 95% of the prescription dose in all analyzed situations for the same minimum dose delivered to 95% of the PTV (D95). Heterogeneity indices were also not compromised because there was no difference between the PTVs that received 108 and 112% of the prescribed dose. In the 10 plans with IMC irradiation, at least 95% of the volume of the IMC PTV received a dose greater than or equal to 40 Gy. A mean incidental dose close to 73.4% of the prescription was administered to the IMC PTV even to plans that did not aim to cover this volume (Table 2).

In the 10 plans with breast treatment alone, the averages of the mean total lung dose (total lung MD), MD to the ipsilateral lung (lung MD), percentage of the lung receiving a 5-Gy dose (lung V5), percentage of the lung receiving a 10-Gy dose (lung V10), and percentage of the lung receiving a 20-Gy dose (lung V20) were 4.97 (3.60–5.90) Gy, 10.66 (8.5–12.20) Gy, 33.67% (26.0–38.0%), 23.44% (19.0–27.0%), and 18.08% (15.0–21.0%), respectively. In the same plans, the averages of the MD to the heart (heart MD), percentage of the heart receiving a 15-Gy dose (heart V15), and percentage of the heart receiving a 25-Gy dose (heart V25) were 3.31 (1.50–4.4) Gy, 4.06% (0–6%), and 3.12% (0–5%), respectively (Table 2).

Table 2. Dosimetric analysis of the averages of the 10 plans in the three analyzed situations (nonparametric Friedman's test).

Dosimetric analysis		Mean	p-value	Comparison between groups	Adjusted p-value
Heart MD (Gy)	No IMC	3.3100	0.027	No IMC/no drainage	1
	With IMC	4.0600		No IMC/with IMC	0.133
	No drainage	3.3100		No drainage/with IMC	0.133
	Total	3.5600			
Heart V15 (%)	No IMC	0.0406	0.895		
	With IMC	0.0560			
	No drainage	0.0406			
	Total	0.0457			
Heart V25 (%)	No IMC	0.0312	0.895		
	With IMC	0.0445			
	No drainage	0.0312			
	Total	0.0356			
Total lung MD (Gy)	No IMC	7.0600	<0.001	No IMC/no drainage	0.057
	With IMC	8.1100		No IMC/with IMC	0.133
	No drainage	4.9700		No drainage/with IMC	<0.001
	Total	6.7133			
Lung MD (Gy)	No IMC	15.0600	<0.001	No IMC/no drainage	0.076
	With IMC	17.2300		No IMC/with IMC	0.076
	No drainage	10.6600		No drainage/with IMC	<0.001
	Total	14.3167			
Lung V5 (%)	No IMC	0.5093	<0.001	No IMC/no drainage	0.057
	With IMC	0.5528		No IMC/with IMC	0.133
	No drainage	0.3367		No drainage/with IMC	<0.001
	Total	0.4663			
Lung V10 (%)	No IMC	0.3568	<0.001	No IMC/no drainage	0.076
	With IMC	0.4136		No IMC/with IMC	0.076
	No drainage	0.2344		No drainage/with IMC	<0.001
	Total	0.3349			
Lung V20 (%)	No IMC	0.2738	<0.001	No IMC/no drainage	0.076
	With IMC	0.3281		No IMC/with IMC	0.076
	No drainage	0.1808		No drainage/with IMC	<0.001
	Total	0.2609			
IMC mean (Gy)	No IMC	36.6800	<0.001	No IMC/no drainage	1
	With IMC	47.4700		No IMC/with IMC	0.02
	No drainage	36.6800		No drainage/with IMC	0.02
	Total	40.2767			
IMC V40 (%)	No IMC	0.5708	<0.001	No IMC/no drainage	1
	With IMC	0.8486		No IMC/with IMC	0.02
	No drainage	0.5708		No drainage/with IMC	0.02
	Total	0.6634			

No IMC: plan without the internal mammary chain and only breast and SCF; With IMC: plan with full drainage, including the IMC; No drainage: plan with the breast alone and no drainage; MD: mean doses; IMC: internal mammary chain.

In the 10 plans with SCF irradiation, the averages of total lung MD, ipsilateral lung MD, lung V5, lung V10, and lung V20 were 7.06 (6.30–8.10) Gy, 15.06 (13.7–16.70) Gy, 50.9% (46–54%), 35.68% (33–38%), and 27.38% (24–31%), respectively. In the same plans, the averages of heart MD, heart V15, and heart V25 were 3.31 (1.50–4.4) Gy, 4.06% (0–6%), and 3.12% (0–5%), respectively (Table 2).

In the 10 plans that included full lymphatic drainage and the IMC, the averages of ipsilateral lung MD, lung V5, lung V10, and lung V20 were 8.11 (6.70–9.80) Gy, 17.23 (15.4–19.90) Gy, 55.28% (49–60%), 41.36% (37–46%), and 32.81% (29–37%), respectively. In the same plans, the mean values of heart MD, heart V15, and heart V25 were 4.06 (1.60–6.0) Gy, 5.6% (0–11%), and 4.45% (0–9%), respectively (Table 2).

Compared with the 10 plans in which only the breast PTV was treated, IMC irradiation increased the MDs, V15, and V25 to the heart, whereas SCF irradiation, with or without the IMC, increased the doses in the lung (Table 2). The values of total lung MD, ipsilateral lung MD, lung V5, lung V10, and lung V20 showed a statistically significant difference via the Friedman's nonparametric test when the plans irradiating the breast alone were compared with those with full lymphatic drainage irradiation ($p<0.001$) (Table 2).Considering the absolute risk of death due to lung cancer or CVD in smokers and nonsmokers, the increase in the relative risk of death for every Gy increment in the mean heart and lung dose (Table 1), and the increase in the mean lung and heart doses after analysis of the 30 plans (Table 2), we estimated that irradiation of the SCF and IMC may increase the risk of death due to lung cancer and CVD in smoking patients by 1.38 and 0.03%, respectively, and that in nonsmokers by 0.1 and 0.01%, respectively.

DISCUSSION

Better systemic treatments have decreased the mortality risk due to breast cancer, local therapy plays a key role in this scenario[11]. A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group showed that RT after conservative surgery or mastectomy is associated with a 20% gain in overall recurrence-free survival at 10 years and an 8.5% decrease in breast cancer mortality at 15 years in patients with lymph node involvement[5,6].

Elective lymph node irradiation represents a key component in the treatment of breast cancer. The IMC is affected in approximately 28–52%[12] of patients with positive axillary lymph nodes. The EORTC 22922 and NCIC MA.20 studies have demonstrated a reduction in the risk of distant metastases with SCF and IMC irradiation[13,14]. At present, the National Comprehensive Cancer Network recommends the inclusion of the IMC in patients with four or more compromised lymph nodes, whereas the ASCO-ASTRO-SSO recommends elective irradiation of the lymphatic drainage in patients with positive lymph nodes after conservative surgery or mastectomy[15]. However, there is no consensus regarding IMC irradiation owing to increased doses to organs at risk[16,17], as demonstrated in this study, as well as the possible side effects of treatment.

There is an association between smoking and breast cancer[18-20], and a meta-analysis with approximately 40,000 patients showed that cigarette smoking increased mortality due to cancer and other causes[20]. In addition, smoking can increase the risk of side effects related to RT, such as CVD and RT-induced secondary neoplasms, particularly in patients with lung cancer[10]. Several studies have correlated the risks of side effects from RT with doses to at-risk organs[21,22]. Taylor et al.[10] estimated a 4 and 11% increase in the relative risk of death due to CVD and lung cancer for every Gy increase in the MDs to the heart and lungs, respectively. In the dosimetric analysis of our study, the increase in the risk of death due to CVDs was less impacted by the inclusion of the elective irradiation of the lymphatic drainage, even in smoking patients. However, the impact of lymph node irradiation on the risk of death due to lung cancer was more significant. We found that compared with the treatment of the breast or chest wall alone, SCF and IMC irradiation may increase the mean risk of death due to lung cancer by 1.38% in smoking patients, which could considerably minimize the oncological benefits of this treatment.

There are other factors that influence the dose distribution in RT planning, such as the technique chosen, positioning, and individual anatomy of the patient. Furthermore, there are ways to reduce doses to risk organs via biofeedback, breath-holding, or prone positioning techniques[21,22]. These techniques can be used either alone or in combination to reduce doses to the lungs and heart and consequently the risk of death due to lung cancer and CVDs; however, their use was outside the scope of this study and was, therefore, not analyzed.

CONCLUSIONS

Smoking status and an increase in the MDs to the heart and lungs are factors that should be considered in the indication of ENI, particularly when this treatment is not mandatory, as in the case of patients with 1–3 compromised axillary lymph nodes. It is important to weigh the risks and benefits of this treatment because an increase in the MDs to the heart and particularly to the lungs of smoking patients can increase the mortality due to other causes and can minimize the oncological benefits of the treatment.

AUTHORS' CONTRIBUTIONS

AAPM: Data curation, Writing – original draft. **PMM:** Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **CQT:** Conceptualization, Methodology, Writing – review & editing. **ACAP:** Conceptualization, Methodology, Writing – review & editing. **FBM:** Conceptualization, Methodology, Writing – review & editing. **RCF:** Conceptualization, Methodology, Writing – review & editing. **MJC:** Conceptualization, Methodology, Writing – review & editing. **MLGS:** Conceptualization, Methodology, Writing – review & editing. **DGC:** Conceptualization, Methodology, Writing – review & editing. **GRMG:** Conceptualization, Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210460

Prognostic nutritional index and the risk of acute kidney injury in patients with acute coronary syndrome

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SUMMARY

OBJECTIVE: Recent studies have linked malnutrition with undesirable outcomes in cardiovascular diseases. However, the underlying mechanism is unknown. Contrast-induced acute kidney injury (CI-AKI) increased cardiovascular mortality after percutaneous coronary intervention (PCI). This study hypothesizes that prognostic nutritional index (PNI) plays a role in the development of CI-AKI in patients with acute coronary syndrome undergoing emergency PCI.

METHODS: This study enrolled 551 patients. PNI was determined as 10× serum albumin (g/dL)+0.005×total lymphocyte count (mm³). CI-AKI was characterized as the increase in serum creatinine ≥0.3 mg/dL level within 48 h after PCI. Patients were classified as either CI-AKI (+) or CI-AKI (–).

RESULTS: CI-AKI has occurred in 72 of 551 patients (13.1%). PNI was significantly lower in the CI-AKI (+) group than in the CI-AKI (-) group (44.4±6.6 versus 47.2±5.8, p<0.001, respectively). Multivariate logistic regression analysis showed that PNI [odds ratio, OR: 1.631, 95% confidence interval (CI): 1.168–2.308, p=0.02] and estimated glomerular filtration rate (OR: 3.26, 95%CI 1.733–6.143, p<0.001) were independent risk factors for CI-AKI.

CONCLUSIONS: PNI is an independent risk factor for CI-AKI. The development of CI-AKI may be the mechanism responsible for the relationship between poor nutritional status and adverse cardiac events.

KEYWORDS: Prognostic nutritional index. Acute kidney injury. Acute coronary syndrome. Percutaneous coronary intervention.

INTRODUCTION

Poor nutritional status is linked to increased morbidity, mortality, hospitalization time, and reduced quality of life in patients with malignancy and renal disease[1,2]. Recent studies also linked malnutritional status with poor clinical outcomes in cardiovascular diseases such as acute heart failure, stable coronary artery disease, myocardial infarction, pulmonary embolism, and prognostic importance[3-5]. However, the pathophysiology is not defined yet.

Contrast-induced acute kidney injury (CI-AKI) is linked to morbidity and mortality in acute coronary syndrome (ACS). Furthermore, CI-AKI is one of the complications that can occur after percutaneous coronary intervention (PCI)[6,7]. The CI-AKI pathophysiology is complex, and the underlying mechanism is unknown[8].

Prognostic nutritional index (PNI) that can be calculated using serum albumin level and total lymphocyte used to evaluate immunonutritional status[9]. We hypothesized that the mechanism underlying poor clinical outcomes

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 06, 2021. Accepted on July 03, 2021.

associated with under nutritional status in patients with ACS can be CI-AKI. The objective of this study was to investigate the relationship between PNI and CI-AKI in patients with ACS who underwent emergency PCI.

METHODS

This study prospectively evaluated 600 patients diagnosed with ACS that underwent emergency PCI. However 49 patients were excluded due to missing serum albumin levels or total lymphocyte count (n=15), end-stage renal disease (n=12), malignancy (n=11), death during PCI (n=5), active infection (n=3), previous chronic inflammatory disease (n=2), and severe liver cirrhosis (n=1). The study was completed with a total of 551 patients. The local ethics committee (Approval #2017,12,07,3028) approved the study. All patients signed a consent form after PCI.

The diagnosis of ACS was based on the guidelines of the European Society of Cardiology and the American College of Cardiology including ST-segment and non-ST segment/unstable angina. CI-AKI was characterized according to the Kidney Disease Improving Global Outcome criteria with an increase in serum creatinine (SCr) ≥0.3 mg/dL or ≥50% from the baseline SCr levels within 48 h after PCI[10]. Patients were classified as CI-AKI (-) or CI-AKI (+). PNI was calculated as 10× serum albumin (g/dL) + 0.005× total lymphocyte count (mm^3)[11].

Blood samples were collected 30 min after emergency admission but before PCI (baseline measurements) for the measurement of serum albumin, SCr, and complete blood count (CBC) within the first 30 min after an emergency admission, before PCI. Serum albumin and SCr were measured with the Olympus AU 600 autoanalyzer (Olympus Optical Co., Ltd., Schimatsu-Mishima, Japan). CBC was measured with an automatized CBC device (Abbott cell Dyn, Chicago, IL, USA). Demographic characteristics and risk factors were asked after PCI, and the patient was stabilized. Patients were not given treatment to prevent CI-AKI before the procedure. Intravenous hydration was given for at least 12 h after PCI. The duration of intravenous infusion was depended on the patient and the physician. All patients received a nonionic, iso-osmolar contrast agent. Coronary intensive care unit and follow-ups were performed by the cardiologist managing the patient. The treatments were arranged according to the current guidelines.

Statistical analysis

All statistical tests were carried out using SPSS version 22.0 (SPSS, Chicago, IL, USA). Continuous variables are shown as mean and standard deviation (SD) or median with interquartile ranges, and categorical variables are shown as percentages (%). Normal distribution was determined with the Kolmogorov-Smirnov test. If variables were normally distributed, the Student's t-test was used. The Mann–Whitney U test was used for continuous variables of non-normal distribution. The between-group comparisons were achieved by χ^2-test for categorical variables. To predict CI-AKI, a multiple stepwise logistic regression analysis with the backward elimination method was performed. The elimination criterion was defined as having a probability of above 0.10. The covariates in the regression model were as follows: age, gender, heart rate, systolic blood pressure, Mehran risk score, cardiogenic shock, urea, basal creatinine value, estimated glomerular filtration rate (eGFR), high-density lipoprotein, ejection fraction, PNI, and contrast amount. A $p<0.05$ was considered significant.

RESULTS

A total of 551 patients with ACS admitted to the coronary angiography laboratory for emergency PCI were enrolled. The average age was 62.5±10.7 years with 63% male (n=347). CI-AKI has occurred in 72 of 551 patients (13.1%). During the study, 17 patients died (3.1%). The demographic characteristics of the patients included in this study are presented in Table 1. Based on the development of CI-AKI development, 479 patients were classified as CI-AKI (-) and 72 were classified as CI-AKI (+). Age was significantly different between the two groups [age (years): CI-AKI (–), 62.1±10.7; CI-AKI (+), 65.1±0.1; p=0.02]. However, gender was not different [male, n (%): CI-AKI (-), 304 (63.5%); CI-AKI (+), 43 (59.7%); p=0.54]. Baseline SCr value, heart rate, Mehran risk score, amount of contrast used, hospital stay, and mortality rate were higher in the CI-AKI (+) group whereas the systolic blood pressure and eGFR rate were increased in the CI-AKI (-) group. Comorbidities such as hypertension, diabetes mellitus, previous myocardial infarction, previous stent implantation, and previous bypass operation were similar between the groups. The clinical features and laboratory results of the two groups are shown in Table 2.

The PNI was significantly lower in the CI-AKI (+) group [PNI: CI-AKI (+), 44.4±6.6; CI-AKI (-), 47.2 ± .8; p<0.001]. The multivariate logistic regression analysis showed that PNI [odds ratio, OR: 1.631, 95% confidence interval (CI): 1.168–2.308, p=0.02] and eGFR (OR: 3.26, 95%CI 1.733–6.143, p<0.001) were independent risk factors for CI-AKI (Table 3).

DISCUSSION

This study shows that PNI and eGFR levels are independent risk factors for the development of CI-AKI in patients with ACS undergoing PCI.

Recent studies have shown the clinical significance of nutritional status in cardiovascular diseases[3-5,12,13]. PNI is a marker

Table 1. Demographic characteristics of patients.

Characteristics	551 of patients
Age (years)	62.5±10.7
Female, n (%)	204 (37)
Body mass index (kg/m^2)	27.6±3.5
Admission heart rate (beats/min)	75.7±15.5
Admission systolic blood pressure (mmHg)	123.8±22.2
Admission diastolic blood pressure (mmHg)	73.4±15.4
Hypertension, n (%)	227 (41.2)
Diabetes mellitus, n (%)	163 (29.6)
Known coronary artery disease, n (%)	110(20.0)
Previous myocardial infarction, n (%)	66 (12.0)
Previous treatments	
Acetylsalicylic acid, n (%)	127 (23.0)
β-Blocker, n (%)	67 (12.2)
Angiotensin-aldosterone system antagonists, n (%)	205 (37.2)
Clinical presentation	
ST-segment elevation myocardial infarction, n (%)	368 (66.8)
Non-ST-segment elevation myocardial infarction, n (%)	122 (22.1)
Unstable angina pectoris, n (%)	61 (2.9)
Hematocrit (%)	41.1±4.8
Urea (mg/dL) median (interquartile range)	36.2 (17.3
Basal creatinine (mg/dL) median (interquartile range)	0.81 (0.24)
Serum albumin (mg/dL)	3.78±0.46
Prognostic nutritional index	46.8±6.0
Contrast amount (mL) median (interquartile range)	160 (70)
Estimated glomerular filtration rate (mL/min/1.73m^2)	89.4±27.1
Left ventricular ejection fraction (%) median (interquartile range)	54 (18)
Transradial approach, n (%)	179 (32.5)
Mehran risk score median (interquartile range)	2.0 (5.0)
Contrast-induced acute kidney injury, n (%)	72 (13.1)
Cardiogenic shock, n (%)	16 (2.9)
Inhospital mortality, n (%)	17 (3.1)

Table 2. Comparison of features of contrast-induced acute kidney injury (–) and contrast-induced acute kidney injury (+) groups.

Variables	CI-AKI (-) (n=479) Mean±SD/ median (IQR)	CI-AKI (+) (n=72) Mean±SD/ median (IQR)	p
Age (years)	62.1±10.7	65.1±10.1	**0.02**
Female, n (%)	175 (36.5%)	29 (40.3%)	0.54
BMI (kg/m^2)	27.5±3.3	27.9±4.2	0.38
Hypertension, n (%)	195 (40.7%)	32 (44.4%)	0.54
Diabetes mellitus, n (%)	138 (28.8%)	25 (34.7%)	0.30
Smoking, n (%)	90 (18.8%)	8 (11.1)	**0.03**
Heart rate (beats/min)	75.2±15.3	79.2±16.8	0.06
Systolic BP (mmHg)	124.6±21.8	118.1±24.0	**0.03**
Diastolic BP (mmHg)	73.9±15.3	69.9±16.0	0.05
Previous stent, n (%)	68 (14.2%)	12 (16.7%)	0.57
Previous CABG, n (%)	24 (5.0%)	6 (8.3%)	0.24
Previous MI, n (%)	55 (11.5%)	11 (15.3%)	0.35
Previous treatments			
β-Blocker, n (%)	57 (11.9%)	10 (13.9%)	0.63
ACE-İ/ARB, n (%)	177 (37.0%)	28 (38.9%)	0.75
Acetylsalicylic acid, n (%)	110 (23.0%)	17 (23.6%)	0.90
Clinical presentation			
STEMI, n (%)	316 (66.0%)	52 (72.2%)	0.55
NSTEMI, n (%)	108 (22.5%)	14 (19.4%)	
UAP, n (%)	55 (11.5%)	6 (8.3%)	
Transradial approach, n (%)	158 (33.0%)	21 (29.2%)	0.51
Ejection fraction (%)	55 (15)	48 (17.5)	**0.004**
LVEDD (cm)	4.7±0.6	4.6±0.6	0.79
LVESD (cm)	3.0±0.8	3.1±0.8	0.11
Mehran risk score	2 (5)	5 (5)	**<0.001**
Glucose (mg/dL)	114 (98–149)	121(101–181)	0.26
Urea (mg/dL)	35.7 (28.7–45.5)	39.4 (30.1–54.4)	**0.04**

Continue...

Table 2. Continuation.

Variables	CI-AKI (-) (n=479) Mean±SD/ median (IQR)	CI-AKI (+) (n=72) Mean±SD/ median (IQR)	p
Basal creatinine (mg/dL)	0.80 (0.71–0.92)	0.90 (0.82–1.23)	**<0.001**
eGFR (mL/min/1.73m^2)	91.6±26.5	75.0±27.1	**<0.001**
Hemoglobin (g/dL)	13.7±1.8	13.4±2.0	0.15
Hematocrit (%)	41.2±4.7	40.1±5.4	0.10
WBC (×10^9/L)	8.3±2.4	8.0±2.1	0.43
Lymphocyte count (×10^9/L)	1.8±0.7	1.6±0.6	**0.03**
Platelet count (×10^9/L)	245.2±75.2	237.6±85.2	0.43
Total cholesterol (mg/dL)	195.3±47.1	186.1±55.2	0.18
LDL (mg/dL)	120.9±41.1	127.0±45.3	0.25
HDL (mg/dL)	36.9±9.7	34.4±11.3	0.08
Triglyceride (mg/dL)	158 (111–217)	147 (116–188)	0.23
Albumin (g/dL)	3.8±0.4	3.6±0.5	**0.007**
Prognostic nutritional index	47.2±5.8	44.4±6.6	**<0.001**
Culprit coronary lesion			
Left anterior descending, n (%)	195 (40.7%)	38 (52.8%)	0.09
Circumflex, n (%)	105 (21.9%)	9 (12.5%)	
Right, n (%)	171 (35.7%)	20 (27.8%)	
Left main, n (%)	1 (0.2%)	1 (1.4%)	
Bypass graft, n (%)	7 (1.5%)	4 (5.6%)	
Contrast amount (mL)	160(60)	180 (81)	**0.01**
Hospital stay (day)	3 (2)	4 (3)	**0.001**
Cardiogenic shock	11 (2.3%)	5 (6.9%)	**0.03**
Inhospital mortality, n (%)	6 (1.3)	11 (15.3)	**<0.001**

CI-AKI: contrast-induced acute kidney injury; IQR: interquartile range; BMI: body mass index; BP: blood pressure; CABG: coronary artery bypass grafting; MI: myocardial infarction; ACE-İ: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blocker; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UAP: unstable angina pectoris; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; eGFR: estimated glomerular filtration rate; WBC: White blood cell; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. Bold numbers indicate statistically significant results (p<0.05).

for the evaluation of nutritional status but is also used for the assessment of immune and inflammatory status[9,14]. The reduction of serum albumin levels, one of the components of PNI, is associated with the increased severity of inflammation[15]. Hypoalbuminemia is an independent predictor of the long-term mortality in patients with ACS treated with primary PCI[15,16]. Other studies have shown that lymphocytes (another component of PNI) are playing a role in the inflammatory response in various stages of atherosclerosis[17]. For example, low lymphocyte counts were associated with complications and mortality in acute myocardial infarction[18].

In light of this information, it is not surprising that PNI is an independent predictor of mortality in patients with acute myocardial infarction[12,14]. However, the pathophysiological mechanism has not been clearly established. Various mechanisms are emphasized. A decrease in serum albumin levels leads to the increased inflammatory process, increased platelet aggregation, and increased blood viscosity, causing deterioration in endothelial function. Low lymphocyte counts contribute to this process due to an inadequate immunological reaction[19-22]. In this study, both albumin and lymphocyte counts were found to be different between groups.

CI-AKI with a sudden loss of renal function after contrast agent exposure occurs in 13.1% of the patient in our study, which is consistent with the literature (2–20%)[13]. The development of CI-AKI after PCI increases morbidity and mortality[23,24]. Interestingly, our study shows that both the hospital stay and the mortality rate were higher in the CI-AKI (+) group. The pathophysiology of CI-AKI has not been established yet and is very complex[25]. Inflammation, oxidative stress, free radical injury, and endothelial dysfunction are the main mechanisms involved in the pathophysiology of CI-AKI. The reduction of albumin, one of the major antioxidant agents in plasma, leads to an increase in oxidative stress. In addition, low serum albumin levels reflecting the inflammation burden in the body cause an increase in blood viscosity and impair endothelial function[8]. Notably, the mechanisms involved in the association of malnutrition with adverse cardiac events and many other mechanisms involved in the development of CI-AKI are similar. Thus, the relationship between poor nutritional status and CI-AKI is not surprising. In our study, the PNI value of the CI-AKI (+) group was significantly lower than that of the CI-AKI (-) group, and PNI was an independent predictor of CI-AKI.

Limitation

This study has limitations. First, this is a single-centered, observational study with relatively low enrollment. Second, the PNI values of the patients were only calculated once a baseline was not at follow-up and discharge. Third, the hormonal changes

Table 3. Independent predictors for contrast-induced acute kidney injury in patients with acute coronary syndrome undergoing emergency percutaneous coronary intervention.

Variables	Univariate analysis			Multivariate analysis		
	OR	(95%CI)	p	OR	(95%CI)	p
Age	2.08	(1.134–3.810)	0.01	1.65	(0.796–3.427)	0.17
Male	0.85	(0.514–1.416)	0.54			
Systolic blood pressure	0.59	(0.319–1.093)	0.09	0.57	(0.301–1.105)	0.09
Heart rate	1.69	(0.747–3.819)	0.20	1.01	(0.995–1.027)	0.17
Ejection fraction	2.25	(1.364–3.710)	0.002	2.01	(1.135–3.558)	**0.01**
Urea	2.01	(1.183–3.435)	0.01	092	(0.467–1.813)	0.81
Basal creatinine	2.50	(1.388–4.515)	0.002	0.91	(0.400–2.089)	0.83
eGFR	3.72	(2.171–6.396)	<0.001	3.26	(1.733–6.143)	**<0.001**
HDL-C	1.72	(0.982–3.038)	0.07			
Prognostic nutritional index	1.74	(1.281–2.708)	0.02	0.28	(1.631–2.308)	**0.02**
Mehran risk score	1.87	(1.139–3.122)	0.01	0.70	(0.348–1.417)	0.32
Contrast amount	3.38	(1.821–6.274)	<0.001	2.64	(1.582–4.916)	**0.01**
Cardiogenic shock	3.17	(1.070–9.422)	0.03	0.17	(0.680–9.144)	0.16

OR: odds ratio; CI: confidence interval; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol. Bold numbers indicate statistically significant results (p<0.05).

may affect PNI values and were not account for in this study. Fourth, specific inflammation and oxidative stress markers were not measured.

CONCLUSION

As a result, low PNI values are an important risk factor in the development of CI-AKI. The development of CI-AKI, in the association between poor nutritional status and increased adverse cardiac events, may be one of the underlying pathophysiological mechanisms. PNI may be guiding in determining patients with a high risk of the development of CI-AKI in patients with ACS who are undergoing emergency PCI, deciding to start preventive treatment earlier, and deciding which patients to monitor their renal function for longer.

AUTHORS' CONTRIBUTIONS

ALS: Project administration. **Aİ:** Writing-original draft. **AA:** Investigation. **ST:** Data curation. **NBA:** Data curation. **YA:** Methodology. **HA:** Data curation

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210509

rs7903146 mutation of Type 2 diabetes mellitus-related gene TCF7L2 is not associated with polycystic ovary syndrome in a cohort of Turkey

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SUMMARY

OBJECTIVE: The aim of this study was to investigate whether TCF7L2 gene mutation rs7903146 is in association with polycystic ovary syndrome (PCOS).

METHODS: A total of 44 PCOS and 48 control participants were recruited for this study. After DNA extraction from peripheral blood, quantitative PCR method was used for genotyping. With a case-control study design, two groups were compared for genotype and allele frequencies as well as clinical characteristics.

RESULTS: Mean testosterone level was significantly higher in PCOS group, whereas mean progesterone level was significantly higher in control group. In PCOS group, mean thyroid-stimulating hormone (TSH) level was significantly higher in polymorphic allele carriers. Genotype and allele frequencies were not different between groups.

CONCLUSIONS: When investigated for the first time in a population from Turkey, no association between PCOS and TCF7L2 gene rs7903146 polymorphism was detected. However, considering contradictory results of other populations and low cohort scale of this study, replication studies with greater cohorts are needed.

KEYWORDS: PCOS. TCF7L2. Rs7903146. Polymorphism. Turkey.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disease of women characterized by polycystic ovaries, as well as high levels of androgens, hyperinsulinemia, and absence of ovulation[1]. It is concluded that both genetic and environmental factors cause PCOS condition. However, etiology of the disease is still unclear. Diagnosis of PCOS may be made according to criteria of two consensuses[2]. First, as declared by the US National Institute of Health (NIH) in 1990 and second, as declared by the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) in 2003, which is called Rotterdam criteria[3,4]. According to Júnior Soares et al.,[2] the most recent and accepted consensus is addressed by the Androgen Excess and Polycystic Ovary Syndrome (AES-PCOS) Society who recommends the presence of hyperandrogenism accompanied by chronic anovulation and/or imaging of polycystic ovaries for diagnosis of PCOS[2]. Clinical manifestations may vary from mild to serious level. Also, women with PCOS are at higher risk of metabolic conditions such as obesity, insulin resistance (IR), and diabetes. IR is one of the most prominent characteristic of the PCOS disease, such that these patients are most likely to develop type 2 diabetes (T2DM)[5]. Also, some PCOS patients may show clinical signs of hirsutism,

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: this work was funded by Karabük University, Committee of Scientific Research Projects.
Received on July 03, 2021. Accepted on July 03, 2021.

alopecia, and acne[6]. The pathophysiological features like IR and hyperinsulinemia of T2DM are similar to PCOS, making T2DM-associated genetic variants plausible candidates for PCOS. On the reproductive physiology side, due to hormonal derangement in PCOS, maturated follicles may not function as fertile eggs[7].

A number of genetic variations have been analyzed and associated with PCOS and selection of the candidate genes investigated before were based on their function and molecular pathway. Also considering approximately 70% of PCOS patients also develop IR, it is concluded that IR may be closely relevant to etiology of PCOS[8]. Additionally, IR-related conditions such as normal body mass index and medication for IR improve PCOS clinical condition such as rebalancing hormones and resuming normal ovulation[9].

Transcription factor 7-like 2 (TCF7L2) gene resides on chromosome 10q25.2 and has 17 exons with approximately 21.5 kb length[10]. TCF7L2 is a transcription factor that participates in Wnt signaling pathway, particularly playing a role in maintaining blood glucose levels by repressing proglucagon gene of intestinal endocrine and pancreatic cells[11]. Wnt pathway participates in multiple processes in the cell-like proliferation, apoptosis, and differentiation[12].

rs7903146 polymorphism is strongly related to T2DM development by Wnt pathway through islet cells of pancreas and interacting with insulin secretion genes[13]. Wnt pathway also regulates proliferation and apoptosis mechanisms of the β-cells of pancreas, thus has the ability to make changes in the insulin activity[14]. Being multitasking and a key to born and survival of the cell, this pathway was found to be related with many degenerative diseases such as cancer and Alzheimer's diseases. Also, it was shown that in PCOS ovaries, Wnt signaling members display altered expression[15]. Another known effect of Wnt pathway is that adolescent girls with Wnt 4 mutations display hyperandrogenism[16]. Furthermore, TCF7L2 protein induces production of various proteins that are involved in insulin secretion and represses proglucagon synthesis across Wnt pathway[17,18]. The link between TCF7L2 (rs7903146) and PCOS comes from being TCF7L2 a transcription factor of Wnt signaling pathway that is included in diabetes mellitus, a frequent accompanying complication of PCOS[19]. Also, it was suggested that TCF7L2 gene was expressed in visceral and subcutaneous tissue for regulating glucose homeostasis via Wnt signaling pathway, indicating a possible link between this polymorphism and PCOS[20]. Also, Lee et al. reported an eye-catching feature of Wnt pathway which activated Wnt pathway in nondiabetic mice fed with high-fat diet[21]. Genetic polymorphisms in TCF7L2 were reported to be clearly associated with T2DM as well as dysfunction of β cells[22]. Wnt pathway also referred as Wnt/b-Catenin pathway also has a function of drug metabolism in primary human hepatocytes that may be used for evaluating drug hepatoxicity[23].

rs7903146 is one of the candidate polymorphisms for the direct association with PCOS among other single nucleotide polymorphisms (SNPs) in the gene. The polymorphic nucleotide resides in an intron, which is a not a coding nucleotide for the protein itself. Since TCF7L2 directly effects insulin secretion that is associated with PCOS, rs7903146 was chosen for investigating its associations with PCOS. Considering its molecular mechanism, TCF7L2 stands as both activator and repressor of Wnt pathway regulatory genes, thus, it is one of the most influential risk genes on developing T2DM condition that is related to PCOS[23].

To date, using candidate gene approach, several genes were investigated in terms of their association with PCOS. Since detailed mechanism of PCOS is still unclear, this approach yielded negative results from studies. In GWAS studies, 11 loci out of 70 candidate genes were found associated with PCOS[24]. Thus, when investigating the association of TCF7L2 with PCOS, rs7903146 stands as one of the most plausible SNPs to investigate. To date, association of rs7903146 with PCOS was investigated in the UK, Finland, Tunisia, Greece, Bahrain, Korea, Brazil, India, Czech Republic, and China[25]. Majority of these studies failed to detect the association, except in the study conducted by Greece.

METHODS

Sample collection

Case group of 44 and control group of 48 individuals were included in this study from Education and Research Hospital of Karabük University. Control and case groups were matched in regard to their age. Individuals who went to hospital for periodic controls were taken as control group, whereas individuals diagnosed with PCOS according to Rotterdam criteria after clinical examination, laboratory testing, and ultrasonography were taken as case group. Relatives, taking medication, and having chronic diseases were set as exclusion criteria. All subjects were informed and signed written consent. Study protocol was approved by ethics committee of medical faculty of Karabük University.

Biochemical analysis

About 2 mL of peripheral blood were draw to EDTA-containing tubes from all participants after 12-h of fasting. Siemens ADVIA Centaur® XP electrochemiluminescence assay was used for hormone level measurement. Biochemical measurements of

blood glucose levels were made with ADVIA® 2400 Clinical Chemistry System that uses spectrophotometry.

DNA extraction and analysis

DNA was extracted from leukocytes of peripheral blood according to attached protocol (GF-1 Blood DNA Extraction Kit, Vivantis, Malaysia). Extracted DNA was stored at -20°C. Specific primers were designed using Primer3 software[26]. Real-time quantitative PCR method was performed in 20 µL PCR mix using Eva Green DNA binding dye (SNP, Turkey). ABI 7,500 Real Time PCR system was used for performing qPCR and analysis of the CT levels (Thermo Fisher Scientific Inc.).

Statistical analysis

Both groups were detected for Hardy-Weinberg equilibrium by chi-square analysis. Normal distributions of all variables were controlled by using Kolmogorov-Smirnov test. Continuous variables were tested using Student's t-test for variables compatible with normal distribution and given as mean±standard deviation. For clinical data not compatible with normal distribution, Mann-Whitney U test was used (progesterone clinical data). Alpha level for statistical significance were determined as p=0.05. Chi-square test was used to determine significant level of genotype and allele frequency distribution between control and PCOS groups. Homogeneity of variances were tested before analysis of variance by Leven's test. ANOVA method was used for testing the differences of clinical data except progesterone between genotypes in PCOS group. Since distribution of progesterone levels do not follow normal distribution, levels between genotypes were tested by Kruskal-Wallis test. For evaluation of effects of genotypes on PCOS, logistic regression analysis was performed. In all tables, data were given for all available subjects.

RESULTS

Testosterone level of PCOS group was significantly elevated compared with controls (p<0.01). Progesterone level in control group was significantly increased than that of PCOS group (p<0.01). Other measurements of clinical data did not give any significant difference between groups (Table 1). In PCOS intragroup comparison between genotypes, only thyroid-stimulating hormone (TSH) level of CT+TT genotypes were significantly higher than that of CC genotype in dominant model (p<0.05).

Table 1. Clinical data of subjects and comparison of clinical characteristics between genotypes in case group.

	Controls (n=33)	PCOS (n=48)	p	Case group	Recessive model		p	Dominant model		p
Age (years)	26.1±7.1	23.7±5.8	>0.05	Genotype	CC+CT	TT		CC	CT+TT	
BMI (kg/m²)	24.9±3.5	24.1±5.4	>0.05	BMI (kg/m²)	24.3±5.6	22.5±3.3	0.45	23.5±5.9	24.5±5.03	>0.05
Insulin (pmol/L)	127±50	109±40	>0.05	Insulin (pmol/L)	107±37	99±36	0.59	108±43	105±32	>0.05
Testosterone (nmol/L)	1.09±0.39	1.58±0.57	<0.01	Testosterone (nmol/L)	1.59±0.60	1.53±0.29	0.831	1.46±0.63	1.68±0.52	>0.05
Fasting glucose (mmol/L)	4.96±0.53	5.04±0.42	>0.05	Fasting glucose (mmol/L)	5.03±0.44	5.16±0.28	0.509	4.99±0.44	5.09±0.41	>0.05
Estradiol (pmol/L)	205.94±90.31	196.03±88.84	>0.05	Estradiol (pmol/L)	204±89	132±66	0.086	197±74	195±101	>0.05
FSH (IU/L)	7.67±2.76	6.96±2.08	>0.05	FSH (IU/L)	6.81±1.96	7.91±2.81	0.227	6.90±2.22	6.98±2.02	>0.05
LH (IU/L)	8.13±3.90	8.59±4.28	>0.05	LH (IU/L)	8.67±4.36	7.93±3.89	0.749	8.86±4.41	8.33±4.24	>0.05
Progesterone (ng/mL) (nmol/L)[1]	15.45±12.75	3.85±7.63	<0.01	Progesterone (ng/mL) (nmol/L)*	3.65±7.70	7.55±3.38	0.408	2.05±1.36	5.29±10.0	>0.05
Prolactin (µg/L)	10.8±5.18	11.7±4.68	>0.05	Prolactin (µg/L)	11.58±4.8	12.90±3.74	0.6	12.63±4.98	11.01±4.43	>0.05
TSH (IU/L)	2.17±1.09	2.47±1.16	>0.05	TSH (IU/L)	2.59±1.13	1.74±1.10	0.095	2.02±0.99	2.80±1.18	0.028

PCOS: polycystic ovary syndrome; BMI: Body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone. *Progesteron levels were compared by Mann-Whitney U test due to noncomformity to parametric test requirements. Only available data were included. Standard deviations are given after±symbol. The values highlighted in bold are intended to draw the reader's attention to statistically significant variables

Genotype and allele frequency comparison is given in Table 2. There was no difference between groups, either for genotype or for allele frequencies (p>0.05).

Logistic regression analysis were given in Table 3. For unadjusted and adjusted models, polymorphism did not have effect on placing in any groups (p>0.05, OR: 1.571, 95%CI 0.675–3.657; p>0.05, OR: 1.810, 95%CI 0.751–4.361, respectively).

DISCUSSION

Here, we aimed to investigate whether rs7903146 polymorphism of the TCF7L2 gene is in association with PCOS in a population from Turkey. Studies from other countries such as Europe, China, Korea, and Brazil yielded negative results[27-31]. In a population from Tunisia consisting of Arabic and Turkish origins; from Bahrain consisting of Jafari Arabs, Sunni Arabs, and Iranians, association between PCOS and rs7903146 was rejected[14,32]. As the first time in a population from Turkey, our goal was to detect whether there is an association between TFC7L2 gene rs7903146 polymorphism and PCOS as well as to compare the clinical data and elucidate polymorphism frequency of the groups. In this regard, we recruited 44 PCOS and 48 control subjects.

In our comparison of clinical data between groups, we have found that testosterone level was significantly higher in PCOS group compared with controls (Table 1; p<0.01). In studies from Greece, Korea, and Brazil, similar testosterone comparison results were reported[28,30,33]. This result is expected since hyperandrogenism displays elevated testosterone levels. This condition physiologically may result from increased production of testosterone from polycystic ovarium. Increased testosterone also may be stimulated by increased insulin levels and IR but we did not detect any significant difference in insulin levels between groups (Table 1; p>0.05). Also, we have found that progesterone level was significantly higher in control group (Table 1; p<0.01). However in Greece study, progesterone comparison gave contradictory result as being higher in PCOS group[33]. We did not encounter more progesterone level comparison in similar studies. Although higher progesterone levels in PCOS patients is expected due to hyperandrogenism, our result may be due to desensitization of hypothalamus as this condition is also presented in PCOS patients.

In our cohort, genotype and allele frequencies did not represent any significant difference between case and control groups (Table 2; p>0.05). Our control group was compatible with Hardy-Weinberg equilibrium. In Greece study, polymorphic T allele frequency was borderline significantly higher in PCOS group creating a weak predisposition to PCOS, although genotype frequencies did not represent an association between rs7903146 polymorphism and PCOS (p=0.04)[33]. In a cohort

Table 2. Genotype and allele frequency comparison.

		Controls (n=44)	PCOS (n=48)	p
rs7903146 n (%)	CC	22 (55)	21 (44)	>0.05
	CT	10 (25)	21 (44)	
	TT	8 (20)	6 (12)	
Allele frequencies C/T		0.67/0.33	0.66/0.34	>0.05
rs7903146 n (%)	CC	22 (55)	21 (44)	>0.05
	CT+TT	18 (45)	27 (56)	

PCOS: polycystic ovary syndrome. Odds ratio for CT+TT between groups is 1,571 (95%CI 0.675–3.657).

Table 3. Logistic regression analysis.

		Unadjusted model		Adjusted model*	
		OR (95%CI)	p	OR (95%CI)	p
Recessive model	CC+CT	1	0.3	1	0.41
	TT	0.571 (0.180–1.812)		0.607 (0.187–1.970)	
Dominant model	CC	1	0.3	1	0.19
	CT+TT	1.571 (0.675–3.657)		1.810 (0.751–4.361)	

OR: odds ratio; CI: confidence interval. *Adjusted for age and body mass index.

from Bahrain, who are ethnically close to Turkey, that includes Turks, rs7903146 was not associated with PCOS (p>0.05)[14]. Similar to this study, Barber et al.[28] had the largest cohort (369 PCOS patients and 2,574 controls for one study and 540 patients and 1,083 patients for another) consisting ethnicities of British, Irish, and Finnish subject, yet they did not detect any association (p>0.05). In a study with Korean population containing 377 patients and 386 control subjects, again association was lacking between rs7903146 polymorphism and PCOS (p>0.05)[28]. In a study from India with 248 patients and 210 control subjects, no association also reported (p>0.05)[24].

We performed intragroup comparison of clinical characteristics for PCOS patients. Unexpectedly, we detected a significant difference of only TSH, being higher in polymorphic carriers (CC versus CT+TT) compared with homozygous normal subjects (Table 1; p<0.05). Although subjects who have known thyroid dysfunction were excluded from the study, this difference may result due to unknown impaired thyroid function of included subjects. Another reason may be that TSH is a structurally similar hormone to follicle-stimulating hormone (FSH), thus may increase as a result of positive feedback in the case of hormone imbalance in PCOS patients, especially for polymorphic allele carriers. We are not able to compare this result with other studies, since they did not represent TSH values of case and control groups due to excluding thyroid dysfunction patients from their cohort.

Regression analysis did not show any influence of rs7903146 polymorphism on having PCOS in both unadjusted and adjusted models (p>0.05). This result is expected since we did not detect any association between the polymorphism and PCOS in chi-square analysis. GWAS studies offered candidate genes for association with PCOS, especially T2DM-related genes. Since PCOS is also an endocrine disorder that is closely related to IR, T2DM-associated genes like TCF7L2 were investigated with GWAS and for association with PCOS. However, many attempts failed to show association with PCOS. Our results that show PCOS is not associated with rs7903146 polymorphism support the conclusion which, although this polymorphism is one of the major genetic determinants of IR, it does not directly affect PCOS.

When we consider case-control studies, the effect of polymorphisms on PCOS seems to be very slight. However, this consideration may result from relatively small sample sizes of conducted studies similar to this study. In this regard, studies with larger cohorts are needed to achieve more powered and accurate statistics.

PCOS susceptibility gene research progress slowly compared with other diseases such as obesity and T2DM. Phenotypic heterogeneity is one of the most preclusive factors which prevents conclusions for which genes and variants may be included in PCOS pathophysiology.

CONCLUSIONS

Limitation of this study is lower recruited sample size compared with similar studies. On the other hand, strength of this study is being the first investigation of rs7903146 in a population from Turkey and exclusion of diabetes mellitus and other metabolic disease carriers, thus focusing on only the association between PCOS and the polymorphism. In this study, we conclude that rs7903146-coded polymorphism of TCF7L2 gene is not associated with PCOS in a cohort from Turkey. Considering that this is a pilot study that has a lower sample size and contradictory results of similar studies, replicating with a larger and more inclusive cohort that better represents the population of Turkey is recommended.

ACKNOWLEDGMENT

We thank to Yeliz Eski (MSc) for contributing to laboratory progress of this study.

AUTHORS' CONTRIBUTIONS

ET: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology Project administration, Resources, Software Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SE:** Conceptualization, Data curation, Investigation, Resources, Visualization, Writing – original draft.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210525

Can copeptin predict the severity of coronavirus disease 2019 infection?

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SUMMARY

OBJETIVE: Coronavirus disease 2019 (COVID-19) has quickly turned into a health problem globally. Early and effective predictors of disease severity are needed to improve the management of the patients affected with COVID-19. Copeptin, a 39-amino acid glycopeptide, is known as a C-terminal unit of the precursor pre-provasopressin (pre-proAVP). Activation of AVP system stimulates copeptin secretion in equimolar amounts with AVP. This study aimed to determine serum copeptin levels in the patients with COVID-19 and to examine the relationship between serum copeptin levels and the severity of the disease.

METHODS: The study included 90 patients with COVID-19. The patients with COVID-19 were divided into two groups according to disease severity as mild/moderate disease (n=35) and severe disease (n=55). All basic demographic and clinical data of the patients were recorded and blood samples were collected.

RESULTS: Copeptin levels were significantly higher in the patients with severe COVID-19 compared with the patients with mild/moderate COVID-19 (p<0.001). Copeptin levels were correlated with ferritin and fibrinogen levels positively (r=0.32, p=0.002 and r=0.25, p=0.019, respectively), and correlated with oxygen saturation negatively (r=-0.37, p<0.001). In the multivariate logistic regression analysis, it was revealed that copeptin (OR: 2.647, 95%CI 1.272–5.510; p=0.009) was an independent predictor of severe COVID-19 disease. A cutoff value of 7.84 ng/mL for copeptin predicted severe COVID-19 with a sensitivity of 78% and a specificity of 80% (AUC: 0.869, 95%CI 0.797–0.940; p<0.001).

CONCLUSION: Copeptin could be used as a favorable prognostic biomarker while determining the disease severity in COVID-19.

KEYWORDS: COVID-19. Mild/Moderate COVID-19. Severe COVID-19. Copeptin. Biomarkers.

INTRODUCTION

In the city of Wuhan in China, a pneumonia outbreak that developed due to a novel coronavirus was detected in December 2019. The outbreak could not be taken under control and it spread all around the world, resulting in a pandemic. The novel coronavirus was defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Accordingly, the disease that resulted from the virus was defined as coronavirus disease 2019 (COVID-19) by the World Health Organization[1,2]. As of May 24, 2021, approximately 167 million COVID-19 cases and more than 3.4 million deaths were reported all around the world[3].

Copeptin is a glycopeptide that consists of 39 amino acids. It is also related to arginine vasopressin (AVP). Copeptin is derived from the C-terminal part of pre-pro-AVP, which is an AVP precursor molecule. Together with AVP, copeptin is expressed from neurohypophysis simultaneously either with osmotic or hemodynamic signals. Therefore, it strongly correlates with plasma levels. AVP is

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 03, 2021. Accepted on June 18, 2021.

a hormone with antidiuretic and vasoconstrictive qualities. Accordingly, it exhibits endogenous stress responses and stimuli, such as hypotension, hypoxia, hyperosmolarity, acidosis, and infections increase its expression. Nevertheless, it cannot be used as a biomarker due to circadian rhythm, short half-life, and unstable molecule status of AVP. On the other hand, copeptin is a peptin that is more stable and its levels can be detected in blood easily[4-6].

In previous studies, it was demonstrated that levels of serum copeptin were increased in diseases, such as community-acquired pneumonia (CAP), ventilator-associated pneumonia (VAP), lower respiratory tract infections, acute exacerbation of chronic obstructive pulmonary disease (COPD), and sepsis, and these increases were related to poor prognosis[7-12].

It is suggested that the assessment and management of COVID-19 should be conducted according to the disease severity. In terms of the initial data that were obtained from China, it was observed that 81% of the patients with COVID-19 experienced mild or moderate diseases, which were similar to cold and mild pneumonia, whereas 14% of the patients had severe diseases in addition to 5% of the patients, who had critical and fatal diseases[13]. At this point, early recognition of severe forms of the disease is vital for early hospitalization and appropriate treatment of the patients. The clinical status, oxygen saturation, and comorbidity mainly determine the need for hospitalization, while certain laboratory parameters can also facilitate the assessment of the severity of the disease[14]. In various studies, it was demonstrated that biomarkers, such as CRP (C-reactive protein), D-dimer, ferritin, cardiac troponin, interleukin-6 (IL-6), and lymphocyte counts, could be used in estimating the severity of the disease in risk classification[15]. In a very recent study, copeptin was found to be a useful biomarker in distinguishing COVID-19-associated pneumonia from CAP[16]. However, in the literature, it was observed that no study evaluated the relationship between COVID-19 severity and copeptin.

In this study, it was aimed to measure the serum copeptin levels in the patients with COVID-19, to evaluate the relationship of serum copeptin levels with disease severity, and to evaluate the relationships between copeptin and certain inflammatory parameters.

METHODS

Study subjects

In this study, 90 consecutive patients with COVID-19 diagnosis, who were admitted to the Pandemic Clinic in the Faculty of Medicine at Firat University between August and October 2020, were included in the sample according to the inclusion criteria. Patients older than 18 years were included in the study.

COVID-19 diagnosis was defined as a SARS-CoV-2 positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, or radiological that suggest COVID-19 infection. In the study, the clinical parameters were recorded as well as the demographic data. Following the investigation of the histories and physical examinations of the subjects, the blood samples were drawn from the patients before the treatment process.

Upon admission to the hospital, the patients with COVID-19 were categorized into three groups by considering the clinical findings, respiratory rates, oxygen saturation (SpO_2) levels, and low-dose chest CT findings[17]. The details of the classification are as follows:

Mild illness: mild clinical symptoms, no sign of pneumonia on low-dose CT.

Moderate illness: mild respiratory symptoms, positive signs of pneumonia on low-dose CT, and SpO_2 ≥94% on room air.

Severe illness: Those who meet any of the following criteria:

1. Respiratory rate >30 times per min;
2. SpO_2 <94% at room air;
3. Lung infiltrates >50% on low-dose CT.

In the study, the exclusion criteria covered the patients who had heart failure, renal failure, COPD, acute myocardial infarction, acute coronary syndrome, interstitial lung disease, any organ malignancy, or immunosuppression (HIV infection, solid organ or stem cell transplantation, or any immunosuppressive treatment). Additionally, pregnancy was an exclusion criterion in the study.

Ethics approval

The study was conducted within the framework of the Helsinki Declaration. The study was also approved by the Ethical Committee of the Medicine Faculty of Firat University (issue: 402252/20,07,2020). The subjects who participated in the study also provided their written consent to be included in the study.

Measurement of serum copeptin levels

In the measurements, the separation of the serum was conducted by centrifuging the samples at 4,000 *g* for 10 min. Then the samples were frozen at -80°C for further analysis. A double-antibody sandwich enzyme-linked immunosorbent assay kit (Catalog No. 201-12-5463 Human copeptin Elisa Kit: Sunred Biological Technology Co. Ltd. Shanghai) was used to measure the serum copeptin levels. The assay had a sensitivity of 0.067 ng/mL. The inter-assay and intra-assay calculation values were <12% and <10%, respectively. Furthermore, the detection range of copeptin was 0.07–20 ng/mL.

Statistical analyses

In the statistical analyses, IBM SPSS Statistics 21 (Version 21, authorization code: d91314f638c364094170, Armonk, NY, USA) software was used. The results obtained in the analyses were stated as mean±SD. The level of statistical significance was regarded as $p<0.05$. To compare two independent samples, the student's t-test was conducted. To compare the distribution of sex between the groups, Chi-square (χ^2) test was conducted. The parametric variables were evaluated by the Pearson correlation analysis. In the study, univariate and multivariate analyses were conducted by binary logistic regression to evaluate the variables that could predict severe COVID-19 disease. In the analysis, a 95% confidence interval (CI) was adopted while calculating the odds ratios (ORs). The receiver operating characteristic (ROC) analysis method was to determine the cutoff value for copeptin. With the ROC curve, the area under curve (AUC) value was determined.

RESULTS

Comparison of groups

In the study population, 35 patients were assigned to a mild/moderate disease and 55 patients were allocated to a severe disease. The mean serum copeptin levels of the patients with mild/moderate and severe COVID-19 were 6.4±2.2 and 11.7±4.6 ng/mL, respectively ($p<0.001$). Comparison of all laboratory data of the patients with COVID-19 was demonstrated in Table 1.

Correlation analysis

In the analyses, it was observed that serum copeptin levels positively correlated with serum ferritin and fibrinogen levels ($r=0.32$, $p=0.002$ and $r=0.25$, $p=0.019$, respectively), whereas negatively correlating with SaO_2 levels ($r=-0.37$, $p<0.001$; Figure 1).

Table 1. Comparison of the demographical and laboratory data of two groups of patients with COVID-19.

	Mild/ moderate disease (n=35)	Severe disease (n=55)	p
Age, years	44.5±14.9	58.8±16.8	**<0.001**
Sex, male, n(%)	18 (51.4)	35 (63.6)	0.25
SaO_2, %	94.7±2.5	88.4±4.4	**<0.001**
Complete blood count			
Leukocyte, $\times10^9$/L	6.4±2.8	6.0±3.2	0.53
Hemoglobin, g/dL	13.5±1.9	13.6±2.0	0.87
Platelet, $\times10^9$/L	194.5±40.7	179.8±83.1	0.33
Biochemical markers			
Urea, mg/dL	32.7±12.7	39.8±16.2	**0.03**
Creatinine, mg/dL	0.81±0.23	0.89±0.25	0.13
ALT, U/L	22.1±10.8	32.9±20.1	**0.004**
AST, U/L	27.0±15.8	40.7±20.2	**0.001**
LDH, U/L	262.9±73.2	344.7±137.8	**0.002**
D-dimer, mg/L	0.8±1.1	1.2±1.8	0.24
Inflammatory markers			
CRP, mg/L	23.8±40.6	84.6±64.2	**<0.001**
Procalcitonin, mg/L	0.34±0.5	0.30±0.41	0.61
Ferritin, ng/mL	185.2±198.0	601.9±364.4	**<0.001**
Fibrinogen, mg/dL	402.7±128.7	536.8±159.9	**<0.001**
Cardiac markers			
CK, U/L	84.6±121.3	162.5±184.6	**0.03**
CK-MB, U/L	20.9±19.5	31.2±32.4	0.09
Troponin I, µg/L	0.02±0.1	0.13±0.8	0.46
Copeptin, ng/mL	6.4±2.2	11.7±4.6	**<0.001**

SaO_2: oxygen saturation; ALT: alanine transaminase; AST: aspartate transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein; CK: creatine kinase. Bold values are statistically significant values ($p< 0.05$).

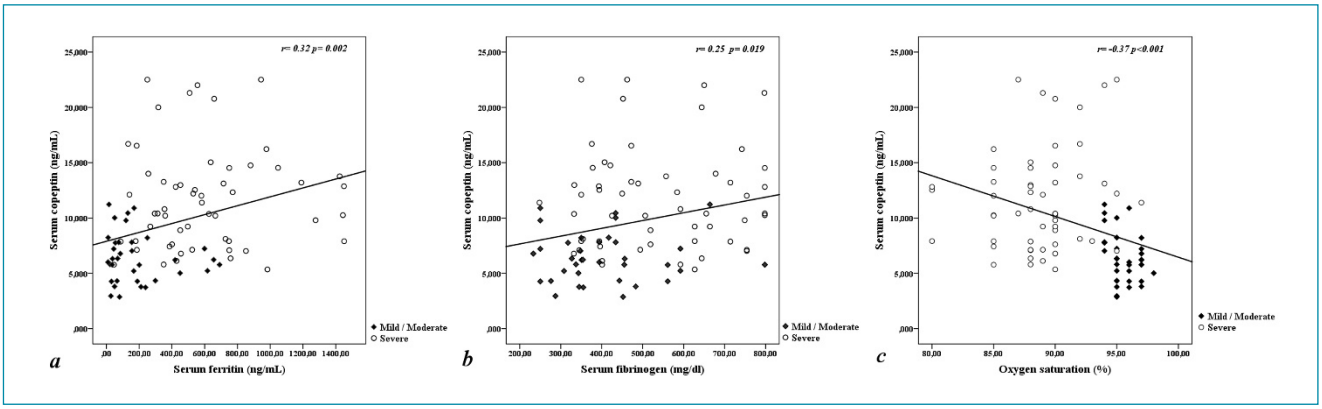

Figure 1. Correlation between serum copeptin levels and (a) ferritin, (b) fibrinogen, and (c) oxygen saturation levels in patients with COVID-19.

Logistic regression analysis

The univariable logistic regression model demonstrated the following parameters that were statistically significant, which included age, copeptin, CRP, fibrinogen, AST, ALT, LDH, and ferritin. In the multivariable logistic regression model, it was observed that that older age (OR: 1.139, 95%CI 1.036–1.251; p=0.007) and increased copeptin (OR: 2.647, 95%CI 1.272–5.510; p=0.009) and ferritin (OR: 1.005, 95%CI 1.000–1.010; p=0.034) levels were independent predictors of severe COVID-19 disease (Table 2).

ROC curve analysis

The efficacy of biochemical and inflammatory markers for the prediction of severe disease was evaluated by ROC analysis. AUC of copeptin, ferritin, CRP, fibrinogen, AST, LDH, and CK were found as 0.869 (95%CI 0.797–0.940; p<0.001), 0.846 (95%CI 0.765–0.928; p<0.001), 0.826 (95%CI 0.734–0.918; p<0.001), 0.743 (95%CI 0.639–0.847; p<0.001), 0.740 (95%CI 0.635–0.845; p<0.001), 0.676 (95%CI 0.563–0.789; p=0.005), and 0.698 (95%CI 0.590–0.807; p=0.002), respectively. Among these parameters, copeptin occupied the maximum area with 0.869. When the cutoff value for copeptin in predicting of severe disease was determined to be 7.84, the sensitivity was determined as 78%, whereas the specificity was 80%.

Table 2. Results of binary logistic regression analysis of potential predictors of severe COVID-19 disease.

	Univariable model		Multivariable model	
	p	OR (95%CI)	p	OR (95%CI)
Age, years	<0.001	1.055 (1.024–1.086)	0.007	1.139 (1.036–1.251)
Sex, male	0.25	1.653 (0.699–3.909)		
Copeptin, ng/mL	<0.001	1.740 (1.362–2.223)	0.009	2.647 (1.272–5.510)
CRP, mg/L	<0.001	1.033 (1.017–1.050)		
Urea, mg/dL	0.57	1.005 (0.988–1.022)		
Fibrinogen, mg/dL	<0.001	1.006 (1.003–1.010)		
AST, U/L	0.003	1.054 (1.018–1.091)		
ALT, U/L	0.008	1.048 (1.012–1.084)		
LDH, U/L	0.005	1.008 (1.002–1.013)		
Ferritin, ng/mL	<0.001	1.006 (1.003–1.009)	0.034	1.005 (1.000–1.010)
CK, U/L	0.06	1.005 (1.000–1.011)		
Troponin, µg/L	0.59	1.616 (0.288–9.075)		

CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CK: creatine kinase.

DISCUSSION

Biomarkers that predict the outcomes of diseases, should be higher in the disease groups compared with the healthy groups and should reflect the severity of the disease. The significance of copeptin in the patients with COVID-19 and its role as a biomarker in predicting disease severity are unknown. Our study is the first one to evaluate the relationship between severity of COVID-19 and copeptin and striking results were obtained in our study. It was determined that copeptin levels of the patients with severe COVID-19 were significantly higher than the patients with mild/moderate COVID-19, and this increase was correlated with disease severity.

It was demonstrated that copeptin played active roles in lung diseases, such as pneumonia, and it was superior to traditional inflammatory markers as a prognostic marker in the patients with CAP[5,18]. The levels of copeptin in the patients with COVID-19 could be increased due to hemodynamic, osmotic, or inflammatory reasons. In the patients with pneumonia, it was discovered that the levels of copeptin were elevated as the severity of sepsis was elevated[12]. Similarly, as the severity of the disease increases in the patients with COVID-19, the expression of copeptin, simultaneously with AVP, from neurohypophysis could be increased with hemodynamic and osmotic signals due to changes in blood pressure and plasma osmolality. Furthermore, it was reported that the endotoxins and inflammatory markers, which increased during respiratory infections, stimulated AVP secretion[4,6]. In our study, it was determined that inflammatory markers, such as CRP, ferritin, and fibrinogen, were elevated in the patients with severe COVID-19, whereas positive correlations were discovered between serum copeptin levels, serum ferritin, and fibrinogen levels. As the severity of the disease was increased, it was believed that the inflammatory markers and cytokines contributed to the increase in copeptin levels. Additionally, it is known that the gas exchange in the lungs during lower respiratory tract infections results in changes in the AVP system. AVP expression could be induced by certain factors such as acidosis, pain, hypoxia, or neuroendocrine stress as well[6]. In the patients with severe COVID-19, it is known that oxygen levels are lower and the stress responses are higher. Conditions such as hypoxia and pain, which develop as the

severity of pneumonia increases, could contribute to copeptin expression. In the current study, it was discovered that the saturation levels were lower in severe patients and saturation levels and copeptin levels were strongly correlated.

Up to date, the prognostic value of copeptin in CAP patients was investigated in several studies in the literature. Masiá et al.[10] evaluated 174 CAP patients and reported that copeptin was an independent marker of mortality. In the current study, it was determined that copeptin yielded high diagnostic accuracy in predicting mortality when the cutoff value was regarded as >18.9 pmol/L (sensitivity: 71.4%, specificity: 79.5%). Similarly, Kolditz et al.[19] evaluated 51 CAP patients and investigated copeptin's diagnostic value in predicting admission to the intensive care unit 7 days from hospitalization and predicting mortality by using ROC analysis. In this study, it was determined that copeptin had 78% sensitivity and 79% specificity when the cutoff value was regarded as 35 pmol/L. In our study, it was observed that copeptin had 78% sensitivity and 80% specificity in terms of distinguishing the patients with severe COVID-19 from those patients with mild/moderate when the optimal cutoff value was regarded as 7.84 ng/mL. According to the findings of our study, copeptin had a higher predictive value in predicting severe disease compared with biochemical and inflammatory markers such as CRP, ferritin, fibrinogen, and LDH used routinely. Furthermore, copeptin was found to be an independent predictor of severe COVID-19 disease in the multivariable logistic regression analysis. Considering the findings of our study, copeptin can be a simple and useful marker for predicting the severity of COVID-19 with high sensitivity and specificity while yielding rapid results. Nevertheless, our study is a first on this subject, and a series of studies are required to support these results.

In conclusion, in this study, it was determined that serum copeptin levels were higher in the patients with severe COVID-19 compared with the patients with mild/moderate COVID-19 and related to disease severity. Moreover, multivariable logistic regression analysis identified copeptin as an independent predictor for COVID-19 severity. Therefore, copeptin could be a useful and prognostic biomarker that can be used in the patients with distinguishing severe COVID-19 from the patients with mild/moderate COVID-19.

AUTHORS' CONTRIBUTIONS

İE: Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing. **KM:** Conceptualization, Methodology, Investigation, Methodology, Resources. **TS:** Methodology, Data Curation, Formal analysis, Investigation, Resources. **ATZ:** Methodology, Data Curation, Investigation, Supervision, Writing – review & editing. **KE:** Formal analysis, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

AVAILABILITY OF DATA

The data that support the findings of this study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210529

Autonomic cardiac modulation in postmenopausal women with dry eye syndrome: a cross-sectional analytical study

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SUMMARY

OBJECTIVE: The aim of this study was to assess cardiac autonomic modulation in postmenopausal women with and without dry eye syndrome (DES) and to identify associations between clinical and socioeconomic factors.

METHODS: A cross-sectional study was carried out at the Institute of Ocular Surgery of the Northeast (ICONE), Brazil. Convenience sample of postmenopausal women, over 40 years old, who were divided into two groups: with and without DES. Clinical, sociodemographic, and ophthalmological characteristics of these women were assessed. Capture of RR intervals was performed using a cardio frequency meter. Differences between the groups were analyzed using the Chi-square test, the Student's t test, and the Mann-Whitney test.

RESULTS: Women with DES were present in 60.4% (n=58), highest median age (63.5 years, 95%CI 62.0–67.9; p<0.001), median length of time menopause (19 years old, 95%CI 10.4–24.0; p<0.001). There was a difference in the standard deviation of all normal-to-normal index between the groups. However, when the differences were adjusted to the clinical model, no association was found between DES and heart rate variability (HRV).

CONCLUSIONS: The analysis of cardiac autonomic modulation in postmenopausal women is similar in the presence or absence of DES. Clinical factors, time of menopause, and intensity of symptoms were not associated with HRV indices.

KEYWORDS: Heart rate. Autonomic nervous system. Postmenopausal. Climacteric. Dry eye syndromes.

INTRODUCTION

Dry eye syndrome (DES) affects 15% of the population aged over 45 years, showing a controversial and unexplained higher prevalence in postmenopausal women using estrogens and associated estrogen and progestogen[1]. It involves factors related to the tear and the ocular surface[2], which is associated with symptoms such as mild eye discomfort, burning, foreign body sensation, photophobia, blurred vision[3], increased risk of ulcerations, corneal infections, and impaired visual acuity[1-3].

Tear production by the lacrimal gland parenchyma and its ocular release are influenced by the autonomic nervous system (ANS) that also controls heart rhythm through sympathetic and parasympathetic endings[1,3-5]. Postmenopause, the

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 16, 2021. Accepted on July 18, 2021.

hypoestrogenism characteristic of ovarian insufficiency, can cause changes in the cardiac autonomic behavior and in the glands involved in tear production[5,6].

Heart rate variability (HRV) is an effective; noninvasive method to evaluate ANS function; being used in different situations, such as postmenopause, vasomotor symptoms (VMS), and their endocrine, nervous, and morbidity relationships. HRV has been considered as a homeostasis imbalance marker in women[7-9].

Understanding autonomic changes in the postmenopausal period, as well as the influence of menopause time associated with DES, becomes relevant in promoting women's health. Thus, the objectives of this study are to evaluate cardiac autonomic modulation in postmenopausal women with and without DES and to identify associations between clinical and socioeconomic factors.

METHODS

Design and ethical aspects

This is an observational analytical study conducted with postmenopausal women in an Ophthalmology Outpatient Clinic at the Northeast Institute of Ocular Surgery (Instituto de Cirurgia Ocular do Nordeste, ICONE), in Recife (PE), Brazil, from December 2017 to December 2018. All procedures were approved by the Research Ethics Committee (2,407,176 and CAAE No. 80490717.4.0000.5200).

Population and eligibility criteria

Study was conducted with women having routine ophthalmological consultations and by nonprobabilistic sampling of convenience. It included women aged over 40 years with a clinical (absence of menstruation for a period longer than 12 months) or laboratory (FSH greater than 30 IU/Ml[5]) diagnosis of postmenopause, who agreed to participate in the study by signing the informed consent form.

Exclusion criteria were use of hormone therapy in the previous 3 months, hysterectomy, cardiovascular diseases, use of systemic or ophthalmological medications, and history of eye infection or surgery.

Sample power

Sample size was calculated using the sample studied and the differences found in the analyses. Thus, we have considered as main parameter the statistical significance found in model II for analyzing the association between DES and HRV indices, r^2 of 0.02 in the initial model, and r^2 of 0.01 in the final model for a sample size of 96 participants, the test power was 0.28.

Data collection instruments

Kupperman-Blatt menopausal index

The Kupperman-Blatt menopausal index (KBMI) analyzes and classifies the intensity of menopausal symptoms through evaluation scales[5,10].

Capture of RR intervals

The RR intervals were captured following the protocols described by Vanderlei et al.[4] and Catai et al.[11] Procedure for capturing RR intervals was performed individually, using a Polar RS800CX HR monitor (Polar Electro, Kempele, Finland) validated equipment for HR capturing beat by beat. Data stored in the Polar RS800CX were used for HRV analysis[12,13].

HRV analysis

HRV was analyzed using the HR recorded beat by beat in RR interval capture. Only series with more than 95% sinus beats were used for analysis[11-13]. RR intervals digitally filtered using the Polar Precision Performance SW software (version 4.01.029), and manually to eliminate ectopic beats and artifacts. After filtering, the last 256 RR intervals were selected to undergo HRV analyses based on nonlinear and linear methods regarding time and frequency[11].

In domain of time, study evaluated the mean RR, the root mean square of the successive differences (RMSSD) between successive normal RR intervals from the analysis of adjacent RR intervals, and the standard deviation of all normal-to-normal (SDNN) RR intervals. RMSSD index translates parasympathetic modulation[14]. SDNN represents global variability[4,12].

In the domain of frequency, low (LF, 0.04–0.15 Hz) and high frequency (HF 0.15–0.40 Hz) spectral components were used to analyze HRV in normalized units that represent the relative value of each component in relation to total power, minus very low frequency (VLF) components in milliseconds squared and the ratio between these components (LF/HF). The spectral analysis was calculated using the Fourier transform algorithm[11,13].

Ophthalmological examination

Biomicroscopy examination analyzes the eyelids and the presence or absence of blepharitis, blepharochalasis, ptosis, ectropion, and entropion. Tear film, the presence or absence of mucus, oiliness, and thickness of the tear meniscus between the eyelid margin and the bulbar conjunctiva are examined[1-3]. Patency, ectopy, and the presence or absence from reflux to expression are evaluated in lacrimal points. Eyelid and bulbar conjunctivae are evaluated for the presence of hyperemia, edema, papillae, follicles, scar areas, and conjunctivochalasis.

The presence or absence of keratitis, irregularities, and cicatricial signs secondary to recurrent erosion should be evaluated in the cornea[1-3].

Statistical analysis

Qualitative variables were described by absolute and relative frequencies. Quantitative variables were described using means and 95% confidence intervals for the variables with normal distribution (Shapiro-Wilk, $p \geq 0.05$), and medians and confidence intervals for those that had no normal distribution (Shapiro-Wilk, $p < 0.05$).

Differences between the groups with and without DES were analyzed using the Chi-square test for qualitative variables, the Student's t-test for quantitative variables with normal distribution, and by the Mann-Whitney test for quantitative variables with no normal distribution.

HRV index differences between groups were analyzed using linear or median regression to estimate adjusted mean differences and adjusted median differences, respectively. The models were created according to the inclusion of all significant variables in the univariate analyses and using clinical criteria. All analyses considered a 5% significance level. The Stata® software (Stata Corp., L.L.C.) version 15 was used in the statistical analysis.

RESULTS

The study included 107 women, of which 11 were excluded due to schizophrenia, hysterectomy, congenital heart disease, and RR interval tracing errors. Sociodemographic and clinical characteristics showed no statistically significant differences (Table 1).

In the comparison of linear HRV indices, there were no statistically significant differences between the groups (Table 2).

Table 3 shows multivariate analyses in three regression models created to estimate differences. There was a difference in the SDNN between groups in model II. However, in model III, there were no association between DES and HRV.

DISCUSSION

These results indicate no differences in cardiac autonomic modulation in postmenopausal women with or without DES. Clinical factors, time of menopause, and intensity of symptoms are not associated with HRV indices.

DES group had a lower BMI and a higher percentage of physical activity practitioners than the control group. Mean chronological age corroborated the studies[5-7] that analyzed hormonal relationships in postmenopausal women with DES. About age at menarche and age at menopause, both groups presented similar results to those found in the literature[5,9,10]. Socioeconomic differences observed have also been described in previous Brazilian studies[5,7,8,10].

Comparison of HRV indices between groups showed no significant differences. When this comparison was adjusted for the different socioeconomic characteristics between groups (ethnicity, marital status, and education), DES group had a lower SDNN. This index represents global variability[4,11,12] that could indicate that some socioeconomic factors associated with DES would decrease global variability. Previous studies presenting global HRV decrease situations in different populations reported worse cardiovascular prognosis[12,13,15].

Jones et al.[14] analyzed the intensity of menopausal symptoms and HRV and reported a decrease in all HRV indices in both groups of postmenopausal women. Studies with different objectives also reported decreased cardiac autonomic regulation in postmenopausal women[7,9,16-18].

However, we do not believe that this difference can have relevant clinical implications since the comparison adjusted by different clinical variables between groups showed no differences in the HRV indices. This indicates that the predominance of age, time since menopause, age at menopause, or menopause symptoms had no influence on cardiac autonomic modulation in the present sample groups.

HRV allows the quantitative evaluation of autonomic balance and describes interval fluctuations between consecutive RR intervals[4,11], which can be an additional resource in the evaluation of menopausal women[16-18] diagnosed with DES. Menopausal women are more likely to develop this condition, probably due to decreased androgens and estrogen production resulting in Meibomian gland dysfunction, and age-related factors[2,6,9,10].

Calio et al.[19] demonstrated that regular physical activity improves or reduces the intensity of menopausal symptoms and improves HRV levels in postmenopausal women. A study on postmenopausal women showed increased post-exercise HRV indices with moderate and high intensity physical exercises. These findings indicate increased parasympathetic tonus, with efficient adaptation of cardiac autonomic modulation and a consequent cardioprotective factor[20]. Rezende Barbosa et al.[18] evaluated women practicing functional training and demonstrated that HRV has greater variability in functional training postmenopausal practitioners.

Regular physical activity represents an important factor to reduce morbidity and mortality rates due to cardiovascular or other causes, being related to improved autonomic control, which has been widely studied through HRV analysis[4,11,16,17]. Different studies[7,16-18] suggest that physical exercise may have a positive relationship with HRV, sometimes reflected by

Table 1. Sociodemographic and clinical characteristics in postmenopausal women with and without dry eye syndrome, Recife (PE), Brazil, 2017–2018.

Variables	Dry eye syndrome				p*
	No (n=38; 39.6%)		Yes (n=58; 60.4%)		
	Median	95%CI	Median	95%CI	p†
Age (years)	54	53.0–55.6	63.5	62.0–67.9	<0.001
Age at menopause (years)	49	48.0–49.5	50.0	49.0–50.9	0.364
Menopause time (years)	5	4.1–9.0	19	10.4–24.0	<0.001
Diastolic blood pressure (mmHg)	80.0	80.0–80.0	80.0	70.0–80.0	0.013
Hot flashes	3	2.0–4.0	1	0.0–2.0	0.019
	n	%	n	%	
Ethnicity					
White	6	12.5	42	87.5	<0.001
No white	32	66.7	16	33.3	
Marital status					
Single/widow/divorced	26	54.2	22	45.8	0.003
Stable union	12	25.0	36	75.0	
Education					
≤8 years	30	90.9	3	9.1	<0.001
>8 years	8	12.7	55	87.5	
Smoking					
No	31	81.6	56	96.6	0.014
Yes	7	18.4	2	3.4	
Alcoholism					
No	35	92.1	30	51.7	<0.001
Yes	3	7.9	28	48.3	
Physical activity					
No	29	76.3	23	39.7	<0.001
Yes	9	23.7	35	60.3	
Comorbidities					
No	29	76.3	42	72.4	0.670
Yes	9	23.7	16	27.6	
Menopausal symptoms (IMKB)					
Mild (≤19)	15	45.5	18	54.5	<0.001
Moderate (20–34)	11	22.9	37	77.1	
Severe (≥35)	12	80.0	3	20.0	
	Mean	95%CI	Mean	95%CI	p‡
Age at menarche (years)	13.3	12.7–13.8	11.7	11.3–12.1	<0.001
Body mass index	28.3	26.7–28.9	26.4	25.4–27.5	0.041
Systolic blood pressure (mmHg)	124.0	119.2–128.8	121.2	118.0–124.5	0.320

95%CI: 95% confidence interval; KBMI: Kupperman-Blatt menopausal index; *Chi-square test; †Mann-Whitney U test; ‡Student's t-test.

Table 2. Linear heart rate variability indices in postmenopausal women with and without dry eye syndrome, Recife (PE), Brazil, 2017–2018.

Variable	Dry eye syndrome				p*
	No (n=38)		Yes (n=58)		
	Median	95%CI	Median	95%CI	
Mean RR	887.5	803.4–967.8	903.0	867.5–946.9	0.727
SDNN	20.1	15.6–24.2	23.3	19.2–26.8	0.121
RMSSD	21.1	14.7–27.6	21.3	19.7–27.4	0.308
NN50	16.0	2.8–43.3	40.0	15.1–65.0	0.264
pNN50	1.4	0.2–5.7	2.6	1.1–5.2	0.351
LFms^2	155.0	103.4–226.2	167.0	128.0–266.8	0.148
LFms^2	144.0	81.6–260.0	190.5	120.0–236.5	0.297
Total	355.5	213.7–596.9	466.0	318.3–638.7	0.179
LFHF	1.3	0.8–1.8	1.1	1.0–1.5	0.810
	Mean	95%CI	Mean	95%CI	p†
LFnu	53.6	47.4–59.8	52.6	47.7–57.6	0.803
HFnu	46.3	40.1–52.5	47.2	42.3–52.2	0.805

95%CI: 95% confidence interval; RR: RR intervals; SDNN: standard deviation of all normal-to-normal; RMSSD: root mean square of the successive differences; NN50: total number of adjacent RR intervals with a difference of duration greater than 50 ms; pNN50: pPercentage of the total number of adjacent RR intervals with a difference of duration greater than 50 ms; LF: low frequency; HF: high frequency; *Mann-Whitney U test; †Student's t-test.

Table 3. Dry eye syndrome and socioeconomic and clinical factors (age, time of menopause, and intensity of menopausal symptoms) associated with linear cardiac autonomic modulation indices in postmenopausal women, Recife (PE), Brazil, 2017–2018.

Variable	Model I	p*	Model II	p*	Model III	p*
	Median difference (95%CI)		Median difference (95%CI)		Median difference (95%CI)	
Mean RR	16.59 (-64.03–97.23)	0.684	-22.4 (-95.5–50.7)	0.544	2.5 (-106.8–111.8)	0.964
SDNN	3.2 (-2.8–9.3)	0.294	8.2 (0.5–15.9)	0.037	6.3 (-1.7–14.4)	0.122
RMSSD	-0.8 (-9.2–7.6)	0.850	-2.1 (-10.9–6.6)	0.630	2.3 (-8.7–13.3)	0.682
NN50	25.0 (-23.0–73.0)	0.304	-14.5 (-113.9–84.9)	0.773	16.1 (-44.8–77.1)	0.601
pNN50	1.2 (-3.8–6.3)	0.638	-2.4 (-11.3–6.4)	0.589	1.9 (-5.3–9.1)	0.604
LFms^2	12.0 (-99.0–123.0)	0.831	65.3 (-133.3–263.8)	0.515	35.5 (-98.2–169.2)	0.599
LFms^2	29.0 (-78.3–136.3)	0.593	-56.8 (-268.1–154.5)	0.594	63.3 (-90.0–225.6)	0.440
Total	112.0 (-128.0–352.0)	0.357	166.9 (-319.9–653.7)	0.497	337.0 (-23.3–697.2)	0.066
LFHF	-0.2 (-0.8–0.3)	0.420	0.004 (-1.1–1.1)	0.994	0.25 (-0.5–1.0)	0.500
	Model I	p*	Model II	p*	Model II	p*
	Mean difference (95%CI)		Mean difference (95%CI)		Mean difference (95%CI)	
LFnu	-0.98 (-8.8–6.8)	0.803	3.1 (-11.8–18.0)	0.682	-2.7 (-13.2–7.8)	0.609
HFnu	1.0 (-6.8–8.8)	0.805	-3.2 (-18.1–11.7)	0.671	2.7 (-7.8–13.2)	0.611

95%CI: 95% confidence interval. RR: RR intervals; SDNN: standard deviation of all normal-to-normal; RMSSD: root mean square of the successive differences; NN50: total number of adjacent RR intervals with a difference of duration greater than 50 ms; pNN50: percentage of the total number of adjacent RR intervals with a difference of duration greater than 50 ms; LF: low frequency; HF: high frequency; *Linear regression. Model I estimated unadjusted linear index differences in both groups. Model II estimated linear index differences adjusted by for all significant variables in Table 1. Model III (clinical model) estimated differences adjusted by age, menopausal time, and intensity of menopausal symptoms (KBMI).

increased vagal regulation, or by a better interaction between sympathetic and parasympathetic components.

In this context, literature[16-18] shows that protocols evaluating HRV after moderate and intense physical activity can provide HRV recovery in postmenopausal women, reestablishing the parasympathetic predominance, especially in women with longer menopausal time. Those authors[16-18] also suggest that lifestyle is an essential component to improve HRV parameters. This fact may be a convenient general recommendation to be given by clinician following up menopausal and DES women.

It is worth mentioning that HRV can also be influenced by other associated factors, such as comorbidities and lifestyle habits[4,5,7,12]. As already mentioned, overweight and other lifestyle habits were not related to the absence or presence of DES in HRV indices analysis. Additionally, considering the volunteers' age and physiological aging could also influence the ANS due to the loss of the system's complexity[13]. However, the presence of temporary or permanent physiological disorders such as menopause in varied stages did not influence the findings[17,18].

This study has some limitations. The first would be related to the fact that cardiovascular risk was not analyzed. Although increased BMI is a risk predictor for mortality from cardiovascular disease in postmenopausal women, this study showed no differences related to this variable in HRV. The second would be that hypoestrogenism causes a progressive and permanent decrease in serum estrogen levels. However, these postmenopausal clinical aspects were not associated with HRV results with and without DES[17,18]. Finally, it has some limitations related to study design and nonprobabilistic sample. Subsequent studies on DES treatment interventions are necessary to evaluate its impact on the ANS.

CONCLUSIONS

Analysis of cardiac autonomic modulation in postmenopausal women is similar in the presence or absence of DES. Clinical factors, time of menopause, and intensity of symptoms were not associated with HRV indices.

AUTHORS' CONTRIBUTIONS

ADAJ: Data curation, Supervision, Writing – original draft. **TDC:** Supervision, Writing – original draft. **ARN:** Data curation. **FWSF:** Formal analysis. **PMM:** Data curation. **LCA:** Conceptualization. **ECB:** Supervision. **JMSJ:** Conceptualization. **ICES:** Conceptualization, Supervision, Writing – original draft.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210545

Patients' understanding of "informed consent" in plastic surgery

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SUMMARY

OBJECTIVE: To assess the patient's understanding of the informed consent form before and after plastic surgery.

METHODS: This was a prospective analytical descriptive study that utilized a questionnaire on informed consent before and after plastic surgery procedures.

RESULTS: Comprehension of informed consent was higher before surgery than after surgery (p=0.016; question 15). The higher the scholarity, the higher the comprehension (s=0.151; p=0.045) before surgery (question 4). For the other questions, it was not possible to find a difference in the pattern of understanding and in the association with the educational attainment level after surgery (s=0.180; p=0.046; question 1). CONCLUSIONS: The patients' level of comprehension of the details, outcomes, possible complications, and postoperative evolutions of surgical procedures, as stated by the informed consent form, is high.

KEYWORDS: Consent forms. Comprehension. Physician-patient relations. Duty to warn. Surveys and questionnaires.

INTRODUCTION

Consent is defined as the permission a person gives for the performance of any type of medical treatment. It should be facultative and informed; the person must be suitable for such a decision. It should also be obtained in advance before the start of the chosen treatment[1,2]. It serves as material proof that the physician fulfilled their obligation to inform the patient and that the patient declared that they understood and agreed to undergo the treatment. Communication before and after any procedure should be clear and done using simple language. There is a risk of the doctor–patient relationship transforming into a formal contract, and the rapport and harmonious bond, which are characteristics of the medical practice, may be lost[3]. In lawsuits on aesthetic plastic surgery, for which informed consent term (ICT) was properly obtained, the judicial expert was mostly favorable toward doctors[4].

The worsening of the doctor-patient relationship, due to the change in the health care model, is associated with the increase in complaints against physicians in Brazil[5].

The exercise of medicine is considered a process-centric activity, without promise of results[6]. As a counterpoint, the courts of justice consider plastic surgery as an end activity, aiming for social acceptance of the individual[7].

The ICT does not include all possibilities in medicine because it is an inexact science. It should include clarifications for the patient that the procedure to be performed will bring some benefits, but that there will be possible complications independent of the skill, training, and performance of the medical professional. The term gives the patient the freedom to choose the most favorable option of treatment, while removing the idea that the doctor is always responsible for the outcome[8,9]. The complexity of the information process is high, and great attention should be paid to this important phase[10].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 11, 2021. Accepted on June 27, 2021.

There is a large increase in the number of lawsuits against plastic surgeons. One reason is the inadequate use and formulation of the ICT[11]. The understanding of patients regarding the ICT for the treatment to be performed is inappreciable. Despite all efforts, there appears to be a great difference in the understanding of this by doctors and courts. The term, as required by law, has not been fully achieved, and the same difficulty has subsisted for decades[12].

Research on patient difficulty in absorbing the information included in the term has determined three related factors: education, health status, and care in and attention to reading the ICT before signing[13].

There have been several studies that utilized questionnaires to evaluate the patient's understanding of the ICT, using several different ways as follows: repeating the term, doubts orally recorded, and standardized term versus reinforcement methods, by video or information by nurses. The results were as follows: the greatest difficulty in understanding was found in patients of different ethnicities due to their schooling and their difficulty in understanding the language[14,15]; information and questions answered orally during consultations were better understood[16]; the vast majority of patients were satisfied with the information given about the procedure to be performed[17]; there was no difference in the understanding and satisfaction of patients who received the standardized term and those who underwent reinforcement methods; and they may, therefore, be unnecessary[18].

In contrast, American studies have observed that the use of supplementary, written, audiovisual, and other materials increase satisfaction after the procedure and may limit litigation[19,20]. In another study, 75% of the plastic surgeons interviewed were defendants in at least one malpractice lawsuit, and most of the investigated cases involved complaints of unsatisfactory results, excessive scarring, or lack of ICT[20].

This study aimed to evaluate the patient's understanding of the informed consent form before and after plastic surgery.

METHODS

This was a prospective descriptive analytical study. Data were collected from July 2017 to September 2018. The study population included people who underwent any plastic surgery, who were seen in the office of any of the 23 participating physicians, and who agreed to participate in the research.

A questionnaire was administered to the patients before the day of the surgery and readministered during the postoperative period in the office of each participating physician. It was distributed in the states of São Paulo and Mato Grosso.

All of the administrants were plastic surgeons recognized by the Regional Council of Medicine of São Paulo (CREMESP) and the Brazilian Society of Plastic Surgery (SBCP).

The questionnaire is composed of 21 questions, with 5 options for each answer, that evaluated the degree of understanding of the patient as follows:

0 = none;
1 = a little;
2 = regular;
3 = moderate; and
4 = very.

The questionnaire was first administered on any date until the day of surgery and was administered for the second time at least 1 month after surgery.

The inclusion criteria were patients who underwent plastic surgery performed by the participating physicians, with the completion of the ICT and questionnaires of this study. The exclusion criteria were those who presented the ICT without the signature of one of the participants (physician or patient) and those who completed them after the stipulated deadline.

The descriptive statistical analyses were performed through measures, such as means and minimum, maximum, absolute, and relative frequencies.

The inferential analyses employed to confirm the descriptive analysis were as follows:

1. Wilcoxon[21], for the comparison of the answers to the questionnaire before and after surgery;
2. Spearman's correlation coefficient[21], in the study of the relationship between schooling and each question in the questionnaire.

The alpha significance level of 5% was used in all the conclusions. The evaluations were performed using the statistical software Statistical Package for the Social Sciences (known as SPSS) version 2019 (IBM Corp., Armonk, NY, USA).

The study was approved by the Research Ethics Committee of UNIFESP, under number 69248/2017 and the approval of the Brazil platform.

The patients signed a consent form to participate in the study.

RESULTS

The research collected 178 questionnaires before and 124 questionnaires after the surgical procedure.

We had 54 unanswered questionnaires after the surgery, which were considered as losses only if the second questionnaire was administered.

The questionnaire was first administered from 103 days before to the day of the surgery.

The questionnaire was readministered from 30 to 320 days after the surgery. The predominant educational attainment levels

Table 1. Number of patients who answered the questionnaire on informed consent, according to sex and education.

Sex	Schooling				
	No study	Fundamental	Medium	Superior	Total
Male	0	0	2	5	7
Female	3	15	75	76	169
Total	3	15	77	81	176*

*Two people did not answer about their schooling.

Table 2. Distribution of responses to the questionnaire on informed consent before and after surgery. (Question 15: Are you aware that the outcome depends on postoperative care?)

Issue	Answer										
	No		Little		Regular		Quite		Very		p
Q15	0	0	1	0.6%	4	2.2%	51	28.7%	122	68.5%	0.016*
R15	0	0	1	0.8%	4	3.2%	38	30.6%	81	65.3%	

*Wilcoxon signed-rank test (p≤0.05).

of the patients were higher education (45.50%), followed by high school (43.25%) (Table 1).

Comparisons were made between the answers of each question before (Q1, Q2, Q3,...Q21) and after (R1, R2, R3,...R21) surgery and whether these differences were statistically different, considering p<0.05.

With the exception of question 15 (Are you aware that the outcome depends on postoperative care?), where understanding before surgery was better than after surgery (p=0.016), there was no difference in the pattern of understanding for the other questions (Table 2).

In the relationship between schooling and each question in the questionnaire, according to the estimates of Spearman's correlation coefficient(s), we noticed that the higher the educational attainment level, the greater the understanding, as shown in the analysis of question 4 (Are the risks and potential complications acceptable?) (s=0.151; p=0.045) from before the surgery and by question 1 (Did you resolve all doubts during the medical consultation about the surgery that is going to be performed?) (s=0.180; p=0.046) after the surgery. For the other questions, this relationship was not confirmed (Table 3).

Table 3. Relationship between the patients' education and each question before and after surgery.

Schooling	Before		Then	
	s	p*	s	p*
Question 1	0.046	0.541	0.180	0.046
Question 2	-0.012	0.876	0.036	0.689
Question 3	-0.060	0.430	0.094	0.302
Question 4	0.151	0.045	0.122	0.177
Question 5	-0.051	0.504	0.030	0.740
Question 6	0.089	0.242	0.115	0.204
Question 7	-0.031	0.686	-0.047	0.604
Question 8	-0.041	0.587	0.058	0.522
Question 9	-0.079	0.296	0.102	0.260
Question 10	0.026	0.732	0.076	0.406
Question 11	0.045	0.552	0.010	0.911
Question 12	0.067	0.378	0.022	0.809
Question 13	0.058	0.443	0.032	0.722
Question 14	-0.023	0.760	0.032	0.729
Question 15	-0.001	0.987	-0.016	0.864
Question 16	0.050	0.513	0.114	0.210
Question 17	0.052	0.491	0.052	0.566
Question 18	0.030	0.696	0.100	0.271
Question 19	0.046	0.546	-0.071	0.432
Question 20	-0.055	0.466	-0.089	0.327
Question 21	0.007	0.924	0.087	0.341

*p≤0.05.

DISCUSSION

The growth of studies and production of data on informed consent have been essential due to the judicialization of medicine in recent years, with the significant increase in lawsuits in Brazil. At any time, the plastic surgeon is faced with a lawsuit simply because the patient is dissatisfied with the outcome of the procedure or with the information previously obtained, although these data are completely subjective.

It is important that the doctor always acts within their area of specialization and is qualified by the CREMESP and SBCP, in the case of plastic surgery. Otherwise, they will be subject to ethical-professional lawsuits and suffer the appropriate punishments if negligence, lack of skill, or imprudence is proven.

The basis of the use of the ICT is the autonomy of the individual, which is a premise of the code of medical ethics. The patient can also make their own decision as to whether it is worth undergoing the procedure with the risks and potential complications inherent to the procedures and possible outcomes. Signing the term confirms awareness and agreement with everything involving the proposed procedure.

From a legal point of view, there is no lack of arguments for the use of the ICT, and the printed form is a physical proof of the patient's consent.

No ideal ICT has yet been found, and there is no protocol to follow in its formulation. This leaves doubts as to what information should be included and how it should be applied with patients for better guidance and understanding, because any area of medicine is an inexact science, and it will always be impossible to list all of the possible complications.

We should remember that the given information and resolved doubts during all preoperative consultations, and in addition, whatever is implicit in the content during the process, must be added to the signed term[4].

There is great difficulty in assessing the patient's understanding of the ICT because when it is evaluated through questionnaires, the result is a great understanding of the information also obtained during the preoperative consultations, in addition to that contained in the term[22].

The understanding of and satisfaction with the ICT is good or excellent in the preoperative period as described[18,23]. At 6 weeks after surgery, there was a drop in the understanding in all the groups, showing that forgetfulness appears to occur quickly. Using several ways in combination does not statistically change the level of understanding.

It is complicated to say currently that the patient or any individual who has access to plastic surgery is fully a layman and does not know that every surgery has inherent risks, because, according to a national survey conducted by IBGE[24], 74.9%, or three of every four Brazilian households had access to information through the Internet in 2017. The proportion of people who accessed the Internet was higher, the higher the level of educational attainment.

The closer and better the physician–patient relationship is, the lower the chance of a future lawsuit, regardless of whether any complication occurred[5].

In a survey by CREMESP[25], 90% of the physicians sued were not specialists. The high incidence of ethical lawsuits involving plastic surgery is due to the invasion of the area by medical and nonmedical specialists, performing procedures specific to the area, without adequate training for such.

The patient should be informed that they may have certain benefits through the procedure and that the occurrence of the expected benefits is limited by risks inherent to the body of each individual and independent of the medical professionals will and skill[8].

CONCLUSION

The level of patient understanding of surgery information, outcomes, possible complications, and postoperative developments is high when they are given an informed consent form.

ACKNOWLEDGMENT

We thank all the physicians and patients who participated in the survey.

AUTHORS' CONTRIBUTIONS

JNN: Conceptualization, Formal analysis, Methodology, Project administration, Research, Software, Writing – original draft, Writing – review & editing. **RACC:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **RRF:** Data curation, Formal analysis, Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210560

Is combined rather than single antibiotic therapy actually reasonable in patients with acute calculous cholecystitis?

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SUMMARY

OBJECTIVE: Acute calculous cholecystitis (AC) is a frequently encountered emergency surgery disease and its standard treatment is cholecystectomy. In patients with high risk in surgery, antibiotic treatment (AT) is important. In routine clinical practices, antibiotics are frequently used either as single or in combination in the treatment of AC. This study examined whether or not combined antibiotic treatment (CAT) had superiority over single antibiotic treatment (SAT) in AC.

METHODS: Patients with cholecystitis who received treatment in the period of 2016–2019 were retrospectively examined. The treatment procedures applied, patient findings, and laboratory data were analyzed using relevant statistical software. The patients were categorized into groups based on the treatment approaches applied, and the effects of SAT and CAT on infection parameters were analyzed.

RESULTS: In all, 184 patients received treatment for AC, with a mean age of 57.7, and the female-to-male ratio was 77:107. Of these, 139 patients received SAT and 45 received CAT. No significant difference was found in terms of effectiveness between the SAT and CAT in the patients who received early cholecystectomy treatment and those who received medical treatment with noninvasive intervention.

CONCLUSIONS: In patients with AC, antibiotics are commonly used either as single or in combination for prophylaxis and therapeutic purposes. As no significant difference was observed between single and combined use in terms of treatment effectiveness and hospitalization duration, CAT is not recommended due to its possibility of allergic side effects, toxicity, and cost-increasing effects.

KEYWORDS: Acute calculous cholecystitis. Antibiotic therapy. Cholecystectomy.

INTRODUCTION

Acute calculous cholecystitis (AC) is a serious infection that generally occurs as a result of a gallstone in the cystic duct or Hartmann's pouch blocking the drainage of bile. However, the process continues, with the participation of anaerobic and aerobic bacteria, especially Gram-negative microorganisms. Based on the severity of the infection, AC was classified into three groups, namely, Grade I: mild; Grade II: moderate; and Grade III: severe according to the Tokyo Guidelines[1].

The standard treatment of AC cases is cholecystectomy. However, especially in patients with severe infection, in order to treat the infection and increase the success of surgical treatment, various antibiotics that are known to be effective on the biliary system are prevalently applied in the preoperative or postoperative period. Many studies have emphasized that bacteria do not have a significant effect in Grade I AC and that the antibiotic treatment (AT) that is applied does not change the prognosis of the patient, whereas AT needs to be applied in Grade II and Grade III cases[2-4]. In empirical AT to be applied in AC cases, there are no precise standards regarding the type of antibiotic, dose of application, and application time. However, TG13 and TG18 provide various recommendations for empirical AT based on the severity of the infection[5].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 19, 2021. Accepted on July 03, 2021.

Antibiotic combinations that are not applied with an appropriate indication, at an appropriate dose, and for an appropriate duration not only increase the development of resistance but also bring about some allergic and toxic side effects. For this purpose, detailed recommendations were provided in the Tokyo Guidelines, and most centers have started to apply treatment procedures that are in compliance with these guidelines[1]. A study with broad participation which investigated changes in the treatment approaches of surgeons after the Tokyo Guidelines reported a significant decrease in the practice of combined antibiotic usage[5].

The present study aimed to group patients with AC based on the AT that was applied, assess the effectiveness of single antibiotic treatment (SAT) and combined antibiotic treatment (CAT), and determine whether or not CAT had significant superiority over SAT.

METHODS

Patients who visited our clinic in the period of 2016–2019 with AC were examined. Changes in hematological parameters were checked in the beginning and at the end of the treatment and compared with hospitalization durations.

The patients who underwent early cholecystectomy were included in Group I, those who were given nonoperative minimally invasive interventions like endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous cholecystostomy were included in Group II, and those who were given only medical treatment and given appointments for 6–8 weeks later for delayed cholecystectomy were included in Group III. The data were analyzed by dividing each group into two subgroups as SAT or CAT. The WBC (white blood cell), HGB (hemoglobin), PLT (platelet), % NE (neutrophil), INR (international normalized ratio), CRP (C-reactive protein), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyl transferase), ALP (alkalinephosphatase), amylase, total bilirubin, and direct bilirubin values measured in the beginning and at the end of the AT and hospitalization durations were analyzed using statistical program. The data were tested for normal distribution. While only the HGB data were normally distributed, other data were non-normally distributed. For statistical analysis, Student's t-test and Mann-Whitney U test were applied. A $p<0.05$ was accepted as statistically significant.

RESULTS

In this study, 184 patients, with a mean age of 57.7 years, received treatment for AC. The most common symptoms associated with AC were epigastric upper right quadrant abdominal pain, nausea, vomiting, and mild fever. The most frequently encountered systemic comorbid diseases were diabetes mellitus and hypertension. Physical examination and laboratory findings were compatible with AC. Radiologically, in addition to the presence of stones or mud in the gallbladder, findings such as wall thickening and pericholecystic fluid collection were also observed. In addition, blood analysis shows an increase in infection markers such as WBC, CRP, and %NE, as well as liver enzymes.

After the diagnosis of AC independently of the treatment option projected for the patients, penicillin-based AT with beta-lactamase inhibitors or AT including cefazolin, cefoperazone, and ceftriaxone was started. Forty-five patients received CAT including ertapenem, imipenem, or meropenem or including levofloxacin and ciprofloxacin with metronidazole. Penicillin-based treatment such as ampicillin/sulbactam was not given to any patient. In patients with severe sepsis findings, in a way to cover Gram-negative, Gram-positive, and anaerobic microorganisms, the combination of ampicillin+cephalosporin+metronidazole or the combination of piperacillin+tazobactam+metronidazole or the combination of imipenem+metronidazole was frequently preferred.

On the days following AT, laparoscopic cholecystectomy (LC) was applied in the low-risk patients, nonoperative interventions like ERCP and percutaneous cholecystostomy were applied on the high-risk patients with more severe infection findings, or in the patients responding well to antibiotic+supplementary medical treatment, appointments were given 6–8 weeks later for delayed cholecystectomy. Group I included 83, Group II included 23, and Group III included 78 patients, whereas 139 patients were given SAT and 45 patients were given CAT. Out of 63 patients in the early cholecystectomy group, 60 (95%) received LC and 3 (5%) received open cholecystectomy, while 55 (93%) out of 59 patients in the delayed cholecystectomy group received LC and 4 (7%) received open cholecystectomy.

The mean age of the patients who were given SAT was 57.3 years and that of those who were given CAT was 57.7 years, and there was no statistically significant difference between the two groups. The female-to-male ratio was 60:79 in the SAT group and 17:28 in the CAT group. The duration of hospitalization varied between 2 and 26 days, and the mean duration was 7.8 in both the groups. When all patients were compared based on their hospitalization durations in Groups I, II, and III and the SAT and CAT groups within these groups, no significant difference was found ($p=0.807$, $p=0.723$, $p=0.759$, $p=0.813$).

The distributions of the WBC, HGB, PLT, %NE, INR, CRP, ALT, AST, GGT, ALP, amylase, total bilirubin, and direct

bilirubin values of the patients at visit to the hospital and at discharge based on their SAT or CAT status and their changes according to all patient group, Group I, Group II, and Group III are presented in Tables 1–3.

When the laboratory values were compared between the first admission and discharge times, although there was a significant reduction in the infection parameters in all patients, in the comparison made based on single or combined antibiotic usage, the difference was significant only in the ALT values in Group I and the ALT, INR, and %NE values in Group III. There was no significant difference based on any parameter between the SAT and CAT in Group II. The patients in all groups were ultimately discharged with full recovery and without any morbidity.

DISCUSSION

The gold standard treatment in AC is LC, and the treatment plan should be established based on the general state of the patient, their comorbidities, and the degree of cholecystitis. In the initial treatment plan for patients who have clinical symptoms and findings, 4–5 days of AT with fluid electrolyte replacement has an important place[6]. It is recommended that early LC is appropriate in Grade I AC and that antibiotics should be used before surgery or during surgery rather for prophylactic purposes. There are many studies suggesting that antibiotic application in the postoperative period is not necessary in these patients[4,7,8].

In elderly patients and those with poor general status who have severe AC findings, the risk of operative mortality is high due to organ dysfunctions. It is recommended to treat these patients with the appropriate medical treatment and antibiotic support using less invasive interventions like ERCP or percutaneous cholecystostomy instead of surgery[9,10]. The benefits of antibiotics and these minimally invasive interventions are limited, and the requirement of surgery arises in some of these patients. Especially in surgeries to be performed on patients who had percutaneous cholecystostomy, laparoscopic intervention becomes difficult due to pericholecystic adhesions, and therefore open cholecystectomy is performed in most cases.

According to some meta-analysis results, there was no significant difference in the treatment outcomes of patients who were given AT and those who were not given AT in AC and therefore antibiotic use is completely unnecessary[11]. However, it is recommended in guidelines to apply broad-spectrum antibiotics that are known to be effective on biliary system infections empirically for certain durations and at certain doses with fluid electrolyte treatment, and this treatment procedure

Table 1. Distribution of white blood cell, hemoglobin, platelet, neutrophil, international normalized ratio, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkalinephosphatase, amylase, total bilirubin, and direct bilirubin values of patients in the cholecystectomy-applied group (Group I) (n=83) based on their single or combined antibiotic treatment status.

Laboratory results	Single antibiotic (n=63)			Combined antibiotic (n=20)			Difference between changes	p-value
	First value (mean)	Last value (mean)	Change (mean)	First value (mean)	Last value (mean)	Change (mean)		
WBC (/mm^3)	14.53	10.05	4.48	12.90	11.10	1.80	2.68	0.33
Hemoglobin (g/dL)	13.41	11.66	1.75	13.54	11.92	1.62	0.13	0.75
PLT (/dL)	270.56	306.05	-35.49	264.70	312.40	-47.70	12.21	0.73
%NE	76.29	67.52	8.77	79.33	71.72	7.61	1.16	0.30
INR	3.51	3.09	0.42	1.22	1.34	-0.12	0.54	0.31
CRP	137.33	95.28	42.05	108.97	69.54	39.43	2.62	0.94
ALT	53.97	42.06	11.91	80.90	29.60	51.30	-39.39	0.03
AST	43.67	37.11	6.56	53.55	35.20	18.35	-11.79	0.99
GGT	97.63	77.98	19.65	193.05	79.75	113.30	-93.65	0.13
ALP	98.63	94.52	4.11	114.70	85.60	29.10	-24.99	0.16
Amylase	66.51	60.63	5.88	225.75	65.70	160.05	-154.17	0.44
Bilirubin total	1.04	0.64	0.40	1.93	0.86	1.07	-0.67	0.37
Bilirubin direct	0.35	0.22	0.13	0.76	0.25	0.51	-0.38	0.87

WBC: white blood cell; PLT: platelet; %NE: neutrophil; INR: international normalized ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; ALP: alkalinephosphatase.

Table 2. Distribution of white blood cell, hemoglobin, platelet, neutrophil, international normalized ratio, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkalinephosphatase, amylase, total bilirubin, and direct bilirubin values of patients in the ERCP-PC-applied group (Group II) (n=23) based on their single or combined antibiotic treatment status.

Laboratory results	Single antibiotic (n=17)			Combined antibiotic (n=6)			Difference between changes	p-value
	First value (mean)	Last value (mean)	Change (mean)	First value (mean)	Last value (mean)	Change (mean)		
WBC (/mm³)	13.89	7.62	6.27	15.52	9.11	6.41	-0.14	0.64
Hemoglobin (g/dL)	13.29	11.86	1.43	13.28	11.47	1.81	-0.38	0.80
PLT (/dL)	261.65	292.59	-30.94	290.83	311.33	-20.50	-10.44	0.14
%NE	79.27	58.56	20.71	81.93	63.60	18.33	2.38	0.40
INR	5.96	5.28	0.68	1.16	1.23	-0.07	0.75	0.56
CRP	153.76	57.50	96.26	196.13	82.39	113.74	-17.48	0.76
ALT	100.00	65.41	34.59	71.50	17.17	54.33	-19.74	0.39
AST	90.29	47.76	42.53	56.17	24.67	31.50	11.03	0.61
GGT	150.35	136.06	14.29	91.33	73.50	17.83	-3.54	1.00
ALP	123.94	160.88	-36.94	104.33	93.50	10.83	-47.77	0.12
Amylase	69.47	87.53	-18.06	78.00	92.67	-14.67	-3.39	0.76
Bilirubin total	5.65	4.65	1.00	13.65	10.20	3.45	-2.45	0.47
Bilirubin direct	0.72	3.02	-2.30	0.55	0.18	0.37	-2.67	0.92

WBC: white blood cell; PLT: platelet; %NE: neutrophil; INR: international normalized ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; ALP: alkalinephosphatase.

Table 3. Distribution of white blood cell, hemoglobin, platelet, neutrophil, international normalized ratio, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, alkalinephosphatase, amylase, total bilirubin, and direct bilirubin values of patients in the Medical Treatment group (Group III) (n=78) based on their single or combined antibiotic treatment status.

Laboratory results	Single antibiotic (n=59)			Combined antibiotic (n=19)			Difference between changes	p-value
	First value (mean)	Last value (mean)	Change (mean)	First value (mean)	Last value (mean)	Change (mean)		
WBC (/mm³)	14.48	8.35	6.13	15.76	8.13	7.63	-1.50	0.63
Hemoglobin (g/dL)	13.26	11.82	1.44	13.11	11.69	1.42	0.02	0.86
PLT (/dL)	261.20	274.07	-12.87	258.53	251.74	6.79	-19.66	0.67
%NE	78.37	59.58	18.79	77.86	64.35	13.51	5.28	0.04
INR	2.70	2.61	0.09	9.41	8.38	1.03	-0.94	0.02
CRP	122.11	57.11	65.00	114.99	55.30	59.69	5.31	0.61
ALT	42.03	39.58	2.45	139.84	39.63	100.21	-97.76	0.05
AST	42.00	29.02	12.98	146.05	29.11	116.94	-103.96	0.35
GGT	93.03	93.88	-0.85	68.58	77.00	-8.42	7.57	0.60
ALP	116.71	109.21	7.50	101.89	90.44	11.45	-3.95	0.40
Amylase	67.39	67.81	-0.42	132.26	92.32	39.94	-40.36	0.40
Bilirubin total	3.43	2.76	0.67	9.05	6.77	2.28	-1.61	0.19
Bilirubin direct	0.29	0.17	0.12	0.46	0.20	0.26	-0.14	0.40

WBC: white blood cell; PLT: platelet; %NE: neutrophil; INR: international normalized ratio; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; ALP: alkalinephosphatase.

is prevalently used at many centers. While selecting antibiotics, it should be kept in mind the potential agent of infection, the allergic or other side-effect history of the patient, and liver and kidney functions of the patients.

It is recommended to keep empirical treatment as short as possible and apply target-oriented treatment by determining the effective antibiotic based on the bile culture and antibiogram results[6,12]. Bacteria cannot be isolated from the bile culture of more than half of patients with AC. For this reason, in order to make the right decision in empirical AT, the results of culture antibiogram performed previously in that region should be considered. The most frequently encountered bacterium in biliary tracts is Escherichia coli. In addition, Gram-negative bacteria like Klebsiella spp, Pseudomonas spp, and Enterobacteria and Gram-positive bacteria like Enterococcus spp and Streptococcus spp are also isolated, and the spectrum of the antibiotics to be selected should cover these microorganisms[5,11,13].

In addition to bacterial resistance, long-term and high-dose antibiotic use leads to gastrointestinal symptoms such as allergic reactions, nausea, vomiting, and diarrhea and causes some hepatorenal toxicities. It has been shown that long-term and unsuitable AT may increase bacterial resistance three times[14]. These objections are applicable to almost all antibiotics, and avoiding unnecessary use of antibiotics is highly important due to these side effects. Additionally, with combined antibiotic usage, the use of broad-spectrum antibiotics has increased, and this has severely raised the costs of hospitalization. This is why avoiding unnecessary multiple antibiotic usage is also important in terms of hospital and health costs.

With the publication of the Tokyo Guidelines, monotherapies have started to be used at all centers instead of CAT. The effectiveness of AT is measured based on the recovery of the pretreatment clinical, radiological, and laboratory findings. It was seen in randomized clinical studies comparing antibiotics used in AC treatment that there was no significant difference between antibiotics[15,16]. Therefore, it is important to investigate whether or not applying the antibiotics that are used either singly or in combination has any difference in the treatment of the disease.

CONCLUSIONS

As a result of this study, no significant superiority of CAT over SAT was observed in terms of hospitalization durations, mortality, and reduction in laboratory parameters in both the cholecystectomy group and the medical treatment group, and it was concluded that the use of CAT is not necessary. We recommend that it is sufficient to apply single-dose prophylactic AT in Grade I AC cases, and in the case of more severe disease indicating therapeutic interventions, SAT by selecting the most appropriate antibiotic would be appropriate rather than CAT as it is not disadvantageous in comparison to multiantibiotic usage in terms of reducing treatment costs, bacterial resistance development, potential allergic reactions, hepatorenal toxic effects, and hospitalization durations.

ETHICAL APPROVAL

The study was conducted at Gulhane Training and Research Hospital and approved by the Ministry of Health of the Republic of Turkey and Republic of Turkey Health Sciences University Gulhane Scientific Research Ethics Committee (dated March 11, 2021, number: 2021/112).

AUTHORS' CONTRIBUTIONS

ÜA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **YSP:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210578

A low phase angle determined by bioelectrical impedance analysis is associated with oropharyngeal dysphagia among institutionalized older adults

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SUMMARY

OBJECTIVE: The aim was to evaluate the prevalence of oropharyngeal dysphagia (OD) and its association with body composition by bioelectrical impedance analysis (BIA) and functionality among institutionalized older adults.

METHODS: A cross-sectional study was conducted. The swallowing function and diagnosis of OD were evaluated with a volume-viscosity swallow test. Activities of daily living were evaluated by the Barthel Index. Body composition was evaluated by BIA, and phase angle (PhA) was determined.

RESULTS: Eighty institutionalized older adults were evaluated. The mean age of the study population was 82±9.5 years, and 65% were females. The OD prevalence was 30%, dependence was 30%, and sarcopenia was 16%. In the multivariate analysis, a low PhA (<3.5°) was independently associated with the presence of OD adjusted by sex and age (OR: 2.60, 95%CI 2.41–2.90, p=0.01).

CONCLUSIONS: A higher prevalence of OD was found. Significant and independent associations were found between low PhA, dependence, and sarcopenia with the presence of OD among institutionalized older persons.

KEYWORDS: Oropharyngeal dysphagia. Sarcopenia. Home for the aged. Dependence. Clinical. Muscle strength. Nutrition. Nurses. Acute care. Clinical research.

INTRODUCTION

The aging process causes changes in the anatomy and function of the muscle mass, and these normal processes result in alterations in the swallowing mechanism[1]. In healthy older adults, these changes in swallowing mechanism are known as presbyphagia and do not necessarily imply a pathological condition[1,2]. When these changes occur in sarcopenic, frail, or malnutrition patients, the risk of oropharyngeal dysphagia (OD) increases[3].

OD is a high prevalence geriatric syndrome. It has been documented that OD affects 30–40% of the population aged 65 years and older, recognizing more its clinical, functional, and social importance in the elderly[4]. The prevalence of OD in institutionalized older patients is higher. It is estimated that 40–51% of institutionalized older patients had the symptoms of OD[5,6].

OD results in clinical and nutritional complications on body composition, nutritional intake, functionality, and prognosis. Over time, the clinical and nutritional complications may lead to frailty, social withdrawal, and mortality[6]. The bioelectrical impedance analysis (BIA) is a noninvasive technique used to estimate body compartments through mechanisms of resistance and reactance and offers an advantage in the assessment of patients with OD. Phase angle (PhA) is an important

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 16, 2021. Accepted on July 14, 2021.

prognosis indicator and a marker of cell membrane integrity evaluated by BIA. Lower PhAs are consistent with muscle mass loss, cell breakdown, and aging cell process, while larger PhAs are associated with large quantities of healthy cell membranes and body muscle mass[7].

The handgrip strength (HGS) is used as an indicator of muscle functional capacity in older adults. A recent study conducted by Carrión et al.[8] demonstrated that 17.4% of older patients with OD in a chronic setting had malnutrition evaluated by Mini Nutritional Assessment (MNA) tool, and 16.7% had Sarcopenia according to the diagnostic criteria recommended by the European Working Group on Sarcopenia in Older People (EWGSOP).

Furthermore, there are few studies that have been evaluated the presence of OD and its association with PhA and HGS in institutionalized older adults. Therefore, the purpose of this study was to evaluate the prevalence of OD and its association with body composition alterations and functionality among institutionalized older persons.

METHODS

A cross-sectional study was performed on institutionalized older persons. The Clinical Research and Bioethics Committee approved this study (REF: 1557). All patients who agreed to participate in the study were screened and evaluated after the procedures were explained. Written informed consent was obtained from each participant or the legally authorized representative if the patient was not able to give it.

Swallowing function

The volume-viscosity swallow test (V-VST)[9] was performed to confirm the diagnosis of OD. The V-VST assesses the ability to drink safely and effectively with different types of viscosity and volume. The bolus volume was 5, 10, and 20 mL. The nectar viscosity (250 cP) was achieved by adding 2 g of the Food Thickener® (Victus Laboratory, FL, USA) to 100 mL of water, and the pudding viscosity (800 cP) was achieved by adding 5.0 g of the thickener to 100 mL of water. Boluses of each volume and viscosity were administered to patients with a syringe during the test to ensure an accurate measurement of the volume. A pulse oximeter was placed on the left index finger before the test, and baseline readings were measured. During the test, the following clinical signs of ineffective swallowing were observed: impaired labial seal, oral residue, and multiple swallows per the bolus. The following clinical signs of unsafe swallowing were also observed according to the V-VST: changes of voice quality, cough, or decrease in oxygen saturation ≥3% to detect silent aspiration[9].

Mini nutritional assessment

The nutritional risk was assessed using the MNA questionnaire, a valid and reliable tool to identify malnutrition in elderly people[10]. The original version of this tool that was used for this study contained 18 questions with a maximum of 30 points. It is considered that a score lower than 17 points represents malnutrition[11].

Barthel index

Dependence on essential activities of daily living was evaluated by the Barthel Index. It is an ordinal scale that consists of 10 items, namely, personal hygiene, bathing, feeding, transferring to and from a toilet, going upstairs and downstairs, dressing, bowel control, bladder control, bed to chair transfer, and walking on a level surface. Patients were classified as severe dependence with a score <60 points[12,13].

Sarcopenia

Sarcopenia was diagnosed according to the diagnosis criteria of 2019 guidelines[14]. In the current research, sarcopenia was diagnosed when both low muscle strength measured with HGS and low Skeletal Muscle Mass (SMM) index measured with BIA were present.

The body composition was performed using a single-frequency BIA equipment (50 kHz, Quantum X, RJL Systems, Clinton Township, MI, USA) with the standard technique[15]. With the resistance and the reactance obtained by the BIA, we estimated the SMM to diagnose sarcopenia. SMM was calculated using the equation of Janssen et al.[16], i.e., SMM (kg): [(Height cm^2/Resistance]×0.401)+(sex×3.825)+(age×-0.071)+5.102. For sex, men=1 and women=0, and age is measured in years. Finally, to obtain the Skeletal Muscle Index (SMI), the SMM was divided by the height squared (m^2) (SMI=SMM/Height m^2). The muscular functionality was evaluated with a handgrip dynamometer (TKK 5001 Grip A, Takei Scientific Instruments CO., LTD, Niigata City, Japan). Subjects were placed standing with arms outstretched parallel to the trunk taking the dynamometer and applying maximum strength with each hand without support. The measurement was repeated three times with a separation of 1 min to avoid fatigue, and the maximum value was recorded.

Statistical analysis

The data are presented as mean±standard deviation or median with interquartile range [25–75 th percentile], depending on the data distribution. The Shapiro-Wilk or the Kolmogorov-Smirnov test for the proper parametric or nonparametric test was performed. For comparisons between groups with OD and those without OD, a Student's t-test or the Mann-Whitney U test was used for continuous variables. The categorical variables are presented as a percentage, and proportions between

groups were compared using the chi-squared test. We hypothesized that there would be an association between OD, body composition analysis, and other geriatric syndromes. To identify potential associations between OD with PhA, sarcopenia, and dependence, a logistic regression analysis was conducted. A $p<0.05$ was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 22.

RESULTS

A total of 80 residents were evaluated and included in this study. The mean age of the residents was 82±9.5 years, and 65% were females. Table 1 shows the demographics and clinical characteristics of our study population. The prevalence of OD at the evaluation was 30%. The mean score of the MNA was 23±4, and the general prevalence of malnutrition (MNA score <17 points) was 20%. The most common diagnosis among residents was neurological diseases (i.e., Alzheimer's disease or other dementias) and metabolic disorders (i.e., diabetes mellitus, hypertension, and metabolic syndrome).

The clinical characteristics between study groups are shown in Table 1. The OD group was older (86±8.0 versus 80±9.4 years respectively, p=0.001) and had the lowest MNA score compared with those residents without OD (20±4 versus 24±3 points, respectively, p=0.001). The residents with OD had the lowest HGS (10±4.9 versus 18±7.5 kg, p<0.001) and PhA compared with those residents without OD (3.5±0.7 versus 4.9±0.8, p<0.001). There were significant differences in anthropometric variables and body composition between groups. There were no significant differences in primary diagnosis between groups.

Table 2 contains the associations of OD with some body composition and functionality. Age >80 years, the presence of dynapenia, severe dependence, sarcopenia, and low PhA were significantly associated with the presence of OD in the bivariate analysis. Severe dependence, sarcopenia, and low PhA were significantly associated with the multivariate analysis adjusted by sex and age. Figure 1 shows the number of subjects with the presence of severe dependence, sarcopenia, and OD. A total of

Table 1. Demographics and clinical characteristics of study subjects.

	Total n=80	With OD n=27	Without OD n=53	p-value
Sex*				
Women, n (%)	52 (65)	35 (44)	45 (56)	0.07
Age (years)†	82±9.5	86±8.0	80±9.4	0.001
Primary diagnosis (%)*				
Neurological disease	27 (34)	14 (50)	15 (28)	0.30
Cardiopulmonary disease	15 (19)	3 (17)	19 (10)	
Metabolic disorders	27 (34)	8 (29)	21 (40)	
Other diseases	11 (13)	2 (4)	7 (13)	
ADLs				
Barthel index score†	82±23	61±24	92±14	<0.001
Dependence n (%)*	24 (30)	20 (74)	10 (18)	<0.001
Body composition and functionality				
Weight (kg)†	57±12	50 ±13	61±11	0.001
Height (cm)†	148±11	144±11	151±11	0.02
BMI (kg/m^2)†	25.4±5.7	23±7.0	27±4.5	0.02
R/H (ohms)†	390±90	440±103	360±68	<0.001
Xc/H (ohms)†	31±11	28±6.5	32±11	0.30
PhA (°)†	4.4±1.1	3.5±0.7	4.9±0.8	<0.001
HGS (kg)†	15±5.7	10±4.9	18±7.5	<0.001

OD: oropharyngeal dysphagia; ADLs: activities of daily living; BMI: body mass index; R/H: resistence/height; Xc/H: reactance/height; PhA: phase angle; HGS: handgrip strength; *Proportions were compared with the χ^2 test; †The student's t-test was used for comparisons between groups.

Table 2. Factors associated with oropharyngeal dysphagia.

	Bivariate analysis		Multivariate analysis*	
	OR	95%CI	OR	95%CI
Age (>80 years)	3.45	1.14–10.37†		
Malnutrition (MNA)	2.47	0.69–8.88		
Dependence (yes/no)	12.40	3.35–45.94†	11.48	2.74–48.06†
Dynapenia (yes/no)	5.70	1.17–27.83†		
Sarcopenia (yes/no)	9.40	1.30–85.81†	9.33	1.63–53.53†
Lower PhA (<3.5°)	3.40	1.84–6.40†	2.60	2.41–2.90†

OR: odds ratio; MNA: mini nutritional assessment, PhA: phase angle; *Multivariate analysis adjusted by sex and age; †Significant results in bold.

9 residents (11.4%) had the triad of geriatric syndromes (i.e., OD, dependence, and sarcopenia).

DISCUSSION

A cross-sectional study was performed to investigate the OD prevalence and its association with dependence and sarcopenia among institutionalized older adults. We identified two important clinical findings. First, the general OD prevalence was 30% among residents. Second, severe dependence and sarcopenia were independently associated with the presence of OD, adjusted by sex and age.

The subjects with OD were older, had a higher Barthel Index Score, and had a lower score of MNA. Previous studies[17,18] have investigated the prevalence and association of malnutrition and dependence in older adults with OD. In a cohort of 1662 hospitalized older persons[3], it was observed that a Barthel Index Score <40 at admission was associated with the presence of OD (OR: 9.71, 95%CI 7.23–12.04), and subjects with OD had a higher prevalence of malnutrition (68.4%). Another study conducted among 874 frail older adults[19] found that dysphagia risk was related to an increased likelihood of malnutrition (OR: 1.30, 95%CI 1.01–1.67). It is important to mention that in these studies the muscle mass index and the muscle strength were not evaluated. In clinical practice, the tools focused to evaluate malnutrition in older adults do not necessarily consider body composition and muscle strength as factors for the diagnosis of malnutrition.

A strength of this study was the evaluation of body composition and the evaluation of muscle strength. A significant association was found between dynapenia and OD. In recent years, the definition and importance of sarcopenic dysphagia have been more studied. Maeda and Akagi[20] found a significant correlation between arm muscle area and efficient swallowing in older adults (r=0.53, p<0.05). In a cohort of 95 older

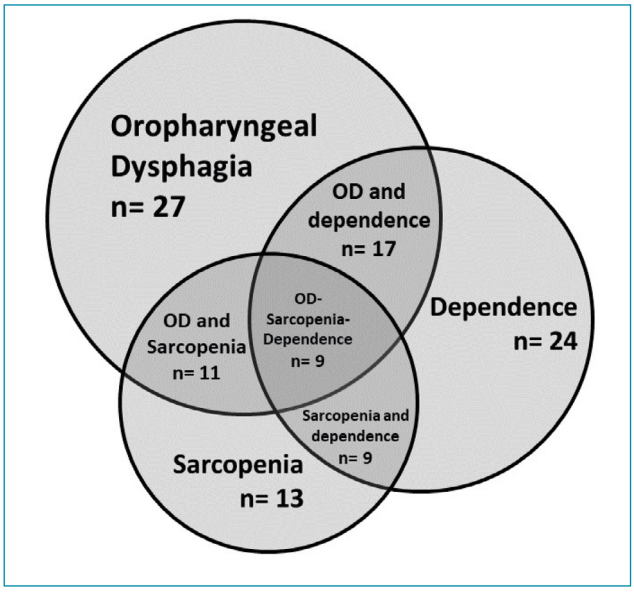

Figure 1. Proportion and association of the three geriatric syndromes studied: oropharyngeal dysphagia, dependence, and sarcopenia.

adults conducted in a care facility, it was found that 77% of the subjects had sarcopenia, and 26% developed sarcopenia, all of whom had sarcopenia (p=0.002). This study concluded that a decreased SMI was associated with the presence of OD (OR: 24.0, 95%CI 3.6–159.0, p=0.001)[8].

Advanced sarcopenia might cause dysphagia, and the loss of activity originated by weakness may result in a reduction in the essential activities of daily living. Although there is an association, it does not imply causality. Some studies have been investigated the association of sarcopenia and impaired swallowing, defined as sarcopenic dysphagia[21,22]. It is important to conduct a complete swallowing evaluation in patients with a diagnosis of sarcopenia or dynapenia to detect alterations in swallowing function. In these older adults with OD and sarcopenia, it is

important to implement strategies to increase the nutritional intake of energy and protein and to improve the functionality in care facilities.

Our study has important limitations. First, this is a cross-sectional study. We cannot explain causality between sarcopenia with OD and dependence, and the scope of this study is merely descriptive. Second, the sample size was reduced to perform a multivariate analysis adjusted with other confusing variables such as comorbidities, polypharmacy, and nutritional intake. Although it is not a novel concept, this study highlights the current high prevalence of swallowing disorders and the importance of evaluating functionality and body composition among institutionalized older persons.

The presence of geriatric syndromes in institutionalized older adults is highly prevalent and associated with morbidity and poor outcomes. In our findings, a considerable proportion of older adults had the triad of OD, sarcopenia, and dependence. Healthcare providers will increasingly encounter older persons with dysphagia, sarcopenia, and dependence. Evaluating swallowing function and functionality must be part of the screening in institutionalized older adults to implement interventions to recover functional status.

CONCLUSIONS

OD is frequent and a condition that is underdiagnosed and underestimated among institutionalized older adults. This important condition has a negative effect on the body composition and on the functionality in older adults living in care facilities. Dependence and sarcopenia are geriatric syndromes that are independently associated with the presence of OD.

ACKNOWLEDGMENT

The authors are grateful to the Centro Gerontológico "Arturo Mundet" for their collaboration in the study.

AUTHORS' CONTRIBUTIONS

CART: Conceptualization, Methodology, Writing – original draft. **LCM:** Formal analysis, Investigation, Resources, Software. **AGRV:** Data curation, Visualization, Writing – original draft. **DVCM:** Data curation, Visualization, Writing – original draft. **AESZ:** Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210586

Automated breast volume scanning combined with shear wave elastography for diagnosis of triple-negative breast cancer and human epidermal growth factor receptor 2-positive breast cancer

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SUMMARY

OBJECTIVE: To explore the values of automated breast volume scanning (ABVS) combined with shear wave elastography (SWE) in the differential diagnosis of triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2–positive breast cancers (HER2+BC).

METHODS: In this study, 28 patients with TNBC and 32 patients with HER2+BC were enrolled. The characteristics of ABVS and virtual touch quantification (VTQ) in SWE of all patients were reviewed. The multivariate logistic regression analysis was carried out and the receiver operating characteristic curves of ABVS and ABVS+VTQ were drawn.

RESULTS: In ABVS imaging, the microcalcification, posterior echo, internal echo, shape, and edge had significant difference between TNBC and HER2+BC groups ($p<0.05$). The regular shape was the independent factor for TNBC ($p=0.04$, odds ratio [OR]=4.479), and the microcalcification in mass was the independent factor for HER2+BC ($p=0.01$, OR=2.997). In VTQ imaging, the shear wave velocity (SWV_{max}, SWV_{min}, and SWV_{mean} in TNBC group were significantly lower than those in HER2+BC group ($p<0.001$). The sensitivity, specificity, and accuracy of ABVS+VTQ in diagnosing TNBC were higher than those of ABVS alone.

CONCLUSIONS: ABVS combined with SWE has certain advantages in differentiating TNBC from HER2+BC, which is helpful for the treatment planning and prognosis judgment.

KEYWORDS: Breast cancer. Ultrasound. Elasticity imaging techniques. Efficiency.

INTRODUCTION

Breast cancer is a malignant tumor in women, causing the highest morbidity and mortality[1]. Triple-negative breast cancer (TNBC) is a particular type of breast cancer that is characterized by its biological aggressiveness, worse prognosis, and lack of prognostic markers or therapeutic targets in contrast with hormonal receptor-positive breast cancer and human epidermal growth factor receptor 2-positive breast cancer (HER2+BC)[2]. Both TNBC and HER2+BC are considered to be the most immunogenic breast cancers and are highly heterogeneous[3]. HER2+BC is sensitive to the targeted molecular therapy, though its prognosis is poor. However, TNBC has high invasiveness and lacks the targeted standard treatment, so its prognosis is worse than HER2+BC[4]. The majority of patients with TNBC die in the first 5 years after treatment[5]. Therefore, improving the diagnostic accuracy of TNBC and HER2+BC plays an important role for the treatment choice and prognosis. Ultrasound is the most common method of breast examination. Automated breast volume scanning (ABVS) is a three-dimensional breast ultrasound technology, which has the advantage of multiplanar reconstruction[6]. Compared with handheld ultrasound, ABUS can overcome the dependence on operators

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 13, 2021. Accepted on July 06, 2021.

and improve the repeatability of inspection. In addition, it can show the structural distortion in coronal plane[7]. Shear wave elastography (SWE) is a new imaging technology based on ultrasonic imaging that can provide the tissue stiffness information[8]. It has the noninvasive, simple, and real-time advantages[8]. In clinics, SWE is used to measure the elastic modulus of tissue and reflect the stiffness properties, contributing to the early diagnosis and assessment of disease[9]. This study investigated the values of ABVS combined with SWE in the diagnosis of TNBC and HER2+BC, for providing more information for effective diagnosis of breast cancer.

METHODS

Subjects

Sixty female patients with TNBC or HER2+BC confirmed by surgery and pathology in our hospital from July 2017 to January 2020 were enrolled in this study. There were a total of 60 lesions. The lesion size was 1.3–3.6 cm, with average size of 2.3±1.4 cm. Out of these 60 patients, 28 had TNBC, and their age was 38–63 years, with average age of 52.3±8.1 years. And 32 patients had HER2+BC, and their age was 31–83 years, with average age of 44.6±7.6 years. All patients had not received any treatment before surgery.

Examination and diagnosis methods

ACUSON S2000 color Doppler ultrasound diagnostic instrument with 14l5BV linear array probe (frequency 5–14 MHz) and corresponding ABVS system (Shanghai Siemens Medical Devices Co., Ltd., Shanghai, China) were used for the examination and diagnosis of breasts. First, the two-dimensional ultrasound was used to scan the fully exposed breasts. The virtual touch quantification (VTQ) mode of acoustic radiation force impulse (ARFI), a new generation of SWE, was selected. The shear wave velocity (SWV, m/s) at the edge of four quadrants of mass was obtained. The SWV_{max}, SWV_{min}, and SWV_{mean} values were recorded. Then, the ABVS mode was selected to scan the breasts at anteroposterior, lateral (or medial), upper, and lower positions. The three-dimensional images of transverse, sagittal, and coronal planes were obtained by workstation[10]. All imaging data were diagnosed by two doctors with 10 years of experience in breast ultrasound diagnosis using double-blind method. The coronary imaging, microcalcification, shape, edge, and other features of mass were analyzed.

Statistical analysis

SPSS version 19.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The enumeration data were expressed as number and rate, and the comparison between groups was performed using χ^2 test. The statistically significant parameters were analyzed by multivariate logistic regression. The measurement data are expressed as mean±standard deviation, and the comparison between groups was performed using t-test. Using immunohistochemistry result as gold standard, the diagnostic efficiencies of ABVS and ABVS+VTQ were analyzed using receiver operating characteristic curve, and the area under curve (AUC) among three methods was compared. A $p<0.05$ was considered statistically significant.

RESULTS

Automated breast volume scanning imaging characteristics of triple-negative breast cancer and human epidermal growth factor receptor 2-positive breast cancer

The single factor analysis of ABVS characteristics of patients in TNBC and HER2+BC groups showed that there was no significant difference in coronal imaging or internal echo between TNBC and HER2+BC groups ($p>0.05$). The microcalcification, posterior echo, internal echo, shape, and edge had significant difference between TNBC and HER2+BC groups ($p<0.05$) (Table 1). Multivariate logistic regression analysis showed that the regular shape was the independent factor for TNBC ($p=0.04$, odds ratio [OR]=4.479) and the microcalcification in mass for HER2+BC ($p=0.01$, OR=2.997). The ABVS images of TNBC and HER2+BC are shown in Figure 1.

Shear wave elastography imaging characteristics of triple-negative breast cancer and human epidermal growth factor receptor 2-positive breast cancer

The VTQ of ARFI showed that the SWV_{max}, SWV_{min}, and SWV_{mean} in TNBC group were 5.2±0.5, 3.7±0.7, and 4.4±0.4 m/s, respectively. The SWV_{max}, SWV_{min}, and SWV_{mean} in HER2+BC group were 6.4±0.8, 4.9±1.0, and 5.7±0.8 m/s, respectively. Each index in TNBC group was significantly lower than that in HER2+BC group (SWV_{max}: $t=6.032$, $p<0.001$; SWV_{min}: $t=4.950$, $p<0.001$; SWV_{mean}: $t=6.991$, $p<0.001$).

Diagnostic efficiency of automated breast volume scanning and automated breast volume scanning+virtual touch quantification for triple-negative breast cancer

In diagnosing TNBC, the AUC of ABVS and ABVS+VTQ was 0.717, 0.632, and 0.768, respectively. The AUC of ABVS+VTQ was larger than that of ABVS. The sensitivity, specificity, and accuracy

Table 1. Single factor analysis of automated breast volume scanning characteristics of triple-negative breast cancer and human epidermal growth factor receptor 2-positive breast cancer.

Characteristics	TNBC group	HER2+BC group	χ^2	p
N	28	32		
Coronal imaging, n (%)				
Convergence sign	0 (0.00)	3 (9.37)	4.117	0.128
Hyperechoic halo	2 (7.14)	5 (15.63)		
Unchanged	26 (92.86)	24 (75.00)		
Microcalcification, n (%)				
Yes	4 (14.29)	24 (75.00)	22.117	0.000
No	24 (85.71)	8 (25.00)		
Posterior echo, n (%)				
Enhance	12 (42.86)	6 (18.75)	8.295	0.016
Sound and shadow	1 (3.57)	9 (28.13)		
No change	15 (53.57)	17 (53.12)		
Internal echo, n (%)				
Hypoechoic	23 (82.14)	20 (62.50)	2.860	0.239
Isoechoic	1 (3.57)	2 (6.25)		
Inhomogeneous echo	4 (14.29)	10 (31.25)		
Shape, n (%)				
Regular (round/oval)	18 (64.29)	5 (15.63)	14.959	0.000
Irregular	10 (35.71)	27 (84.37)		
Edge, n (%)				
Smoothing	20 (71.43)	7 (18.75)	17.177	0.000
Microlobulation	7 (25.00)	13 (25.00)		
Angulation/burr	1 (3.57)	12 (56.25)		

TNBC: triple-negative breast cancer; HER2+BC: human epidermal growth factor receptor 2-positive breast cancer.

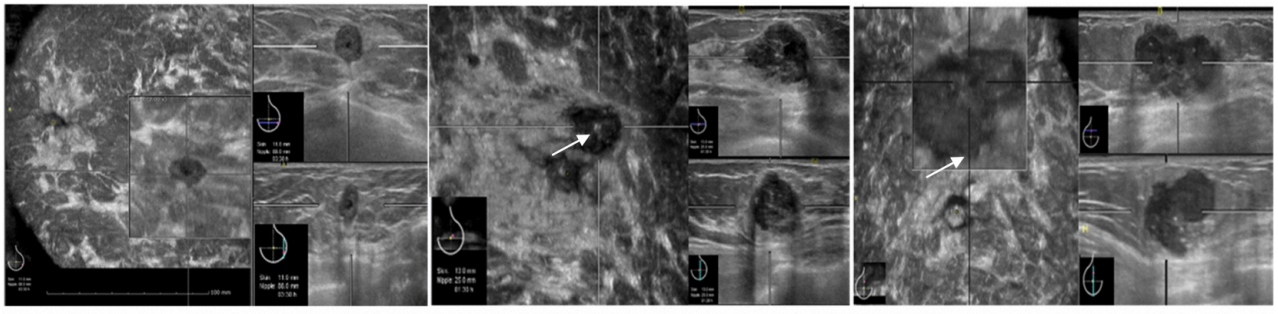

Figure 1. (A) automated breast volume scanning image of triple-negative breast cancer. The shape of mass was regular, and there was no microcalcification. (B) automated breast volume scanning image of human epidermal growth factor receptor 2-positive breast cancer. There was obvious microcalcification in mass on the coronal plane (arrow). (C) automated breast volume scanning image of human epidermal growth factor receptor 2-positive breast cancer. There was obvious angulation on the edge of coronal plane and sagittal plane (arrow).

of ABVS were 71.4, 71.9, and 70.5%, respectively. The sensitivity, specificity and accuracy of ABVS+VTQ were 78.6, 75.4, and 75.0%, respectively. Therefore, the sensitivity, specificity, and accuracy of ABVS+VTQ were higher than those in ABVS alone (Figure 2).

DISCUSSION

Due to the standardization of scanning procedure, ABVS has better repeatability, higher consistency, and more comprehensive information than conventional two-dimensional ultrasound. It can display the differential resolutions of image and tissue anatomical characteristics and spatial relationship, which is of great significance in the localization and diagnosis of breast cancer[11]. The sagittal view of ABVS has advantage in observing the angulation in edge, the coronal view has advantage in observing the burr in edge, and the cross-sectional view has the highest resolution[12]. In the absence of mass background, ABVS has a higher detection rate of microcalcification than conventional ultrasound, which plays an important complementary role in the detection of microcalcification[13].

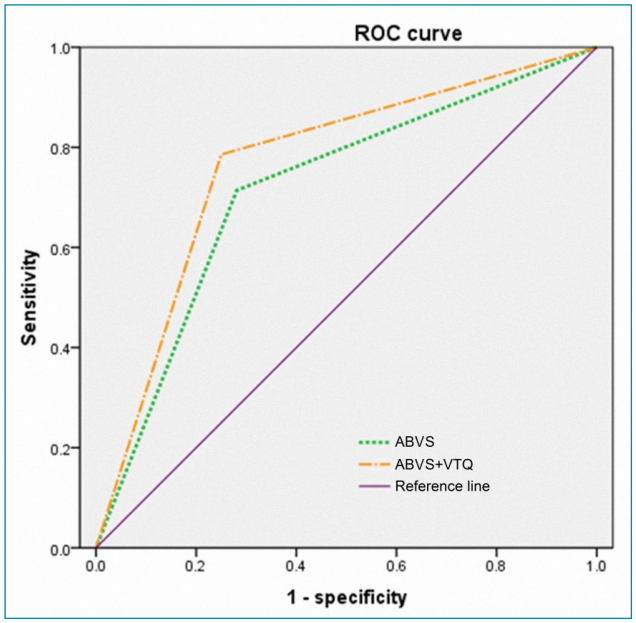

Figure 2. Receiver operating characteristic curves of automated breast volume scanning and automated breast volume scanning+virtual touch quantification in diagnosing triple-negative breast cancer.

Some scholars[14] have studied the ABVS-related manifestations and proposed that the marginal burr sign of breast cancer is positively correlated with the positive expression of estrogen receptor and progesterone receptor and that the microcalcification in mass is positively correlated with HER2-positive expression. Both TNBC and HER2+BC have negative estrogen receptor and progesterone receptor expressions, but HER2+BC has positive HER2 expression. Results of this study showed that in TNBC and HER2+BC, the convergence sign of ABVS was rare and hyperechoic halo was not obvious. However, the microcalcification in mass was the independent factor for HER2+BC. This can be used for differentiation of HER2+BC from TNBC.

Results of our study indicate that SWE could provide the additional information for the quantitative diagnosis of TNBC and HER2+BC. In our study, the SWV_{max}, SWV_{min}, and SWV_{mean} values in TNBC group were significantly lower than those in HER2+BC group. ABVS+VTQ can show the relatively low stiffness of TNBC, so the sensitivity, specificity, and accuracy of ABVS+VTQ were higher than those in ABVS alone.

CONCLUSIONS

ABVS combined with SWE has certain advantages in differentiating TNBC from HER2+BC, which is helpful for the treatment planning and prognosis judgment. The limitation of this study is that, due to the relatively small sample size, the clinical tumor node metastasis stage of selected patients is not considered. Next, the sample size should be further increased, and the in-depth study should be conducted to put forward the advantages of the combined differential diagnosis method.

ACKNOWLEDGMENTS

This work was supported by the Major Scientific and Technological Project in Xiaoshan District (2017218).

AUTHORS' CONTRIBUTIONS

WC: Supervision, Validation, Writing – review & editing. **RR:** Conceptualization, Funding acquisition, Investigation. **FW:** Data curation, Formal analysis, Software. **ML:** Methodology, Project administration, Resources, Writing – original draft.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210589

Laparoscopic cholecystectomy by the modified bikini line approach as a simple and safe technique

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SUMMARY

OBJECTIVE: The gold standard technique for laparoscopic cholecystectomy (LC) is using four ports in the upper abdomen. However, this operative approach may not provide aesthetic satisfaction for some patients because of visible incision marks. This study sought to demonstrate that these incision marks can be hidden by safely changing the port locations.

METHODS: For patients with symptomatic cholelithiasis undergoing LC between March 2019 and March 2020, the modified bikini line approach was used. With the patient in the supine position with open legs, the first trocar (10 mm) was inserted into the abdomen through an 11-mm incision in the umbilicus. The other three trocars were placed in the abdomen at the bikini line with the help of a camera. The standard equipment for LC was then used to perform the surgery.

RESULTS: The modified bikini line approach to LC was used for 38 patients. Average operative time was 28.65 min, and the average hospital stay was 1.07 days. No perioperative or postoperative complications occurred. Follow-up was at 1 week, 1 month, and 6 months. Cosmetic results were satisfactory for all patients.

CONCLUSIONS: As an alternative to the standard LC approach, the modified bikini line technique is safe and useful in patients for whom postoperative aesthetic appearance is important. The modified approach is simple to learn and use and is effective to hide the incision marks well.

KEYWORDS: Laparoscopy. Cholecystectomy. Bikini line.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most common surgical procedures performed globally. However, LC may not be cosmetically satisfactory because of visible scars[1]. Although many new techniques have been developed for better cosmetic results, these methods have not become widespread because of application and learning difficulties. Two best known methods are natural orifice transluminal endoscopic surgery (NOTES) and single-incision laparoscopic surgery (SILS)[2,3]. In NOTES, the peritoneal cavity can be accessed through transvaginal, transgastric, transcolonic, and transurethral approaches, without abdominal incisions[4]. Widespread use of this method in surgical practice is limited, however, because of its high cost, unsafe orifice closure, and a prolonged learning period. In SILS, the incision is made at the umbilicus, and all the ports are inserted through this single incision. Although this method is safer than NOTES, the lack of angulation between the trocars prolongs the operative time. In addition, extra instrumentation is mandatory[5]. For these reasons, SILS has not become a widely used method throughout the world.

The placement of laparoscopic ports in less visible areas of the body, such as the bikini line — termed alternative port site selection — may result in further improved cosmesis[6]. Bachmann et al. described a new laparoscopic technique using the umbilicus and bikini line area in a patient undergoing hysterectomy. In their technique, a 5-mm camera was placed in the umbilicus; other trocars were placed at the bikini line; and LC was performed with long-handle instruments[7].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 08, 2021. Accepted on July 15, 2021.

In the technique described by Ersoz et al., all port entries were placed in the bikini area using a closed method. Although the desired results for cosmesis were achieved, the approach was difficult in practice[8]. In addition, the use of this technique creates a risk of trocar injuries in patients who have undergone previous pelvic surgery.

With the high frequency at which LC is performed globally, new techniques are needed with more aesthetic results, easy application, and low risk of complications. In the technique defined in this current study, the first 10-mm trocar was placed at the umbilicus incision site with an open technique and then the other three ports were placed in the bikini line area with camera guidance. In this way, the surgical team aimed to prevent possible organ and vascular injuries and to provide an adequate cosmesis.

METHODS

For patients with a diagnosis of symptomatic cholelithiasis who underwent LC between March 2019 and March 2020 at the authors' institution, the modified bikini line approach was used. Exclusion criteria were incision scars in the upper abdomen due to previous surgery, body mass index >40, and age >65 years. The study was conducted in accordance with the Declaration of Helsinki and was approved by local ethics committee (KAEK-50, decision number: 2,479). Informed consent was obtained from all patients and their relatives.

Procedure for modified bikini line approach to LC

All patients were placed in the reverse Trendelenburg position with open legs under general anesthesia. First, an 11-mm median incision was made into the umbilicus by working on the right of the patient in a straight position. The peritoneum was reached with a 1-cm median incision made to the fascia through this opening. The abdomen was insufflated with carbon dioxide at a pressure of 14 mmHg. At the bikini line, one 10-mm trocar was placed at the midline and two 5-mm trocars were placed on the right side (Figure 1). The laparoscope was operated through a 10-mm trocar on the bikini line. While working with 5-mm trocars located medially in the bikini area and in the umbilicus, the 5-mm trocar located in the lateral in the bikini area was used for retraction. However, depending on the intra-abdominal characteristics of the individual patient, all ports could be used as working ports.

Standard LC equipment was used throughout the entire procedure. Dissection and clipping of the artery and ductus cysticus was performed through a 10-inch trocar in the umbilicus. The gallbladder was separated from the bed with a hook, working in a retrograde manner. The gallbladder was visually removed from the trocar in the umbilicus. The laparoscope was inserted into the umbilicus, and any bleeding in the other trocar areas was observed by removing trocars and intervening as needed. When necessary, a drain was placed through the rightmost 5-mm trocar (Figure 2).

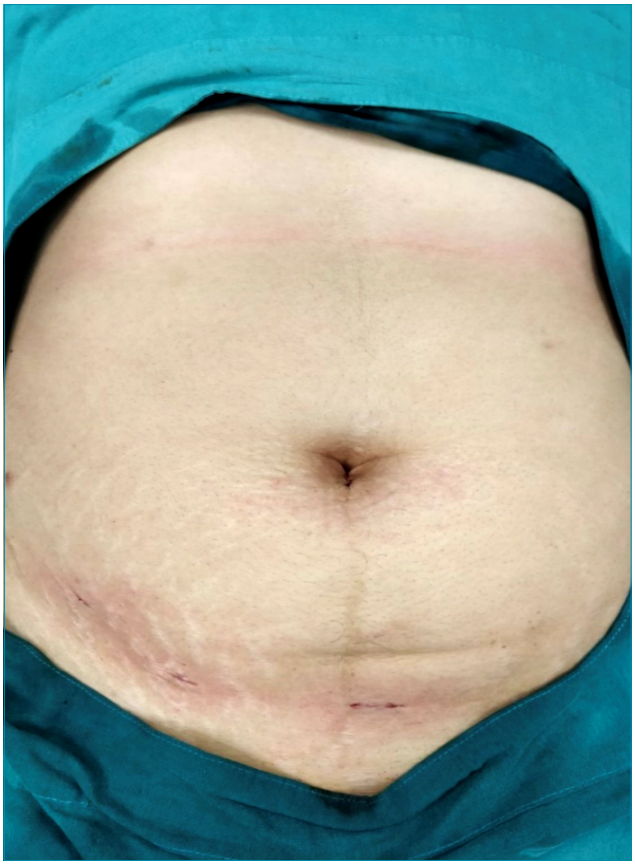

Figure 1. Trocar positions for the modified bikini line approach to laparoscopic cholecystectomy.

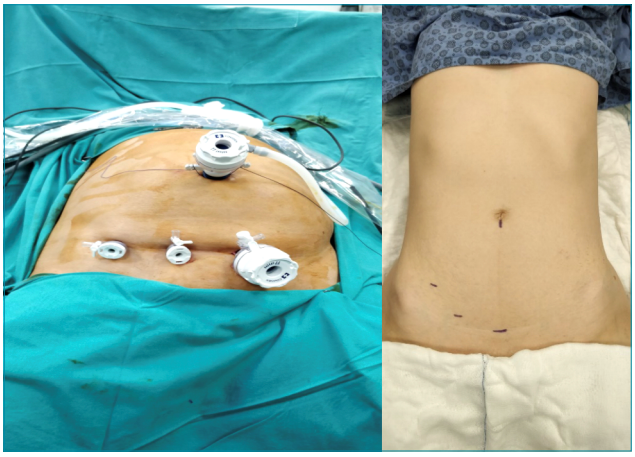

Figure 2. Postoperative view of incisions in the operation room.

Postoperative follow-up was conducted at 1 week, 1 month, and 6 months. Cosmetic satisfaction of the patients was questioned at each follow-up visit.

RESULTS

The modified bikini line approach to LC was used for 38 patients: 35 women and 3 men. The age of patients ranged from 15 to 65 years; average age was 42.7 years for women and 50.3 years for men. Mean body mass index was 27.9 kg/m^2 in women and 30.4 kg/m^2 in men.

Indications for LC were acute cholecystitis in 5 (13.16%) patients, chronic cholecystitis in 11 (28.95%), and symptomatic gallstones in 22 (57.89%). Concurrent umbilical hernia was detected in 5 (13.15%) patients; all underwent herniotomy and Mayo repair. Surgical history of the 38 patients included section in 10 (26.31%) patients, hysterectomy in 2 patients, endoscopic retrograde cholangiopancreatography in 2 patients, bladder operation in 1 patient, and open appendectomy in 1 patient. Significant adhesions were observed in the pelvic area in three patients who had previous surgery in the lower abdominal and pelvic area. Classical LC was performed in three patients due to adhesions in the pelvic area during exploration with a trocar entered from the navel at the beginning of the operation.

The gallbladder was removed from the umbilicus in all patients. A gangrenous gallbladder was removed with an endobag in two patients because of a large stone (>2 cm), for which the median incision in the umbilicus was enlarged and gallbladder was removed from the same incision. Average operative time was 28.65 (15–42) min.

No complications developed in any patient during postoperative follow-up at 1 week, 1 month, and 6 months. Drains were removed on the first postoperative day for all, except for two patients whose drains were removed on the second day. The average hospital stay of the patients was 1.1 days. At all follow-up visits, all 38 patients reported that the cosmetic results were satisfactory.

DISCUSSION

The gold standard procedure for gallbladder removal is LC. The traditional laparoscopic approach results in better cosmetic outcome than open cholecystectomy. In addition, the postoperative hospital length of stay, pain, and time to recovery are better in the classic laparoscopic method than with open surgery. As the two main other approach, both NOTES and SILS were developed as minimally invasive procedures[2-4]. In the NOTES technique, cholecystectomy is performed by making an internal incision[4]. Although the benefits of NOTES are not yet clear, less postoperative pain and fewer complications are expected[9], especially if the transvaginal route is used. Marescaux et al. published the first report of transvaginal endoscopic cholecystectomy as the first example of NOTES; however, this surgery was not a complete NOTES because they used an umbilical port or upper abdominal port[10]. In addition, both NOTES and SILS are expensive, have a prolonged operative time, and have a long learning curve[11].

A systematic review of the transvaginal approach in laparoscopic surgery in nongynecological intra-abdominal procedures to assess the risk of complications found an overall complication rate of 4.4%. Conversion rate to open surgery was 3.4%. Mean operative time was 119 min. Mean hospital length of stay was 3.1 days[12]. The risk of peritonitis is also present with the transvaginal approach and especially in the transgastric and transcolonic approaches. Also, no safe closure method has been found to date for the transvaginal approach. Moreover, the infection rate in animal models is 10–20%[13]. In addition, sociocultural and psychological barriers can be important issues for transvaginal access[14]. During the preoperative interview, most of female patients declined transvaginal cholecystectomy, not for medical concerns, but instead for personal reasons[14-17]. For all these reasons, the number of transvaginal cholecystectomies was very limited and could not be widely reviewed.

Therefore, many new methods have been tried to facilitate cholecystectomy. One of these methods is SILS, which was developed with the aim of reducing the invasiveness of LC. With SILS, only one umbilical incision is made and three ports are inserted into the abdomen through this single access[2,3]. In this technique, reticulator instruments were used to create the necessary operative angle because their insertion points are very close to one another[2,5]. Also, the gallbladder is emptied by a percutaneous needle and needs two sutures to the suspensions of the gallbladder from the abdominal wall. In this procedure, the peritoneal area can become contaminated by bile, which may cause biliary peritonitis. Also, the operative time is longer than for classic LC. In contrast to NOTES, SILS does not require the opening of a hollow organ, such as the stomach, colon, or vagina; therefore, complications such as gastrostomy or colostomy leakage are avoided. However, SILS has a longer operative time than LC and has a notable learning curve. Furthermore, because all instruments are closely placed together in SILS, conflict occurs between the operative instruments and camera[2,5]. After LC, the rate for infection and herniation is reported as 2% and 5.2%, respectively[10]. In SILS, the umbilical incision is larger than the LC incision, which may lead to local complications[18,19].

Although the LC-modified bikini line approach used in the present study is similar to the technique described

by Bachmann et al., the selected trocar diameters, entrance technique, and entry placements of the trocars are different[7]. In contrast, Ersoz et al. described the "full bikini line cholecystectomy" and aimed to keep the scars completely in the bikini area by carrying all the ports to the bikini area versus using one port in the umbilicus as in the current study[8]. However, in the technique used by Ersoz et al., the fact that the first trocar is entered into the abdomen with a Visiport optical trocar in the midline bikini line area may cause organ injuries, especially in patients with a history of pelvic field surgery. In addition, the fact that all ports are away from the operative area may cause the technique to be difficult to use in patients who are tall, obese, or have intensive gallbladder adhesions.

The current technique described herein is a modified version of the techniques described by both Bachmann et al.[7] and Ersoz et al.[8]. Thanks to the 10-mm port placed at the umbilicus with the open technique, the current approach provides safe access to the abdomen, safe placement of other ports, better control of the operating area, and a safe LC, even in patients with acute cholecystitis. In this technique, a 10-inch trocar inserted through the umbilicus can be used as both a camera and a working port. This site of trocar provides not only an appropriate angle in the dissection of the ductus cysticus and arteria cystica but also significant convenience in clipping. In this technique, interference of instruments is prevented by the distance between the trocar entrances. The application of the technique is difficult in patients with a body mass index >40 and in cases in which abdominal obesity is present. When placing the trocars in the bikini area, the epigastric arteries should be visualized and then the trocars should be placed. Long-hand instruments may be preferred in patients with a long distance between the gallbladder and the bikini area. The gallbladder is preferably visually removed from the umbilicus. In this way, it can be protected from possible strain, perforations, bile leakage, and falling abdominal stones. The fact that all 38 patients expressed significant satisfaction with the cosmetic result showed that the aesthetic results of the technique were highly acceptable.

CONCLUSIONS

In patients with symptomatic cholelithiasis undergoing LC, the use of the modified bikini line approach can be a satisfactory and safe method for patients who care about cosmesis and desire hiding all incision scars in the umbilicus and bikini area (Figure 3). At the same time, the surgeon does not need special training and does not use special laparoscopic equipment, which are important advantages of this technique.

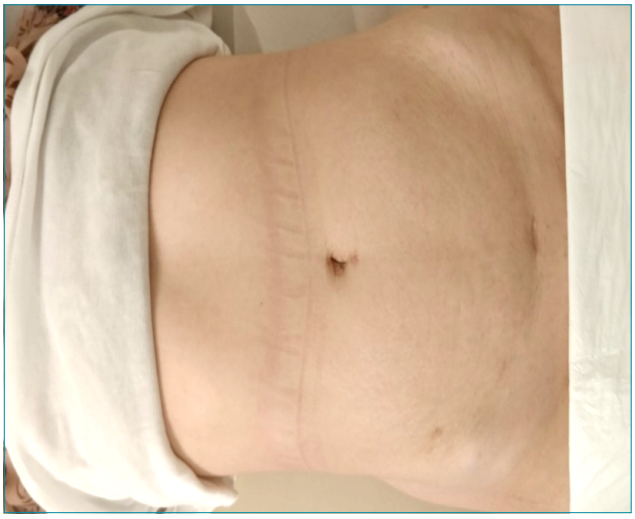

Figure 3. Cosmetic appearance of incisions at 6-month follow-up.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210608

Endurance and high-intensity interval training improve the levels of anxiety and quality of life in overweight men

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SUMMARY

OBJECTIVE: Body mass index (BMI) values of 25 kg/m² or more have been associated with poor cognitive outcomes, reduced health-related quality of life (HRQoL), and mental health disorders. Participating in regular exercise may improve these negative outcomes. However, the optimal exercise prescription remains to be clarified. The purpose of the present study is to compare the effects of moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) on HRQoL, depression, and anxiety levels in middle-aged overweight men.

METHODS: Twenty-five sedentary, overweight men participated in the 8-week training intervention. Subjects were randomized into MICT or HIIT and performed exercise sessions three times per week for 8 weeks. Participants answered the Physical Activity Readiness Questionnaire, the Short Form-36 survey, the Beck Depression Inventory-II, and the Beck Anxiety Inventory. Statistical analysis was carried out using the GraphPad Prism 7.0, and the level of significance was set at 5% to quantitative variables.

RESULTS: HRQoL scores were enhanced to all domains of both the groups. MICT and HIIT did not significantly change the depression levels in middle-aged overweight men ($p>0.05$). Nevertheless, MICT was capable to reduce the anxiety levels in middle-aged overweight men ($p<0.05$). However, there was not a significant change in the anxiety levels at the HIIT group.

CONCLUSIONS: HIIT may be a useful treatment to improve the HRQoL, but MICT alone can positively impact the anxiety levels in middle-aged overweight men.

KEYWORDS: Physical exercise. Physical activity. Quality of life. Mood disorders. Brain.

INTRODUCTION

The prevalence of overweight and obesity is increasing worldwide[1]. Body mass index (BMI) is one of the main personal factors that can influence mood and behavior[2]. Previous studies indicated that being overweight, for example, is related to changes in lifestyle variables, such as the quality of life

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Research Support Foundation of the State of Minas Gerais (FAPEMIG – Finance code APQ 01436-15) and Coordination for the Improvement of Higher Personnel Education (CAPES – Finance code 001), Brazil. Received on June 25, 2021. Accepted on July 18, 2021.

(QoL)[3] and mental health[4]. It has been suggested a reciprocal relationship between depression and obesity, indicating that obesity increases the risk of depression and depression is predictive of developing obesity[5]. Thus, weight status may impact health-related QoL (HRQoL)[6]. A growing body of evidence suggests that engaging in regular physical activity may be an effective strategy to improve anxiety, depression, and HRQoL[7,8].

Depression is a common cause of morbidity and mortality worldwide[3]. It was reported an inverse association between fitness and depression symptoms[9]. Moderate-intensity continuous training (MICT) is a type of physical exercise performed at moderate intensity for 30–60 min, 3–5 times per week. Another type of physical exercise is the high-intensity interval training (HIIT) that consists in short bouts of vigorous and intense exercise interspersed by periods of passive or active recovery. However, the comparison effects of MICT versus HIIT on the HRQoL and mood in overweight adult men are not found in scientific literature. The aim of this study was to evaluate the effects of MICT and HIIT on the HRQoL, anxious profile, and depressive behavior in middle-aged overweight men.

METHODS

Participants were included in the study if they met the following inclusion criteria: nonsmoker, aged 30–50 years, overweight or obese (BMI ≥25 kg/m^2), and no regular participation in a physical exercise program in the past year. Exclusion criteria included prescription drug use, limited physical exercise capability, or any contraindication to physical exercise as determined by the Physical Activity Readiness Questionnaire[10].

Study design

At the first preintervention visit, participants performed a shuttle run test to estimate oxygen maximum consumption (VO_{2max}). At the second preintervention visit, anthropometric data were collected, and subjects completed health and affective questionnaires. During the training intervention, subjects performed either MICT or HIIT three times per week for 8 weeks. Prior to the physical exercise intervention, subjects completed a 20-m multistage shuttle run test to estimate maximal velocity and VO_{2max}, as previously described[11].

Training protocols

Subjects randomized to HIIT performed repeated 200-m sprints (10×20 m) interspersed with 1-min bouts of passive recovery. The beep sounds were individualized for each subject and listened to through headphones, allowing them to run at 85% (weeks 1–2), 90% (weeks 3–6), 95% (week 7), or 100% (week 8) maximum velocity. Subjects randomized to the MICT group were instructed to run continuously on a 300-m track at a prescribed speed for a prescribed distance.

Health-related quality of life

To assess HRQoL, the Short Form-36 survey was administered[12].

Depression and anxiety

The Beck Depression Inventory-II was administered to determine individual severity of depressive symptoms[13]. To assess anxiety symptoms, the Beck Anxiety Inventory was administered[14].

Statistical analysis

The normality of the data was verified by the Shapiro-Wilk test. Student's nonpaired *t*-test was used to evaluate the participants' characteristics. The possible effects of the proposed interventions on the dependent variables between the groups were tested through two-way analysis of variance for repeated measures, with Tukey post hoc test. Data are presented as mean and standard deviation. The level of significance was fixed at $p<0.05$.

RESULTS

MICT and HIIT subjects had an average VO_{2max} of 44.02 and 45.48 mL/kg/min and an average BMI of 29.37 and 27.76 kg/m^2, respectively. This body mass mean classifies both groups as overweight. No significant difference was observed in baseline age, BMI, or VO_{2max} between the groups ($p>0.05$). Then, HRQoL scores were evaluated (Table 1).

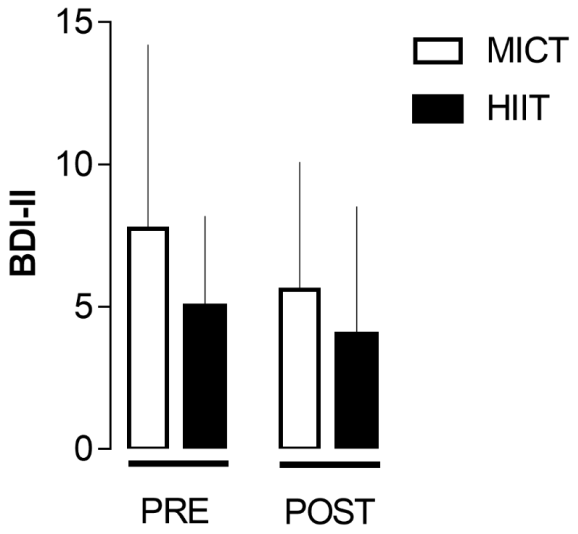
The scores of QoL were enhanced to all domains of both groups, MICT and HIIT. The evaluation of the QoL has a qualitative compound and not quantitative. It was also identified a significant effect of the treatment (exercise) on the mental component score, while an effect of the time can be seen in the physical component score. These results together indicate that MICT and HIIT are capable to improve the QoL of middle-aged overweight men, and the endurance exercise has an important effect over mental health.

Next, we evaluated the anxiety (Figure 1) and depression levels (Figure 2). MICT and HIIT did not significantly change the depression levels in middle-aged overweight men. Nevertheless, MICT was capable to reduce the anxiety levels in middle-aged overweight men. However, there was not a significant change in the anxiety levels at the HIIT group. We also performed a linear regression (results not showed) between all variables, but no significant results were seen.

Table 1. Health-related quality of life.

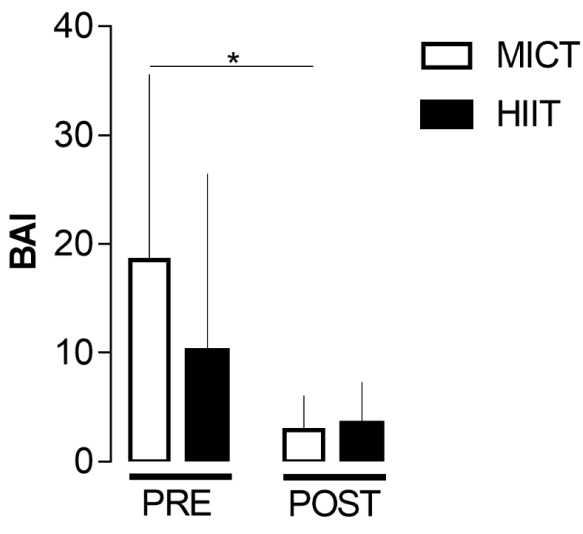
SF-36 domains	MICT (n=12)			HIIT (n=13)			Treatment	Time	Interaction
	Pre	Post	p-value	Pre	Post	p-value	p-value	p-value	p-value
Physical function	92.9±12.5	96.8±3.61	0.8800	88.6±13.3	95±8.4	0.3931	0.0287*	0.5723	0.1084
Physical role	79.1±29.8	87.9±22.4	0.8033	83±23.6	92.3±18.8	0.7540	0.5421	0.1871	0.9706
Pain	79.8±23.1	82.8±19	0.9747	70.1±13.9	77.2±12.6	0.7298	0.1291	0.3129	0.6807
General health perception	75.8±14.8	84.8±13.1	0.7382	72.4±16.5	82.3±16.6	0.4442	0.6836	0.0821	0.7618
Vitality	67.9±18.5	78.5±7.9	0.3642	61.8±12.8	71.5±20.5	0.4073	0.1495	0.0278*	0.9202
Social function	81.3±21	93.5±11.5	0.5282	73.1±23.3	81.7±27.8	0.7499	0.1138	0.1004	0.7730
Emotional role	88.8±21.8	98.8±4	0.4962	89.4±22	92.3±14.6	0.9735	0.5499	0.1944	0.4722
Mental health	80.6±16.6	83.4±4.9	0.9642	67.5±14.4	76±17.8	0.4451	0.0157*	0.1734	0.4890
Physical component score	53.8±14.3	61.42±6.4	0.2488	50.2±7.42	57.6±9.8	0.2403	0.1923	0.0102*	0.9689
Mental component score	52.08±7	55.9±3.13	0.6037	47.65±8.1	51.1±9.9	0.6500	0.0357*	0.0950	0.9312

SF-36: Short Form-36 survey; MICT: moderate-intensity continuous training; HIIT: high-intensity interval training. Data are presented as mean±standard deviation and compared scores between baseline (PRE) and follow-up (POST) training protocol of MICT and HIIT with their respective p-values, and also the p values relative to the treatment (physical exercise), time, and interaction by a two-way analysis of variance with Tukey post hoc test. *p<0.05.



BDI-II: Beck Depression Inventory-II; MICT: moderate-intensity continuous training, HIIT: high-intensity interval training.

Figure 1. Moderate-intensity continuous training and high-intensity interval training do not significantly change depression levels in middle-aged overweight men. Assessment of the Beck Depression Inventory-II scores in middle-aged overweight men with main effect of treatment (exercise) F (1,46)=2.569 and p=0.1158; time F (1,46)=1.372 and p=0.2475; and interaction F (1,46)=0.1862 and p=0.6681. Scores were compared between baseline (PRE) and follow-up (POST) training protocol of moderate-intensity continuous training (p=0.6845) and HIIT (p=0.9504) through a two-way analysis of variance followed by Tukey post-hoc test. Data are expressed as mean±standard error mean.



BAI: Beck Anxiety Inventory; MICT: moderate-intensity continuous training, HIIT: high-intensity interval training.

Figure 2. Moderate-intensity continuous training reduces the anxiety levels in middle-aged overweight men, while high-intensity interval training does not cause significant change. Assessment of the Beck Anxiety Inventory scores in middle-aged overweight men with main effect of treatment (exercise) F (1,46)=1.306 and p=0.2590; time F (1,46)=10.45 and p=0.0021; and interaction F (1,46)=1.697 and p=0.1992. Scores were compared between baseline (PRE) and follow-up (POST) training protocol of moderate-intensity continuous training (*p=0.0141) and HIIT (p=0.4966) through a two-way ANOVA followed by Tukey post-hoc test. Data are expressed as mean±S.E.M, *p<0.05.

DISCUSSION

To our knowledge, no studies have examined the relationship between MICT and HIIT in overweight or obese individuals simultaneously. The main findings of our study indicate that both MICT and HIIT can improve HRQoL, while MICT alone reduces the anxiety levels. No effect of either exercise intervention, MICT or HIIT, was observed on the depression levels.

A recent prospective study suggested that low fitness is much more strongly related to the onset of elevated depressive symptoms than fatness[15]. Depressed individuals often suffer from physical fatigue, which can lead to physical inactivity[16], while overweight individuals present a higher risk factor for developing depression[15]. Many explanations for establishing a relationship between obesity and depression have been suggested, such as psychological, sociological, and biological factors[8,17].

Physical exercise programs can be used as a nondrug method of maintaining brain health and treating psychiatric conditions[18]. It has been reported that the antidepressant effect of physical exercise is significantly higher in participants diagnosed with major depressive disorder when compared to participants with subclinical levels of depression[19]. Thus, the failure to see a significant change in depression scores in the present study may be due to the relatively low baseline levels of depression identified.

It has been shown that physical exercise interventions can improve symptoms of anxiety[20]. In our study, middle-aged overweight men who engaged in the MICT group for 8 weeks presented a significant reduction in the anxiety levels. However, this change was not seen in the HIIT group. Although the causal relationship between anxiety and obesity is not well understood, researchers speculate a bidirectional relationship between these factors. For example, the overweight status may increase the risk of developing an anxiety disorder, but, on the other hand, anxiety may also lead to increased appetite and subsequent weight gain through hypothalamic-pituitary-adrenal axis dysregulation[21].

CONCLUSIONS

Eight weeks of MICT or HIIT improved HRQoL. No exercise effect of MICT or HIIT was observed on depression scores. MICT was capable to reduce the anxiety levels, but HIIT did not induce this change. Future research should aim to elucidate the mechanisms responsible for mental health improvements after MICT and HIIT in middle-aged overweight men. Findings from the present study implicate that both MICT and HIIT may be a useful treatment to improve the HRQoL, but MICT alone can positively impact the anxiety levels in middle-aged overweight men.

ACKNOWLEDGMENTS

The authors would like to thank Fundação de Amaparo à Pesquisa do Estado de Minas Gerais and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

ETHICAL STATEMENT

This study was approved by the Research Ethics Committee of the Federal University of the Valleys Jequitinhonha and Mucuri (protocol number 667.788). This study was performed in accordance with the Declaration of Helsinki and CONSORT guidelines.

AUTHORS' CONTRIBUTIONS

RALS: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **FTA:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **NSL:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **FG:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **CODM:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **SHP:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **MFDP:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **RSMJ:** Conceptualization, Formal analysis, Investigation, Methodology. **KB:** Conceptualization, Formal analysis, Investigation, Methodology. **RCC:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Supervision, Writing review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210616

Intervention with a Pilates program in the primary health care of leprosy patients: an experimental study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the influence of a Pilates program on the perception of quality of life of leprosy patients suffering from physical disabilities and who are undergoing treatment or who have been discharged.

METHODS: This is an experimental study in which 48 participants were included; however, the final sample consisted of 5 participants. We performed a standardized and systematic dermatological–neurological examination to define the Eye-Hand-Foot score. Comparisons between preintervention and postintervention were performed using the paired t and Wilcoxon tests with a significance level of 0.05.

RESULTS: We did not find significant values for the quality-of-life outcome in the domains and skills observed. We identified a significant value for the level of physical activity after the intervention.

CONCLUSIONS: Quality of life between preintervention and postintervention with the Pilates program did not show significant improvement through self-report.

KEYWORDS: Leprosy. Public health. Primary health care. Exercise.

INTRODUCTION

Leprosy affects peripheral nerves and skin and can generate important deformities and physical disabilities. Physical disabilities that may arise before, during, and after treatment are more common in multibacillary individuals in cases of large neural impairment. These disabilities become stigmatizing factors of society and cause exclusion, prejudice, fear, and low quality of life[1].

Follow-up is based on routine assessments, such as muscle strength testing and sensitivity in the eyes, hands, and feet. Thus, it is possible to measure the degree of impairment on a scale ranging from 0 to 2, in which 0=absence of alteration; 1=decrease in muscle strength in the eyes, hands, and feet; and 2=notable deficiencies. Diagnosis, treatment, and monitoring are performed by primary health care services with multiprotection care, guidance on the disease, and regular physical exercises[2].

In this context, Pilates program emerges as a way to complement the stages of treatment up to the postdischarge moment, by structuring itself in movements and strategies, guided by professionals, capable of improving the loss of sensitivity, providing group interaction, social reintegration, and improvement of self-esteem and quality of life. Since Pilates practice is used in interventions of numerous pathological conditions and has a large scientific contingent of recommendation sat in the world[3].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This work was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), finance code 001.
Received on June 25, 2021. Accepted on July 18, 2021.

However, it is still unclear in the scientific literature whether the physiological effects of Pilates contribute to the increase in the quality of life of patients affected by disabilities due to leprosy. Thus, the present study aims to evaluate the influence of a Pilates program on the perception of quality of life of leprosy patients affected by physical disabilities and who are undergoing treatment or who have been discharged.

The hypothesis of this study is that a Pilates program, in patients with different degrees of disability caused by leprosy, generates benefits that can be observed through the self-report of these patients.

METHODS

This is an experimental study conducted in two Centros de Saúde da Comunidade (CSC) of Território Xerente 1 (Palmas, Tocantins, Brazil). All procedures were previously approved by the ethics committee on research with human Beings (code: 3251050).

The sample calculation was performed using the Software Ene, version 3.0, based on the detection of the minimum clinically important difference of 12.9 points for the Physical Health of the WHOQOL-Bref between preintervention and postintervention[4], assuming a standard deviation of 3.1 points. We consider a statistical power of 80% and alpha of 5% and estimate the minimum number of three participants.

Inclusion criteria were patients with disability due to leprosy, over 18 years of age, under treatment or discharged between 2018 and 2019, and who had as reference the CSC of Território Xerente 1 (Laurides Milhomen e Liberdade). Recruitment occurred after the identification of participants through the Notifica-SUS disease notification system.

We performed simplified neurological assessments, as recommended by the manuals of the Ministry of Health, such as muscle strength test, thermal, tactile, and painful evaluation, with the achievement of the Eye-Hand-Foot (EHF) score[5].

Evaluation of quality of life by the abbreviated versions of the WHO Quality of Life Instrument (WHOQOL-100) scale is adapted for Brazilians aged 18 to 59 years and the WHOQOL-Old for the elderly from 60. The scores were calculated using the syntaxes provided by WHO by converting them into scales from 0 to 100. Higher scores indicate a better perception of quality of life[6].

Socioeconomic and demographic data were classified according to the Brazilian Association of Research Companies[7]. We did a standardized and systematized dermato-neurological physical examination to define the EHF score of 8. The EHF score scales the severity of physical disability impairment in grade 1 or 2 for the eyes, hands, and feet segments and generates a score that can range from 0 to 2 on the left and right sides of each of these segments; and the final score ranges from 0 to 12. The higher the score, the greater the commitment in each of these segments[8]. The level of physical activity was measured using the International Physical Activity Questionnaire (IPAQ), a short version, validated for the Brazilian population by Matsudo et al.[9].

The Pilates program was conducted in a group, two times per week with 45-min sessions, supervised by a physical education professional experienced in the Pilates method, according to international guidelines[10]. The intervention took place for 12 weeks at the reference center of social assistance (May to November 2019). Each Pilates session was composed of stretching and muscle strengthening exercises in open and closed kinetic chains in the powerhouse system, which includes the abdominals, glutes, and paravertebral and lumbar[11].

Statistical analysis

Statistical analysis was performed using STATA statistical package version 14.2. The normal age of the variables was verified by the Shapiro-Wilk test. The parametric variables were presented in mean and standard deviation and others in frequency and percentiles. For the comparative analysis of the preintervention and postintervention, the paired t-test and Wilcoxon test were used, both using $p<0.05$ as reference.

RESULTS

Forty-eight participants who met the eligibility criteria were included. After four attempts, only 16 people attended the first week of the intervention with the Pilates program. Eleven participants were excluded for the following reasons: 1 due to worsening of the clinical picture and 10 for not attending the intervention. The final sample consisted of five participants affected by leprosy who had grade 1 or 2 disability. Socioeconomic, demographic, and clinical characteristics are presented in Table 1.

We did not find significant values, through the paired *t*-test, for the outcome of quality of life in the physical, psychological, social relations, and environment domains, nor for the observations such as sensory skills; autonomy; past, present, and future activities; social participation; death and dying; and intimacy (Table 2). In the evaluation of the level of physical activity, using the Wilcoxon test, we observed a significant value ($p=0.0522$) before and after the intervention.

Table 1. Socioeconomic, demographics, and clinical characteristics of the participants of the Centro de Saúde e Comunidade of Laurides Milhomen e Liberdade, Palmas (TO), 2019 (n=5).

Variables	n (%)
Sex	
Male	1 (20)
Female	4 (80)
Racial classification	
White	1 (20)
Black	1 (20)
Brown	3 (60)
Age (years)	
41–60	2 (40)
60 or above	3 (60)
Average size of households	
1 person	1 (20)
2 persons	2 (40)
3 persons	1 (20)
4 persons	1 (20)
Employment relationship	
Autonomous	1 (20)
Unemployed	2 (40)
Retired	2 (40)
Economic classification	
D-E	4 (80)
B2	1 (20)
Clinical characteristics	
Dimorfa	5 (100)
Disability	
Degree 1	4 (80)
Degree 2	1 (20)
Number of lesions	
<5	4 (80)
≥5	1 (20)
EHF	
<6	2 (40)
≥6	3 (60)
Affected nerves	
>1	5 (100)

D-E: average income R$ 768,00; B2: average income R$ 4.852,00; EHF: Eye-Hand-Foot.

DISCUSSION

We did not observe an improvement with statistical significance in the perception of quality of life in the comparison between preintervention and postintervention. However, there was an improvement in the physical domain and a worsening in the domain of the social relation according to the WHOQOL-Bref. There was an improvement in the facet social participation and worsening in facets sensory abilities and death and dying, as evaluated by the WHOQOL-Old. The physical activity level (NAF) of the participants obtained a statistically significant improvement.

The practice of physical exercises is initiated for various reasons, such as disease prevention, aesthetics, and physical, mental, and social well-being, but not everyone can combine this practice with their daily lives, leaving it aside in various phases of life. In the present study, only 33.3% began to participate in the Pilates program, a number that decreased to 10.4% at the end of the study[12].

The literature still has a scarcity of studies on this subject, and this makes it difficult to conduct a deeper discussion. However, certain barriers are presented to practice exercises in the face of pathological conditions, such as lack of time and energy, demotivation, and especially priority. This fact worsens even more due to issues such as economic class, confirmed in the present study, in which 80% of the participants belong to the economically disadvantaged class, due to the work routine to provide family maintenance[13].

Pilates practice brings important benefits over age and acts as an artifice capable of slowing physiological declines caused by aging, preventing chronic degenerative diseases, and promoting the readaptation of disabilities arising from other diseases, such as leprosy, helping the quality of life and social participation[3].

Although we did not find statistically significant improvements in the analyses of the perception of quality of life before and after the practice of Pilates, a fact that can be explained by the reduced number of the sample, according to the descriptions of Loureiro et al.[14], we can observe improvements in the physical domains and facet social participation, as well as the worsening of the observations for sensory abilities and death and dying.

Pain, physical disability, and physical inactivity are intrinsically related to a low assessment of the perception of quality of life of those affected by leprosy[15]. Thus, after the practice of physical exercises, it was possible to observe an improvement in the physical domain, maintaining a good evaluation, with mean values between 41 and 60.

Social participation, which refers to personal relationships, sexual activity, and social support of friends or groups of people, can generate different behaviors and emotions[16]. In this study, the social participation domain had a slight worsening

but remained with average values (41–60). On the other hand, the social participation facet evaluated in the elderly, despite the nonsignificant, obtained a small improvement.

Physical exercises performed in groups are more effective than compliments and advice, provide encouragement for the continuity of their practice, and promote a positive relationship among their practitioners. This strategy is seen as fundamental for individuals who are in the aging process because it provides more independence in performing cotidiana activities and autonomy, skills that are shaken by leprosy[16]. With aging, there is a decrease in the sensitivity of the body and the reduction of the physical capacity of individuals, a fact that is enhanced in leprosy patients since the disease decreased the sensitivity of the body and can cause pain and discomfort. This factor may explain the reduction of the sensory abilities facet, which nevertheless remained well evaluated. Multibacillary leprosy has a treatment proposed by the Ministry of Health of 12 months, and in its course, there may be type 1 and 2 reactions that may aggravate the clinical picture of the affected[8].

Analyzing the death and dying facets, we observed that it was the only one with an evaluation considered bad and that it also did not improve. This may be related to the aging process, due to decreased physiological capacity and the emergence of degenerative conical diseases, which decrease the quality and life expectancy of individuals[17].

The advent of technology has brought facilities to move through various means of transport; thus, currently less physical effort is made, increasing the number of physically inactive people. Physical inactivity, in addition to favoring the onset of diseases, can cause injuries to those associated with the fragility of the immune system and prognosis of leprosy[8]. In the present study, 80% of the individuals were insufficiently active at the beginning of the exercise program, which went to 40% physically active and 60% very physically active, an important fact that should be highlighted since the group was composed of people with grade 1 and 2 disabilities caused by leprosy.

This study has limitations that should be highlighted, such as small sample size and difficulty in adhering to recruits. Thus, new research is suggested to better understand the physiological adaptations of physical exercise in this population.

CONCLUSION

The quality of life between preintervention and postintervention with the Pilates program did not show significant improvement through self-report.

ACKNOWLEDGMENTS

We would like to thank the Coordination for the Improvement of Higher Education Personnel through the Dean of Research Program, Universidade Federal do Tocantins.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 2. Perception of quality of life before and after intervention with Pilates program in participants with leprosy of Centro de Saúde e Comunidade of Laurides Milhomen & Liberdade, Palmas (TO), 2019 (n=5).

Domain	Pre		Post		p‡
	Mean	SD(±)	Mean	SD(±)	
Physical*	47.86	8.96	51.43	10.29	0.5862
Psychological*	56.00	13.87	57.00	10.37	0.7865
Social relations*	63.34	4.57	58.43	13.17	0.3961
Environment*	58.75	12.38	57.50	16.03	0.7865
Sensory skills†	58.33	13.01	54.17	3.61	0.4142
Autonomy†	56.25	6.25	54.17	3.61	0.3173
Activities PPF†	58.33	3.61	56.25	12.50	0.7815
Social participation†	54.17	3.61	62.50	27.24	0.4142
Death and dying†	37.50	6.25	35.42	3.61	0.3173
Intimacy†	60.42	7.22	60.42	3.61	1.0000

SD: standard deviation; *WHOQOL-Bref: WHO Quality of Life – scale abbreviated version; †WHOQOL-Old: World Health Organization Quality of Life for Older Persons; PPF: past, present, and future activities; ‡Paired t-test.

AUTHORS' CONTRIBUTIONS

AMB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SCG:** Visualization, Writing – original draft, Writing – review & editing. **APS:** Validation, Visualization, Writing – original draft, Writing – review, editing. **FRPQ:** Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE
https://doi.org/10.1590/1806-9282.20210373

Simulators for endoscopic retrograde cholangiopancreatography training: systematic review and meta-analysis

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable technique for evaluating pancreatic and biliary ductal anatomy in a wide variety of clinical situations[1]. The first report of successful cannulation of the major duodenal papilla, which is the main stage of the procedure, was conducted in the United States in 1968 by McCune et al.[2] The first endoscopic biliary sphincterotomies were reported almost simultaneously in 1974 by Kawai from Japan and Classen from Germany[3]. ERCP has evolved substantially: it has gone from a diagnostic procedure to a therapeutic tool thanks to technological innovations in endoscopes and accessories[4]. The learning process is long, and the main and essential step of the procedure is the cannulation of the major duodenal papilla[5]. ERCP can present severe complications (i.e., pancreatitis, hemorrhage, cholangitis, and perforation), especially in the hands of inexperienced endoscopists. The use of a simulator could be a valid tool for training and performing ERCP more effectively and safely[6].

In this study, the systematic review and the meta-analysis were performed to clarify whether the use of simulators in ERCP training increases the cannulation rate of the duodenal papilla more than the traditional "master-student" teaching method.

METHODS

Source of data and research

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[7]. No language or year of publication restrictions was applied. The following databases were searched: MEDLINE, EMBASE, CENTRAL, Web of Science, and LILACS. The gray literature included ProQuest Dissertations & Theses Global and clinical trial records (clinicaltrials.gov). The date of the search was July 20, 2020. The search used the following keywords combined with Boolean logical operators, appropriate for each database: "ERCP," "simulator(s),' 'training(s)," and "model(s)."

Selection of studies

Only randomized clinical trials (RCTs) were included in which the intervention group was trained with ERCP simulators before the practice of ERCP in supervised patients. The control group practiced ERCP directly on supervised patients ("master-student") without previous training on simulators. Two authors independently evaluated all studies identified by the survey using Review Management Website Covidence (http://www.covidence.org). A third review author resolved any disagreements.

Data extraction and quality assessment

Information on the study design, description of the participants, type of simulator[8-11], type of training, description of the control group, and each outcome explored in the studies were extracted.

All included studies were evaluated for their methodological quality using the Cochrane Collaboration Risk of Bias tool (RevMan 5)[12]. The tool measures nine bias categories (i.e., selection, allocation, masking of data and statistical collectors, performance, detection, attrition, selective reporting of outcomes, and other biases). The items were scored as positive (low risk of bias), negative (high risk of bias), or insufficient information (uncertain risk of bias). The GRADE method was used to classify the level of evidence of the outcomes (i.e., high, moderate, low, and very low) using GRADEproGDT (https://gradepro.org/)[13-17].

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 06, 2021. Accepted on June 12, 2021.

Statistical analysis

RevMan version 5.3 was used for the statistical analyses.

RESULTS

The search identified 3,310 studies. After duplicate studies were excluded, 2,386 studies were evaluated based on the title and abstract, of which 2,335 were excluded. Full-text studies were retrieved for 51 titles, of which 46 were excluded.

Four studies were included in the review[18-21], although five publications were identified. It is noteworthy that two publications by Meng et al.[21] and Meng et al.[22] have the same method and same authors, and the beginning of the study of the 2019 publication[21] was in 2016[22], according to the information obtained at clinicaltrails.gov. We believed that one of the publications, Meng et al.[22], served as a pilot study or initial publication and was incorporated into the publication referenced as Meng et al.[21], so only the latter was enrolled in this review.

The findings of the studies[18-21] are summarized in Table 1.

Table 1. Characteristics of the included studies.

	Lim et al.[18]	Liao et al.[19]	Hritz et al.[20]	Meng et al.[21]
Type of publication	Article Completed	Article Completed	Abstract	Abstract
Centers	Multicenter	Multicenter	Multicenter	Not reported
Location	USA	Taiwan	Hungary	China
Number of participants	16 (8 control, 8 intervention)	16 (8 control, 8 intervention)	15 (9 controls, 6 intervention)	12 (6 controls, 6 intervention)
Characteristics of participants	Maximum 30 ERCPs	1,000 EGDs done, 0 ERCPs	Experience in EGD, 0 ERCPs	No previous endoscopic experience
Length of follow-up after training	16 weeks	12 weeks	Not specified	Not reported
Type of simulator	Mechanical (EMS)	Mechanical (EMS)	Computational (AccuTouch®)	Mechanical (EMS)
Number of ERCPs	265 (139 intervention and 126 control)	190 (98 intervention and 92 control)	59 (25 intervention and 34 control)	300 (150 intervention and 150 control)
Mean ERCPs per student	17±10	11.875	3.93	25
Description of interventions	Theoretical and simulator training, repeated after 8 weeks. In the ERCP, if in 10 min the trainee failed after two attempts, he/she received manual help from the supervisor	Theoretical classes on ERCP. The group in 2008 received only one 6-h practical class in the simulator. In 2009, the group received biweekly practical classes in the simulator for 12 weeks. In ERCP, unlimited verbal instructions and manual help after 5 min of attempts. After a second failure with manual help, the supervisor took over	Theoretical of 2 h and training in the simulator. There was no report on the supervision of the ERCP	Training with verbal instructions for 20 h in the simulator. In ERCP, verbal instructions and manual help, if necessary. If failure after 20 min of attempts, the supervisor took over
Description of the group control	Theoretical training without training in the simulator	Theoretical classes on ERCP only	A 2-h seminar on ERCP, without simulator training	Only training with verbal instructions and manual assistance, if necessary, during ERCP
Outcome main	Cannulation success rate	Cannulation success rate	Note successful cannulation	Cannulation success rate
Definition of success in cannulation	Deep biliary cannulation in 10 min of attempts with fewer than three manual aids from the supervisor	Deep biliary cannulation with up to two manual aids from the supervisor for 10 min	Deep biliary cannulation	Selective biliary cannulation in 20 min

ERCP: Endoscopic retrograde cholangiopancreatography; Endoscopic retrograde cholangiopancreatography: mechanical simulator.

Methodological quality of the included studies

Figure 1 shows the evaluation of the risk of bias of the four included studies[18-21].

Meta-analysis

Using a meta-analysis with the random-effects model, a significant difference was found between ERCP simulator training and traditional teaching in the outcome cannulation success rate (three studies with sufficient data were included[18,19,21]). A relative risk of 1.40 (95%CI 1.24–1.58) was found in favor of the simulator group (heterogeneity I^2=0% and p<0.00001) (Figure 2).

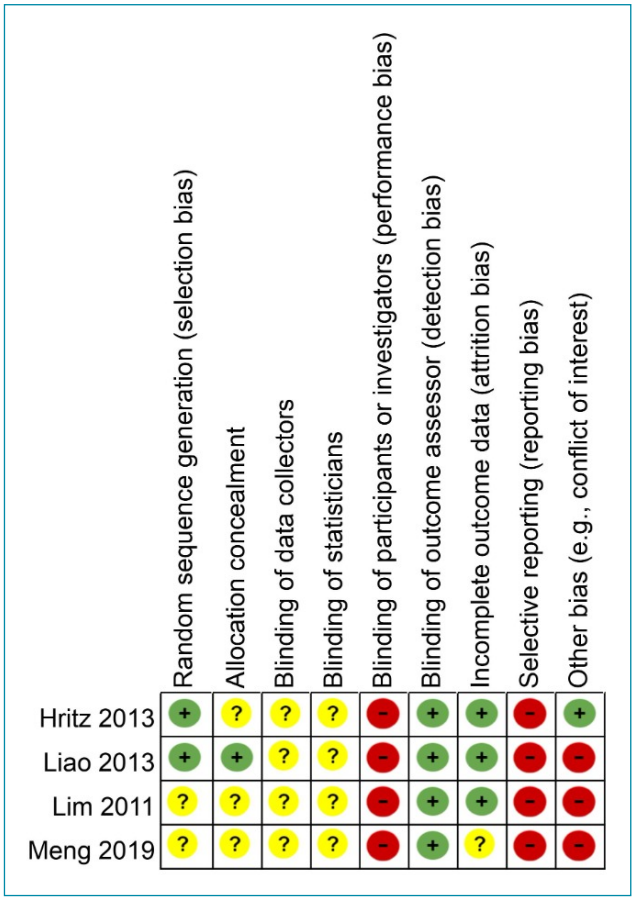

Figure 1. Summary of risk of bias of the included studies.

DISCUSSION

No other systematic review on ERCP simulators was found in the literature.

Considering the data on the cannulation success rate of the three studies included in the meta-analysis[18,19,21], there was a significant increase in the training group with simulators compared with the traditional teaching method. This result, which is favorable to the use of the simulator, may have obtained from the better knowledge of how to manipulate the endoscope (duodenoscope) and accessories for the ERCP before practice in patients[23,24].

A systematic review by Ekkelenkamp et al.[25] evaluated simulators for endoscopy in general. They found 14 studies related to students who were trained in ERCP simulators and cited an RCT[18] without analyzing it. Considering the quality of the studies in this meta-analysis[18-21], more full-text studies (not just abstracts) and improvements are needed to perform and describe randomization and allocation concealment. The masking of data collectors and statisticians was uncertain in all studies. Due to the nature of the intervention, masking of the participants was not possible.

A low risk of bias was identified regarding the blinding of outcome evaluators and the risk of incomplete results. The selective outcome report was considered high risk due to the absence of ERCP complication rates in patients. A high risk of bias from the conflict of interest was considered in three studies[18,19,21], as one of the authors was the developer of the simulator used, a fact that could influence the study design.

Regarding the evaluation of the quality of the evidence for the success rate of cannulation using the GRADE system, it

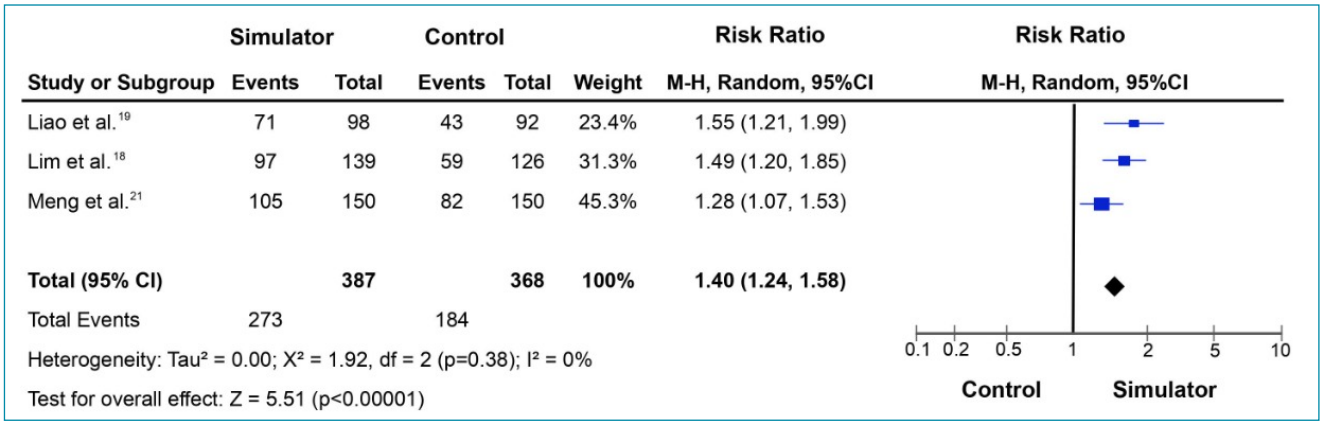

Figure 2. Meta-analysis of the outcome success rate at cannulation.

can be concluded that our findings have moderate confidence, taking into account the risk of bias, inconsistency (heterogeneity), indirect evidence, imprecision, and publication bias[26]. The evidence found in this systematic review may be altered by new studies, modifying the confidence in the estimation of the effect, and may even modify the estimate[26].

The limitations of this study are based on the small number of RCTs that met the selection criteria, which may have influenced the calculation of the results. The strategy to get around this limitation was a broad and exhaustive search so that no relevant RCTs were excluded.

CONCLUSIONS

Evidence of moderate confidence suggests that the training of physicians with ERCP simulators, when compared to the traditional teacher-student method, improves the success rate of cannulation of the greater duodenal papilla. Future studies may present such evidence in a more incisive and reliable way.

AUTHORS' CONTRIBUTIONS

STNA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ELD:** Data curation, Formal analysis, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing. **MAD:** Formal analysis, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **LGBR:** Supervision, Visualization, Validation.

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REVIEW ARTICLE
https://doi.org/10.1590/1806-9282.20210404

Effect of vitamin D supplementation on depression treatment

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INTRODUCTION

Depression is a mental disorder that has drawn attention because of its high incidence. The World Health Organization (WHO) reported that the number of cases of depression increased by 18% between 2005 and 2015; 322 million people have depression globally, and most of them are women. In Brazil, depression affects 11.5 million people (5.8% of the population)[1].

Depression is characterized by the impairment of the physical and mental states of an individual. Its main symptoms are constant sadness, lack of energy, irritability, anxiety, and loss of interest in activities that usually produce a feeling of pleasure, low self-esteem, and changes in sleep and appetite. For the diagnosis of depression, symptoms should persist for at least 2 weeks[2,3].

Depression is also associated with serious disabilities, mortality, and medical expenses. Despite the development of biological, psychological, and environmental theories, the underlying pathophysiology of depression is still unknown and may involve several mechanisms[4,5].

There has been a long-standing interest in the role of nutrition and its relationship to depression; some studies have shown a strong relationship between vitamin D and depression. Several dietary factors have been implicated in the development and treatment of depression. The changes in vitamin D receptors impact several brain neurotransmitters and, therefore, suggest a potential role of vitamin D in causing and correcting mood disorders[6].

Vitamin D is involved in several brain processes, including neuroimmune regulation, neurotrophic factor regulation, neuroprotection, neuroplasticity, and brain development. Therefore, biologically speaking, this vitamin may be related to depression, and its supplementation may play an important role in the treatment of the disease[7,8]. Therefore, this study aimed to review the recent literature on the effect of vitamin D supplementation in the treatment of patients with depression.

METHODS

A systematic review of vitamin D supplementation in patients with depression was performed. For the guiding question, the PICO strategy was used, which represents the population (P) to be studied, the intervention (I), comparison (C), and outcome (O). The question to be raised was whether vitamin D supplementation, compared with placebo, helps in the treatment of patients with depression. Each PICO item represents an element: (P) patients with depression, (I) vitamin D supplementation, (C) placebo, and (O) improvements in patient health.

The review was carried out from September to December 2020 and included all articles published up to the time of the research retrieved from the PubMed, SciELO, and ScienceDirect databases. The following combination of descriptors was used in the search for articles: supplementation and (depression or depressive symptoms) and vitamin D registered in the Medical Subject Headings.

Original articles and randomized (RCTs) and placebo-controlled clinical trials addressing vitamin D supplementation

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 15, 2021. Accepted on May 30, 2021.

in patients with depression with different clinical conditions and at different ages were included. Duplicate original articles and articles that could not be accessed were excluded. The research was registered with the Research Coordination of the UNINOVAFAPI University Center under case number 104/2020.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was used to ensure the quality of this study. For the quantitative analysis and risk of methodological bias, the Jadad scale was used to classify articles from 0 to 5 based on the methodological criteria and adequacy of results, and the Cochrane collaboration tool was used to classify articles with a low risk of bias, high risk of bias, and uncertain risk of bias.

RESULTS

The bibliographic research, according to the pre-established strategy, resulted in 830 articles. Of these, 46 were from the PubMed database, 784 were from ScienceDirect, and 0 were from SciELO. After the duplicate article selection and removal process, six original RCTs were identified as eligible for this systematic review. Figure 1 shows the flowchart of the search results for the sources of information and the selection and inclusion of original articles in the systematic review, according to the PRISMA protocol.

The clinical trials showed a homogeneous methodological quality based on the risk of bias assessment using the Cochrane tool (Table 1)[9-14]. Random generation and allocation concealment were adequately reported in 83.35% (5/6) of the studies; blinding of participants and professionals was reported in 100% (6/6) with a low risk of bias; blinding of the outcome evaluators was reported in 50% (3/6) with a low risk of bias; incomplete outcomes were reported in 66.66% (4/6) with a low risk of bias; selective outcome reporting was reported in 100% (6/6) with uncertain risk of bias; and other sources of bias were reported in 16.6% (1/6) with low risk of bias. Table 1[9-14] presents the results of the quality assessment of the articles analyzed according to the Jadad scale. Regarding the items assessed, all articles adequately described the aspects assessed using that scale.

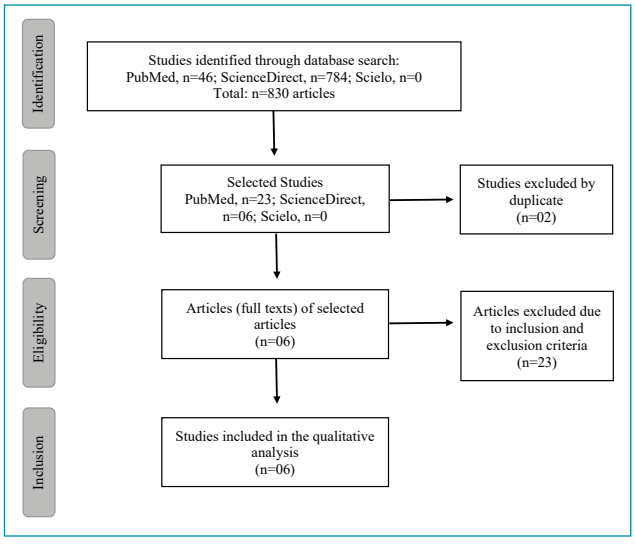

Figure 1. Flowchart for the database search and screening, eligibility, and inclusion of articles in the systematic review.

The data presented in Table 2[9-14] integrate the results of the articles reviewed, including authors, year of publication, study sample size, dose, assessment instrument, duration of supplementation, and main outcomes. The supplemental doses of vitamin D ranged from 2,800 to 50,000 IU, and the duration of intervention ranged from 8 weeks to 2 years.

The main variable investigated was the relationship between vitamin D supplementation and depressive symptoms. Three studies showed a positive effect of supplementation on disease activity, and three studies showed no improvement in disease activity after supplementation.

DISCUSSION

Of the clinical trials present in this review, three found improvements with the use of vitamin D supplementation in depression symptoms: Alavi et al.[11], Omidian et al.[13], and Zheng et al.[14] Three other studies found no improvement: Hansen et al.[9], Marsh et al.[10], and Kjærgaard et al.[12]

Hansen et al.[9] randomized patients with depression into two groups (intervention or control) in blocks of four to receive vitamin D (70 µg vitamin D3 [2,800 IU]) or placebo for 12 weeks. At baseline, 23 patients had a normal 25-hydroxyvitamin D (25(OH)D) concentration (≥50 nmol/L), 22 had insufficiency (<25 nmol/L), and 17 had deficiency (25–50 nmol/L). At the end of the treatment, vitamin D supplementation did not reduce the symptom scores among the patients with depression. The study may not have shown significant outcome data, as they did not reach the estimated sample size and did not exclusively include patients with low vitamin D content.

In the study by Marsh et al.[10], the participants were allocated in a 1:1 ratio. The participants received 5,000 IU vitamin D3 (cholecalciferol) capsules daily or placebo for 12 weeks. The mean serum 25(OH)D concentration increased by 9.9±8.2 ng/mL in vitamin D in the supplemented group and by 1.3±4.3 ng/mL in the placebo group for 12 weeks. At the end of the experiment, there was no improvement in the symptoms of depression with treatment relative to placebo. The absence of

Table 1. Analysis of methodological quality and risk of bias according to the Cochrane collaboration and Jadad scale.

Cochrane tool						
Variables	Hansen et al.[9]	Marsh et al.[10]	Alavi et al.[11]	Kjaergaard et al.[12]	Omidian et al.[13]	Zheng et al.[14]
Random Sequence Generation	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Uncertain bias risk	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants and professionals	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of outcome evaluators	High risk of bias	Uncertain bias risk	Uncertain bias risk	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcomes	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias
Selective outcome report	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk
Other sources of bias	High risk of bias	Low risk of bias	High risk of bias	Uncertain bias risk	Uncertain bias risk	High risk of bias
Jadad scale						
Variables	Hansen et al.[9]	Marsh et al.[10]	Alavi et al.[11]	Kjaergaard et al.[12]	Omidian et al.[13]	Zheng et al.[14]
Was the study described as randomized?	Yes	Yes	Yes	Yes	Yes	Yes
Has randomization been described and is it adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any comparisons between the results?	Yes	Yes	Yes	Yes	Yes	Yes
Have comparisons and results been described and are they adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Have losses and exclusions been described?	Yes	Yes	Yes	Yes	Yes	Yes
Total	5	5	5	5	5	5

results in the study may be related to the small number of participants, low concentrations of vitamin D supplementation, and the short period of the study.

Alavi et al.[11] randomly assigned eligible participants to receive vitamin D (n=40) or placebo (n=40) for 8 weeks. The vitamin D group received 50,000 units of vitamin D3 weekly for 8 weeks at mealtime, and the control participants received a placebo weekly at the same time. All patients had vitamin D deficiency (vitamin D concentration of less than 30 ng/mL) before the intervention. The mean baseline 25(OH)D3 concentration was 22.57±6.2 ng/mL in the vitamin D group and 21.2±5.8 ng/mL in the placebo group (p=0.16). Vitamin D increased to 43.48±9.5 ng/mL in the vitamin D group and 25.9±15.3 ng/mL in the placebo group. Both groups showed a significant increase in vitamin D concentration, although the increase was approximately fourfold greater in the vitamin D group. After the intervention, it was observed that vitamin D supplementation was effective in reducing depression scores in people aged 60 years or older. The results of the study may have been positive, as all participants had vitamin D deficiency

Table 2. Synthesis of studies evaluated regarding the effect of vitamin D supplementation in aiding the treatment of depression.

Authors	Sample	Variables analyzed	Intervention	Outcome
Hansen et al.[9]	n=62	- To examine whether vitamin D3 supplementation in patients with depression would result in improved disease activity. - Assessment instrument: International Classification of Diseases (CID-10) (F32.X).	- Randomization: 2,800 IU of vitamin D3 or placebo. - Duration: 12 weeks.	- No significant reductions in depression scores were found.
Marsh et al.[10]	n=33	- To examine improvements after vitamin D3 supplementation in bipolar depression activity. - Reduction in mood elevation or anxiety symptoms. - Assessment instrument: Hamilton Anxiety Rating Scale, Young Mania Rating Scale.	- Randomization: 5,000 IU vitamin D3 or placebo. - Duration: 12 weeks.	- There was no significant reduction in depressive symptoms. - Vitamin D supplementation did not improve reduction in mood elevation or anxiety symptoms.
Alavi et al.[11]	n=78	- To examine the effect of D3 supplementation in the treatment of depression in the elderly population. - Assessment tool: Geriatric Depression Scale-15 questionnaire and 25-hydroxyvitamin D3 to assess the level of depression.	- Randomization: 50,000 IU vitamin D3 or placebo. - Duration: 8 weeks.	- Vitamin D supplementation can improve depression scores in people aged 60 years and older.
Kjaergaard et al.[12]	n=344	- To examine improvements after vitamin D3 supplementation in patients with low serum levels of 25-hydroxyvitamin D. - Low and high serum levels of 25-hydroxyvitamin D. - Assessment instrument: Beck Depression Inventory, Hospital Anxiety and Depression Scale, Seasonal Pattern Rating Scale, and Montgomery-Åsberg Depression Rating Scale.	- Randomization: 40,000 IU vitamin D3 or placebo. - Duration: 6 months.	- No significant effect of vitamin D supplementation was found on depressive symptom scores. - Low serum 25-hydroxyvitamin D levels are associated with depressive symptoms, but no effect was found with vitamin D supplementation.
Omidian et al.[13]	n=68	- To examine the effect of vitamin D3 supplementation in type 2 diabetes mellitus patients with depressive symptoms. - Assessment instrument: Beck Depression Inventory-II (BDI-II-PERSIAN).	- Randomização: 4,000 IU vitamin D3 or placebo. - Duration: 12 weeks.	- Vitamin D supplementation in diabetes mellitus type 2 patients may protect these patients against the onset of major depressive disorder.
Zheng et al.[14]	n=413	- To examine the effect of vitamin D3 supplementation in patients with knee osteoarthritis with depressive symptoms. - Assessment instrument: Patient Health Questionnaire (PHQ-9, 0-27).	- Randomization: 50,000 IU vitamin D3 or placebo. - Duration: 8 weeks.	- Vitamin D supplementation can improve depression scores in people aged 60 years and older.

before the intervention, and the supplemented dose was higher than in other studies.

Kjærgaard et al.[12] studied participants with low and high serum 25(OH)D concentrations and a randomized clinical trial comparing placebo or 40,000 IU vitamin D supplementation for 6 months. In this intervention study, there was no significant effect of high-dose vitamin D on depressive symptom scores. The study had some limitations that may have contributed to its negative results, such as a short study period, distribution of participants in groups, and the exclusion of participants with high scores for depression from the intervention. Consequently, most participants had no or only mild depressive symptoms. This may have influenced the results, as participants who were not sick were more likely to respond to the placebo.

In a study by Omidian et al.[13], randomized type 2 diabetes mellitus patients with depressive symptoms were divided into two groups to receive 4,000 IU vitamin D or placebo. The results of this study showed that vitamin D supplementation is effective in improving depressive symptoms in patients with type 2 diabetes and mild-to-moderate depressive symptoms. Vitamin D supplements significantly improve depressive symptoms, and they also significantly decrease HbA1c, insulin, and TG concentrations in diabetic patients with vitamin D deficiency. A suggested mechanism for this effect may be related to vitamin D and insulin secretion, as vitamin D facilitates the release of insulin from beta-cells.

Zheng et al.[14] studied randomized patients to verify the effect of vitamin D supplementation on depressive symptoms in patients with knee osteoarthritis (OA). The participants were randomized in a 1:1 ratio to receive a 50,000 IU vitamin D3 oral capsule or placebo monthly for 24 months. The serum 25(OH) D concentrations increased from 43.7±11.8 to 84.5±17.3 nmol/L in the vitamin D group and increased from 43.8±12.7 to 50.6±17.5 nmol/L in the placebo group. The study concluded that vitamin D supplementation and the maintenance of vitamin D at sufficient concentrations above 24 months may have beneficial effects on depression symptoms in patients with knee OA. The study results suggest that vitamin D supplementation may have a positive effect on depressive symptoms when serum vitamin D concentrations become optimal. The study hypothesized that vitamin D may have a neuroprotective effect on the brain when vitamin D deficiency is corrected.

The studies analyzed in this review show that the initial vitamin D status (deficient or normal) may have been one of the factors that most influenced the improvement of depressive symptoms in patients. In addition, the severity of depressive symptoms, sample size, age of the individuals, dose of vitamin D offered, and duration of the intervention may have contributed to the outcome of the results.

CONCLUSIONS

The results of the studies indicated that vitamin D can improve depressive symptoms; however, this improvement depends on several factors such as dose and duration of supplementation as well as the initial state of health of the patient before supplementation. We emphasize the need for more clinical studies to verify the most efficient forms of supplementation for different clinical conditions.

AUTHORS' CONTRIBUTIONS

RTM: Project administration, Conceptualization, Data curation, Formal analysis, Investigation, Methodology Writing – original draft, Writing – review & editing. **LARLR:** Project administration, Conceptualization, Data curation, Formal analysis, Investigation, Methodology Writing – original draft, Writing – review & editing. **LMF:** Data curation, Formal analysis, Investigation, Writing – review & editing, Supervision. **JMC:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **LCCL:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **OSRF:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **KMGF:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing.

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REVIEW ARTICLE
https://doi.org/10.1590/1806-9282.20210582

Current updates on clinical management of COVID-19 infectees: a narrative review

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged the current public health crisis, thus resulting in medical emergencies worldwide. This virus likely originated from bats, through an unknown intermediary vector, and then transmitted to humans in Wuhan city of China in December 2019[1]. The virus was designated as a novel coronavirus (2019-nCOV) by WHO and then widely used as coronavirus disease 2019 (COVID-19)[2]. The prevalence and severity of coronavirus depend on several factors such as viral serotypes, tropics, and genetic makeup of local people and also on the pandemic management protocols and the medical services[3]. This study aims to narrate and analyze the available key guidelines and recommendations to manage the COVID-19 pandemic as no study is available until now covering all aspects of COVID-19 from clinical features, diagnosis to management, and healthcare guidelines. Thus, a comprehensive approach needs to be addressed to minimize the confusion regarding the treatment and management of COVID-19 patients.

Clinical features

The clinical symptoms of COVID-19 infection are fever, productive cough, myalgia, fatigue, sputum expectoration, dyspnea, arthralgia, headaches, sore throat, chills, nausea, vomiting, diarrhea, pleuritic chest pain, nasal congestion, palpitations, chest tightness, and hyposmia. Complications are acute respiratory distress syndrome (ARDS), acute myocardial injury, raised troponin I levels, myocardial infarction, sudden cardiac arrest, secondary bacterial infections, sepsis, multiorgan failure, lymph histiocytosis, and the cytokine storm syndromes. Deaths are more prevalent in elderly patients and already medically ill patients like malignancy and interstitial lung disease[4]. The COVID-19 patients with diabetes are at higher risk of severe pneumonia due to the release of certain enzymes, the vicious cycle of inflammatory cascades, and hypercoagulable states[5]. Similarly, the patients with chronic obstructive pulmonary disease (COPD) may far seriously affect[6].

The diagnostic indication of COVID-19 varies from patient to patient depending on patients' medical history, clinical examination, medical baseline, and the test's specificity. The real-time polymerase chain reaction (RT-PCR) expressed 60–97% sensitivity. However, some cases have been reported to exhibit negative RT-PCR results whereas high-resolution CT (HR-CT) scans turned out to be positive for the same patients. So the inclusion of radiological features in diagnostic criteria increases the specificity of testing[7]. Few radiographs and CT images showing consolidation and thickened pleura are shown in Figure 1.

The drugs that have potential activity against coronavirus include remdesivir, ritonavir, lopinavir, lopinavir/ritonavir combined with interferon-β (INF-β), monoclonal antibodies, and antimalarial drug (i.e., hydroxychloroquine)[8]. Anticoagulant therapy with low molecular weight heparin (LMWH) appears to be associated with a better prognosis in treated patients vs. nontreated ones concerning mortality (40.0 versus 64.2%, p=0.029)[9].

Clinical management

If patients have been screened as positive for common flu-like symptoms, a surgeon should consider delaying any surgical procedures until the patient stabilizes, and if the surgery is

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 14, 2021. Accepted on June 27, 2021.

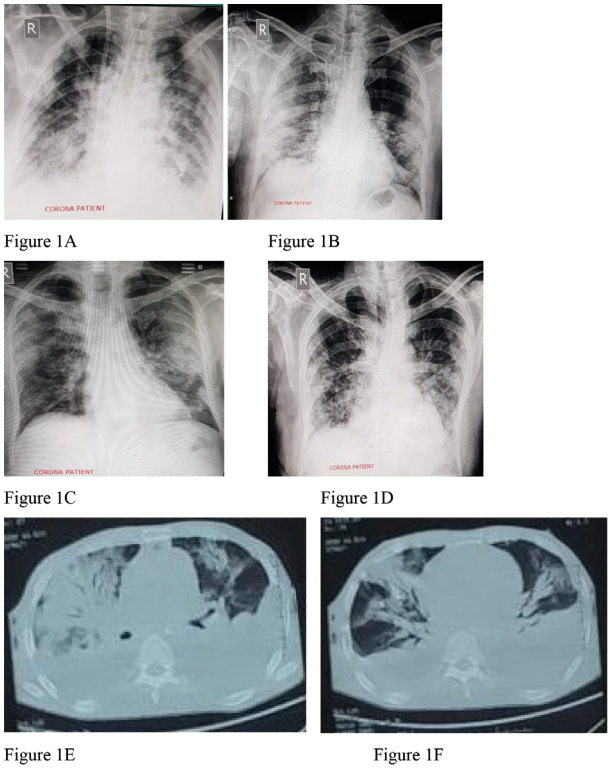


Figure 1. Representative radiographs: (A) honeycomb appearance (ARDS), (B) bronchopneumonia, (C) hyperinflation with consolidation, and (D) hyperemia with basal consolidation; and the computed tomography scan images at axial view showing (E) consolidation with air bronchogram and (F) fibrotic band and pneumonic patches.

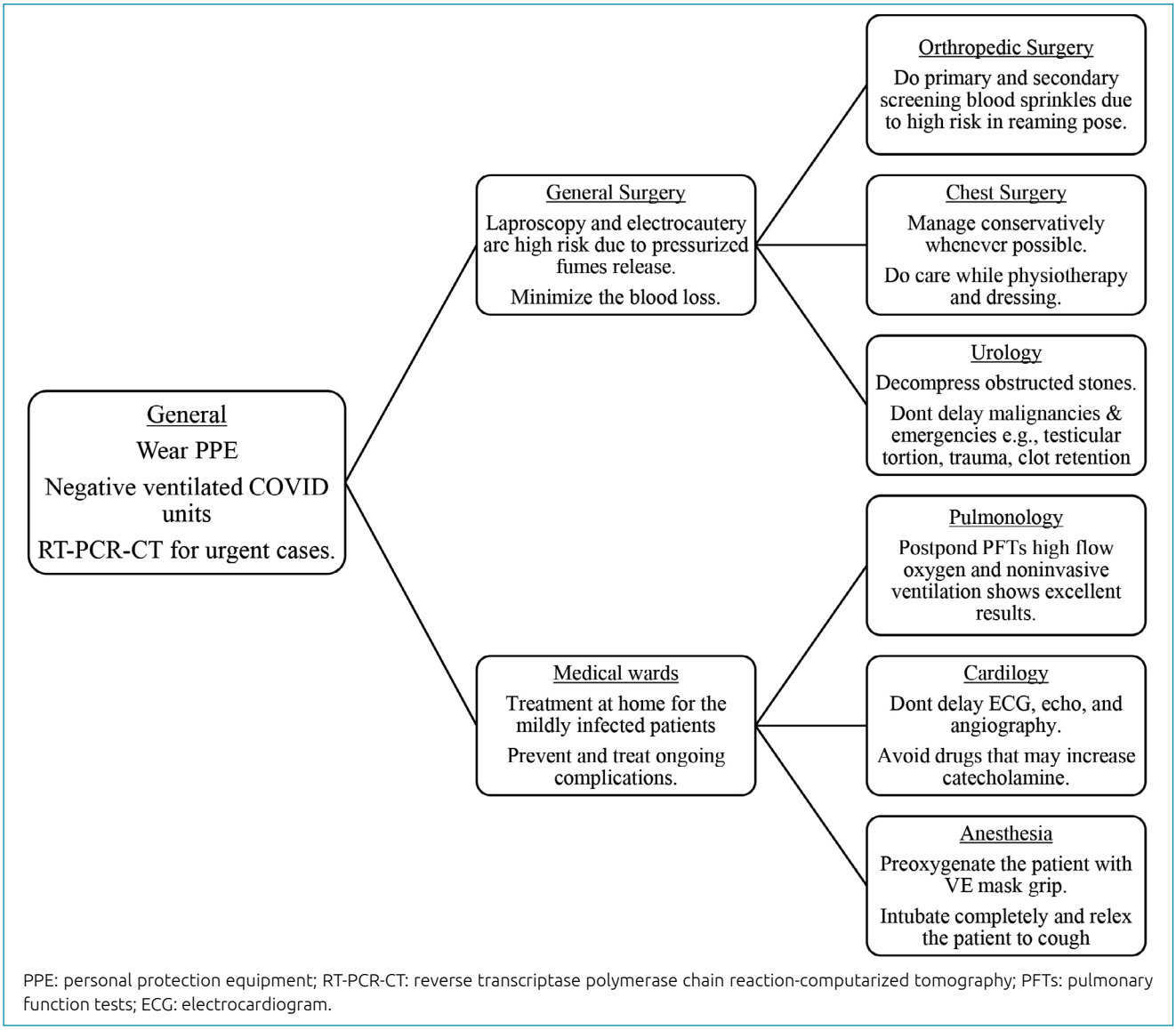
unavoidable, such patients must undergo urgent RT-PCR testing[10]. The American Academy of Orthopedic Surgeons (AAOS) recommends patients' ELIZA or PCR testing for COVID-19 72 h before surgery or on the day of surgery, and the healthcare workers (HCWs) before performing any surgical procedures. The following guidelines should be followed while treating/operating patients during this pandemic[11]:

1. Resuscitate the patient, rule out all other injuries via primary survey;
2. Do secondary survey as there are high chances of missed injuries in light of COVID suspicion;
3. Whenever possible, manage conservatively and keep the patients in isolation wards;
4. Provide masks to patients and attendants, and minimize patients' and attendants' mobility;
5. Expedite the process of operation and discharge to lessen the load over the health system, and these patients should be attended by separate team surgeons;
6. Keep follow-up of outdoor patients in a separate area for dressing, suture removal, and plaster removal;
7. Manage the patient conservatively whenever possible, and preventive measures must be followed at every level;
8. There should be separate triage room and dedicated COVID operating room with trained staff;
9. Maintain negative pressure ventilation in operation theaters;
10. Minimize operation time and blood spillage;
11. Postoperatively, the patient should be shifted to COVID wards and discharged only after COVID results are negative;
12. Special care must be taken during the hospital stay to wound dressing, physiotherapy, bedsores, and deep vein thrombosis (DVT) prevention; and
13. There should be proper disposal of surgical waste. The clinical management summary of COVID-19 patients in various departments is illustrated in Figure 2.

The lungs are the primary organ affected by COVID-19 and transmission through aerosols, while thoracic surgery makes it a high-risk procedure for the HCW. Thoracic surgery is significantly associated with high mortality rates in COVID-19-infected patients. It had been concluded that COVID-19 patients undergoing thoracic operation are associated with a poor prognosis, especially for those who are suffering from COPD. However, comprehensive protective measures are required to prevent and control COVID infection[12]. Thereby, the following precautions are necessary:

1. Perform the procedure in an isolated negatively ventilated room;
2. Limit the number of participants and time of surgery;
3. Make a small incision and place an air seal tie around the tube;
4. Use high-efficiency particulate air (HEPA) filters on suction equipment; and
5. Avoid entry into room 10 min after the surgery due to the persistence of droplets into the air[13].

Respiratory management has a key role in COVID-19 treatment. Apart from the abovementioned treatment guidelines, certain other steps are deemed necessary while treating patients with pulmonary function tests (PFTs) is required for assessing asthma and chronic pulmonary disorders. For that purpose, a patient under investigation needs to blow into a peak flow meter that may increase the risk of aerosol spreading. It is therefore strongly recommended that the PFT procedures for the suspected or confirmed cases of COVID-19 may be delayed during this pandemic if it is not imperative. Disposable 99% effective filtering devices should be used during the PFTs if deemed necessary. More attention is required on the disinfecting and sterilization of the equipment used using PFTs[14]. A passive mobilization of



PPE: personal protection equipment; RT-PCR-CT: reverse transcriptase polymerase chain reaction-computarized tomography; PFTs: pulmonary function tests; ECG: electrocardiogram.

Figure 2. Clinical management summary of COVID-19 patients in various departments.

the patient is necessary to prevent skin lesions and bed sores. In spontaneous breathing patients, variation in position could modify the perfusion/ventilation ratio. Airway clearance is required only when it is indispensable. The patients should wear a face mask even during high nasal flow (HNF) oxygen therapy, and closed suctioning circuits are preferable when compared with endotracheal suctioning while disconnecting the circuit[15].

In the anesthesiology, the rapid sequence induction (RSI) approach must be considered in the following steps:

1. Preoxygenate the patient with a well-fitting mask for 4–5 min;
2. In the distressed patients, the RSI may result in hypoxia so a delayed sequence tracheal intubation (DSTI) technique may be the best option;
3. In the case of cardiovascular instability or DSTI, 1–2 mg/kg ketamine is used for the induction of anesthesia;
4. Before proceeding to tracheal intubation, ensure full neuromuscular blockade and maintain patency through the guided airway;
5. Using two-person, two-handed technique with a VE-grip is effective in COVID-19-infected patients to suppress the dissemination of the virus;
6. A video laryngoscope is a correct option to be utilized;
7. Nasogastric tube may be required after tracheal intubation and ventilation to minimize the complications; and
8. Collect lower respiratory tract sample if COVID diagnosis is not confirmed. During anesthesia, drugs to minimize coughing such as dexmedetomidine, lidocaine,

and opioids could be administered[16]. An overview of COVID-19 spread and management strategies is expressed in Figure 3.

DISCUSSION

The COVID-19 infection has inspired us to revisit all infection management strategies. Some drugs indicated effective in mild cases were found to be ineffective in severe cases. This occurred with lopinavir/ritonavir and other antiretrovirals in the clinical outcomes of severe cases, which might partly be due to the variable severity of the disease, viral load, different underlying disease, and clinical presentations[17]. Another cohort study included 102 adult patients; among patients who survived, they were younger and less likely to suffer from comorbidities. They suffered the least from complications and were less likely to require admission to the intensive care unit. There was no marked difference in drug treatment rates between the survival and non-survival groups. The trials showed that there were no differences in mortality among those who did or did not receive antimicrobial or glucocorticoid drug treatment[18]. Evidence was collected after the trial of remdesivir that the patient started improving on the 8th day of admission. The self-defense mechanism plays a key role in fighting against the coronavirus. The COVID-19 disease is self-limiting but it may persist for weeks due to complications and secondary infections developing after the disease[19]. The antiviral activity is required against viral replicating enzymes, protein-synthesizing enzymes, assembly proteins, and entry receptors. Studies have shown that some natural products inhibit viral entry, replication, transcription, and translation limiting viral virulence and the spread of disease. The natural products have antiviral activity in the nanomolar concentration, e.g., curcumin, homoharringtonine, lycorine, Silvestre L, ouabain, tylophorine, and 7-methoxycryptopleurine, and silver nanoparticles[20]. These could further lead to drug development on their own or as a template. Besides, the major constituents of some common dietary supplements with anti-coronavirus activity may be used to boost the body's immunity against

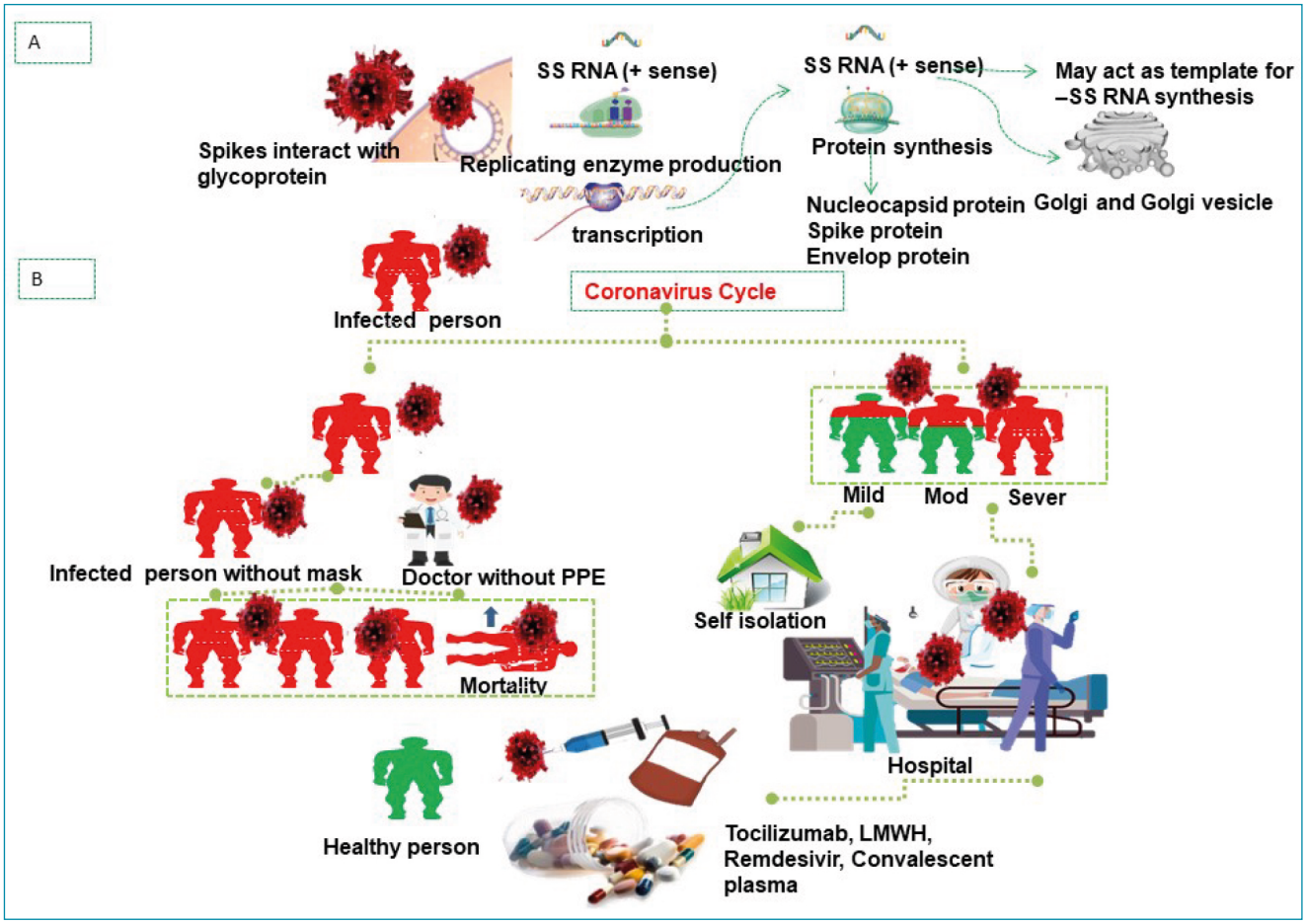


Figure 3. An overview of COVID-19 spread and management strategies: (A) the replication cycle of the corona virus. (B) the spread of the virus and COVID-19 management options.

coronavirus[21]. The main factor leading to pulmonary dysfunction in SARS survivors after recovery was pulmonary fibrosis, declining the quality of life. Extensive epidemiological, current clinical evidence supports the possibility that COVID-19 patients may face pulmonary fibrosis after the resolution of the coronavirus. Thus, some patients recovering from this infection may have diseased lungs and low quality of life when compared with a pre-pandemic state[22]. Further research is required for clinical trials, especially for developing the vaccine, this is the only way to get rid of this.

CONCLUSION

COVID-19 is the greatest pandemic health crisis of mankind. This study is designated to explain available guidelines and recommendations in major medical fields to minimize the risk of error. The clinical data of different drugs have been published, but large randomized control trials (RCTs) and cohort studies are required to prove the definitive role of anti-COVID drugs. Following clinical and practical guidelines, the dissemination of the COVID among HCWs and patients can be minimized as there is also an imbalance of demand and supply of personal protective equipment. Besides preventive measures, the COVID status of the patient needs to be documented in elective cases/nonemergency cases. Keeping in mind the COVID load in the general public, both morbidity and mortality of HCW defer all unnecessary procedures and follow recommendations to make a safe way through this pandemic.

AUTHORS' CONTRIBUTIONS

MT: Investigation, Methodology, Writing – original draft. **FHSG:** Supervision. **MT:** Data curation. **ZAR:** Project administration, and Writing – review & editing. **MZH:** Formal analysis.

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REVIEW ARTICLE
https://doi.org/10.1590/1806-9282.20210587

Impact of the central auditory processing disorder on children with phonological deviation: a systematic review

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INTRODUCTION

The phonology acquisition process requires the acquisition and organization of sounds, in addition to the normal functioning of the structures of the oral myofunctional system as well as the auditory and central nervous systems. The correct sound production process occurs around the age of 5; however, this does not occur satisfactorily for some children, resulting in phonological deviations[1] in which the distinctive features of the sounds are not jointly achieved[2].

Central auditory processing (CAP) refers to the capacity and efficiency of the central nervous system to use auditory information[1]. Its functions are noted by the ability to locate the sound source, focus, discriminate, recognize, and/or understand auditory stimuli. To fulfill these functions, it is necessary that the auditory structures, related to the central and peripheral auditory systems, are preserved. If this does not occur, alterations in auditory processing (AP) skills can be occur, causing problems in receiving, analyzing, and organizing auditory information[3].

Difficulties in oral language may be associated with AP disorders, since hearing is an essential entry point for its acquisition. Central auditory processing disorder (CAPD) can be defined as a group of complex and heterogeneous alterations that are related to hearing and learning difficulties, with normal peripheral hearing[2].

The present study aims to characterize, through a systematic literature review, the impact of CAPD in children with phonological disorders, in order to answer the following research question: What is the impact of central hearing processing disorder in children with phonological disorders?

METHODS

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[4]. Searches for scientific articles were reported by two independent researchers in electronic databases (PubMed, CAPES, SciELO, LILACS, BIREME, MEDCARIB), between 2010 and 2020, without time and location restrictions. The search was conducted in De cember of 2020. The gray search used the same strategy and was performed using Google Scholar. The survey was structured and organized in the form PICOS, an acronym for the target population, intervention, comparison, outcome (outcomes), and study (Table 1).

Table 1. Description of the PICOS components.

Acronym	Definition
P	Children
I	Central auditory processing
C	Phonological disorder
O	Impact
S	Cross-sectional studies Observational studies Case reports Case-control studies Controlled clinical trials Cohort studies

Source: Developed by the authors.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 14, 2021. Accepted on June 24, 2021.

Research strategy

The descriptors were selected from the medical subject heading terms dictionary. For the searches, the following descriptors and Boolean operators were used: (central auditory processing therapy) and (phonological disorder therapy).

Eligibility criteria

Studies without language and location restrictions were included between 2010 and 2020. The admitted study obtained a score of 12 in the modified protocol by Pithon et al.[5] to assess their quality.

Data analysis

Data extraction for the study eligibility process was performed using a specific form prepared by two researchers in Excel® Program, in which the extracted data were added by one of the researchers and then checked by another researcher. Initially, they were selected according to title; then, the abstracts were analyzed, and only those that were potentially eligible were selected. Based on the abstracts, articles were selected for full reading, those that met all the predetermined criteria designed for this research were admitted.

Method of selection of the studies

Initially, the eligibility reviewers (LFG, EAP) were calibrated to carry out a systematic review by PH and KMV. Those that presented a title within the scope, but abstracts were not available, were also obtained and analyzed in full. Studies outside the preestablished scope, case reports, letters to the editor and/or editorial, literature reviews, indexes, abstracts, and studies on animals were excluded. Subsequently, the full texts of the preliminary eligible studies were obtained and evaluated.

RESULTS

The results obtained in this research and presented in Figure 1 highlight that exclusions were carried out due to duplicity, title, abstract, and complete reading. At the end of the selection process, the study was considered adequate for all eligibility criteria. The type of study included in this analysis was a clinical experimental study.

Study characteristics

The study included[6] 21 patients (both sexes) diagnosed with phonological disorder, aged between 7.0 and 9.11 years. According to the results of the CAP assessment, 10 subjects without CAPD were allocated to the control group (CG) and 11 subjects with CAPD to the study group (SG). All participants were Brazilian Portuguese speakers. As inclusion criteria, the child needed to have speech errors in the phonological test and adequate performance for age in the vocabulary, fluency, and pragmatic assessments of the ABFW Child Language Test.

Severity indices were calculated from percentage of correct consonant (PCC) and corrected-revised consonant percentage index (PCC-R); the number of different types of phonological processes; and the occurrence of each process. The phonological processes analyzed were Syllable Reduction (RS), Consonant Harmony (HC), Fricative Plosive (PF), Posteriorization to Velar (PV), Posteriorization to Palatal (PP), Velar Frontalization (FV), Palatal Fronting (FP), Liquid Simplification (SL), Simplification of the Consonant Meeting (SEC), Final Consonant Simplification (SCF), Sound of Plosiva (SP), Fricative Sound (SF), Plosive Deafening (EP), and Fricative Deafening (EF). For the evaluation of the CAP, identification tests of figures with white noise, dichotic digits test, frequency pattern test, and duration pattern test were used. The criterion for identifying CAPD in the tested subjects was the presence of alterations in at least two of the four tests administered[6].

Auditory processing, phonological processes, and deviation severity

In the analysis performed by sex in both groups, it was noted that most subjects were male, both in the CG (7) and SG (8). Regarding the number of different types of phonological processes in the phonological tests, the results showed that the SG participants used, on average, four types of phonological processes in each test. On the other hand, CG participants used an average

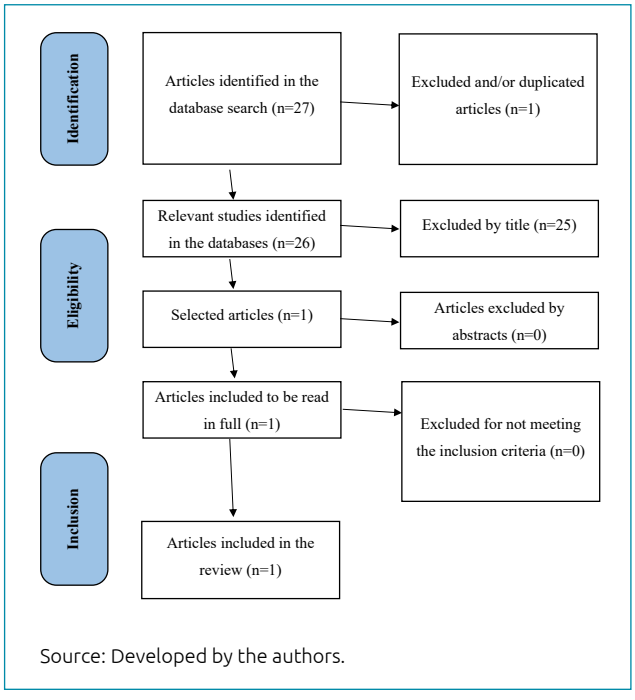

Figure 1. Flowchart of the article search and analysis process.

of three types of phonological processes. Although the SG had a higher mean number of phonological processes regardless of the phonological test, this difference was not significant in relation to word imitation or picture naming. The phonological processes that presented the highest occurrence were EP, EF, SL, and SEC. The distributions of these processes were compared between the two groups (CG and SG), with a difference only found for SEC in the word imitation test, indicating a higher occurrence of this process in the SG. Thus, the group with AP disorder (SG) had a greater severity of phonological disorders[6]. The information regarding the selected studies is presented in Table 2.

DISCUSSION

Individuals with CAPD) have some characteristic behaviors, such as alterations in oral communication or in the use of grammatical rules; inversions of graphemes; alterations in the notion of laterality, agitation, hyperactivity, or apathy; impaired auditory memory; and difficulty in understanding an acoustic message in noisy environments[7]. Furthermore, substitutions in oral production involving the phonemes/r/and/l/and difficulties in understanding reading are also manifestations found in individuals with CAPD, which may be related to phonological, learning, and language problems resulting from problems in the processing of acoustic stimuli[8].

For the evaluation of the CAP, identification tests of figures with white noise, dichotic digits test, frequency pattern test, and duration pattern test were used. The criterion for identifying CAPD in the tested subjects was the change observed in at least two of the four tests administered[6]. One study[9] compared a group of children with and without speech sound disorder (SSD) who underwent a temporal processing test and found altered results in most children with SSD. Regarding the group without DF (phonological deviation), the results were within the normal range in most individuals[9].

Individuals who have language disorders may have deficits in temporal processing, manifested by limited abilities to identify brief phonetic elements in specific speech contexts and poor performance in identifying or sequencing short-term stimuli presented quickly[10]. Regarding the analysis by gender, it was observed that most individuals were male, both in the CG (7) and SG (8)[6]. Some studies[11-14] have confirmed the prevalence of phonological disorders or other speech and/or language disorders in men. Regarding age, the admitted study[6] included individuals aged between 7 and 9 years, and four phonological processes were found for each SG and CG. One study[15] sought to analyze the occurrence, types, and average of phonological processes in subjects with phonological disorder, with and without a history of otitis media, and found that, on average, three phonological processes were found for each group.

Another study[7] pointed out the interference of neural maturation in the performance of AP tests, which included individuals from 8 to 10 years of age, and indicated that they can perform better in the 10-year-old range. As in a study[16] carried out with children aged 7–12 years, the authors observed that the performance on the tests was better according to the increase in age of the individuals. According to the study of Simon and Rossi[17], who carried out a survey with individuals aged 8–10 years, the difference in their performance in AP tests was statistically significant and was considered positive, as it indicates the test's ability to assess the maturation of the central auditory nervous system.

Regarding DF and CAP abilities, the authors[18] pointed out that children with deviant speech show poor performance in relation to children without DF, with the main deviant abilities being temporal resolution, location, memory for sounds in sequence, figure-background, and auditory closure. Furthermore,

Table 2. Síntese dos artigos incluídos.

Author/year/ Place of publication	Objective	n	Method	Results	Conclusion
Barrozo et al.[6], 2016 Brazil	To study phonological measures and auditory processing in children with phonological disorders.	21	Clinical and experimental study with 21 subjects with phonological disorder, between 7.0 and 9.11 years old, separated into two groups: with and without auditory processing disorder. Phonology, speech inconsistency, and metalinguistic skills tests were evaluated.	The group with auditory processing disorder showed greater severity of phonological disorder.	The comparison of the performance of the tests evaluated in the two groups showed differences regarding some phonological and metalinguistic aspects. Children with an index value above 0.54 showed a strong tendency to present alterations in the auditory processing, and this measure was effective in indicating the need for evaluation of children with phonological disorders.

studies[19,20] indicate that conductive hearing loss caused by recurrent otitis media can be a risk factor for the development of CAPD, which will consequently have negative impacts on language acquisition and development.

CONCLUSION

It can be concluded that CAPDs have an impact on children with phonological disorders, as the studies found in this study corroborate the idea that these individuals have greater losses in AP tests, indicating a close correlation between the two, demanding greater attention for this population, and highlighting the need for assessments in children with phonological disorders and subsequent auditory training.

AUTHORS' CONTRIBUTIONS

EAP: Conceptualization, Data curation. **LFG:** Formal analysis, Investigation, Methodology. **PH:** Methodology, Visualization. **APBD:** Project administration, Writing – review & editing. **KMP:** Supervision, Writing – original draft. **JVS:** Validation.

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COMMENTARY
https://doi.org/10.1590/1806-9282.20210688

Comment on "Vitamin D status influences cytokine production and MALAT1 expression from the PBMCs of patients with coronary artery disease and healthy controls"

Tinghui Li[1], Lianping He[1]*

Dear Editor,

We were glad to read the interesting study published by Nowrouzi-Sohrabi et al.[1] and his study team. They revealed that in vitamin D deficient individuals a decreased level of long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lncRNA MALAT1) was related to cluster of differentiation (CD) 36 expression and increased interleukin(IL)-22 production. Vitamin D supplementation may act as a part to reduce MALAT1/CD36/IL-22 mediated complications, such as type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD), especially in vitamin D deficiency. Although this study is of great significance for the prevention and treatment of vascular complications, there are some issues should be further discussed.

To begin with, statistical methods should be included in the methods section. We suggest that the statistical methods used in this study should be supplemented in the method section of the summary. It will also be helpful to explain in detail the specific methods used in each data analysis, such as the categorical data were tested by Fisher exact test and presented by frequency and percentile among others. The purpose of this study is to investigate the lncRNA MALAT1 expression and its role in cytokine production from peripheral blood mononuclear cells (PBMCs) in patients with CAD and non-CAD (NCAD) participants. However, the samples collected in this survey report are non-random samples, which may lead to biases in the experimental conclusions. And the limitation of cross-sectional study is that causal inference cannot be made. Therefore, it cannot be simply concluded that vitamin D supplementation can increase the level of MALAT1 in PBMCs, nor can it simply establish a relationship between the level of IL-6 in PBMCs and CD36.

In addition, we could not find Table 1 mentioned in the conclusion of this article, please confirm whether you have missed it. Furthermore, we cannot find the Table S1 mentioned in your results and the supplementary materials you mentioned. What's more, "association between clinical and biochemical characteristics with MALAT1" cannot be found either. We found that A and D in Figure 1 lack legends, please confirm whether the legends of these two parts are the same as the other legends in Figure 1. Last but not least, we suggest providing detailed demographic characteristics of the sample, such as occupation, gender, and home address, to analyze whether the conclusions of this experiment are dependent on occupation or another aspect.

AUTHORS' CONTRIBUTIONS

THL: Conceptualization, Data Curation, Formal analysis, Writing – original draft, Writing – review & editing. **LPH:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 17, 2021. Accepted on July 18, 2021.