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EDITORIAL PRODUCTION

EDITORIAL
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Editorial policies of Brazilian journals about guidelines

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The *guidelines* or writing guides are protocols structured as a check-list to improve the methodological quality of scientific research by increasing its external validity, in addition to ensuring an improved examination by reviewers, encouraging transparency and minimizing the omission of critical information in the method sections, inadequate reporting of adverse events, and misleading result presentations[1-3].

In March 2020, instructions to authors of 95 Brazilian biomedical journals found in the Scientific Electronic Library Online collection were evaluated and divided into eight major areas, namely:

1) Biomedicine;
2) Nursing;
3) Physiotherapy;
4) Medicine;
5) Multidisciplinary;
6) Dentistry;
7) Collective Health; and
8) Others – other major areas that did not present at least five journals in isolation.

The 27 guidelines included herein (AGREE, AMSTAR, ARRIVE, CARE, CASP, CHEERS, CODE, CONSORT, COPE, COREQ, GATHER, MIAME, MOOSE, PAIN, PREPARE, PRISMA, PROCESS, RATS, REMARK, SAGER, SPIRIT, SQUIRE, SRQR, STARD, STROBE, STROCSS, and TREND) in the instructions to authors were evaluated. One point was attributed to each guideline identified in the instructions to authors, and thus the score of a journal varied from zero to 27 points.

The mean score of guidelines per journal was 1.34±2.27 guidelines, with zero being the lowest score and 11 the highest. A total of 56 (58.94%) journals did not discriminate any guidelines in the instructions to authors. This result indicates the need to modify the editorial policies of Brazilian journals. When compared with the world scenario[4-6], Brazilian journals are similar to other journals, but inferior to high-impact journals, evidencing the importance of requesting these editorial guidelines.

When comparing major areas, nursing and physiotherapy journals presented the best results, and biomedicine, multidisciplinary, and others had the worst results. This fact could be related to how long the journal has been published as journals on the newest major areas presented the worst results. However, there is a need for more studies to confirm this conclusion.

No journal reported even half the protocols evaluated. The five most present guidelines were CONSORT (28–29.47%), PRISMA (26–27.37%), STROBE (15–15.79%), STARD (11–11.58%), and COPE (8–8.42%). Four protocols (AGREE, PREPARE, PROCESS, and STROCSS) were not mentioned by any of the journals. The journals should not describe all the guidelines already developed in their instructions to authors, but they should at least indicate those that are related to their area as well as the main study designs to ensure higher methodological quality and reduce the reviewers' work.

Overall, it is noticeable that Brazilian biomedical scientific journals use a small number of guidelines in their instructions to authors, and the ones that use them favor the oldest and best-known protocols, showing a growth potential for Brazilian biomedical science.

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RKCT: Conceptualization. Methodology. Project administration. Supervision. Validation. Writing – review & editing. **ALJCP:** Investigation. Methodology. Writing –original draft. **MESLV:** Data curation. Investigation. Writing – original draft. **DSN:** Investigation. Writing – original draft. **FCC:** Conceptualization. Data curation. Formal analysis. **DRS:** Conceptualization. Investigation. Methodology. **NPA:** Investigation. Writing – original draft.

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LETTER TO THE EDITOR
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Spontaneous Perforation of the Colon - A possible Third Classification

Amanda Prado[1], Ricardo Pedrini Cruz[1]*

Dear Editor,

The article by Moon et al.[1] brings a very important differential diagnosis of spontaneous perforation of the colon (SPC), pathology seldom recognized by surgeons. The frequency of this emergency condition may be underestimated and consequently rare reported. SPC was first described in 1894[2], as being classified as stercoral or idiopathic perforation[2-4]. Stercoral perforation of the large bowel is a rare event (with less than 100 cases reported in the literature), and idiopathic perforation is even more rarely reported[4].

A 46 years old white man was admitted complaining of abdominal pain and distension in the past 2 days, partially relieved with powdered magnesium sulfate. The pain worsened in the last 24 hours, without elimination of flatus or feces. He had a history of arterial hypertension (treated with captopril and hydrochlorothiazide), alcohol and tobacco consumption, and chronic constipation. Stercoral perforation usually occurs in patients with chronic constipation[1,5]. The patient reported constipation in the last 30 years, worsening in the last 9 years. During this period, daily laxative use (powdered magnesium sulfate and senna leaves compound) was necessary for symptom alleviation. He denied previous hospitalization or surgery. In the admission, the patient had no fever, presenting distended abdomen, diffuse abdominal pain and rebound tenderness on physical exam. Laboratory tests showed 9600 leukocytes with 41% of younger white cells (bands and metamyelocytes). An abdominal CT scan was performed, showing a sigmoid wall perforation, no fecaloma, and pneumoperitoneum (Figure 1). A laparotomy was indicated, showing fecal peritonitis and sigmoid colon perforation, treated with Hartmann's procedure. No tumor, fecaloma, or diverticulosis were found. The sigmoid colon had a hypertrophic muscular wall and a narrowed lumen with a 0.5 cm circular perforation on the antimesenteric tenia, with necrotic borders. Pathology analysis evidenced an area of necrosis on the antimesenteric sigmoid border, precisely in the colic tenia. There were no signs of previous pathologies, such as ulcers, or diverticula. Ciprofloxacin, metronidazole and fluconazole were used for 15 days. He was discharged without any complication. Colonoscopy was performed without

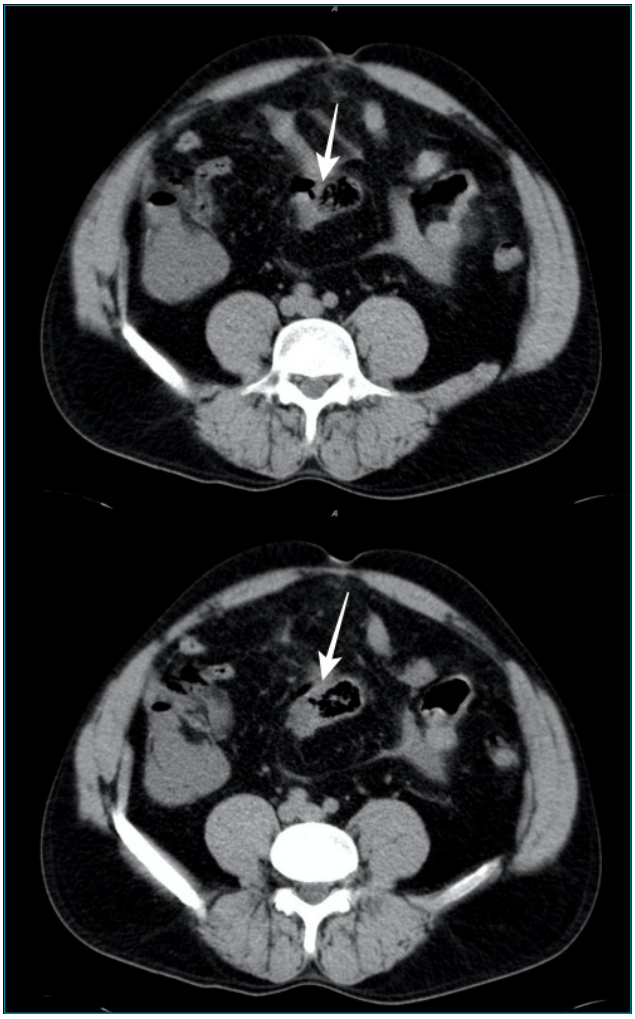

Figure 1. Abdominal CT showing a sigmoid wall perforation, no fecaloma, and pneumoperitoneum (white arrows).

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any abnormality. The bowel transit was reconstructed 2 months after the first surgery. He reported improvement of constipation after sigmoid resection, without any constipation thereafter.

SPC is defined as a sudden perforation of the normal colon in the absence of tumors, diverticulosis, or external injury[5]. Stercoral perforation occurs more frequently on the antimesenteric border of the rectosigmoid, an area more prone to ischemia because of anatomical vascularization[2]. The SPC has been classified as stercoral and idiopathic[1,2]. Stercoral perforations are those with rounded shape perforation with more than 1 cm in diameter; the colon should be full of stool, which diffuses to the abdominal cavity through the perforation; microscopical examination should evidence ischemia and necrosis of colonic mucosa leading to feculent ulcer and acute inflammatory reaction surrounding the perforation site; and external injury or other diseases such as obstruction, tumors, and diverticulosis must be excluded. The idiopathic SPC occurs due to asymmetrical distribution of intraluminal pressure at the pelvirectal angle in the absence of obvious impacted fecal matter[4,5]. According to Kasahara et al.[6] idiopathic SPC has a linear perforation and the feculent ulcer cannot be seen at microscopic examination. Other characteristics are a clear mucosal edge that does not extend to the serosa, and a regular broken end of the muscular layer[5]. Our patient had chronic constipation with laxative abuse, a narrowed lumen with a hypertrophic muscular wall in the sigmoid colon, and necrotic 0.5 cm diameter perforation on the antimesenteric tenia without fecaloma. Although a higher association with a layered-enhancing wall thickening was described in the stercoral SPC[1], the absence of a fecaloma and a colon perforation of only 0.5 cm without surrounding acute inflammatory reaction in the perforation site, prevent its classification as stercoral SPC. The idiopathic SPC classification is neither possible: no linear perforation was evidenced and there is no evidence that an asymmetrical distribution of intraluminal pressure at the pelvirectal angle could be a reasonable explanation of the perforation. Moreover, the patient had bowel wall hypertrophy with a narrowed lumen, aspects not present in the previous classifications.

Chronic constipation has an important association with indiscriminate laxative use. There is some evidence about colon ischemia by hyperosmotic laxatives[7], probably by the rapid shift of fluids from the vascular space of the colonic wall circulation into the luminal space resulting in local hypoperfusion. The mechanism of bowel ischemia by stimulant laxatives is a combination of colon motility stimulation with the increase of bowel luminal pressure, decreasing consequently the colonic perfusion by splanchnic circulation compression[7]. Our patient used senna leaves compound (a nonspecific bowel laxative stimulant/irritant) and powdered magnesium sulfate (a luminally active laxative agent). These laxatives may have contributed to impaired perfusion of the colon wall, leading to its ischemia and spontaneous perforation.

In conclusion, there is probably another pathophysiological mechanism that differs from those two described in the literature. The SPC associated with chronic constipation and laxative abuse is characterized by a narrowed sigmoid lumen, hypertrophic bowel wall musculature, no fecaloma, and perforation on the antimesenteric taenia of sigmoid, in the absence of other diseases (as tumors, diverticulosis, ulcers, or infection signs). Many stercoral SPC reported in the literature may be in fact, an SPC associated with laxative abuse.

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RPC: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing. **AP:** Data Curation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft.

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POINT OF VIEW
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Stress management in Medicine

Valentina Coutinho Baldoto Gava Chakr[1]*

SUMMARY

Stress and burnout can result in errors, reduction in patient safety, and decreased productivity. They can cause absenteeism, depression, destructive behavior, alcohol, drug abuse, and even suicide. Several factors lead to professional stress, many of which are out of one's control, thus making intervention impossible. Physicians often neglect their health and ignore stress and burnout. They often deny the existence of stress as a way of adapting to it, which is an ineffective method of coping with this problem that can lead to negative coping strategies. For managing stress and burnout, it is paramount to recognize situations/conditions that may trigger them, identify their signs, and invest in well-being strategies. In this article, well-being promotion is addressed with a focus on strategies that can be used at the individual level. Topics such as stress management and resilience should be valued in medical training and profession. As long as they form a part of the "hidden curriculum", well-being will continue to be undervalued, when in fact it should be seen as fundamental to the health of professionals and patients.

KEYWORDS: Mental health. Occupational stress. Psychological burnout. Psychological resilience. Physicians. Medicine.

Stress does not discriminate when it comes to occupation, career length, or seniority and no health professional is immune to it[1]. Stress and burnout can result in errors (since they affect attention, concentration, and decision-making ability), reduction in patient safety, and decreased productivity. They can cause absenteeism, depression, destructive behavior, alcohol, and drug abuse, and even suicide[2,3].

Stress is a complex phenomenon composed of three key elements: source (stressors), effects, and individual differences[4].

Stressors can be classified as being extrinsic and intrinsic[1]. Extrinsic factors include the following: high goals at work/college; excessive work/study hours; lack of resources required to do a good job; lack of socialization, good relationships, and support at work; sexual/racial discrimination; inadequate time for sleep; lack of proper feedback; lack of work recognition and autonomy; conflicts between personal values and organizational values; excessive bureaucracy; increased responsibility (especially for residents); and negative events in one's personal life. Intrinsic factors include the following: being extremely self-demanding (perfectionism); denying vulnerability (denying stress or having difficulty recognizing it); being overly meticulous, idealistic, controlling, and/or self-critical; lack of determination; low self-esteem and self-confidence; pessimism; and feeling that one's work is meaningless[1,3,5,6]. Traits such as compulsion, guilt, and self-denial (reflected as self-care negligence) can contribute to success in medical training. However, eventually, they become harmful[5]. Some personality types are risk factors for stress, such as neurotic personalities. Individuals with this personality type are usually nervous, oversensitive, tense, concerned, and have low frustration tolerance[7].

Stress becomes harmful when the person realizes that they are not able to deal with excessive demands and when adaptive

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responses become counterproductive, leading to decreased performance[1]. Stress also affects the learning process because it has a negative impact on memory. Stressful situations are internally evaluated for damage, loss, threat, or challenge based on the person's capabilities and resources when facing such situations. The confrontation process comes from the individual's efforts to balance demands with their available internal resources. In addition, the emotional experience of stress is influenced by the cognitive assessment of demand versus coping capacity. This explains why some stressors are seen as positive (challenges), while others are seen as negative (threat or damage). Stress is influenced by personal characteristics including emotions, self-esteem, and resilience. People can experience completely different emotions from a stressful situation, even when the external stressors are identical[8].

Longstanding, unresolved stress can result in burnout. This occurs when meaningful and challenging work becomes unpleasant and no longer brings satisfaction, when enthusiasm gives way to emotional exhaustion, and when effectiveness turns to inefficiency. Physicians experiencing burnout have reduced capacity to feel compassion and to practice empathy, in addition to having less time and ability to support their patients[1,9].

Many physicians neglect their health and ignore stress and burnout. They often deny stress as a way of adapting to it, which is an ineffective method of coping with this problem that can lead to negative coping strategies. Some physicians simply have trouble realizing they are under stress and suffering from burnout, which is also harmful[10].

Therefore, for managing stress and burnout, it is paramount to recognize situations/conditions that may trigger them (to avoid them when possible), as well as identifying their signs as shown below[1,9].

- Stress characteristics: isolation, retraction/introversion, rumination, procrastination, anger, crying easily, self-depreciation, excessive caution, lack of enthusiasm, reluctance to ask for help, inflexibility, difficulty in taking rest breaks, difficulty in concentration, irritability.
- Burnout characteristics: excessive emotional exhaustion, cynicism, loss of empathy, detachment (treating patients coldly and like objects), indifference and apathy towards work, feelings of failure and incompetence (even if they are not real), not feeling fulfilled at work.

Unfortunately, a lot of stressors are out of one's control making intervention impossible. Thus, to manage stress, efforts should be focused on controllable elements that can promote resilience and improve global well-being[1,11].

When experiencing a stressful situation, self-reflection and self-awareness are fundamental, either individually, or with the help of friends, co-workers, a mentor, or a mental health professional[1,5]. Self-awareness means being aware of one's thoughts, emotions, and behaviors. It is essential for developing cognitive flexibility, which is the ability to mentally adapt to challenging situations, to accept that mistakes can happen, and to deal with uncertainties[12].

The following questions can help in the practice of self-reflection and self-awareness: How have I faced difficult situations and succeeded in dealing with them? What has worked out, despite these difficulties? What was decisive for overcoming these situations? Why haven't I dealt so well with other situations (e.g., skipping meals, not having enough time to rest)? What were the difficulties (e.g., lack of time management and establishment of priorities)? Which signs have demonstrated that I am not coping well with a situation (e.g., feeling frustrated, tired, irritated, having headaches and/or muscle contractures)[1,5]? Some people believe that keeping a diary may be useful for self-reflection[12].

Using the wheel of life tool is an interesting exercise to assist in the process of self-awareness and in the development of strategies to establish an action plan for lessening the impact of stress on the person. A wheel of life is made of pre-defined domains that represent ways of describing life. Each domain should be classified according to its degree of satisfaction. For example, if the social life domain is classified as 7, its numbers from 0 to 7 are colored. Ranking all of the domains will result in a complete overview of the wheel of life. In this way, the focus will be on those areas that need to be improved and what can be done to improve them[5]. Within the health domain, there are issues such as the adequate amount of sleep, nutrition, and exercise[12]. For resident physicians, in particular, the wheel of life is usually found to be unbalanced, because their investment in professional growth affects other areas related to family, social life, physical and mental health, spirituality, and finances[13].

It has been noted that resilience is fundamental to be able to deal with stress. Resilience is the ability to overcome and recover from adversities, to bend rather than break, and to persevere and adapt when circumstances are difficult. It is the ability to develop and to adapt to challenges and to discover new ways to move forward without negative consequences for individual well-being. Improving resilience results in learning how to deal with stress in a way that protects mental health. A person with good resilience has the ability not only to survive troubled times but also to boost personal and professional development[1]. Optimism and flexibility are important for resilience[8]. Some techniques that have been proven to increase the level of optimism are sharing good news, reflecting on daily successes and achievements, and showing people gratitude whether personally or in writing. In addition, other

factors that can contribute to greater resilience are a sense of purpose and meaning to life, high-quality leisure time, and a sense of humor[12].

Actions that provide well-being should be promoted to avoid stress. Below are five key attitudes for promoting well-being[1]:

1. Connect: It is important to have support from family, friends, co-workers, and/or mentors. Reliable social relations (family, friends) bring a sense of safety so that individuals can be "themselves", providing a stress outlet[1,12]. Good relationships help build a sense of belonging and create opportunities to share positive experiences and to provide and receive emotional support. Some recommendations could be: have dinner with the family; meet friends you haven't seen in a while; have lunch with a co-worker; have a conversation or play a game with friends/family instead of watching TV; visit a friend or family member who needs help; volunteer; make video calls, and avoid keeping in touch only through text messages on social media channels[11,14]. In general, physicians neither support each other nor provide positive feedback (acknowledgments, compliments) to co-workers. In this sense, a change of attitude contributes to improving the quality of relationships in the workplace[10].
2. Be active: Physical activity reduces the intensity of emotions related to stress and increases self-esteem. Any physical activity is better than none. Physical exercise can release adrenaline (such as aerobic activities) or bring relaxation (such as eastern body-mind practices). People should try to be active every day, turning it into a habit. Doing exercise while listening to music or a podcast, in a group, or with the help of applications, helps to maintain motivation[1,11,14].
3. Be aware: People should use mindfulness to develop an awareness of their internal, emotional, and cognitive processes, as well as of their environment. This practice identifies stressors by their early signs and helps to balance emotions. It also ensures that actions are taken that optimize well-being before it is too late[1,12,14]. An important part of mindfulness is the reconnection with present thoughts and feelings. Being aware of our thoughts makes it easier to analyze their influence on our behavior[14]. By promoting professional and personal development, we understand more deeply our life history, experiences, personality, and how we see ourselves in comparison to how others see us. All of these factors influence our behavior and understanding their results in better management[12]. Many free applications assist in mindfulness practice, some of which are recommended by the United Kingdom National Health Service (NHS)[15].
4. Learn new things: Having a proactive attitude to seeking out challenges reduces stress. Learning new things improves self-confidence and self-esteem, and helps to build a sense of purpose and connections with other people. Some examples are: learning a new sport, a new language, or a new hobby, cooking a new dish, trying to do things on your own (like fixing a bicycle or hemming pants), and taking on new responsibilities at work. Using mistakes as learning experiences help to overcome their negative effects on a person's well-being[1,11,14].
5. Help others: Devoting time and compassion to co-workers and patients prevents burnout because it creates positive feelings and a sense of reward. It also builds a sense of purpose and helps a person to connect with people. Other ways of helping include spending time with friends or relatives who need support or company, and asking how a friend, a co-worker, or relative is, and listening to them[1,11,14].

Finally, it is important to emphasize that unhealthy habits should not be used (use of alcohol, cigarettes, and caffeine) as a means of coping with stress[11].

Topics such as stress management and resilience should be valued in medical training and profession[16]. As long as they form part of the "hidden curriculum", well-being will continue to be undervalued, when in fact it should be seen as fundamental to the health of professionals and patients.

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SHORT COMMUNICATION
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Eruptive vellus hair cyst syndrome or exuberant atypical keratosis pilaris?

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Dear Editor,

A generally healthy 35-year-old man presented with complaints of trunk skin lesions since his early childhood. He reported no symptoms and lesions were stable so far. Clinical examination revealed slightly hyperchromic, multiple, and disseminated perifollicular small papules on the anterior aspect of the trunk (Figure 1). No lesions were found at any other place on full-body skin examination. Eruptive vellus hair cyst (EVHC) syndrome was considered as a main diagnostic hypothesis, but the patient declined to undergo a skin biopsy for diagnostic confirmation. Treatment with a compounding cream of 20% urea plus 5% salicylic acid was prescribed and the patient reported moderate improvement after 3 months of use.

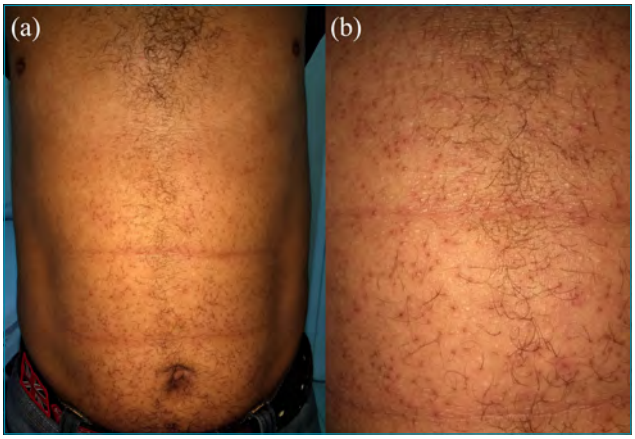

Figure 1. (a) shows the patient's frontal aspect of the trunk, covered by slightly hyperchromic, multiple, and disseminated perifollicular small papules on the anterior aspect of the trunk; (b) presents a closer view of skin lesions.

EVHC, firstly described by Esterly et al. is considered a rare condition that affects equally different genders and ethnicities1-3. There is a predilection to adolescents and young adults2, as in the current report. Even though most reports present sporadically, some believe its pathogenesis comes from autosomal dominant inheritance and follicular occlusion by keratin and folding of multiple vellus hairs2-4. Clinical features are as described in our patient and can affect limbs, face, abdomen, gluteal and genital region, as well as the trunk2,4. Keratin-17 mutations were described on EVHC patients5.

Clinical differential diagnosis of EVHC includes keratosis pilaris, acneiform eruptions, steatocystoma multiplex, milia, contagious mollusk, and folliculitis2-5. Definitive diagnosis is confirmed by skin biopsy exam1-5. Our patient did not want to undergo a skin biopsy because of personal concerns with scar raising. Thus, the exact diagnosis of the current case remains unclear.

As for clinical practice, though, we considered an exuberant and atypical form of keratosis pilaris as the main differential diagnosis for the current case, given its presentation. Both conditions are benign skin lesions and may be managed with topical keratolytic agents, such as urea, retinoids, salicylic acid, and lactic acid2,4,5. Laser, surgical and oral treatment is also described, but with limited results5.

This communication aims to stress that even though without a precise and definitive diagnosis, the current case

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examples a patient with skin lesions that invasive investigation would not lead to a better therapeutic decision or prognostic statement. We agree that microscopic examination of lesions would enrich this report. However, authors consider it noteworthy to say that complementary investigation should be done wisely, and patients' choices on refusing procedures must be respected, as well as daily practice skin conditions investigation should be oriented by well-established clinical, therapeutic and prognostic criterion. Additionally, we have to say that EHVC may be considered as a rare syndrome due to underdiagnosed, histopathological-confirmed cases, as the current communication.

AUTHOR'S CONTRIBUTIONS

BOR: Conceptualization of the study, Literature review, Dermatological examination, Drafting, Reviewing, Editing the final paper. **HVCS:** Literature review, Drafting, Reviewing, Editing the final paper. **JDF:** Supervision, Dermatological examination, Editing the final paper.

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ORIGINAL ARTICLE
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The impact of COVID-19 and social avoidance in urgent and emergency surgeries – will a delay in diagnosis result in perioperative complications?

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SUMMARY

OBJECTIVE: The sudden COVID-19 outbreak has changed our health system. Physicians had to face the challenge of treating a large number of critically ill patients with a new disease and also maintain the essential healthcare services functioning properly. To prevent disease dissemination, authorities instructed people to stay at home and seek medical care only if they experienced respiratory distress. However, there are concerns those patients did not seek necessary health care because of these orientations. This study aims to see how the pandemic has influenced the severity of the disease, complication, and mortality of patients undergoing emergency cholecystectomy and appendectomy.

METHODS: Retrospective review of medical records of patients admitted to the emergency department and undergoing to cholecystectomy and appendicectomy in the periods from March to May 2019 and 2020.

RESULTS: We observed that COVID-19 did not change the severity of presentation or the outcome of patients with gallbladder disease, but caused a 24.2% increase in the prevalence of complicated appendicitis ($p<0.05$). However, disagreeing with what was expected, we did not identify a greater number of perioperative complications in patients undergoing an appendectomy.

CONCLUSION: Therefore, it seems that in a university tertiary referral center COVID-19 did not influence the management and outcome of inflammatory diseases treated in the surgical emergency department.

KEYWORDS: COVID-19. Pandemics. Surgery. Emergency. SARS-CoV-2. Appendectomy. Cholecystectomy.

INTRODUCTION

The COVID-19 outbreak has affected healthcare systems across the world, and Brazil was not an exception - the country was one of the epicenters of the disease for months. In this context, as well as in other services worldwide, we hypothesized an increase in the severity of other pathologies, probably due to the delay in seeking medical care due to the isolation and fear of exposure to the hospital environment[1]. In addition, due to the sharp increase in the demand for medical services, mainly for emergency and intensive care units, the health system was saturated and there was a consequent difficulty in accessing care.

Among the main causes for seeking urgent care and emergency medical care are acute appendicitis (AA) and gallbladder diseases (GBD)[2], which can serve as a "thermometer" for the emergency surgical service.

Gallbladder lithiasis is a common condition, with a prevalence of 72% in the literature described in the general population[3]. The most common complication of this pathology is

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acute cholecystitis (7–11%) and typically appears in patients in whom cholelithiasis is symptomatic[4]. The most serious complication in this context is perforation, but it is rare and occurs most commonly in men[5]. In the GBD group, the benefits of early surgery (within 24 to 72 hours of symptoms) have already been well documented in the medical literature[6], but achieving this "better" treatment during the pandemic may be difficult.

AA is the most common reason for an urgent abdominal operation, with a lifetime incidence of 7–15%[1,2,7,8]. The risk of complications seems to be directly related to the duration of symptoms, being higher after 36 hours, in addition to being influenced by age and comorbidities[7].

Thus, we chose to study these pathologies to determine whether there was an impact of COVID-19 on the severity and perioperative complications of patients in the surgical emergency of a university hospital in southern Brazil. We evaluated patients that were not infected with coronavirus but were affected by the impact of social isolation and service saturation, with the hypothesis of an increase in severe cases and a consequent greater number of complications.

METHODS

Retrospective review of medical records of patients admitted to the emergency department and undergoing laparoscopic cholecystectomy due to cholecystitis or cholelithiasis with refractory pain and laparoscopic or conventional appendectomy for treatment of appendicitis at the Hospital de Clínicas de Porto Alegre from March to May 2019 (our control group, showing how the diseases used to present in previous years) and from March to May 2020 (with the influence of lockdown and social restrictions imposed by the government). The following variables were analyzed: gender, age, time of symptom until medical care, comorbidities, surgical findings, and perioperative complications. The severity of intraoperative findings was assessed using the Parkland scale[9] – for laparoscopic cholecystectomy – and those who underwent appendectomy were divided according to the intraoperative macroscopic findings into uncomplicated AA (catarrhal, phlegmonous, and ulcer-phlegmonous) and complicated AA (suppurative, gangrenous, and perforated). The only exclusion criterion was being under 15 years old at the time of surgery. For statistical analysis, Chi-Square and Mann-Whitney tests were used using SPSS software version 23.0.

RESULTS

A total of 301 medical records of patients undergoing laparoscopic cholecystectomy and laparoscopic and conventional appendectomy were evaluated. In the period from March to April 2019, a total of 31 surgeries for the treatment of AA and 152 GBD were performed, while for the same period in 2020, 40 and 78 were performed respectively.

The profile of the patients was similar between the two years: age, comorbidities, and sex remained within the same pattern. For patients with AA in 2019, 17 (54.8%) were men and the average age of these patients was 31.7 (±13.4). In 2020, 26 patients (65%) were men and the average age was 36.3 (±17.1). For patients with GBD in 2019, 37 (24.3%) were men and their average age was 52.1 (±15.5). In 2020, 20 patients (25.3%) were men with an average age of 46.4 (±17.9).

The difference of comorbidities between the groups after controlling for potentially confounding variables such as age, gender, alcoholism, smoking, neoplastic disease, immunosuppression, diabetes, hypertension, renal dysfunction, liver dysfunction, and cardiopulmonary disease in the analysis, was statistically insignificant and the most prevalent being systemic arterial hypertension. The time from symptoms to medical evaluation for GBD was significantly shorter in 2020 (p=0.003), on the other hand, the time from symptoms to medical evaluation for AA did not present significant differences (p=0.650).

The most prevalent intraoperative findings were Parkland grade 1 to 3 for GBD in both years studied. Complicated AA was found in 50% of cases in 2020 and only in 25.8% in 2019, a finding with statistical significance (p<0.05) (Table 1).

The rates of perioperative complications were 15% in 2019 and 6.8% in 2020 after cholecystectomy (p = 0.153) and, in appendectomy, the rate was 25.8% in 2019 and 12.5% in 2020 (p=0.259). The most prevalent complication was of pulmonary origin in both years for both procedures (Table 2).

Table 1. Severity of intraoperative findings.

	Cholecystectomy		Appendicectomy	
	2019	2020	2019	2020
Uncomplicated (%)	127 (86.6)	67 (85.9)	23 (74.2)	20 (50)
Complicated (%)	25 (16.4)	11 (14.1)	8 (25.8)	20 (50)
p-value	Not significant		<0,05	

Regarding the severity of this complication, no significant differences were found in the present study (Table 3). The length of hospitalization was an average of 2 days in 2019 and 3 days in 2020 for both procedures (p=0.122 for cholecystectomy and p=0.455 for appendectomy).

DISCUSSION

In March 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic[10]. During the pandemic, health systems around the world faced the need to reorganize to deal with a new disease and, at the same time, maintain the provision of essential health services. However, due to overcrowding, the risk of system collapse and the need to prioritize care for the most serious patients, some diseases were left in the "background". Patriti et. al. reports that in Italy "80% of surgical departments changed their practices"[11], this reality was also present in Brazil, causing a greater chance of delay in the diagnosis and surgical procedure of several pathologies.

Government officials advised patients with fever to stay in isolation at home and go to the emergency room only in case they had breathing difficulties. This was of paramount importance for controlling the spread of the disease and reducing the lines in healthcare services. However, some patients did not have a fever due to COVID-19, but due to abdominal inflammatory / infectious disease, which may have worsened the clinical condition before an adequate medical evaluation.

Table 2. Postoperative complications.

Postoperative complications	Cholecystectomy			Appendicectomy		
	2019	2020		2019	2020	
Adynamic ileus (%)	0	1 (1.4)	NS	2 (6.5)	1 (2.5)	NS
Bruise (%)	2 (1.3)	0	NS	0	0	–
Seroma (%)	4 (2.6)	0	NS	3 (9.7)	1 (2.5)	NS
Surgical wound infection (%)	2 (1.3)	0	NS	3 (9.7)	0	NS
Deep infection (%)	3 (2.0)	0	NS	1 (3.2)	1 (2.5)	NS
Aponeurosis dehiscence (%)	0	1 (1.4)	NS	0	0	–
Bleeding with transfusion (%)	2 (1.3)	0	NS	0	0	–
Pulmonary complication* (%)	57 (37.5)	3 (4.1)	p<0.05	12 (38.7)	1 (2.5)	p<0.05
Arrhythmia (%)	1 (0.7)	0	NS	0	0	NS
Deep vein thrombosis (%)	0	0	–	0	1 (2.5)	NS
Stroke (%)	0	0	–	0	0	–
Others (%)	12 (7.9)	0	NS	1 (3.2)	1 (2.5)	NS

NS: not significant.

Table 3. Severity of complication.

Severity of Complication	Cholecystectomy		p	Appendectomy		p
	2019	2020		2019	2020	
Hassle free (%)	126 (82.9)	70 (95.9)	NS	24 (77.4)	35 (87.5)	NS
Delay of discharge or need for readmission (%)	18 (11.8)	2 (2.7)	NS	6 (19.4)	3 (7.5)	NS
New invasive procedure (%)	1 (0.7)	1 (1,4)	NS	1 (3.2)	0	NS
ICU readmission (%)	4 (2.6)	0	NS	0	2 (5.0)	NS
Death (%)	3 (2.0)	0	NS	0	0	NS

NS: not significant.

Although the number of appendectomies remained similar between the periods analyzed, the number of cholecystectomies was influenced by the pandemic. This fact occurred due to a reduction in the number of cases referred to the service (reference in COVID-19).

In our sample, no statistically significant differences were found in the assessed items (severity of presentation, perioperative complications, length of hospitalization) in the period of laparoscopic cholecystectomies. There was no delay in the diagnosis of acute conditions, although the diagnosis time was significantly shorter. This fact can be easily explained by the inclusion of pathologies without inflammation, such as refractory symptomatic cholelithiasis and by having maintained the procedures in patients with comorbidities, which would not be recommended to postpone until after the pandemic. In addition, fear of coronavirus infection and misinformation left the general population more aware of any symptoms, inhibiting home management with symptomatic patients in respiratory conditions or abdominal pain, mainly. In addition to this, even though it is difficult to prove, the dietary change due to long-term homestay may have contributed to an increase in cases of symptomatic cholelithiasis and acute cholecystitis in patients who previously waited for elective surgery.

For intraoperative findings in laparoscopic cholecystectomy, our numbers are compatible with those described in the literature (about 65% in mild degree, 30% in moderate degree and 5% in severe degree)[9]. The reported incidence of trans-operative complications related to the gallbladder is 10–40%[12], this number is lower than described in the literature (14.5% in 2019 and 6.8% in 2020).

The relationship between duration of symptoms and the risk of progression to complicated AA has been demonstrated in several studies[2,13]. AA has a 5% increase in the risk of perforation every 12 hours after 36 hours, especially in young patients and those over the age of 50[1,13]. As complicated acute appendicitis is an independent risk factor for the formation of surgical site abscess after laparoscopic appendectomy and mortality is <0.1% in uncomplicated AA and reaches 5% in the case of perforation, early diagnosis is of great importance[1,2,14]. In the present study, complicated AA was diagnosed in more cases during the pandemic, however, the time spent before seeking medical care and the execution of treatment were similar. In addition, even with a percentage increase of 24.2% in severe cases ($p<0.05$), there was no change in the incidence of perioperative complications, mortality or increased length of hospital stay compared to the previous year, as shown in the results.

During the peak of COVID-19 in Italy, there was a reduction in the number of urgent cases, at the expense of an increase in severity, attributed to the delay in diagnosis[10]. Here in Brazil, despite the small number of cases, we managed to reach the same result in the evaluation of patients with AA, but not in cases of GBD, however, we can assume that in GBD there are more biases and that a larger study should be enlightening.

Contrary to the main findings in the literature, we found no difference in the incidence of perioperative complications, increased length of hospital stay, or mortality between uncomplicated and complicated AA. Regarding GBD, our data are consistent with those in the literature, maintaining the pattern of early treatment and treatment results.

CONCLUSIONS

In this paper, it was possible to identify the increase in the severity of presentation of AA occurrences during COVID-19. However, the same effect was not observed in GBD. Despite these findings in patients with AA, the repercussions were not harmful to the patients and the outcomes were similar to the previous year.

This study was carried out in a university hospital in the south of Brazil that is renowned for treating COVID-19 patients. The study shows a short period of observation because we selected the moment of greatest restriction and social isolation. Possibly the data found here were influenced by this factor and to circumvent this bias larger and multicenter studies are necessary.

The small number of patients in this study increases the chance of type two error for most of our results and there is a risk of some patients who underwent cholecystectomy due to cholelithiasis has been included in our sample. Further studies and larger samples are required to understand better the impact of the COVID-19 worldwide.

AUTHORS' CONTRIBUTIONS

RPS: Data Curation, Methodology, Project Administration, Supervision, Writing – Original Draft. **TLC:** Data Curation, Formal Analysis, Methodology. **AGT:** Formal analysis, Methodology, Visualization, Writing – Original Draft. SB: Data Curation, Investigation. **ECK:** Data Curation, Investigation. **JARP:** Data Curation, Investigation. **CG:** Data Curation, Investigation. **DCT:** Data Curation, Investigation. **VVD:** Methodology, Writing – Original Draft, Writing – Review & Editing. **LTC:** Conceptualization, Supervision, Writing – Review & Editing

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ORIGINAL ARTICLE
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The effect of treatment of obstructive sleep apnea syndrome on overactive bladder symptoms

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SUMMARY

OBJECTIVE: To evaluate the effect of the treatment of obstructive sleep apnea syndrome on overactive bladder symptoms.

METHODS: All patients who applied to the outpatient clinic with complaints of snoring and apnea were evaluated by polysomnography between years 2017 and 2019. obstructive sleep apnea syndrome severity was evaluated according to the apnea-hypopnea-index. All patients were filled with questionnaire form as overactive bladder symptoms score, international quality of life, international consultation on incontinence questionnaire short-form, and 3-day bladder diary before polysomnography and three months after continuous positive airway pressure therapy and surgical treatment.

RESULTS: A total of 125 patients, 34 (27.2%) patients with mild obstructive sleep apnea syndrome, 27 (21.6%) patients with moderate obstructive sleep apnea syndrome, and 64 (51.2) patients with severe obstructive sleep apnea syndrome were included in the study. The prevalence of overactive bladder symptoms in three obstructive sleep apnea syndrome groups were 67.6, 53.8, and 48.4%, respectively, and there was no statistical difference between the groups (p=0.190). obstructive sleep apnea syndrome treatment such as surgical treatment or continuous positive airway pressure therapy was applied to 45.5% (31 patients) patients with obstructive sleep apnea syndrome and overactive bladder. Three months after treatment, the overactive bladder symptoms score significantly decreased from 16.1±7.9–12.80±9.82, international quality of life was significantly increased from 105.0±23.2–110.4±22.2, and incontinence questionnaire short-form decreased from 11.9±4.0–10.4±5.6 (p=0.009, p=0.023, and p=0.248, respectively). There was a significant decrease between before and after treatment in terms of mean day-time frequency and mean urgency episodes of patients (p=0.007, p=0.002).

CONCLUSIONS: Both surgery and continuous positive airway pressure treatment of obstructive sleep apnea syndrome improved overactive bladder symptoms, overactive bladder symptoms score, international quality of life, day-time frequency, and urgency episodes.

KEYWORDS: Sleep apnea, obstructive. Urinary bladder, overactive. Continuous positive airway pressure.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is defined as complete or partial obstruction of the upper respiratory tract during sleep, resulting in airflow reduction or cessation[1]. The standard method for diagnosis of OSAS is polysomnography (PSG), which measures the apnea-hypopnea index (AHI)[2]. AHI is defined as the sum of apneas and hypopneas per hour of sleep, and OSAS can be classified as mild, moderate, and severe according to AHI[3]. In the treatment of patients with OSAS, lifestyle changes, oral cavity tools, medical treatment,

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surgical treatment, and continuous positive airway pressure (CPAP) therapy are used[4].

Overactive bladder (OAB) prevalence rates range from 49.6 to 79.3% in patients with OSAS[5,6]. Despite extensive study, the etiopathogenesis of OAB has not been clearly explained, and the relationship between OSAS and OAB is still under investigation[6,7]. Some studies have explained the relationship between OSAS and OAB by urinary visceral dysfunction caused by hypoxia. However, the effect of severity and treatment of OSAS on the improvement of OAB in patients with OSAS is still unclear and the prevalence studies of OAB in OSAS patients are quite limited[5,6,8].

In this study, the prevalence of OAB in OSAS severity and the effect of disease treatment on OAB symptoms were evaluated.

METHODS

Patients who applied to the outpatient clinic with complaints of snoring and apnea were retrospectively evaluated by PSG after routine otorhinolaryngologic examinations between years 2018 and 2019. Patients diagnosed and treated with benign prostate hyperplasia, interstitial cystitis, neurogenic urinary bladder, urinary tract infection, hematuria, previous urogenital operations, neurological disorders, patients who were taking anticholinergic, α1-blockers and 5α-reductase inhibitor, patients who had inadequate and incomplete tests, and patients with AHI score below 5 were excluded from the study.

PSG tests of patients were performed at the sleep laboratory of Çukurova University, School of Medicine, Department of Chest. The severity of OSAS was determined AHI (mean number of apnea+hypopnea per hour of sleep). In this study, AHI was classified as mild (5–15), moderate (16–30), and severe (>30)[9]. Patients were offered CPAP therapy or surgery according to OSAS severity and patients' clinic.

All patients who applied to the Sleep Disorders Center were filled with a 3-day bladder diary and before PSG was performed and 3 months after CPAP therapy and surgery treatment, all patients were filled with questionnaire form as Overactive Bladder Symptoms Score (OAB-V8), International Consultation on Incontinence Questionnaire Short-Form (ICIQ-SF), and International Quality of Life (I-QOL).

An overactive bladder questionnaire (OAB-q) consists of 33 questions is the first questionnaire form specific to OAB disease and can be used in both wet and dry OAB patients[10]. OAB-V8 consists of the first 8 questions of OAB-q evaluating the daytime frequency, nighttime frequency, urgency, and emergency incontinence and recommended as OAB screening and awareness test[11]. OAB-V8 is preferred for its ease of use in clinical practice. Patients with a total OAB-V8 score ≥8 were considered to be OAB patients[12]. In our study, OAB was defined as ≥8 points on the OAB-V8.

I-QOL is a 22-item questionnaire form into 3 subscales: Avoidance and Limiting Behavior (eight items), Psychosocial Impacts (nine items), and Social Embarrassment (five items). The total I-QOL is calculated by summing the unweighted item score and transforming them to a 100 point scale where 0=most severe, and 100=no problem.

The ICIQ-SF is formed of six items in the past 4 weeks that evaluate urinary continence. Scores range from 0 to 21 points. Only it was filled by patients with urge incontinence.

In this study, OAB-V8, I-QOL, ICIQ-SF, and nocturia of the patients were compared according to OSAS severity, whose parameters were compared before and 3 months after treatment of OSAS.

Statistical analysis

All analyses were performed using IBM SPSS Statistics statistical software package, Version 20.0. χ^2 test was used to compare categorical variables between the groups. For comparison of continuous variables between two groups, the Mann-Whitney U test was used. To compare two related continuous variables, Wilcoxon Signed Rank test or the Repeated Measurements Analysis were used, where appropriate. For comparison of more than two groups, Oneway ANOVA or Kruskal Wallis test was used. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

A total of 125 patients with the mean age of 49.9±11.6 years (range 25–81 years) were included in the study. Of them, 98 (78.4%) were male and 27 (21.6%) were females (p=0.013). Patients were classified according to AHI; 34 (27.2%) patients had mild OSAS, 27 (21.6%) had moderate, and 64 (51.2%) had severe OSAS. The mean AHI of mild, moderate, and severe OSAS groups were 8.1±2.9, 24.0±9.3, and 55.8±19.6, respectively (p<0.001). A comparison of demographic and clinical characteristics between the OSAS groups are presented in Table 1. Gender, age, diabetes mellitus (DM), hypertension (HT), smoking, and alcohol do not differ statistically between the OSAS groups (p>0.05).

Overactive bladder was observed in 68 patients (54.4%). Urge urinary incontinence was present in 22 (32.3%) of patients with OAB. The mean AHI value of 68 patients with OAB was 34.9±27.2. The prevalence of OAB in three groups of OSAS were 67.6, 53.8, and 48.4%, respectively (p=0.190). The mean OAB-V8 of patients with OAB was 16.9±8.3 and no significant difference in patients' OAB-V8 scores was found between

Table 1. Baseline characteristics of the study population.

	OSAS severity			
	Mild (n=34)	Moderate (n=27)	Severe (n=64)	p-value
AHI value[a]	8.1±2.9 7.0 (5.0–15.0)	24.0±9.3 22.0 (12.0–61.0)	55.8±19.6 52.5 (23.0–135.0)	<0.001
Age (years)[a]	49.5±10.7 48.5 (31.0–73.0)	52.3±13.0 51.0 (29.0–78.0)	49.2±11.5 49.0 (25.0–81.0)	0.512
Gender[b]				0.013
Male	21 (61.8)	21 (77.8)	56 (87.5)	
Female	13 (38.2)	6 (22.2)	8 (12.5)	
HT[b]	15 (44.1)	12 (44.4)	28 (43.8)	0.998
DM[b]	10 (29.4)	7 (25.9)	21 (32.8)	0.800
Smoking[b]	20 (58.8)	19 (70.4)	37 (57.8)	0.514
Alcohol[b]	4 (11.8)	3 (11.1)	9 (14.1)	0.908
Treatment[b]				<0.001
Follow up	23 (67.6)	11 (40.7)	24 (37.5)	
Surgery	9 (26.5)	8 (29.6)	10 (15.6)	
CPAP	2 (5.9)	8 (29.6)	30 (46.9)	

OSAS: obstructive sleep apnea syndrome; AHI: apnea-hypopnea index; HT: hypertension; DM: diabetes mellitus; CPAP: continuous positive airway pressure. [a]Data are expressed as mean±standart deviation, median (min–max). [b]Data are expressed as n (%). Note: bold values indicate statistical significance (p<0.05).

the groups (p=0.281). The mean I-QOL of these patients was 104.7±22.1 and was similar between the groups (p=0.539). The mean ICIQ-SF of patients with urge incontinence was 11.3±5.2 and was similar between the groups (p=0.320). The mean voided volume (MVV), mean day-time frequency, mean urgency episodes, and mean frequency of nocturia of patients with OAB were 262.0±123.5, 8.2±2.7, 4.2±4.7, and 2.7±1.5, respectively, and there was no significant difference between OSAS groups in terms of these parameters (p=0.965, p=0.120, p=0.210, and p=0.524) (Table 2).

Surgical treatment or CPAP therapy was applied to 45.5% (31 patients) of patients with OAB; (11 patients had surgery, 20 patients with CPAP). There were no significant differences between surgical treatment or CPAP therapy in terms of variables in Table 3 except for the mean voided volume in the 3rd month. The mean voided volume was found to be significantly lower in the surgical treatment group than in the CPAP therapy group (p<0.003). Hence, due to the insufficient sample size of each treatment group, the patients gathered in one group and comparisons of before and after treatment were applied to this sample (n=31). Three months after treatment, the OAB-V8 score significantly decreased from 16.1±7.9–12.80±9.82 (p=0.009). Also, in 9 of 31 patients, the OAB-V8 score decreased below 8, 3 months after treatment. After treatment, the I-QOL significantly increased from 105.0±23.2–110.4±22.2 (p=0.023). There was a significant decrease between before and after treatment in terms of mean day-time frequency and mean urgency episodes of patients with OAB (p=0.007, p=0.002). There was no significant difference between before and after treatment in terms of the MVV and mean frequency of nocturia of patients with OAB (p=0.356, p=0.205). In patients with urgent urinary incontinence, ICIQ-SF decreased from 11.9±4.0–10.4±5.6 after treatment (p=0.248). Although ICIQ-SF decrease after treatment, the difference was not statistically significant although there was a trend toward significance, which may become significant with larger group sizes (Table 3).

DISCUSSION

OSAS is causing urologic pathologies, such as erectile dysfunction (ED), nocturia, and OAB[10,13-15]. Although the pathogenesis of ED and nocturia is clearly demonstrated in patients with OSAS, the mechanism between OAB symptoms and OSAS is still uncertain[6,10,13]. Pathogenesis of OAB is thought to be morphologic changes of the detrusor (e.g., patchy denervation of detrusor muscle bundles), metabolic causes (e.g., disturbed

Table 2. Comparison of questionnaire form and bladder diary of patients with overactive bladder between obstructive sleep apnea syndrome groups.

	OSAS severity			
	Mild n=23	Moderate n=14	Severe n=31	p-value
AHI value[a]	8.5±2.8 7.0 (5.0–15.0)	25.0±11.3 22.0 (15.0–61.0)	57.3±23.4 49.0 (23.0–135.0)	<0.001
OAB[b]	23 (67.6)	14 (53.8)	31 (48.4)	0.190
OAB-V8[a]	18.7±8.6 17.0 (8.0–35.0)	17.9±9.2 16.0 (8.0–32.0)	15.1±7.5 12.0 (8.0–32.0)	0.281
I-QOL[a]	104.1±23.5 115.0 (62.0–132.0)	99.6±24.5 106.0 (65.0–126.0)	107.5±20.1 109.0 (64.0–132.0)	0.539
ICIQ-SF[a]	13.7±5.0 14.0 (5.0–21.0)	11.2±3.3 11.0 (8.0–15.0)	9.7±5.7 10.0 (0.0–20.0)	0.320
Day-time frequency[a]	8.9±2.5 8.0 (6.0–15.0)	8.7±3.7 7.0 (5.0–18.0)	7.5±2.2 7.0 (4.0–13.0)	0.120
Urgency episodes[a]	4.7±4.2 3.0 (0.0–17.0)	5.7±6.7 2.0 (0.0–21.0)	3.2±3.7 2.0 (0.0–16.0)	0.210
Frequency of nocturia[a]	2.5±1.3 3.0 (0.0–5.0)	2.6±1.8 2.0 (1.0–7.0)	2.9±1.4 3.0 (0.0–7.0)	0.524
The mean volume voided[a]	256.1±113.7 214.0 (80.0–571.0)	259.9±136.4 268.0 (67.0–600.0)	267.4±128.2 250.0 (108.0–625.0)	0.965
Total daily urine volume (mL)[a]	2,160.8±856.9 1,800.0 (1,200.0–4,000.0)	1,950.0±646.5 2,000.0 (1,000.0–3,000.0)	1,890.3±893.4 1,700.0 (1,000.0–5,000.0)	0.436
Total Night-time urine volume (mL)[a]	439.1±231.0 400.0 (0.0–1,000.0)	450.0±250.3 400.0 (200.0–1,000.0)	570.9±440.6 500.0 (0.0–2,000.0)	0.608

OSAS: obstructive sleep apnea syndrome; AHI: apnea-hypopnea index; OAB: overactive bladder; OAB-V8: overactive bladder symptoms scores; I-QOL: international quality of life; ICIQ-SF: international consultation on incontinence questionnaire short form. [a]Data are expressed as mean±standard deviation, median (min–max). Note: bold values indicate statistical significance (p<0.05).

Table 3. Comparison of questionnaire form and bladder diary of patients with overactive bladder between before and after obstructive sleep apnea syndrome treatment.

	Before treatment	After treatment	p-value
OAB-V8[a]	16.1±7.9 13.0 (8.0–32.0)	12.8±9.8 9.0 (1.0–36.0)	0.009
I-QOL[a]	105.0±23.2 109.0 (64.0–132.0)	110.4±22.2 120.0 (52.0–132.0)	0.023
ICIQ-SF[a]	11.9±4.0 12.0 (6.0–20.0)	10.4±5.6 11.5 (0.0–17.0)	0.248
Day-time frequency[a]	8.4±3.0 8.0 (4.0–18.0)	7.7±3.3 7.0 (4.0–18.0)	0.007
Urgency episodes[a]	4.3±5.2 2.0 (0.0–21.0)	3.4±5.8 1.0 (0.0–22.0)	0.002
Frequency of nocturia[a]	2.6±1.7 3.0 (0.0–7.0)	2.4±2.7 1.0 (0.0–10.0)	0.205
The mean volume voided (mL)[a]	230.6±131.2 214.3 (66.7–625.0)	235.2±177.0 250.0 (75.0–625.0)	0.356
Total daily urine volume (mL)[a]	1,748.4±860.2 1,500.0 (1,000.0–5,000.0)	1,924.0±830.8 1,800.0 (1,000.0–5,000.0)	0.001
Total Night-time urine volume (mL)[a]	567.7±468.6 500.0 (0.0–2,000.0)	380.0±329.5 200.0 (0.0–1,200.0)	0.013

OAB-V8: overactive bladder symptoms scores; I-QOL: international quality of life; ICIQ-SF: international consultation on incontinence questionnaire short form. [a]Data are expressed as mean±standard deviation; median (min–max). Note: bold values indicate statistical significance (p<0.05).

serotonin metabolism), age-related causes of urinary dysfunction, and neurologic changes (e.g., ischemic nerve damage)[13]. Considering these mechanisms that can cause OAB, the relationship between OSAS and OAB is thought to be related to nerve damage caused by hypoxia due to OSAS, as in erectile dysfunction[6,13]. The other possibility is that malfunction of the central nervous system leads to dysregulation of sleep and voiding. The hypothalamus is responsible for the regulation of sleep and arousal, as well as for sending afferent signals directly to the pontine micturition center. Continuous activation of the hypothalamus, which might induce urgency, might fail in its regulation of sleep and arousal[16]. Our study showed that the prevalence of OAB is quite high in patients with OSAS; however, there is no difference according to prevalence between OSAS severity and it was demonstrated that the treatment of OSAS, regardless of surgery or CPAP therapy, improved OAB symptoms. It was also found that OSAS treatment not only improved the OAB-V8 score but also improved quality of life. In addition, an improvement in day-time frequency and urgency episodes were found.

Ipekci et al. assessed 140 female patients diagnosed with OSAS and reported that OAB symptoms were observed in 79.3% of patients, but unlike our study, they defined OAB as OAB symptoms score of ≥4. They found no statistically significant differences between OSAS severity with the prevalence of OAB[6]. Similarly, Tuncer et al. evaluated the 194 patients diagnosed with OSAS and found no significant difference between OSAS severity in terms of OAB symptoms urgency urinary incontinence[5]. However, Kemmer et al. argued that patients with moderate and severe OSAS had a significantly higher prevalence of OAB than patients with mild OSAS and control group patients[13]. In this cohort, it had been shown that the prevalence of OAB, urgency urinary incontinence, parameters of bladder diary were similar between OSAS severity.

In the study, Ipekci et al. investigated whether CPAP therapy administered in OSAS patients improves OAB and they concluded that the OAB, OABSS, and ICIQ-SF scores improved in women with severe and moderate OSAS 3 months after treatment[6]. Similarly, in another study consisted of 73 patients, Dinç et al. concluded that CPAP therapy improved OAB symptoms[8]. The present study evaluated the effect of surgery as well as CPAP on OAB symptoms and concluded that both surgery and CPAP improved OAB symptoms, I-QOL, day-time frequency, and urgency episodes.

Limitations of the study

The limitations of this study are the low number of patients with OSAS and OAB receiving treatment and the small number of women included in the study. Another limitation is that urodynamic studies were not used for the diagnosis of OAB, only questionnaire forms and bladder diary were made.

CONCLUSIONS

The prevalence of OAB was higher in OSAS patient; however, there was no difference in the prevalence of OAB between OSAS severity. Both surgery and CPAP therapy of OSAS improved OAB symptoms, I-QOL, day-time frequency, and urgency episodes.

AUTHORS' CONTRIBUTION

MD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft. **OS:** Data curation, Investigation, Methodology, Project administration, Supervision. **SK:** Data curation, Writing – review & editing. **IT:** Data curation. **NA:** Formal analysis, Visualization. **SPY:** Formal analysis. **VI:** Project administration, Supervision, Writing – review & editing. **MD:** Validation, Visualization.

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ORIGINAL ARTICLE
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Recommendation and physical activity practice in Brazilians with chronic diseases

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SUMMARY

OBJECTIVE: To analyze the prevalence and factors associated with professional recommendation and leisure-time physical activity (LTPA) in Brazilian individuals diagnosed with hypertension (HBP), diabetes, and/or hypercholesterolemia.

METHODS: This is a cross-sectional population-based study with a representative sample of the Brazilian population (aged ≥20 years) in 2013, with self-reported HBP (n=11.098), diabetes (n=3.176), and/or hypercholesterolemia (n=7.252). Prevalence and gross odds ratios were estimated and adjusted for both outcomes.

RESULTS: Professional recommendation and LTPA were more prevalent in individuals who received recommendation and presented with hypercholesterolemia (85.9 and 23.4%, respectively). Adjusted analysis showed an association in people 40 to 59 years of age and public programs in most diseases. Higher educational level was associated with receiving recommendations in all non-communicable diseases (NCDs). LTPA was associated in people 40 to 59 years of age for HBP and diabetes and in all investigated NCDs, higher educational level, positive perception of health, and a favorable environment in those who received recommendation.

CONCLUSIONS: Education presented the greatest magnitude in the associations, clearly showing the need for equitable methods to increase recommendation and LTPA levels for the most vulnerable population. Further studies analyzing other variables and NCD are needed, corroborating the Ministry of Health.

KEYWORDS: Physical activity. Adherence, patient. Chronic disease. Non-communicable. Health surveys. Health personnel.

INTRODUCTION

Non-communicable diseases (NCDs) are responsible for 41 million deaths in the world[1] annually. In Brazil, approximately 45% of the adult population presents at least one NCD[2]. The main risk factors for NCDs are smoking, excessive consumption of alcoholic beverages, poor food quality, overweight, and insufficient physical activity on prescription (PAP)[1,3]. PAP accounts for the annual costs for health systems worldwide, which is estimated to exceed $50 billion[4]. Conversely, sufficient PAP has a positive effect on the prevention of health-related diseases, in addition to contributing to control and prevention of early mortality attributed to NCDs[5].

Environmental, demographic, socioeconomic, and psychocognitive factors[6] are PAP conditioning factors. In addition, the literature indicates the important role of health professionals and services in stimulating PAP. Some studies show that the recommendation of physical activity by health professionals to service users[7], especially by physicians[8,9], is associated with behavioral changes and an increase in PAP[7,10]. However, few

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studies have investigated this association in Brazil[7,8,11], especially in Brazilian individuals with NCDs.

Investigating the knowledge on PAP recommendation by health professionals in individuals with a NCD is particularly important in middle-income countries, such as Brazil, which have high social and individual costs attributed to NCDs and scarce resources to deal with such health conditions[2,4,12]. Moreover, Brazil has the goal of increasing the prevalence of leisure-time PAP (LPAP) and decreasing the growth of obesity among Brazilian adults, according to the Strategic Action Plan for NCDs[3].

This study aimed to analyze the prevalence and factors associated with professional recommendation and LPAP in Brazilian individuals diagnosed with HBP, diabetes, and/or hypercholesterolemia.

METHODS

This is a cross-sectional study based on microdata from the 2013 National Health Plan (PNS) conducted by the Brazilian Institute of Geography and Statistics (IBGE). This study has a domiciliary characteristic, national representativeness, and a population base with three-stage sampling by conglomerates. The questionnaire was completed by 60,202 adults[13].

This study included adults aged ≥20 years who self-reported HBP, diabetes, and/or hypercholesterolemia. To identify the pathological condition, they were asked: "Has any doctor ever diagnosed you with [*pathology*]?" with the option of answering "yes" or "no."

The *professional recommendation for physical activity* variable was also self-referred (yes, no), and the *enough leisure-time physical activity* variable considered sufficiently active participants those who performed at least 150 min/week of light or moderate PAP or at least 75 min/week of vigorous PAP at leisure time, or a combination of moderate and vigorous activities totaling 150 min a week[5]. The classification of the activity intensity was based on weekly frequency, duration, and intensity[14,15].

The exploratory variables were sex (male or female); self-reported race/skin color (black, brown, white); age group (20–39, 40–59, ≥60 years); marital status (married, separated/divorced/widowed, single); education (no education, incomplete/complete elementary school, incomplete/complete high school); self-perception of health status (positive, good and very good; negative, other answers); self-reported presence of public space near the household for PAP (yes, no); and self-reported presence of public programs that stimulate PAP (yes, no) in the city.

The analyses described the prevalence of the outcomes and their 95% confidence intervals (95%CI) by exploratory variables. Subsequently, logistic regression was performed, and gross odds ratio (OR) values were estimated and adjusted with the respective 95%CI. The Stata 12.0 software was used, considering individual sample weights and complex sampling.

RESULTS

The study sample consisted of individuals with hypercholesterolemia (n=7,252), diabetes (n=3,176), and hypercholesterolemia (n=11,098), and its distribution included more women and individuals aged ≥40 years, were whites and brown were married, had completed elementary school education, had negative health perception, and reported no space for PAP or public programs that stimulate PAP. The prevalence of both professional PAP and LPAP in those who received recommendation were higher in individuals with hypercholesterolemia (85.9 and 23.4%, respectively). In all NCDs, the two outcomes investigated were less prevalent in older individuals, who had a lower educational level and negative health perception (except for recommendations to individuals with diabetes), and to those who declared to have no space and PAP public programs (Table 1).

An adjusted analysis showed distinct associations among different investigated NCDs. Individuals with HBP aged 40–59 years had a 27% higher chance of receiving a recommendation than older individuals. Public space and public programs were also associated with PAP. In individuals with diabetes, those aged 40–59 years who were white had 105 and 60% higher chances of receiving a recommendation, respectively, compared to older and black individuals. Married individuals with hypercholesterolemia had a 46% higher chance of receiving a recommendation compared to separated/divorced/widowed individuals. For all investigated NCDs, an educational level of high school or college was positively associated with receiving a recommendation (Table 2).

Among those who received a PAP recommendation, an adjusted analysis in all NCDs showed that a positive self-perception of health, the presence of space and PAP public programs, and a high educational level were positively associated with adequate LPAP. A high educational level increased the chances of LPAP 2.5 times in individuals with HBP, 2.1 times in those with diabetes, and 3.1 in those with hypercholesterolemia compared to individuals with a low educational level (Table 3).

Table 1. Prevalence of "having received a recommendation for physical activity on prescription from a health professional" and "leisure-time physical activity on prescription in people who received a recommendation" in adults (≥20 years) with HBP, diabetes, and hypercholesterolemia. Brazil, 2013.

Variables	Received PAP recommendation			LPAP in individuals who received a recommendation		
	Hypertension	Diabetes	Hypercholesterolemia	Hypertension	Diabetes	Hypercholesterolemia
	95%CI	95%CI	95%CI	95%CI	95%CI	95%CI
Total sample	81.8 (80.5–83.1)	83.9 (81.8–86.0)	85.9 (84.4–87.3)	18.2 (16.8–19.5)	18.0 (15.4–20.6)	23.4 (21.5–25.3)
Sex						
Female	81.9 (80.4–83.5)	83.5 (81.1–85.8)	86.0 (84.4–87.7)	17.5 (15.8–19.2)	18.7 (16.0–21.4)	22.9 (20.7–25.0)
Male	81.7 (79.7–83.6)	84.5 (82.0–87.0)	85.6 (83.1–88.1)	19.3 (17.2–21.3)	17.0 (13.8–20.2)	24.4 (21.2–27.7)
Age group (years)						
20–39	84.8 (82.6–87.0)	90.1 (87.7–92.6)	89.2 (86.1–92.3)	19.8 (16.6–23.0)	22.0 (18.5–25.4)	29.0 (24.4–33.6)
40–59	84.8 (82.9–86.7)	89.8 (87.7–91.9)	87.3 (85.5–89.1)	20.6 (18.3–22.9)	22.5 (18.7–26.4)	24.4 (21.7–27.1)
≥60	78.0 (76.0–80.0)	78.6 (75.8–81.3)	82.3 (80.0–84.7)	15.0 (13.2–16.8)	13.4 (10.7–16.2)	19.0 (16.5–21.5)
Race/skin color						
Black	79.4 (75.8–83.0)	77.6 (73.6–81-5)	84.9 (81.8–88.0)	14.2 (10.7–17.8)	16.2 (13.1–19.4)	17.5 (13.0–21.9)
Brown	79.9 (78.2–81.7)	82.9 (80.8–84.9)	84.3 (81.7–86.9)	18.7 (16.8–20.6)	16.1 (13.6–18.7)	23.3 (20.6–26.1)
White	83.9 (82.2–85.5)	85.7 (82.6–88.8)	87.5 (85.7–89.3)	18.5 (16.5–20.5)	19.2 (15.3–23.2)	24.1 (21.5–26.8)
Marital status						
Separated/divorced/widowed	79.4 (77.0–81.8)	83.1 (80.2–85.9)	81.9 (79.0–84.8)	16.3 (14.3–18.4)	16.4 (13.4–19.4)	21.6 (18.6–26.7)
Single	79.4 (77.1–81.7)	83.7 (81.8–85.6)	85.8 (83.5–88.2)	17.9 (15.7–20.1)	14.4 (11.6–17.2)	25.0 (21.2–28.7)
Married	83.8 (82.1–85.4)	84.4 (81.6–87.2)	87.4 (85.3–89.4)	19.0 (17.2–20.9)	20.0 (16.5–23.5)	23.4 (21.0–25.9)
Education						
No education	71.1 (68.4–73.7)	72.9 (69.6–76.1)	76.7 (73.6–79.8)	11.3 (9.2–13.5)	11.4 (8.2–14.7)	13.0 (10.5–15.6)
Completed elementary education	80.0 (78.0–82.0)	84.2 (81.7–86.6)	82.4 (79.8–85.0)	15.0 (13.2–16.7)	14.0 (11.2–16.9)	17.2 (14.7–19.7)
Completed high school education	89.0 (87.2–90.9)	92.4 (90.1–94.7)	91.2 (89.4–92.9)	22.1 (19.2–25.0)	26.8 (20.0–33.7)	25.8 (22.6–29.1)
Completed higher education	94.6 (92.9–96.2)	92.2 (88.0–96.3)	95.7 (94.5–96.9)	30.8 (26.3–35.3)	29.3 (24.7–33.9)	41.5 (36.8–46.2)
Self-perception of health						
Negative	79.1 (77.4–80.8)	82.6 (80.4–84.8)	83.2 (81.3-85.1)	14.3 (12.5–16.1)	15.1 (12.3–18.0)	15.8 (13.7–17.9)
Positive	85.6 (83.6–87.6)	87.1 (83.4–90.9)	88.9 (87.1-90.7)	23.2 (21.0–25.4)	24.8 (21.1–28.5)	31.5 (28.5–34.5)
Public space for PAP						
No	78.2 (76.3–80.0)	81.4 (78.4–84.4)	83.7 (81.9-85.6)	13.9 (12.4–15.5)	15.1 (12.0–18.2)	17.5 (15.3–19.7)
Yes	86.8 (85.2–88.5)	87.3 (84.8–89.8)	88.5 (86.8-90.2)	23.5 (21.2–25.8)	21.7 (17.8–25.6)	30.2 (27.2–33.2)
Public programs that stimulate PAP						
No	79.9 (78.4–81.4)	82.8 (80.5–85.1)	83.8 (82.0-85.5)	15.8 (14.4–17.2)	15.1 (12.5–17.7)	20.3 (18.2–22.4)
Yes	88.3 (86.2–90.3)	87.6 (84.3–90.8)	92.2 (90.2-94.3)	25.4 (22.8–28.0)	27.4 (23.1–31.7)	32.2 (28.8–35.6)

Source: Brazilian Institute of Geography and Statistics; 2013. *p<0.001 (χ^2 test). PAP: physical activity on prescription; LPAP: leisure-time physical activity on prescription

Table 2. Gross and adjusted odds ratio of "having received a recommendation for physical activity on prescription from a health professional" in adults (≥20 years) with hypertension blood pressure, diabetes, and hypercholesterolemia. Brazil, 2013.

Variables	Hypertension				Diabetes				Hypercholesterolemia			
	Crude		Adjusted[A]		Crude		Adjusted[B]		Crude		Adjusted[C]	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Sex												
Female	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Male	0.98	(0.83–1.16)	0.88	(0.74–1.05)	1.08	(0.79–1.48)	0.92	(0.65–1.29)	0.97	(0.75–1.24)	0.78	(0.60–1.01)
Age group (years)												
≥60	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
40–59	1.57	(1.30–1.91)	1.27	(1.03–1.56)	2.40	(1.65–3.51)	2.05	(1.34–3.14)	1.48	(1.15–1.89)	1.12	(0.86–1.46)
20–39	1.58	(1.23–2.02)	1.16	(0.87–1.55)	2.49	(1.21–5.14)	1.60	(0.85–4.49)	1.77	(1.20–2.63)	1.05	(0.66–1.69)
Race/skin color												
Black	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Brown	1.04	(0.80–1.34)	1.03	(0.80–1.33)	1.40	(0.95–2.06)	1.41	(0.93–2.12)	0.96	(0.61–1.49)	0.88	(0.57–1.38)
White	1.35	(1.04–1.75)	1.14	(0.88–1.47)	1.73	(1.12–2.66)	1.60	(1.03–2.48)	1.24	(0.82–1.88)	0.95	(0.63–1.45)
Marital status												
Separated/divorced/widowed	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Single	1.00	(0.81–1.24)	0.86	(0.68–1.10)	1.05	(0.70–1.56)	0.78	(0.48–1.26)	1.34	(0.97–1.85)	1.17	(0.79–1.73)
Married	1.34	(1.11–1.61)	1.15	(0.95–1.40)	1.10	(0.80–1.51)	0.82	(0.59–1.15)	1.53	(1.13–2.07)	1.46	(1.07–1.98)
Education												
No education	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Completed elementary education	1.63	(1.36–1.96)	1.40	(1.15–1.70)	1.98	(1.43–2.73)	1.68	(1.19–2.37)	1.42	(1.06–1.91)	1.29	(0.97–1.72)
Completed high school education	3.30	(2.59–4.22)	2.49	(1.91–3.26)	4.54	(2.69–7.65)	3.12	(1.79–5.48)	3.14	(2.25–4.39)	2.78	(1.95–3.97)
Completed higher education	7.11	(4.85–10.43)	5.00	(3.31–7.55)	4.39	(1.56–12.37)	2.93	(1.04–8.29)	6.81	(4.50–10.29)	5.40	(3.14–8.53)
Self-perception of health												
Negative	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Positive	1.57	(1.29–1.90)	1.21	(0.99–1.49)	1.43	(0.93–2.19)	1.14	(0.73–1.78)	1.62	(1.28–2.05)	1.07	(0.83–1.39)
Public space for PAP												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	1.85	(1.53–2.22)	1.47	(1.20–1.79)	1.58	(1.13–2.20)	1.39	(0.98–1.97)	1.50	(1.17–1.91)	1.11	(0.85–1.45)
Public programs that stimulate PAP												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	1.89	(1.52–2.36)	1.40	(1.11–1.77)	1.46	(0.92–2.33)	1.07	(0.65–1.76)	2.29	(1.67–3.14)	1.89	(1.33–2.67)

Source: Brazilian Institute of Geography and Statistics, 2013. All variables were kept in the adjusted analysis, with sex[B], age-group[A,C], race[C], marital status[B], health status[B,C], program[B], and space[C], p>0.20.
OR: odds ratio; PAP: physical activity on prescription.

Table 3. Gross and adjusted odds ratio for sufficient leisure-time physical activity on prescription in adults (≥20 years) with hypertension blood pressure, diabetes, and hypercholesterolemia who received recommendation from health professionals. Brazil, 2013.

Variables	HBP				Diabetes				Hypercholesterolemia			
	Crude		Adjusted[A]		Crude		Adjusted[B]		Crude		Adjusted[C]	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Sex												
Female	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Male	1.13	(0.94–1.36)	1.05	(0.87–1.28)	0.89	(0.63–1.26)	0.73	(0.51–1.03)	1.09	(0.87–1.37)	0.97	(0.77–1.22)
Age group (years)												
≥60	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
40–59	1.47	(1.20–1.81)	1.26	(1.00–1.59)	1.86	(1.35–2.60)	1.66	(1.13–2.43)	1.37	(1.10–1.72)	1.13	(0.88–1.45)
20–39	1.40	(1.05–1.86)	1.08	(0.80–1.47)	1.81	(1.04–3.17)	1.72	(0.91–3.24)	1.74	(1.29–2.34)	1.03	(0.74–1.43)
Race/skin color (3)												
Black	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Brown	1.38	(0.97–1.99)	1.45	(0.99–2.13)	0.99	(0.62–1.58)	0.99	(0.59–1.66)	1.44	(0.93–2.21)	1.30	(0.82–2.06)
White	1.37	(0.96–1.94)	1.20	(0.84–1.72)	1.23	(0.75–2.01)	1.10	(0.65–1.85)	1.50	(0.99–2.27)	1.07	(0.69–1.66)
Marital status												
Separated/divorced/widowed	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Single	1.11	(0.85–1.46)	0.99	(0.73–1.33)	0.85	(0.53–1.39)	0.71	(0.40–1.26)	1.21	(0.89–1.64)	0.97	(0.71–1.32)
Married	1.20	(0.97–1.49)	1.01	(0.80–1.27)	1.27	(0.85–1.91)	1.14	(0.73–1.77)	1.11	(0.87–1.41)	0.99	(0.75–1.30)
Education												
No education	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Completed elementary education	1.38	(1.06–1.80)	1.18	(0.90–1.55)	1.26	(0.80–2.00)	0.90	(0.57–1.42)	1.39	(0.97–1.99)	1.19	(0.81–1.74)
Completed high school education	2.22	(1.64–2.99)	1.63	(1.19–2.22)	2.84	(1.67–4.82)	1.91	(1.11–3.31)	2.32	(1.61–3.36)	1.66	(1.11–2.48)
Completed higher education	3.48	(2.50–4.85)	2.49	(1.76–3.51)	3.21	(1.82–5.66)	2.07	(1.14–3.75)	4.74	(3.24–6.94)	3.07	(2.03–4.64)
Self-perception of health												
Negative	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Positive	1.81	(1.48–2.21)	1.48	(1.21–1.81)	1.85	(1.29–2.65)	1.62	(1.13–2.32)	2.45	(1.98–3.03)	1.75	(1.38–2.22)
Public space for PAP												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	1.90	(1.57–2.29)	1.59	(1.29–1.95)	1.56	(1.11–2.20)	1.42	(0.99–2.03)	1.56	(1.11–2.20)	1.56	(1.25–1.97)
Public programs that stimulate PAP												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	1.81	(1.50–2.19)	1.49	(1.21–1.83)	2.12	(1.41–3.21)	1.85	(1.19–2.89)	1.87	(1.51–2.31)	1.64	(1.30–2.07)

Source: Brazilian Institute of Geography and Statistics, 2013. All variables were kept in the adjusted analysis, with sex[A,C], age-group[A,C], race[A,B,C], and marital status[A,B,C], p>0.20. OR: odds ratio; PAP: physical activity on prescription; HBP: hypertension blood pressure.

DISCUSSION

The results showed that receiving a PAP recommendation was positively associated with the age group 40–59 years (except for hypercholesterolemia), with being white (in individuals with diabetes), with being married (in individuals with hypercholesterolemia), and with having space (in individuals with HBP) and public PAP programs (except for individuals with diabetes). Educational level was the only variable associated with the outcome in all NCDs. In those who received a recommendation, LPAP presented positive association with higher educational level, positive self-perception of health, and presence of space and public PAP programs in all NCDs.

In Brazil, approximately 59.3% of individuals received some recommendation for adopting a healthy behavior in primary care[9]. One of the associated factors is the presence of an NCD[8,11,16], justifying the high prevalence of recommendations. Corroborating the results of this study, other studies also reported higher prevalence of both PAP recommendation[11,16] and sufficient LPAP[10,14,15,17] in married individuals, with a higher educational level, and access to public spaces and programs.

As for the age group, there was a higher prevalence of recommendations for older adults and younger elderly individuals[16]. The demand for health services and professional recommendation is highly prevalent in elderly individuals[7] but, with advancing age, NCD and physical limitations may hinder PAP, reducing recommendations for older individuals who cannot perform them. LPAP was more prevalent among adults, which may be justified by better health status and lower limitations resulting from NCD in this group[13]. Although there was a higher prevalence of recommendations and PAP in individuals with positive health perception, only PAP showed an association in an adjusted analysis, corroborating a study investigating the same NCD[17]. Positive health perception presupposes greater susceptibility to adhere to LPAP[6], which may justify the association.

As in other studies, the favorable environment for PAP was associated with receiving recommendations[11] and LPAP[10,17,18]. Places such as health units, gym centers, and green spaces in the area increase recommendations and LPAP[11], possibly because the health professional considers that the user would be able to comply with the recommendations. Decision making for PAP considers the effects of space and context[19], highlighting a person's sense of safety, urbanization, geography, and climate[6,18]. Some studies highlight the importance of environments built to address PAP inequalities. Although wealthier individuals have more knowledge on the existing public programs, individuals with lower income participate more often in these programs[20]. Adequate spaces for PAP close to the household are associated with higher PAP[18]; therefore, public health promotion policies can help fight inequalities when aimed at the most vulnerable regions.

Having a higher educational level increased the chances of both outcomes. Studies identified the same bias for recommendation[11] and LPAP[10,14,15,17]. The lower occurrence of recommendation for individuals with a lower educational level replicates a perverse logic, in which those who need it most have less access or use a service of lower quality. Similar behavior was found in patients with high cardiovascular risk, where those with lower income had less access to diagnostic health services[21]. Considering the positive relationship between education and income[22], higher education provides individuals with objective conditions to meet the recommendations. Professional recommendation is a way to promote health and, according to the principle of equity, greater attention to the most vulnerable population is expected. They need more social support, objective conditions, and motivation for behavioral changes[23]. Another hypothesis for the results obtained would be the greater engagement of individuals with higher educational level for LPAP since they were more knowledgeable[15].

One limitation of this study is its cross-sectional design, which makes it impossible to infer causality, and self-reported NCD leads to a memory bias of the participants. Considering that the presence of NCD is associated with an increased use of health services, a possible selection bias cannot be excluded, especially because individuals with undiagnosed disease are not included in the analyzed sample.

CONCLUSIONS

Being in the 40–59 years of age group and having a higher educational level, a positive perception of health, and the existence of public spaces and PAP programs were associated with both receiving professional PAP recommendation and being more leisure-time physically active in individuals who received professional recommendation.

Educational level was the variable associated with the greatest magnitude, pointing to the need for strategies capable of attenuating the evident inequalities found to increase LPAP recommendation in the most vulnerable population.

AUTHORS' CONTRIBUTIONS

PSCS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **TRL:** Conceptualization, Data curation, Writing – review & editing. **LJB:** Conceptualization, Writing – review & editing. **AFB:** Conceptualization, Formal analysis, Methodology, Validation, Writing – review & editing.

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The effect of the use of a physical-activity mobile application on body composition and sleep quality of overweight children

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SUMMARY

OBJECTIVE: To analyze the use of a mobile physical activity application and its influence on body composition and sleep quality in overweight children.

METHODS: Prospective study with 37 patients from the Child and Adolescent Obesity Clinic at Unicamp Hospital das Clínicas, between 2018 and 2019. Anamnesis and anthropometry were performed. We oriented the use of the application for six weeks, five days/week for ten minutes.

RESULTS: Among 37 patients, 28 (mean age 10.7±2.0 years, 50% boys) used the application. The average use of the application ranged from 1.93±2.18 to 3.25±1.84 times/week, with a peak in the second week and a progressive decrease during follow-up. The paired t-test showed, on average, lean mass (t (27)=-2.91), weight (t (27)=-3.11) and height (t (27)=-3.79). After using the application, these were higher than before (all $p<0.05$). There was a significant difference in the proportion of children who presented difficulty sleeping ($\chi 2$ (1)=5.143) and insomnia (χ^2 (1)=4.167).

CONCLUSIONS: There was an improvement in sleep quality and an increase in lean mass, but no significant changes in BMI z-score, waist circumference, and body fat percentage.

KEYWORDS: Physical activity. Obesity. Child. Mobile application.

INTRODUCTION

Prevention and control of obesity among children and adolescents present a challenge to healthcare professionals as they involve improvement in dietary behavior, physical activity, and sleep quality. New technologies, such as mobile health applications, have emerged as an aid in this process[1]. These applications allow users to customize their goals and plans, and to switch between activities[2]. Most patients can benefit from these services, even if they live in remote communities and have limited access to places that provide care, because they are reliable, accurate, and inexpensive[3].

Mobile-health applications present an effective and sustainable solution that can help users promote significant and consistent changes in their behavior towards an active and healthy lifestyle[3]. Studies indicate that they offer a fun alternative for users to improve their physical condition, concentration, and

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sleep. These applications can motivate users to play sports, and can be used outdoors as well as in groups[4,5].

Given the current concerns regarding weight-management and increased screen time among children, this study aimed at evaluating the effect the use of a mobile application, by promoting physical activity, might have on the body composition and sleep quality of overweight children.

METHODS

This prospective, interventional study was conducted between February 2018 and August 2019, and included male and female patients who were in follow-up care at the Child and Adolescent Obesity Clinic of the Unicamp Hospital das Clínicas. Ten new cases of children between the ages of two and seventeen were admitted to the clinic every month.

Cases that met the inclusion criteria were selected. We selected 37 patients between the ages of seven and thirteen who had a suitable smartphone, were able to understand the application's functionality and the exercises, and were either overweight or obese. Patients signed an Informed Consent or a Minor Informed Consent form. Among the exclusion criteria were the presence of former psychiatric disorders, other concomitant illnesses such as endocrine, renal, pulmonary, or cardiovascular diseases, and girls who had started menstruating.

For the intervention, we used the Tabata Timer® application for physical activity, and instructed patients to use the application at least five days a week, for six consecutive weeks. This application is available for free on several platforms, and it helps users to structure and modify the intensity of their exercises, supporting short-duration workout sessions. We helped patients set up the application, the time settings, and structured the proposed activities. We selected the following age-appropriate motor coordination and strength exercises, which were performed sequentially in timed intervals: jumping jacks; stationary single-leg hop exercises (hopscotch); squats; and the plank. The activities were structured as follows (with time set in seconds): 10s preparation – 20s jumping jacks – 10s pause – 20s stationary single-leg hop exercises – 10s pauset – 20s squats – 10s pause – 20s plank – 50s pause to end the cycle. This sequence was performed in a set of four cycles, totaling ten minutes a day. During this period, the researcher and the children's parents communicated via WhatsApp Messenger® to receive a brief report of the activities. Right after each session, the Borg Rating of Perceived Exertion[6] scale was presented: 1–2 easy, 3–5 moderate, and ≥6 very difficult. We took anthropometric (physical) and bioimpedance (body-composition) measurements at the beginning and at the end of the six-week period. We assessed sleep quality before and after patients used the application by asking the following questions:

1) Do you have trouble sleeping? and
2) Do you have or have ever had insomnia? We considered sleep time to be the reported in the number of hours between sleep onset and wakefulness.

We took weight and height measurements[7] and calculated BMI and BMI z-scores for age and gender, in order to classify the subjects as being overweight or obese[8]. We also measured their waist circumference (WC)[9] and used tetrapolar bioimpedance with the Bioimpedance Analyzer – BIA 310®10.

For statistical analysis, we used the SPSS® program, version 16, with a significance level of $p<0.05$. We used the Shapiro-Wilk test to assess normality, and the paired t-test or McNemar's test to compare the variables.

RESULTS

Seven among the 37 patients did not use the application at any time, and two patients were excluded due to irregular adherence and drop-out. As a result, we examined 28 patients.

The average age was 10.7±2.0 years (11.0±1.9 for males and 10.4±2.2 for females), with 2 overweight and 26 obese children.

Figure 1 illustrates the patients' average use of the application and the Borg Rating over six weeks.

Table 1 presents a comparison of the body composition and total sleep time before and after the subjects used the application. The paired t-test showed that lean mass ($t(27)=-2.91$, $p=0.007$), weight ($t(27)=-3.11$, $p=0.004$), and height ($t(27)=-3.79$, $p=0.001$) were statistically higher after the children used the application. BMI Z-scores ($t(2)=0.678$), WC ($t(27)=0.465$), body fat percentage ($t(27)=1.04$), and the total sleep time ($t(27)=1.14$) did not present statistically significant differences.

In Table 2, the exact McNemar test demonstrated a significant difference in the proportion of children who had trouble sleeping ($\chi2(1)=5.143$; $p=0.016$) and those who had insomnia ($\chi2(1)=4.167$; $p=0.03$) before and after using the application.

DISCUSSION

In this study, we assessed the effect that the use of a physical-activity mobile application has on the body composition and sleep quality of overweight children. There was little compliance with the recommended use of the application and a progressive decline in activity during the week, resulting in almost zero activity on weekends. However, participants who followed the recommendations were able to perform the exercises with less effort, thus increasing their lean mass and improving their sleep quality.

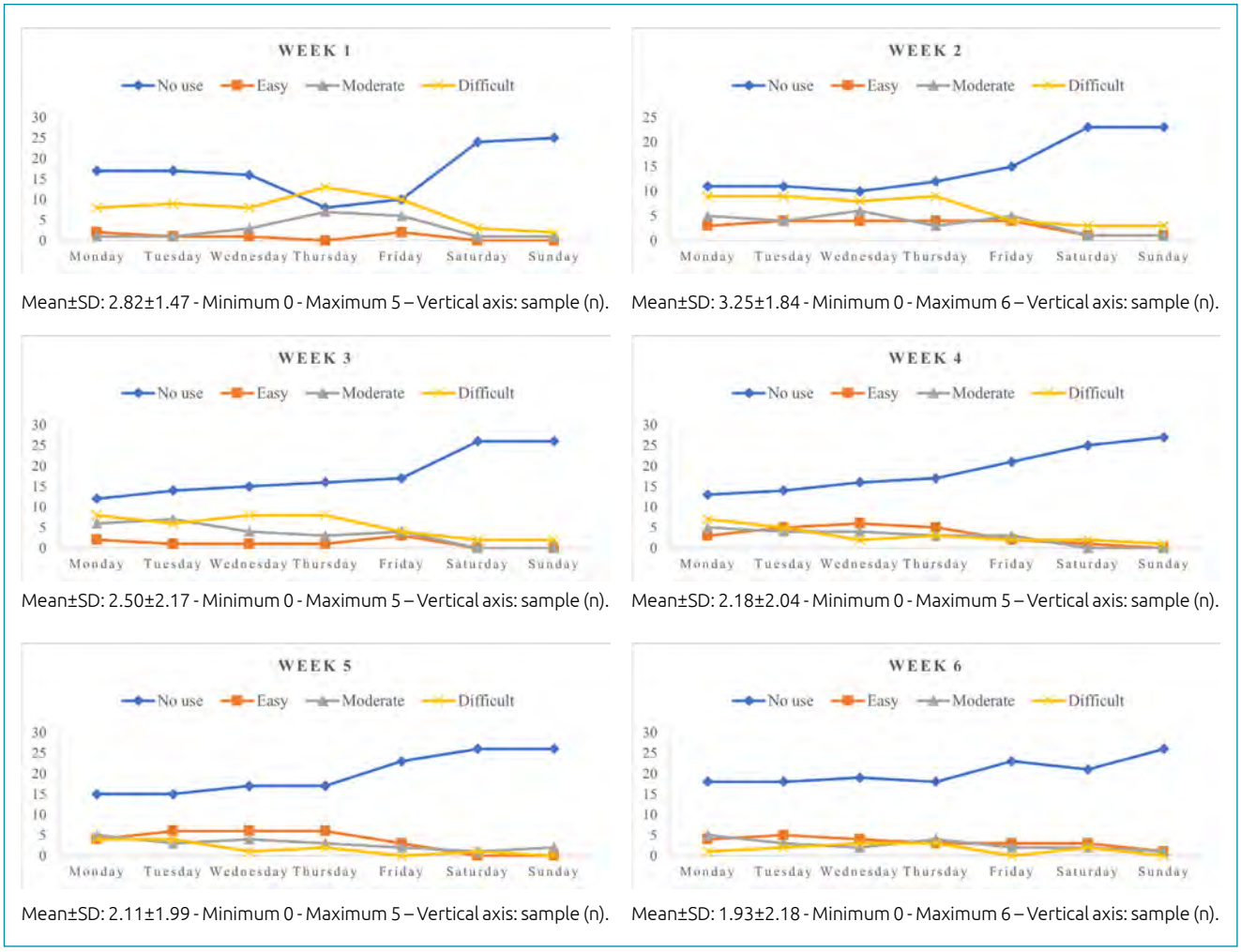

Figure 1. Daily perceived exertion ratings on the Borg Scale for 6 weeks.

Table 1. Comparison of body composition variables and total sleep time before and after using the mobile application.

Variables	Before using the mobile application (n=28)	After using the mobile application (n=28)	p-value[a]
Weight, kg	66.67±14.75	67.82±15.32	**0.004**
Height, m	1.49±0.10	1.50±0.10	**0.001**
Height z-score	1.08±1.40	1.06±1.38	0.70
BMI, kg/m^2	29.62±4.84	29.80±5.11	0.28
BMI z-score	2.26±0.38	2.25±0.41	0.50
Waist circumference, cm	86.99±9.40	86.66±9.85	0.65
Total fat mass, kg	22.58±7.60	22.57±7.48	0.99
Total lean mass, kg	44.08±8.20	45.42±9.20	**0.007**
Body fat percentage, %	33.16±5.38	32.62±5.19	0.31
Sleep time, hours/day	9.51±1.21	9.14±1.31	0.26

BMI: body mass index [a]Paired t-test. Data presented as mean±standard deviation.

Table 2. Sleep quality before and after using the mobile application.

			Trouble sleeping after using the application		Total	p-value[a]
			Yes	No		
Trouble sleeping before using the application	Yes	n (%)	2 (22.2)	7 (77.8)	9 (100.0)	0.016
	No	n (%)	0 (0.0)	19 (100.0)	19 (100.0)	
			Insomnia after using the application		Total	p-value[a]
			Yes	No		
Insomnia before using the application	Yes	n (%)	1 (14.3)	6 (85.7%)	7 (100.0)	0.031
	No	n (%)	0 (0.0)	21 (100.0)	21 (100.0)	

[a]Exact McNemar test.

The lower than recommended adherence to the application can be explained by the subjects' resistance to begin physical activities, the level of difficulty of the exercises, and a disturbed routine. The low level of interest may also be due to preferences for browsing or using other digital platforms[11]. It has been found that personalizing the frequency and intensity of the exercises, setting goals, knowing the benefits of exercise, and self-monitoring in real-time can promote adherence. Furthermore, encouragement from family members and healthcare professionals also plays an important role to promote children practicing physical activity[5,11].

In this study, the decline in the use of the application on weekends suggests little family involvement in the development of healthy habits in children. Studies have shown a reduction in physical activity and an increase in sedentary behavior in obese parents and children on weekends, which indicates a difficulty in promoting games that are fun and stimulating for a child's healthy development[12,13]. It must be noted that family support is crucial for the development of healthy behaviors[14].

The decrease in the level of difficulty and effort required to perform the proposed exercises can be explained by the continuous use of the application. Contact with the researchers via WhatsApp Messenger® may also have facilitated the patient's compliance with the recommended exercises. The study suggests that parents have a positive outlook towards messages that are clear and objective, and which contain practical instructions[14].

As for body composition, there was a statistically significant increase in weight, height, and lean mass but no significant changes in BMI and BMI z-scores. The mean waist circumference, total fat mass, and body fat percentage were lower after the evaluations, but there were no statistical differences. We noted that the use of the application, even for just ten minutes a day for six weeks, generated positive results. The increase in physical activity led to an increase in energy expenditure and possibly reduced adiposity, since muscle activity is the primary form of energy consumption. However, the rapid increase in height may be related to weight gain, resulting in a decreased BMI[15].

The average sleep time after the intervention was between nine and eleven hours, which is appropriate for this age group[16]. The patients had less trouble sleeping and less insomnia, which highlighted the effects of physical activity on sleep quality. Children who sleep less than nine hours a day and have poor sleep quality are more likely to increase their caloric intake and sedentary activities, which consequently leads to an increase in adiposity[17]. Nevertheless, physical activity can have a direct impact on these harmful habits and promote health benefits[18].

Aside from regular contact with the researcher, the positive changes may also be related to consistent follow-up care at the multidisciplinary clinic. It has been found that lifestyle changes will have a positive impact only when they are consistently maintained in the long run, which indicates the importance of creating intervention strategies that can be incorporated gradually and engagingly[19].

The strengths of the study included the use of a free and user-friendly mobile application to promote the health of patients in follow-up care, at a specialized outpatient clinic that was difficult to access, under remote supervision of researchers. It is important to note that during the pandemic, when social distancing was a safety measure, mobile applications emerged as a potential tool for healthcare professionals to help children remain active.

One of the limitations of the study was that the application was not specific to the age group of the study; it did not have specific goals, nor was it very playful. In addition, the sample size was small. These reasons may explain patients' low adherence to the use of the application and the progressive decline in its use during the six weeks of the intervention, especially on weekends. Those who followed the recommendations benefited by being able to perform the exercises with less effort, increasing their lean mass, and improving their sleep quality. We

believe that playful applications with an interactive and "gamified" interface could generate better results for this age group.

CONCLUSIONS

The patients' use of the physical activity application led to an improvement in their quality of sleep and an increase in their lean mass, while there were no significant changes in BMI z-scores, waist circumference, and body fat percentage.

AUTHORS´ CONTRIBUITIONS

FF: Conceptualization, Data curation, Research, Methodology, Project management, Writing – review and editing. **CCS:** Data curation, Formal analysis, Software, Writing – review and editing. **RTM:** Formal Analysis, Visualization. **MÂRGMA:** Formal Analysis (Leadership), Supervision (Leadership), Writing – review and editing (Leadership). **MPZ:** Formal Analysis (Leadership), Financing acquisition (Leadership), Supervision (Leadership), Writing – review and editing (Leadership).

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Platelet/Lymphocyte ratio independently predicts the outcome of severe aplastic anemia patients treated with antithymocyte globulin

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SUMMARY

OBJECTIVE: The aim of this study was to determine the clinical role of platelet/lymphocyte ratio and neutrophil/lymphocyte ratio in severe aplastic anemia patients treated with antithymocyte globulin.

METHODS: The outcomes of consecutive severe aplastic anemia patients treated with rabbit or swine antithymocyte globulin plus cyclosporine (n=159, from January 2012 to December 2018) were analyzed retrospectively.

RESULTS: In a total of 159 patients, the actuarial 5-year survival rate was 85.6%. Low platelet/lymphocyte ratio (PLR≤55) was significantly associated with less complications at 1 month and 24 months after the antithymocyte globulin treatment (p=0.048 and 0.028, respectively). The univariate and multivariate analyses revealed that low platelet/lymphocyte ratio was an independent predictor of overall survival (p=0.03 and 0.04, respectively). Patients with low neutrophil/lymphocyte ratio (NLR≤0.18) had shorter survival time, but there was no significant difference (p=0.056). PLR was positively correlated with neutrophil/lymphocyte ratio (r=0.38, p<0.0001) and age (r=0.17, p=0.0379), while it was negatively correlated with IgG level (r=–0.18, p=0.0309). The ratio of CD4/CD8 was significantly higher in low platelet/lymphocyte ratio group (p=0.005).

CONCLUSION: The platelet/lymphocyte ratio reflects the immune abnormality of SAA. Notably, low platelet/lymphocyte ratio is an independently positive prognostic factor for severe aplastic anemia patients treated with antithymocyte globulin.

KEYWORDS: Anemia, aplastic. Antithymocyte globulin. Neutrophils. Platelet. Lymphocyte.

INTRODUCTION

Acquired aplastic anemia (AA) is primarily ascribed to activated T lymphocytes, which induce destruction to hematopoietic stem cells, while the antigenic exposure leading to the expansion of dysregulated $CD4^+$ T-cell populations[1]. For severe AA (SAA) patients, who are transfusion-dependent and in the absence of a human leukocyte antigen (HLA)-matched sibling, antithymocyte globulin (ATG) is recommended[2]. Young and less severe disease had a much higher probability of 10-year survival, but none of them significantly predicted response to ATG at 6 months[3]. Although patients with baseline absolute reticulocyte count (ARC) $\geq 25\times10^9$/L and absolute lymphocyte count (ALC) $\geq 1\times10^9$/L had a better response to ATG at 6 months, they did not significantly predict the overall survival

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(OS) in children[4]. Thus, how to predict the response and outcome of AA patients treated with ATG remained to be further investigated.

Further evidence indicated that autoimmune and inflammatory processes induced the apoptosis of $CD34^+$ progenitor cells, influencing the disease course as well as response rate to ATG in AA patients[5]. Platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) are novel markers of systemic inflammation, which have shown to be effective predictors of prognosis and therapy response in various immune diseases such as systematic lupus erythematosus and dermatomyositis[6,7]. In hematological disease, PLR and NLR were also relevant to poor prognosis in peripheral T-cell lymphoma and diffuse large B-cell lymphoma[8,9]. In this study, it was suggested that baseline PLR and NLR were associated with lymphocyte subsets. The ratio of CD4/CD8 was significantly higher in low PLR group. However, to the best of our knowledge, no study till date has investigated the association between PLR as well as NLR and the prognosis of SAA patients treated with ATG. In this study, we retrospectively analyzed 159 SAA patients treated with ATG and intended to assess the prognostic roles of PLR and NLR in treatment-naïve SAA cases.

METHODS

Study design

This study is to determine the clinical role of PLR and NLR in SAA patients treated with ATG.

Participants

The eligibility criteria were as follows:

1. newly diagnosed SAA patients older than 2 years of age;
2. patients treated with first-line ATG from January 2012 to December 2018 at Blood Diseases Hospital, Chinese Academy of Medical Sciences;
3. patients or legal guardians were informed of the study which was approved by the Institutional Committee for Medical Care and Safety, and therefore performed in accordance with Declaration of Helsinki.

All the data were collected through the follow-up in the outpatient department or phone call until December 2019.

Variables

The definition and disease severity of AA patients included were defined according to the Camitta criteria[10].

Two types of ATG regimens were included in this analysis:

1. rabbit ATG (rATG) (Thymoglobulin®, Genzyme, Sanofi Company, Cambridge, MA, USA) was administered at a dose of 1.97 mg/kg per day for 9 days;
2. swine ATG (sATG) (Wuhan Institute of Biological Products Co., Ltd., Wuhan, China) at a dose of 20–30 mg/kg per day for 5 days, as previously described[11]. Cyclosporine was administered at a dose of 5 mg/kg per day (3 mg/kg per day for children under 18 years of age), which was adjusted according to the serum creatinine levels.

Data sources/measurement

Both PLR and NLR were calculated by dividing the platelet count and absolute neutrophil count by the lymphocyte count, respectively. The data were collected at the time of diagnosis without transfusion of platelet and recombinant human granulocyte colony-stimulating factor (rhuG-CSF) treatment within 1 week.

Statistical methods

The optimal cut-off values for classifying NLR and PLR as low or high for the subsequent analysis were 0.18 and 55, respectively, which was determined using the receiver operating characteristic curve analysis for OS. The Mann–Whitney *U* test and χ^2 test were used to compare continuous and categorical variables, respectively. OS correlations were assessed using Kaplan–Meier curve with log-rank statistics. Furthermore, the univariate and multivariate Cox regression analyses were performed to calculate their respective hazard ratios (HRs) and 95% confidence intervals (CIs). The statistical analyses were performed using SPSS software (version 22; IBM Corp., Armonk, NY, USA). $p<0.05$ was considered as statistically significant.

RESULTS

Participants

Between 2012 and 2018, 159 SAA patients treated with ATG were included for the evaluation in this study.

Descriptive data

The characteristics of all the study participants were included in Table 1.

Outcome data

The number of patients who died within 3 months from the ATG treatment (early mortality) was 6 (3.8%), and 14 (9.6%) patients died beyond day +90 (late mortality). The causes of early mortality were infections (n=5) and hemorrhage (n=1).

Table 1. Clinical characteristics of 159 SAA patients.

Factors	Values
Patients, n	159
Median age (years, range)	22 (3–57)
Age groups	
<20 years, n (%)	70 (44)
20–40 years, n (%)	68 (42.8)
>40 years, n (%)	21 (13.2)
Gender, n (%)	
Male	87 (54.7)
Female	72 (45.3)
Etiology, n (%)	
Idiopathic	156 (98.1)
Post-hepatitis	3 (1.9)
Severity, n (%)	
SAA	80 (50.3)
VSAA	79 (49.7)
Median follow-up after ATG (months), mean (range)	41 (1–92)
Peripheral blood counts	
Hb (g/L), (median, range)	30 (76–131)
PLT ($\times 10^9$/L), (median, range)	21 (1–115)
ANC ($\times 10^9$/L), (median, range)	0.43 (0.01–4.36)
ARC ($\times 10^9$/L), (median, range)	9.3 (0.54–128.9)
ALC ($\times 10^9$/L), (median, range)	1.35 (0.13–5.29)
NLR	
≤0.18, n (%)	49 (30.8)
>0.18, n (%)	110 (69.2)
PLR	
≤55, n (%)	140 (88.1)
>55, n (%)	19 (11.9)
PNH clone, n (%)	
Positive	25 (15.7)
Negative	134 (84.3)
ATG agent, n (%)	
rATG	98 (61.6)
sATG	61 (38.4)
Interval from diagnosis to ATG (days) (median, range)	32 (10–134)

SAA: severe aplastic anemia; VSAA: very severe aplastic anemia; PLT: platelet count; ANC: absolute neutrophil count; ARC: absolute reticulocyte count; ALC: absolute lymphocyte count; NLR, neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; PNH: paroxysmal nocturnal hemoglobinuria; rATG: rabbit antithymocyte globulin; sATG: swine antithymocyte globulin.

In this study, 38% (60/158) of patients showed complete and partial responses (CR and PR) within 3 months. At 6 months, the overall response rate (CR and PR) was 57.2% (83/145). Until the end of follow-up, the best response rate was 71.7% (114/144).

The strongest predictor of response was the severity of disease; the response rate was 25.3% at 3 months and 41.4% at 6 months in very severe AA (VSAA) patients compared with 50.6% at 3 months and 72% at 6 months in SAA patients (HR=0.3; p=0.001 and HR=0.3; p<0.001, respectively). The second prognostic factor was the diagnosis-to-treatment interval, 0–32 or >32 days from diagnosis; the response rates at 3 months were 46.9% and 28.6% (HR=2.2; p=0.018).

The most common complications after ATG treatment within 1 month were infection (25.8%) and hemorrhage (5.7%). Low PLR (≤55) predicted less complications after ATG treatment within 1 month and at 24 months: 30 versus 52.6% (p=0.048) and 4.2 versus 33.3% (p=0.028), respectively.

Main results

The platelet/lymphocyte ratio was positively correlated with NLR (r=0.38, 95%CI 0.23–0.50, p<0.0001) and age (r=0.17, 95%CI 0.01–0.31, p=0.0379). However, PLR was negatively correlated with IgG level (r=-0.18, 95%CI -0.33 – -0.02, p=0.0309).

There was a significant difference in lymphocyte subsets between low PLR group and high PLR (PLR>55) group (Figure 1). The ratio of lymphocyte/nucleated cell, $CD3^+CD4^+$ cell/lymphocyte, $CD19^+$ cell/lymphocyte, and CD4/CD8 was found to be significantly higher in low PLR group (78.5 versus 57.8%, p<0.0001; 42.2 versus 31.3%, p=0.001; 14.3 versus 8.5%, p=0.028; 1.7 versus 1.1, p=0.005, respectively), while the ratio of $CD3^+CD8^+$ cell/lymphocyte and $CD3^-CD56^+$ cell/lymphocyte tended to be higher in high PLR group (34.2 versus 28.7%, p=0.023; 15.0 versus 7.3%, p<0.0001, respectively). Only the ratios of lymphocyte/nucleated cell and $CD3^+CD4^+$ cell/lymphocyte were significantly higher in NLR≤0.18 group (88.6 versus 70.1%, p<0.0001; 45.3 versus 38.6%, p=0.005, respectively). There was no significant difference between NLR≤0.18 group and NLR>0.18 group in other lymphocyte subsets.

With a median follow-up of 41 months (range: 0–92 months), the OS rate at 5 years was 85.6±3.3% (Figure 2A). Posttreatment status at 3 months strongly predicted the long-term survival; the 5-year OS rates of patients with response and no response were 96.5±2.4% and 75.3±5.4% (p=0.002); low PLR predicted a higher 5-year survival (87.0±3.2% *versus* 71.8%±10.7%, p=0.03) (Figure 2C); patients with ALC >1×10^9/L at diagnosis had significantly higher 5-year OS (90.1±3.2%), as compared with patients with ALC ≤1×10^9/L (74.4±6.8%, p=0.018); the severity of disease was also predictive, with a 5-year survival of 90.7±3.7% and 79.1±5%

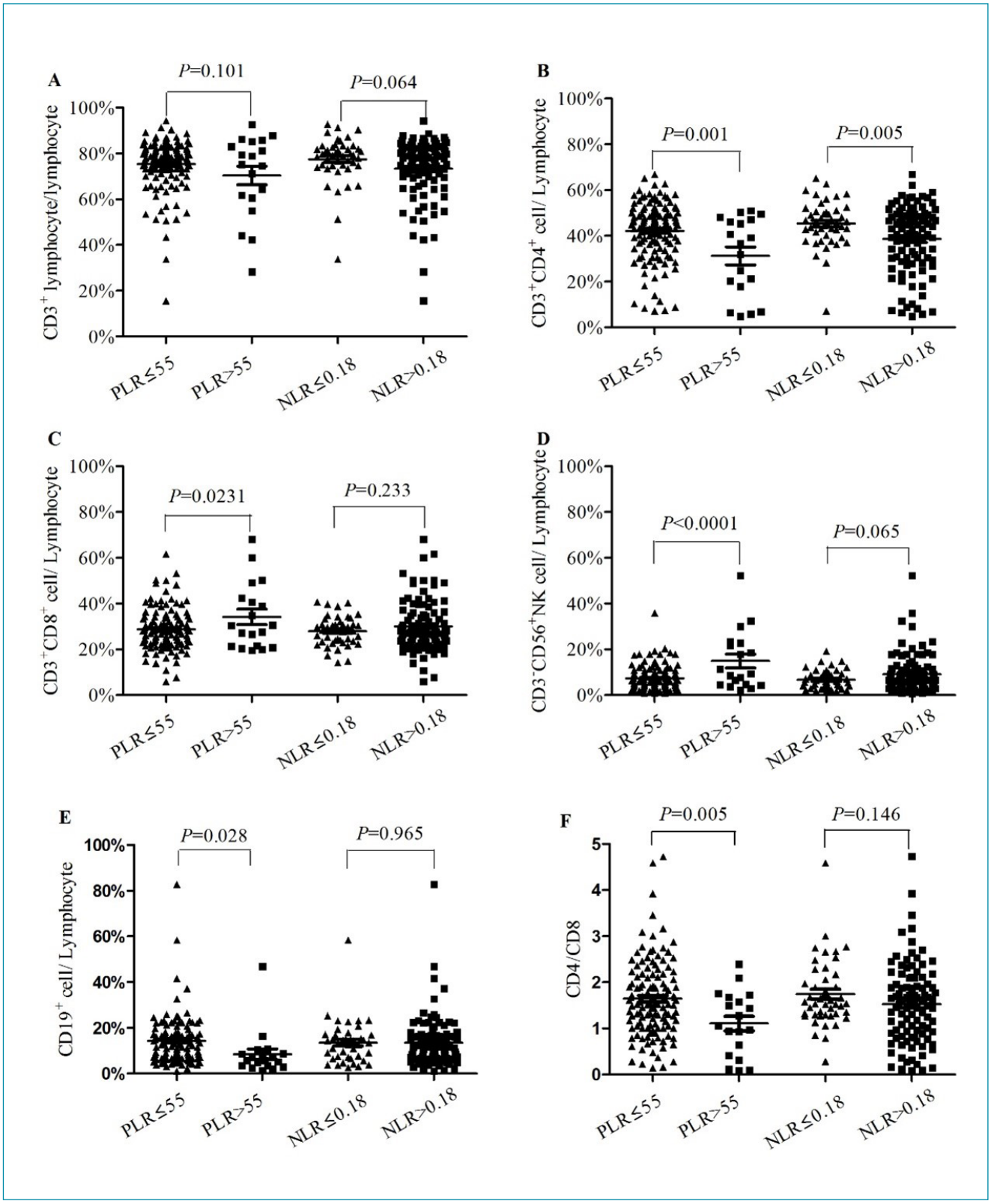

Figure 1. Baseline PLR and NLR correlated to lymphocyte subsets. Neither PLR nor NLR correlated with the percentage of $CD3^+$ lymphocyte/lymphocyte (A). Patients with PLR≤55 had higher $CD3^+CD4^+$ lymphocyte/lymphocyte (B), lower $CD3^+CD8^+$ lymphocyte/lymphocyte (C), lower $CD3^+CD56^+$ NK cell/lymphocyte (D), higher $CD19^+$ cell/lymphocyte (E), and higher CD4/CD8 (F). PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

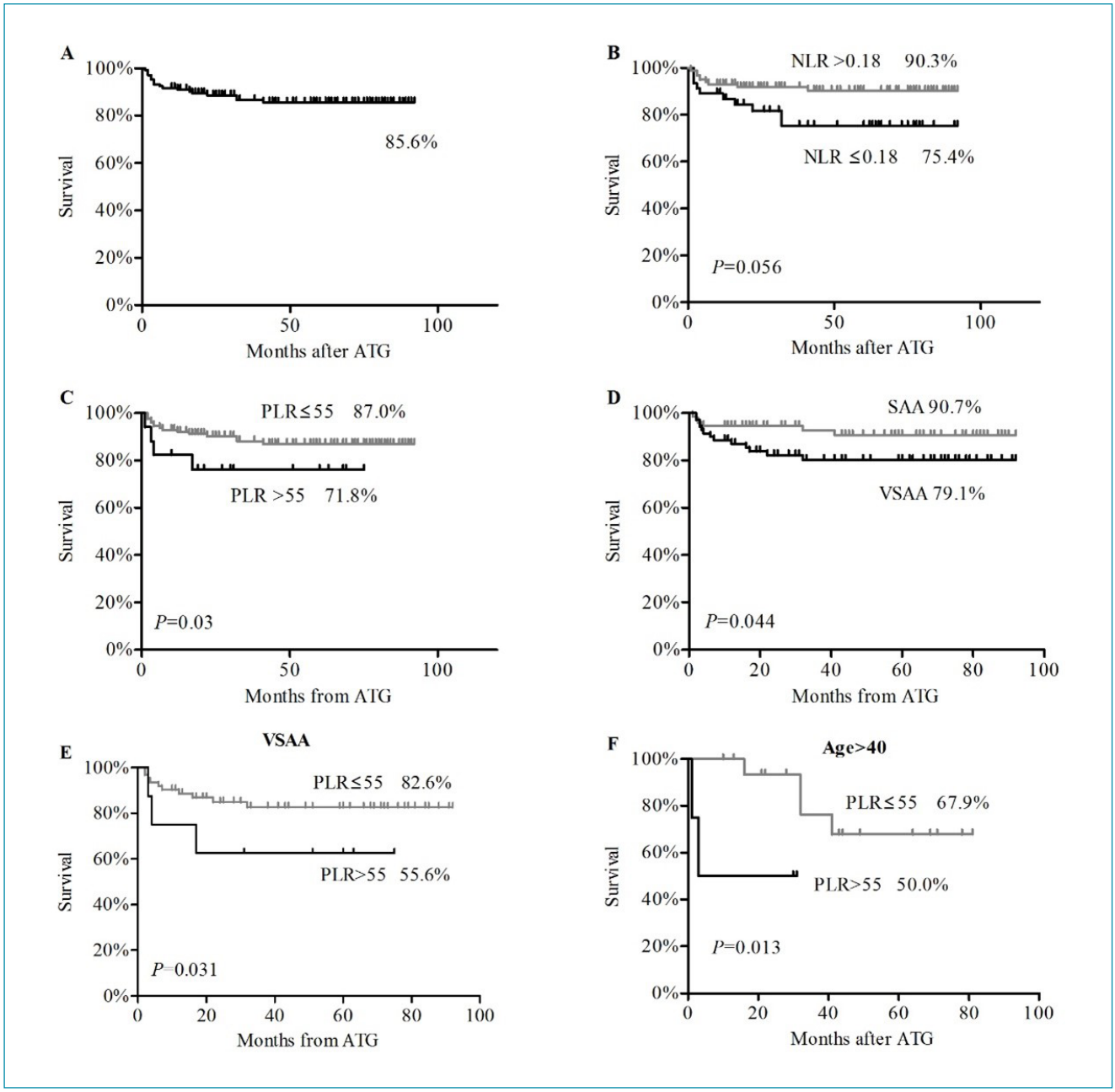

Figure 2. Kaplan–Meier curves of overall survival. (A) Five-year overall survival of 159 patients with AA treated with ATG. (B–D) Survival of patients stratified according to NLR, PLR, and severity of disease: a significant positive effect was seen for patients with PLR ≤55 and SAA patients. (E and F) Comparison of the impact of PLR on overall survival according to the severity of disease and age separately. AA, aplastic anemia; ATG, antithymocyte globulin; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SAA, severe aplastic anemia; VSAA, very severe AA.

for SAA and VSAA patients (p=0.044) (Figure 2D), respectively. However, age, NLR, ARC, and paroxysmal nocturnal hemoglobinuria (PNH) clone did not significantly affect the OS.

As the severity of disease was a significant predictor of prognosis, we classified the patients into two groups: SAA and VSAA. Low PLR (PLR ≤55) was still a positive predictor in VSAA group (Figure 2E). Although PLR was positively correlated with age as described earlier, low PLR still predicted the better prognosis in patient group aged >40 (Figure 2F).

Since PLR was significantly correlated with age, both ALC and NLR factors were excluded in the multivariate analysis. Factors such as gender, PLR, ARC, PNH, and the severity of disease were included. As expected, PLR was the independent predictive factor for patients treated with ATG [HR=0.34, (95%CI 0.12–0.95), p=0.04].

DISCUSSION

Antithymocyte globulin (ATG) is often recommended as a first-line therapy for AA patients who lack a matched sibling donor, especially for SAA and VSAA patients. In this study, the 3-month (37.7%), 6-month (52.2%), and best response rates (71.7%) were higher than the previous reports[12,13], respectively, due to our optimized ATG therapy[11]. The 5-year survival and early mortality for AA patients with ATG were 85.6 and 3.8%, respectively, and in our center, the results were compared with those reported in the earlier foreign studies[3,14].

In this cohort, we determined that the patients with diagnosis-to-treatment interval <32 days had better response to ATG at 3 months than those with longer ones (46.9 versus 28.6%, p=0.018). Response to ATG in VSAA patients at 3 months was worse than that of SAA patients (25.3 versus 50.6%, p<0.001). But there were no significant difference in other factors such as age, ARC, ALC, NLR, and PNH clone. These results were consistent with the long-term follow-up consequences of a multicenter study in Europe and Asia[3].

Various studies had investigated the risk factors that predicted the OS: age, the diagnosis-to-treatment interval, severity of AA, ALC, ARC, PNH clone, and telomere length[3,12,14-16]. In consistent with the previous studies[3,4], we determined that ALC >1×10^9/L and SAA were correlated with longer survival. Although an evidence suggested that a minor population of PNH-type cells and ARC was the positive predictors of ATG[16,17], other studies showed that there was no difference in outcome related to these factors[4,18]. Thus, until now, there are no sufficient practical and reliable factors to predict the outcomes of ATG therapy.

At present, this is the first study to investigate the relationship between PLR as well as NLR and the outcomes of AA patients treated with ATG. More importantly, we found that low baseline PLR level (PLR≤55) in SAA patients was an independent positive prognostic factor (HR=0.34, p=0.04). Since PLR and NLR were the novel markers of systemic inflammation, we determined that baseline PLR and NLR were associated with lymphocyte subsets in our data. Besides, PLR was positively correlated with NLR and age, however it was negatively associated with IgG level.

Lymphocytes play a central role in the pathogenesis of AA. Activated T lymphocytes mediate autoimmunity through producing pro-inflammatory cytokines and thereafter lead to bone marrow destruction[1]. ATG is a purified antibody, which can ablate abnormal T lymphocytes as well as reverse the "immune-mediated" pathogenic mechanisms in AA[19]. As expected, we demonstrated that the patients with low PLR have better prognosis. It is worth to mention that these patients had higher ratio of CD4/CD8. Indeed, $CD4^+$ cells played an important role in the pathogenesis of AA, especially Th1 cells. A polarization of $CD4^+$ cells toward a type-1 response leads to the activation of cytotoxic $CD8^+$ cells and finally to hematopoietic stem cell destruction[20]. Thus, we hypothesized that PLR as well as NLR predicted the abnormal quality and function of lymphocyte subsets, and low PLR was more likely correlated with severe immunity of this disorder. Therefore, it is plausible and necessary to include PLR and NLR into factors predicting the outcomes of ATG.

There were some limitations in this study. First, this study was based on the retrospective data collection and completed at a single center. Second, the patients in this study were included with rATG and sATG. However, there was no significant difference between them as studied previously[21].

Despite the above-mentioned limitations, this study had some clinical implications. First of all, this is the first study that evaluates the role of PLR and NLR in the treatment of SAA. Second, we found that PLR could predict initial response to ATG treatment of SAA patients. Low PLR was a positively significant predictor of better response, fewer complications, and longer survival after ATG. Furthermore, PLR and NLR were closely related to lymphocyte subsets, which reflected immune abnormality in SAA patients. This finding might guide clinicians to judge the treatment response of SAA patients to ATG earlier and determine better therapy scheme, which has the meaningful and useful implications for clinical practice. Finally, PLR can be acquired at low cost in clinical practice, so it has potential to be a simple, convenient predictive, and stratification factor to assist with clinical decision-making for SAA patients.

CONCLUSION

The platelet/lymphocyte ratio reflected immune abnormality in SAA patients, and a low PLR was an independently significant predictor of SAA patients treated with ATG.

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ETHICAL APPROVAL

The retrospective protocol of this study was approved by the ethics review board of Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science and Peking Union Medical College (Grant No. HG2020016-EC-1).

AUTHORS' CONTRIBUTIONS

PD: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MG:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **YZ:** Conceptualization, Writing – Review & Editing. **XL:** Data Curation, Formal Analysis, Writing – Review & Editing. **XR:** Data Curation, Formal Analysis, Writing – Review & Editing. **HW:** Data Curation, Formal Analysis, Writing – Review & Editing. **JH:** Data Curation, Formal Analysis, Writing – Review & Editing.

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ORIGINAL ARTICLE
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The evaluation of patients with essential thrombocythemia in terms of risk of thrombosis

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SUMMARY

OBJECTIVE: The aim of this study was to compare the incidence of factors associated with an increased risk of thrombosis in patients with essential thrombocythemia.

METHODS: A total of 200 patients followed-up in our unit with a diagnosis of essential thrombocythemia in 13 years were analyzed retrospectively.

RESULTS: Of the study participants, 60.5% were females and 39.5% were males, with an overall mean (±SD) age of 54.93 (±14.21) years. In 119 patients, Janus Kinase 2 was positive with 56.3% of cases. When two patient categories were defined as those with or without history of thrombosis, no significant differences were found in terms of Janus Kinase 2 positivity, mean age, as well as white blood cells and platelet counts ($p>0.05$). Also, no significant differences in thrombotic event incidence were found between patient categories defined on the basis of cut-off values for white blood cells (cut-off values of $15\times10^3/mm^3$ and $8.7\times10^3/mm^3$) and platelets (cut-off values of $1500\times10^3/mm^3$) ($p>0.05$).

CONCLUSION: Although our results are generally in line with the published data, some divergence from previous results has been observed with respect to risk factors for thrombotic events. Absence of a correlation between leukocytosis and thrombosis may be related with the significant decline in white blood cells after treatment. Also, a significant reduction in platelet counts occurring in association with treatment is linked with a lowered incidence of thrombosis. Janus Kinase 2-positive patients had a similar thrombosis frequency with that reported in the literature.

KEYWORDS: Thrombocythemia, essential. Janus kinase 2. White blood cell count. Platelets. Thrombosis.

INTRODUCTION

Essential thrombocythemia (ET) is a clonal stem cell disorder that is characterized by isolated thrombocytosis and thromboembolic complications, and it exhibits phenotypic and pathogenetic resemblance with other myeloproliferative neoplasms (MPNs), particularly with polycythemia vera (PV) and primary myelofibrosis (PMF). Our knowledge on the pathogenesis of this disorder remained relatively limited until 2005, when acquired JAK2 mutations were reported in approximately 50% of ET patients and in great majority of PMF patients[1,2]. Nearly 55% of ET patients have JAK2V617F mutations, while JAK2 exon 12 mutations are rare[3]. MPL mutations are seen in approximately 4% of ET patients[4]. MPL mutations cluster at exon 10, most frequently at MPL W515LVK[5]. Presence of JAK2 mutations has been associated with an increased risk of arterial thrombosis and lower post-ET MF risk in ET patients[6].

Several parameters have been used to distinguish higher risk groups from lower risk groups among ET patients, and these

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include age, white blood cells (WBC) count, platelet count, and history of thrombosis[7]. An increased incidence of thrombotic events has been reported in patients over 60 years of age and/or in those with leukocytosis and thrombocytosis.[8,9,10] JAK2 mutations have been associated with an increased risk of thrombosis, and JAK2 homozygous status was found to increase the risk of vascular complications[11,12].

This study was undertaken to compare the frequency of factors associated with an increased risk of thrombosis in ET patients.

METHODS

Selection of study patients

This retrospective study was undertaken with the participation of 200 patients followed-up and treated with a diagnosis of ET between 2000 and 2013 at the Hematology Unit, Ankara Research and Training Hospital, Turkey. Hemoglobin (Hb), WBC, platelet, and cytogenetic test results at baseline (pre-treatment) were recorded. At the last assessment time-point (post-treatment), Hb, WBC, and platelets were remeasured. Age, gender, and history of thrombosis and/or bleeding were also recorded in the case data form.

Statistical analysis

All the data obtained throughout this study were analyzed using "Statistical Package for the Social Science" (SPSS) version 11.5 for Windows. Descriptive statistics were expressed as frequency, percent distribution, and median values (min–max). Pre- and post-treatment complete blood count parameters were compared with Wilcoxon signed-rank test, while the comparison of WBC between those with or without the history of thrombosis was performed with Mann–Whitney U test. Categorical variables were compared with Fisher's exact test and Yates χ^2 test. The value $p<0.05$ was considered statistically significant.

RESULTS

The mean age of study participants (n=200) was 54.93±14.21 years. A total of 39.5% of the patients were male and 60.5% female. JAK2 analysis was available for 119 patients. JAK2 results of 56.3% of patients were positive and 43.7% negative. Pre-treatment WBC, Hb, and platelet counts were significantly higher than post-treatment counts ($p<0.001$, for all comparisons). The comparison of WBC, Hb, and platelet counts measured at different time points was shown in Table 1. A total of 13.5% of patients had a history of thrombosis, while 1% had bleeding, and 1.5% had both thrombosis and bleeding. About 3.5% of patients had myocardial infarction (MI), 6% cerebrovascular events (CVE), 1.5% portal venous thrombosis, 1.5% deep venous thrombosis (DVT), 18.5% peripheral arterial thrombus, 0.5% pulmonary embolism (PTE), 1.5% GIS bleeding, and 0.5% had abdominal aortic thrombosis. The frequency of thrombotic events in JAK2-positive patients was similar to that in JAK2 negative patients (p=0.540). Patients with or without history of thrombosis did not differ significantly in terms of age (p=0.125) as well as pre-treatment WBC (p=0.442) and platelet (p=0.804) counts. Comparison of age, WBC, and platelets between patients with or without thrombosis is shown in Table 2. Also, no statistically significant differences were found between patients with or without a history of thrombosis with respect to patient categories defined on the basis of age (p=0.199), pre-treatment WBC (p=0.121 for a cut-off value of $15\times10^3/mm^3$ and p=0.357 for a cut-off value of $8.7\times10^3/mm^3$), and platelet count (p=0.508). Distribution of patients with or without history of thrombosis with respect to patient categories defined on the basis of age, WBC, and platelet count is shown in Table 3.

DISCUSSION

The clinical course of ET is characterized by microcirculatory disorders and increased risk of arterial and venous thrombosis[13]. In this study, our aim was to evaluate the factors that increase the risk of thrombosis as well as the history of thrombosis and/or bleeding in a sample of ET patients.

Table 1. Comparison of WBC, Hb, and platelet counts measured at different time points.

	Time points										p
	Pretreatment					Posttreatment					
	Mean	SS	Median	Min	Max	Mean	SS	Median	Min	Max	
WBC ($\times10^3/mm^3$)	12.6	7.7	12	4.1	80.9	7.3	2.4	7.3	2.8	21.8	<0.001
Hb (g/dL)	13.6	2.1	13.5	7.5	18.4	12.8	1.88	12.8	7.8	17.4	<0.001
Platelet ($\times10^3/mm^3$)	1074	446	997	514	4213	431	154	431	98	1150	<0.001

WBC: white blood cells; Hb: hemoglobin.

Table 2. Comparison of age, WBC, and platelets between patients with or without thrombosis.

	History of thrombosis										p
	Yes (n=36)					No (n=134)					
	Mean	SS	Median	Min	Max	Mean	SS	Median	Min	Max	
Age (years)	58.1	13.9	58.5	20	83	54.2	14.2	55	17	80	0.125
WBC ($\times 10^3/mm^3$)	13.6	7.3	12.4	4.1	36.8	12.4	7.8	11.6	4.2	80.9	0.279
Platelets ($\times 10^3/mm^3$)	1030	330	1000	562	1985	1083	468	978	514	4213	0.804

WBC: white blood cells.

Table 3. Distribution of patients with or without history of thrombosis with respect to patient categories defined on the basis of age, WBC, and platelet count.

		History of thrombosis				p
		Yes (n=36)		No (n=134)		
		n	%	n	%	
Age (years)	≥60	17	47.2	56	34.1	0.199*
	<60	19	52.8	108	65.9	
WBC ($\times 10^3/mm^3$)	≥15	10	27.8	25	15.2	0.121*
	<15	26	72.2	139	84.8	
WBC ($\times 10^3/mm^3$)	>8.7	29	80.6	117	71.3	0.357*
	≤8.7	7	19.4	47	28.7	
Platelets ($\times 10^3/mm^3$)	≥150000	3	8.3	21	12.8	0.580**
	<150000	33	91.7	143	87.2	

WBC: white blood cells. *Yates χ^2 test; **Fisher's exact test.

In a study, the reported rate of JAK2 mutation positivity was 54%, while Duletic et al. reported a positivity rate of 58%[14,15]. The observed JAK2 positivity rate among our clinical sample was 56.3%.

While 26% of the ET patients in the study by Duletic et al. had vascular events, the reported rates of hemorrhage and thrombosis in the study by Chou et al. were 18.5% and 19.2%, respectively, with 2.1% of the patients having a history of hemorrhage prior to diagnosis[14,16]. In another study, 19% of the patients had thrombosis and 6% had bleeding at the time of follow-up, while 4% of the patients had MI, 4% had CVE, 1% had peripheral arterial thrombus formation, <1% had PTE, and 3% had portal venous thrombosis[5,17]. In this study, 13.5% of the subjects had a history of thrombosis, 1% had bleeding, and 1.5% had both thrombosis and bleeding. Also, history of MI, CVE, portal venous thrombosis, DVT, peripheral arterial thrombus formation, abdominal aortic thrombus formation, PTE, and GIS bleeding was present in 3.5, 6, 1.5, 1, 18.5, 0.5, 0.5, and 1.5%, respectively.

Risk grading systems have been proposed for ET patients to assist in predicting the risk of thrombotic complications[18]. Risk factors that utilized to define risk categories in ET patients (low, 0 risk factor; high, 1 or 2 risk factors) include age, WBC count, platelet count, and history of thrombosis[7].

In the multicenter retrospective analysis of Turkish patients, 708 patients who were diagnosed between 1987 and 2014, 55.1% of all patients had ET. JAK2 mutation was found positive in 51.5% of patients with ET. At diagnosis, thrombosis was observed in 15.12% and bleeding occurred in 9% of ET patients. The incidence of JAK2 mutation, the history of thrombosis, and the median age at diagnosis were lower than in the literature[19]. JAK2 mutation, observed in 50–60% of patients with ET, has been an independent risk factor for thrombosis, but less is known about the underlying mechanism of this relation[20]. However, in this study, patients with JAK2 positivity did not exhibit a significant increase in thrombotic events as compared with patients who were JAK2 negative. The main limitation of this study is the retrospective and observational data collection techniques, which restricts making causal assumptions.

Advanced age is an important risk factor for thrombosis, with patients over 60 years of age having an increased occurrence of thrombotic events[8]. Although ET patients

with thrombotic events were slightly older than those without such events, the difference did not reach statistical significance in our study.

Previous research has provided evidence for an increased risk of thrombosis in ET patients with leukocytosis[8,9]. WBC count higher than $8.7\times10^3/mm^3$ or higher than $15\times10^3/mm^3$ was proposed to represent an independent risk factor for thrombotic events[17]. Although ET patients with a history of thrombosis had higher WBC counts than those without such a history, the difference was insignificant. Therefore, our results suggest that no associations may be present between thrombotic event frequency and the two separate cut-off values for WBC. The absence of a correlation between leukocytosis and thrombosis may be related to the significant reduction in WBC counts with treatment in our patients. In the last decade, several studies have investigated the association between leukocytosis and risk of thrombosis in patients with MPN, but the conclusions were not univocal. Furthermore, even in studies concluding that leukocytosis was associated with thrombosis, no consensus was found on the numerical cut-off that should be used to define leukocytosis[21].

Another important consideration in reducing the risk of thrombosis involves the prevention of thrombocytosis[22]. Platelet count of $<1000\times10^3/mm^3$ in a patient over 60 years of age or a platelet count $\geq1500\times10^3/mm^3$ in those less than 60 years of age may be considered an indication for the use of agents that reduce the number of platelets[10].

The hypercoagulability state is a condition that may induce the thrombosis phenomenon. The markers of this state were identified in patients who received estrogen associated with progestagens. Furthermore, patients who received oral estrogen plus medroxyprogesterone showed a decrease in antithrombin III, which is a risk factor for thrombosis. Therefore, this association may lead to a procoagulant state in ET patients who received estrogen plus medroxyprogesterone[23]. Also, the inflammatory changes are part of coronavirus disease 2019 (COVID-19) pathophysiology and this might generate a higher thromboembolic risk in patients using combined hormonal contraception and menopausal hormone therapy. The thrombosis risk of ET patients affected by COVID-19 using combined hormonal therapy should also be evaluated in this respect[24].

Our results are in disagreement with the previous reports in terms of the incidence of thrombotic events in patients with leukocytosis, increased platelet count, or JAK2 positivity. The absence of a correlation between leukocytosis and thrombosis may be related to the significant reduction in WBC counts with treatment in our patients. Similarly, significant reductions in platelet counts that achieved by treatment have been associated with reduced frequency of thrombosis. JAK2 mutations could be evaluated in only 119 of our patients due to technical constraints between the years 2000 and 2006. In this regard, the inconsistency between the previous reports and this study in terms of the thrombotic events in JAK2-positive patients may be related with the small sample size.

CONCLUSION

The thrombo-hemorrhagic events occur in patients with ET. JAK2 mutation, leukocytosis, and thrombocytosis are associated with a high risk of thrombosis. We concluded that the effective control of WBC and platelet counts can reduce the risk of thrombosis.

AUTHORS' CONTRIBUTIONS

CS: Writing – Review & Editing. **AG:** Investigation. **GA:** Data Curation. **YK:** Resources. **FC:** Methodology. **SD:** Validation. **GO:** Supervision.

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ORIGINAL ARTICLE
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Relations of heart-type and brain-type fatty acid-binding proteins with postoperative cognitive dysfunction in elderly patients undergoing spinal surgery

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SUMMARY

OBJECTIVE: The aim of this study is to analyze the relations of heart-type fatty acid-binding protein (H-FABP) and brain-type fatty acid-binding protein (B-FABP) with postoperative cognitive dysfunction (POCD) in elderly patients undergoing spinal surgery.

METHODS: One hundred and twenty-five patients who underwent spinal surgery were enrolled in this study. According to whether patients had POCD within 5 days after surgery, the participants were divided into POCD group and non-POCD group. Before surgery and 6 h after surgery, the serum H-FABP and B-FABP contents were detected.

RESULTS: There were 33 (26.4%) patients in POCD group, and 92 (73.60%) patients in non-POCD group. After surgery, the serum H-FABP and B-FABP contents in POCD group were significantly higher than those before surgery, respectively ($p<0.05$), and those in non-POCD group were significantly lower than those before surgery, respectively ($p<0.05$). After surgery, the serum H-FABP and B-FABP contents in POCD group were significantly higher than those in non-POCD group, respectively ($p<0.05$).

CONCLUSION: The serum H-FABP and B-FABP contents are positively related to the occurrence of POCD in elderly patients undergoing spinal surgery.

KEYWORDS: H-FABP. B-FABP. Postoperative cognitive dysfunction. Elderly patients. Spinal surgery.

INTRODUCTION

With the increase of elderly patients, the brain dysfunction that appears after general anesthesia is receiving more and more attention[1]. The neurocognitive changes related to surgery and anesthesia mainly include postoperative delirium and postoperative cognitive decline[2]. Although there is some overlap area, there are still differences in the occurrence time and clinical manifestations[3]. Complications of the central nervous system after surgery in the elderly patients are manifested as confusion, anxiety, personality changes, and memory impairment. These changes in personality, social ability, and cognitive ability and skills after surgery are called postoperative cognitive dysfunction (POCD)[4]. POCD is one of the common complications in elderly patients that may lead to delayed rehabilitation[5]. Early and accurate prediction of the occurrence of POCD is the key to prevention and control of POCD[6].

Fatty acid-binding protein (FABP) is a group of low-molecular weight proteins existing in cytoplasm. FABP is distributed in the tissues with active fatty acid metabolism and has the function of binding fatty acids and regulating cell metabolism. There are many types of FABP[7]. The study has found that the serum heart-type FABP (H-FABP) and brain-type

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FABP (B-FABP) levels have high susceptibility for judging the brain injury[8]. Kok et al.[9] have studied the POCD in patients receiving heart surgery and they found that in patients with POCD, the serum B-FABP level 24 h after surgery is higher than that before surgery. Therefore, we hypothesized that the serum H-FABP and B-FABP were related with POCD in elderly patients undergoing spinal surgery. This study was designed to analyze the relations of serum H-FABP and B-FABP levels with POCD in elderly patients undergoing spinal surgery, in order to provide a scientific basis for the prediction of POCD in these patients.

METHODS

Patients

One hundred and twenty-five patients who underwent spinal surgery in our hospital from January 2019 to October 2019 were enrolled. There were 67 males and 58 females. There were 75 cases of lumbar spine surgery (among them, 25 cases with one-segment lumbar surgery, 32 cases with two-segment lumbar surgery, and 18 cases with three- or more segment lumbar surgery) and 50 cases of cervical spine surgery (24 cases with anterior cervical surgery and 26 cases with posterior cervical surgery). According to whether patients had POCD, the participants were divided into POCD group and non-POCD group. The demographic and clinical data of patients were shown in Table 1. There was no significant difference between two groups (p>0.05). This study was approved by the Medical Ethics Committee of People's Hospital of Jiangbei District, and informed consent was signed with patients or their families.

Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: the patients aged ≥60 years, the ASA grade was I–III, and the estimated operation time was ≥2 h. Exclusion criteria were as follows: the patients had severe respiratory or circulatory diseases; the patients had acute and chronic infections before surgery; the preoperative biochemical examination revealed renal dysfunction (i.e., blood creatinine >177 μmol/L) or active liver disease; the patients had history of myocardial infarction and cerebral infarction; the patients had a history of mental nervous system or taking related drugs; and the preoperative Mini-Mental State Examination (MMSE) score showed illiteracy level <17 points, primary school level <20 points, middle school level <22 points, and college and higher level <24 points.

Anesthesia method

All patients were fasting for 8 h and drinking for 6 h before surgery. The patients were routinely monitored for aterial blood pressure (ABP), electrocardiogram (ECG), oxygen saturation (SpO_2), and bispectral index (BIS) after entering the room. Before the operation, a right internal jugular vein puncture was performed. The central venous catheter was routinely placed, and central venous pressure (CVP) was monitored. The anesthesia induction used 0.3 μg/kg sufentanil, 1.5–2.5 mg/kg propofol, and 0.6 mg/kg rocuronium bromide. A tracheal intubation anesthesia machine was used to control the breathing. The respiratory rate (RR) was 12 times/min, and the tidal volume (Vt) was 8–10 mL/kg. The anesthesia maintenance used target-controlled infusion of 2–4 μg/mL plasma concentration of propofol and intraoperative continuous pumping of rocuronium to maintain muscle relaxation. For intraoperative adjustment of

Table 1. Comparison of demographic and clinical data between postoperative cognitive dysfunction group and non-postoperative cognitive dysfunction group.

Variables	POCD group	Non-POCD group	t/χ^2	p
n	33	92		
Gender (n)			0.081	0.782
Male	17	50		
Female	16	42		
Age (years)	69.53±5.41	67.14±6.49	1.892	0.061
Body mass index (kg/m²)	22.26±2.29	21.97±2.75	0.522	0.603
Surgery type (n)			0.007	0.934
Lumbar spine surgery	20	55		
Cervical spine surgery	13	37		
Operation time (h)	2.89±0.82	2.62±0.83	1.58	0.117
Blood loss (mL)	339.84±26.51	331.42±25.03	1.631	0.105

the dose of anesthetic drugs to maintain BIS at 40–60, intraoperative blood pressure fluctuations should not exceed 30% of the basic value. All patients were given patient-controlled intravenous analgesia (PCIA) after surgery. Of note, 2 μg/kg sufentanil+1 μg/kg dexmedetomidine+15 mg tropisetron were diluted to 100 mL with normal saline. The parameters were set to a background dose of 2 mL/h, an additional dose of 2 mL each time, and a lock time of 20 min. After the operation, the patient was sent to post-anesthesia care unit (PACU), and the tracheal tube was removed after awakening. After the hemodynamics was stable and the steward score was >4 points, the patient returned to the ward.

Blood specimen collection and assessment of cognitive function

A 3 mL of central venous blood was collected before and after surgery. Cognitive function of patients was assessed with the MMSE scale on 1 day before surgery and 5 days after surgery. The total score was 30 points, and the normal value was 27–30 points. Those with a decrease of 2 points or more were considered to have cognitive decline and were diagnosed with POCD. The same number of patients with POCD as those with similar general conditions as sex, weight, ASA classification, blood loss, etc., were selected from patients who had never had POCD, and the serum H-FABP and B-FABP contents were determined together.

Detection of H-FABP and B-FABP

The ELISA method was used to determine the serum contents of H-FABP and B-FABP before and 6 h after surgery. The specific method was performed according to the kit instructions.

Statistical analysis

This study used SPSS 19.0 software for the statistical analysis. The enumeration data were presented as number and rate and were compared using χ^2 test. The measurement data were presented as mean ± SD and were compared using *t*-test. $p<0.05$ was considered as statistically significant.

RESULTS

Occurrence of POCD

A total of 33 (26.40%) patients (POCD group) developed POCD at 5 days after surgery. Among them, 15 cases did not recover at 3 days, 10 cases did not recover at 5 days, 7 cases occurred newly 1–3 days after operation, and 1 case occurred 3–5 days after operation. Other 92 (73.60%) patients (non-POCD group) did not develop POCD.

Comparison of serum H-FABP and B-FABP contents between POCD group and non-POCD group

Before surgery, the serum H-FABP and B-FABP contents in POCD group were significantly lower than those in non-POCD group, respectively ($p<0.05$). After surgery, each index in POCD group was significantly higher than that before surgery ($p<0.05$), and that in non-POCD group was significantly lower than that before surgery ($p<0.05$). In addition, after surgery, the serum H-FABP and B-FABP contents in POCD group were significantly higher than those in non-POCD group, respectively ($p<0.05$) (Figure 1).

Comparison of serum H-FABP and B-FABP contents between male and female patients

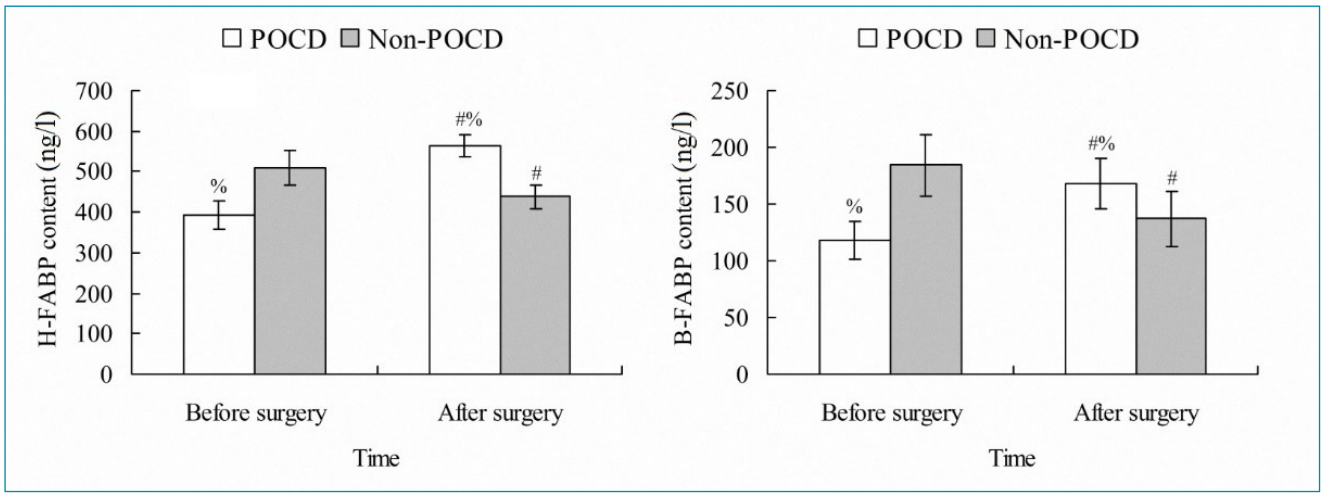

Figure 1. Comparison of serum heart-type fatty acid-binding protein and brain-type fatty acid-binding protein contents between postoperative cognitive dysfunction group and non- postoperative cognitive dysfunction group. #p<0.05 versus before surgery; %p<0.05 versus postoperative cognitive dysfunction D group.

Before and after surgery, there was no significant difference of serum H-FABP or B-FABP content between male and female patients, respectively (p>0.05). After surgery, the B-FABP content was significantly lower than before surgery for each gender (p<0.05) (Figure 2).

DISCUSSION

The postoperative cognitive dysfunction is a common neurological complication in elderly patients[10]. In this study, the incidence of POCD within 5 days after surgery was similar to that reported by Moller et al.[11]. Changes in S100β protein and neuron-specific enolase (NSE) in serum can reflect brain damage and have been used to predict the occurrence of POCD[12]. Finding specific and sensitive predictive indicators of POCD is the key to prevent and control POCD. FABP is a group of low-molecular-weight proteins in the cytoplasm, which are involved in the regulation of fatty acid uptake and transport and enzyme activity. This study suggests that H-FABP and B-FABP are more sensitive and specific than S100 protein and NSE in the judgment of acute brain injury[8].

The results of this study show that compared with patients with non-POCD, the serum H-FABP content in patients with POCD increased significantly 6 h after surgery compared with that before surgery, and the results were similar to the earlier reports. Vupputuri et al.[13] found that H-FABP could hardly be detected in the peripheral circulation of normal people. When brain cells were damaged, it began to increase 1–3 h and reached a peak 6 h after operation. The content of B-FABP in serum was significantly increased 24 h after the study, and the incidence of POCD was significantly positively correlated with the changes of H-FABP and B-FABP contents. The results suggest that the increase of H-FABP and B-FABP in postoperative serum is closely related to the occurrence of POCD in patients. Kok et al.[9] confirmed that during the perioperative period of cardiac surgery neurocognitive dysfunction, the level of B-FABP in serum of patients with POCD 24 h after surgery was significantly higher than before surgery.

The pathogenesis of POCD is still unclear, involving disorders of the central nervous system, endocrine system, and immune system[14]. It is generally believed that POCD is based on the degeneration of the central nervous system in elderly patients, and it is caused by various factors such as acetylcholine, serotonin, norepinephrine, glutamic acid, and gamma-aminobutyric acid. Acute mental disorder syndrome is caused by further disorders of the neurotransmitter system. Cognitive dysfunction caused by elevated FABP may be related to its ability to regulate inflammatory cytokines through intracellular fatty acid-mediated signaling pathways. This study has shown that the downregulation of FABP can significantly reduce the synthesis of TNF-α and IL-6[15], and the overexpression of FABP can lead to increased synthesis of IL-7 and IL-18[16].

This study still has some limitations. First, the sample size of this study is relatively small, especially for the POCD group, which may affect the results. Second, the correlations of H-FABP, B-FABP, and other parameters have not been discussed. These issues should be solved in more in-depth research to make the outcomes more convincing.

CONCLUSIONS

The serum H-FABP and B-FABP contents are positively related to the occurrence of POCD in elderly patients undergoing spinal surgery. This study has provided a certain scientific basis for the prediction of POCD in elderly patients undergoing spinal surgery.

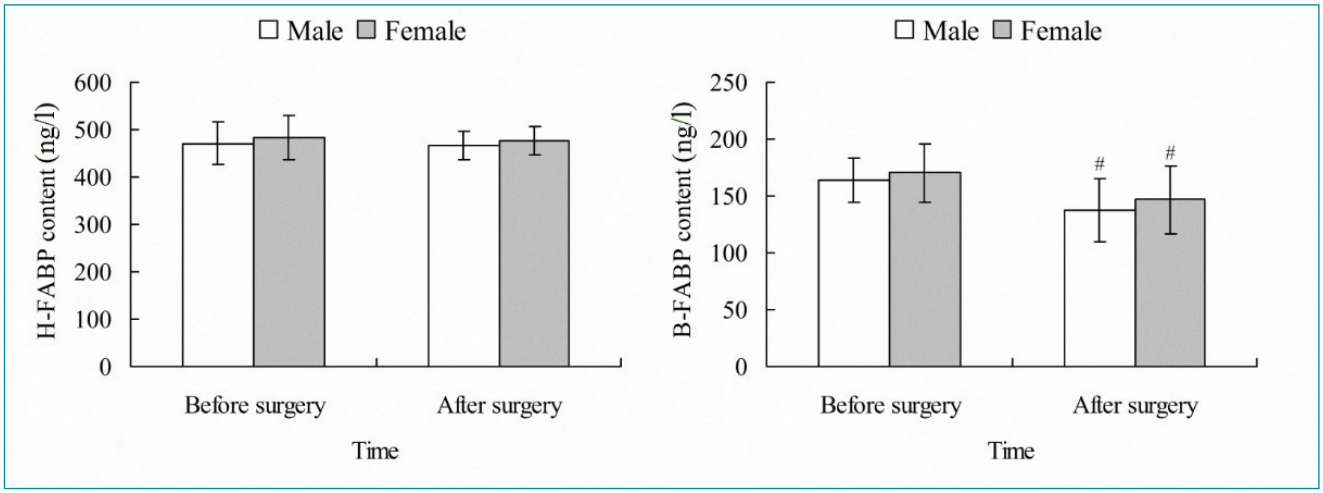

Figure 2. Comparison of serum heart-type fatty acid-binding protein and brain-type fatty acid-binding protein contents between male and female patients. #p<0.05 versus before surgery.

AUTHORS' CONTRIBUTIONS

MJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing-original draft. **YL:** Conceptualization. **LC:** Data curation, Software. **JT:** Project administration, Supervision, Validation, Writing—review and editing. **DW:** Project administration, Supervision, Validation, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Effects of four types of chinese medicines as concomitant drugs with azithromycin for the treatment of mycoplasma pneumonia in children in China: a network meta-analysis

Lairun Jin[1], Ping Chen[1], Yan Xu[1]*

SUMMARY

OBJECTIVE: The purpose of this study was to evaluate the efficacy of the use of four concomitant Chinese medicines with azithromycin in the treatment of mycoplasma pneumonia in children (MPC) by using network meta-analysis (NMA) and ranking them according to their performances.

METHODS: There were a total of 130 randomly controlled trials of four different concomitant Chinese medicines with azithromycin for the treatment of MPC in many databases, and an NMA was conducted in them by using Stata (version 13.0) software to evaluate the odds ratio (OR) and sequence of the different combinations. The included studies were divided into two groups: control group (azithromycin alone) and observation group (one of four azithromycin combinations).

RESULTS: A total of 13119 cases were included in this study, and the results showed that the pooled OR and 95% confidence interval (CI) of MPC improvement compared with azithromycin alone were 4.76 (3.18–7.14) for azithromycin and Reduning, 5.66 (4.50–7.12) for azithromycin and Tanreqing, 4.84 (3.35–7.01) for azithromycin and Xiyanping, and 4.58 (3.59–5.83) for azithromycin and Yanhuning, respectively. This study shows the significant efficacy of Chinese concomitant drug. The combination of azithromycin with Tanreqing is the best candidate of concomitant drug in terms of clinical efficacy. Its surface under the cumulative ranking (SUCRA) score was 85.5, while the SUCRA score for the azithromycin and Yanhuning combination was the worst, which is 48.4.

CONCLUSIONS: The combination of azithromycin with Tanreqing is the most promising group among four combinations for the treatment of MPC.

KEYWORDS: Network meta-analysis. Azithromycin. Pneumonia, mycoplasma. Randomized controlled trials as topic. Self efficacy.

INTRODUCTION

Mycoplasma pneumonia in children (MPC) is mild or absent in the early stage, but the disease progresses rapidly, and extrapulmonary complications are diverse[1,2]. The first choice of antibacterial drugs is macrolides, which are represented by azithromycin[3,4]. Due to the long treatment time, the incidence of gastrointestinal symptoms will increase accordingly[5]. Traditional Chinese medicine has certain advantages in improving efficacy, shortening the course of disease, and reducing toxic and side effects[6].

Network meta-analysis (NMA) is developed from the traditional meta-analysis, from the standard analysis of two sets of processing factors to a number of different processing factors[7].

The aim of this study is to evaluate the efficacy of four types of Chinese medicine as concomitant drugs, while azithromycin is administered in the treatment of MPC using NMA,

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and to rank them according to their performances. These four schemes are most widely used to treat MPC. This includes the combination of azithromycin with Reduning, Tanreqing, Xiyanping, and Yanhuning injections. This study may provide a significantly important guide for the selection of clinical medications for MPC.

METHODS

Search strategy

The databases used for this study included Wanfang, China National Knowledge Index, Chongqing VIP Network, China Academic Journal Network Publishing, China Biomedical Medicine, Chinese Science Citation, China Science and Technology Journal, PubMed, Cochrane Library, EMBASE, Web of Science, BIOSIS Previews, SciFinder, and SINOMED. Search strategies were adapted to each database, and they are the variations of the search words, wildcard symbols, and Boolean operators that combine terms. The searching date is from the establishment of the database to February 1, 2020. The search words are as follows: "azithromycin", "combination therapy", "Reduning", "Tanreqing", "Xiyanping", "Yanhuning", "injection", "efficacy", "pneumonia", "mycoplasma", "primary atypical pneumonia", "mycoplasma ovipneumoniae infection", "mycoplasma dispar infection", "children", "child", "child-mycoplasma pneumonia", and "pediatric pneumonia".

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1) Randomly controlled trials;
2) Patients who met the requirement of diagnosis of MPC[8];
3) Patients aged 14 years and below;
4) The results of the effective number of cases of both the control group and the observation group are provided; and
5) Studies that used azithromycin alone as control group, while the observation group was one of the azithromycin combinations for the treatment of MPC.

The exclusion criteria were as follows:

1) Children with severe dementia or mental illness;
2) Patients with severe tumor, lung, heart, liver or kidney damage, or immune diseases;
3) Purely descriptive studies with no control group;
4) Research types that were reviews, theoretical discussions, summaries of experience, case reports, and animal-based experiments; and
5) Studies with provision of incomplete or repeated data.

Data extraction and quality evaluation

Two reviewers independently searched the literature and screened all the titles and abstracts of potentially eligible trials based on the inclusion and exclusion criteria, and then, they extracted all the relevant data in each included study. This research extracted the characteristics of participants and interventions, outcomes reported and collected, sample size (control and observation) in each arm, numerical results, and quality indicators of publications. The data extracted were cross-checked, and disagreements were referred to a third reviewer. This study adopts the Jadad quality scoring standard to evaluate the quality of the publications.

Statistical analysis

This study conducts the network meta-analysis by using Stata software version 13.0 and commands network package. The efficacy of interventions was ranked according to the value of surface under the cumulative ranking (SUCRA) curve. SUCRA values were presented in percentages. The greater the SUCRA value, the better the intervention. The selected indicators were count data, while OR was used as the concomitant effect, and the confidence interval (CI) was set at 95%. The probability value of $p<0.05$ was defined as statistically significant.

RESULTS

Characteristics of included studies

This study identified 130 eligible studies published between 2007 and 2019 eventually. A total of 13119 cases including 6509 control cases and 6610 observation cases were included. Basic classifications of included studies are presented in Table 1.

Network meta-analysis

Network plot of four types of integrated chinese and western medicines

Of the 130 publications, the combination of azithromycin with Tanreqing was the most common one, while azithromycin with Reduning was the least frequent one. Figure 1 shows that the azithromycin-alone group had the largest number of subjects, while azithromycin and Reduning had the least number of subjects.

Confidence interval

The pooled OR and 95%CI of MPC improvement compared with azithromycin alone were 4.76 (3.18–7.14) for azithromycin+Reduning, 5.66 (4.50–7.12) for azithromycin+Tanreqing, 4.84 (3.35–7.01) for azithromycin+Xiyanping, 4.58 (3.59–5.83)

Table 1. Classification of included studies.

Comparison	Year	Area	Number of publications	Observation group		Control group		Duration (days)	Jadad quality score
				Total effective cases	Total cases	Total effective cases	Total cases		
B versus A	2011–2019	China	14	667	700	563	698	5–21	3–4
C versus A	2006–2019	China	61	2787	2887	2367	2878	3–15	2–4
D versus A	2011–2019	China	18	962	1002	816	990	4–11	2–4
E versus A	2007–2019	China	37	1929	2021	1594	1943	5–10	2–5

A: azithromycin; B: azithromycin+Reduning; C: azithromycin+Tanreqing; D: azithromycin+Xiyanping; E: azithromycin+Yanhuning.

for azithromycin+Yanhuning, respectively. This study shows a significant difference in efficacy. No significant difference was found in the comparison between azithromycin combinations.

Publication bias

Figure 2 shows that publication bias may have existed due to the asymmetry in the results of studies.

Ranking of clinical efficacy

The distribution of probabilities for each treatment is being ranked for their efficacy in MPC according to SUCRA values, and the order of SUCRA values for four types of concomitant Chinese medicine and azithromycin combination is as follows: azithromycin+Tanreqing (85.5), azithromycin+Xiyanping (59.3), azithromycin+Reduning (56.7), and azithromycin+Yanhuning (48.4). As shown earlier, the combination of azithromycin with Tanreqing had the best clinical efficacy.

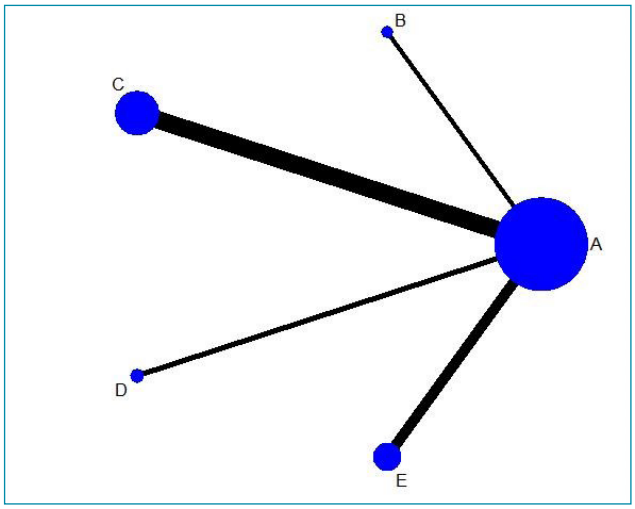

Figure 1. Network plot of different interventions for the treatment of mycoplasma pneumonia in children. The size of the point in the network graph is proportional to the number of subjects, while the thickness of the line is proportional to the number of studies. A: azithromycin; B: azithromycin+Reduning; C: azithromycin+Tanreqing; D: azithromycin+Xiyanping; E: azithromycin+Yanhuning.

DISCUSSION

The network meta-analysis is mainly used to compare the clinical efficacy of three or more interventions[9]. In this study, four types of combined Chinese medicine with azithromycin for treatment of MPC were analyzed. The combinations of azithromycin with Reduning, Tanreqing, Xiyanping, and Yanhuning were more effective when compared to azithromycin alone in the treatment of MPC. The combination of azithromycin with Tanreqing had the highest SUCRA value and probability of being the best treatment option.

Mycoplasma pneumonia in children is a common respiratory disease in pediatrics[10]. After mycoplasma pneumonia (MP) invades the respiratory tract, toxic metabolites, such as hydrogen peroxide, were produced, and antigen structures in the patient's body were changed[11-13].

Anti-infection therapy is the main clinical practice, and azithromycin is the first choice for the treatment of MPC[14]. As the third-generation semi-synthetic 15-membered macrolide antibiotic,

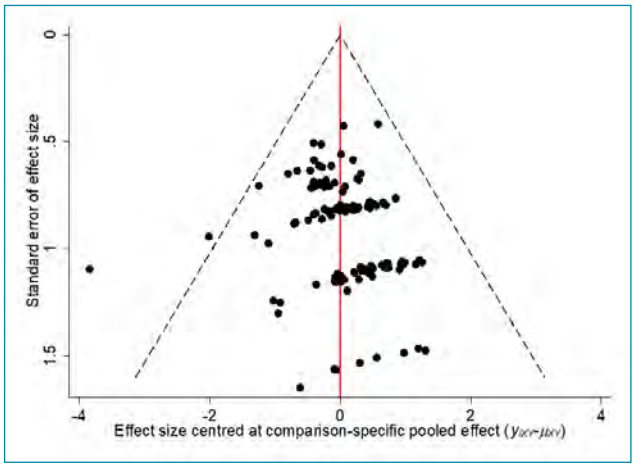

Figure 2. Funnel plot for publication bias in selected studies.

azithromycin can interfere with the protein synthesis of microorganisms by binding to the 50S ribosomal subunit of the microorganism. It has good antibacterial effect on MP and the characteristics of long plasma half-life, strong acid resistance, and strong permeability[14]. However, azithromycin-resistant strains often appear in clinical practice[15]. Exploring effective treatment for MPC has become a difficult task in pediatric clinic. Treatment with azithromycin alone may prolong the course of treatment and increase the risk of infection in other systems of patient[16,17].

At present, the clinical application of Chinese medicine injection in adjuvant treatment of MPC has achieved good results, showing that traditional Chinese medicine, including Reduning, Tanreqing, Xiyanping, and Yanhuning, combined with azithromycin has significant therapeutic advantages in MPC treatment[18].

Our findings show that the combination of azithromycin with Tanreqing is the most promising candidate for treatment. Tanreqing injection is a kind of Chinese patent medicine, and its main ingredients include *Scutellaria baicalensis*, bear bile powder, goat horn, honeysuckle, and forsythia[19]. *S. baicalensis*, bear bile powder, and goat horn perform the functions of clearing away heat, detoxification, expectorant, and cough suppressant, and they can effectively relieve the symptoms of MPC. Honeysuckle and forsythia have the effect of removing damp heat and enhancing immunity. Due to its advantages of safe application, minor side effects, and resistance to drug resistance, it is selected for clinical use in China[20,21]. This study may provide a guide of great importance for the selection of MPC clinical medications.

CONCLUSIONS

This study may be very helpful for the clinical treatment of MPC, but there are some limitations in this study. The research examined only the Chinese studies, and there were no consistencies in the treatment dose, duration of treatment in the included publication, and a quantitative analysis of immune system cytokines. Moreover, the result of safety assessment is absent. Therefore, high-quality randomized controlled trials are needed in the future to evaluate the efficacy of the combining traditional Chinese medicine and azithromycin in MPC.

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Ethical Statement: All analyses were adapted from previous published work. Thus, no ethical approval and patient consent were required.

AUTHORS' CONTRIBUTIONS

LJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft. **PC:** Methodology, Project administration, Resources, Software, Supervision. **YX:** Validation, Visualization Writing – review & editing. All authors approved the final version of the submitted manuscript.

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ORIGINAL ARTICLE
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Judicialization of coagulation factors in severe hemophilia: compliance with the care protocol and associated factors Judicialization and severe hemophilia

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SUMMARY

OBJECTIVE: This study aimed to analyze the compliance with the assistance protocol and factors associated with the judicialization of coagulation factors in severe hemophilia patients.

METHODS: A retrospective, cross-sectional study was conducted from June 2015 to May 2016 in adults with severe hemophilia in the Federal District, Brazil using data from their medical records and the Hemovida Web Coagulopathies System.

RESULTS: One-hundred and three patients from Federal District, the capital of Brazil, were included in the study. The mean age of the patients was 34.6±10.1. Ninety-three received prophylactic treatment (90.3%) and 53 received recombinant coagulation factors (51.7%). Judicialization occurred in 21 cases (20.4%), 13 of whom disagreed with the assistance protocol (12.6%). In the univariate analysis, an association was observed between reduced judicialization and treatment (4.8 vs. 47.6%; p<0.001) in the hemophilia treatment center and an increase that was associated with use of the recombinant coagulation factor in disagreement with the protocol (38.1 vs. 6.1%; p<0.001). In the multivariate analysis, the odds ratio for judicialization was 0.081 (95% confidence interval [CI] 0.010–0.055) for treatment at the hemophilia treatment center and 5.067 (95%CI 1.392–18.446) for the use of recombinant coagulation factor not in compliance with the protocol. More inhibitor development in judicialized patients (33.3 vs. 4.9%; p<0.001) was found.

CONCLUSIONS: The effectiveness of judicialization should be questioned, especially regarding coagulation factor prescriptions that are not in compliance with the protocol. The expense resulting from judicialization has not shown any benefit, and an even greater development of inhibitors during treatment in judicialized patients was found.

KEYWORDS: Legislation, jurisprudence. Hemophilia A. Hemophilia B. Factor VIII. Factor IX. Pharmaceutical services. Health services. Health services accessibility.

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INTRODUCTION

Hemophilia is a rare, inherited disorder linked to the X chromosome characterized by the deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B), which leads to bleeding. The treatment is the replacement of coagulation factors (plasma or recombinant)[1,2], which aims to reduce bleeding and prevent sequelae and high mortality rates.

Brazil has the fourth largest population of hemophilia patients worldwide (12,432 people) according to the 2017 Annual Global Survey of the World Federation of Hemophilia, behind the United States, India, and China[3]. To guarantee treatment, the Brazilian Ministry of Health (MS) acquires and distributes coagulation factors free of charge to users of the Unified Health System (SUS)[4], which has incorporated innovations during the last decade for the care of people with hemophilia. These innovations have been incorporated as the national registry of users with hereditary hemorrhagic disorders (Hemovida Web Coagulopathies System)[5] and include the implantation of primary prophylaxis with regular replacement of coagulation factors for patients below 36 months of age[6] and secondary prophylaxis for older people and young children[7]. In 2013, in hemophilia A, recombinant FVIII was incorporated for patients under the age of 30 years[8].

In the Federal District (FD), prophylactic treatment for hemophilia was implemented in 2011[9] and revised in 2012 to adapt to the MS guidelines[10]. From the disclosure of the protocol among the assisting professionals, an adjustment of the demand for the products was foreseen with reduction of the judicialization, given that the availability was compatible with the demand. However, a persistence of lawsuits has occurred[11].

Legal actions related to the right to health, described now as the judicialization of health, have been increasing in Brazil. As an example, between 2016 and 2017, an increase of approximately 50% in these processes was found[11,12]. In the FD, a study showed that there was an increase in lawsuits over time related to the right to health care without further discussion of the economic aspects since when a claim is granted; the Executive Branch is forced to reduce investment in other health-related actions or policies. This privileges the individual at the expense of the collective, which is contrary to the principle of equity and isonomy leading to the detriment of efficiency itself[11]. Another study in the FD showed that all processes were individual and not collective actions[13].

In this context, this study aimed to analyze compliance with the care protocol and factors associated with the judicialization of coagulation factors in patients with severe hemophilia.

METHODS

This study was conducted as a retrospective cross-sectional study from June 2015 to May 2016 based on data from patient medical records and the Hemovida Web Coagulopathies System of MS[5], including patients with severe hemophilia, those who were aged 18 or above, and those who resided in FD or in the municipalities of RIDE-FD (n=103). In addition, records of product dispensations were also consulted in the pharmacy of Fundação Hemocentro de Brasília (FHB).

Data, including age, weight, place of treatment (FHB or other), place of residence, type of treatment (demand or prophylaxis), access to treatment (judicial or not), dose by infusion, number of weekly doses, and type of coagulation factor prescribed (plasma or recombinant), tests for inhibitory antibodies, and serology for blood-borne infectious diseases (hepatitis viruses B and C [HBV and HCV, respectively], human immunodeficiency and human T-lymphotropic viruses [HIV and HTLV, respectively], and Chagas disease), were collected. Serological tests were performed using the chemiluminescence method (Abbott) in the FHB laboratory. Severe hemophilia was defined by the levels of clotting factors <1%[3].

The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Quantitative data were expressed as mean ± standard deviation (SD) or median and the 25–75% interquartile range (IQ 25–75%). Categorical variables were expressed as numbers and percentages (%). When appropriate, the Student's *t*-test or Mann–Whitney *U* test was used to compare quantitative variables. For categorical variables, contingency tables and Pearson's chi-square (χ^2) or Fisher's exact test were used as appropriate. To assess independent factors associated with judicialization, noncollinear variables with a $p<0.20$ in the univariate analysis were assessed by binary logistic regression analysis using the stepwise method. Data were analyzed by using the IBM Statistical Package for the Social Sciences (SPSS) software program, version 20.0 for Mac (SPSS, Chicago, Illinois, USA). Statistical significance level was defined as two-tailed $p<0.05$.

The study was approved by the Research Ethics Committee of the Health Sciences Teaching and Research Foundation (FEPECS), Brasília, Distrito Federal, Brazil.

RESULTS

The mean age of the included patients (n=103) was 34.2±10.1 years. Approximately 70.9% were residents of the FD and 38.8% underwent treatment at the referral care unit, the FHB. Ninety-three patients received prophylactic treatment (90.3%) and 53 patients (51.7%) received recombinant factors. In 13 cases, use was at odds with the protocol (12.6%). Judicialization occurred in 21 cases (20.4%). The median consumption of clotting factors per kg was 37.0 IU of FVIII (IQ 25–75%: 31.0–41.0) and 40.0 IU of FIX (IQ 25–75%: 35.5–54.0) as shown in Table 1.

Table 2 presents the univariate and multivariate analyses of the factors associated with judicialization. In the univariate analysis, a significant association was observed between reduced judicialization and treatment in the reference care unit (p<0.001). On the contrary, using recombinant FVIII in disagreement with the protocol was associated with greater judicialization (p<0.001). No significant differences were found in relation to other variables. In the multivariate analysis, a significant association was maintained between increased judicialization and the use of recombinant FVIII in disagreement with the protocol (p=0.014) and a reduction associated with treatment in the reference care unit (p=0.018). The odds

Table 1. Baseline data of adult patients with severe hemophilia (*n*=103).

Age, years, mean (SD)	34.2 (10.1)
Hemophilia A, n (%)	79 (76.7)
Judicial treatment, n (%)	21 (20.4)
Residence in the Federal District, n (%)	73 (70.9)
Use of the reference care unit for treatment, n (%)	40 (38.8)
Presence of inhibitor, n (%)	11 (10.7)
Prophylactic treatment, n (%)	93 (90.3)
Use of recombinant coagulation factor, n (%)	53 (51.5)
Use of recombinant coagulation factor in disagreement with protocol, n (%)	13 (12.6)
Coagulation factor VIII	
Infusion IU in patients with hemophilia A, median (IQ 25–75%)#	3.000 (2.500–3.000)
Infusion IU and weight in patients with hemophilia A, IU/kg, median (IQ 25–75%)#	37.0 (31.0–41.0)
Doses per week in patients with hemophilia A, median (IQ 25–75%)#	4.0 (3.0–4.0)
IU dispensed per month in patients with hemophilia A, median (IQ 25–75%)#	48.000 (30.000–60.000)
Coagulation factor IX	
Infusion IU in patients with hemophilia B, median (IQ 25–75%)*	3.000 (3.000–3.500)
IU by infusion and weight in patients with hemophilia B, IU/kg, median (IQ 25–75%)*	40.0 (35.5–54.0)
Doses per week in patients with hemophilia B, median (IQ 25–75%)*	3.0 (2.0–3.0)
IU dispensed per month in patients with hemophilia B, median (IQ 25–75%)*	35.500(16.875–46.000)

IU: international units of coagulation factor; SD: standard deviation; IQ 25–75%: interquartile range 25–75%; #79 patients with hemophilia A; *24 patients with hemophilia B.

Table 2. Univariate and multivariate analyses of factors associated with judicialization in adult patients with severe hemophilia (*n*=103).

	Judicialized (n=21)	Not judicialized (n=82)	Univariate analysis: p-value	Multivariate analysis: p-value
Age, years, mean (SD)	34.2 (9.1)	34.2 (10.4)	0.991	–
Hemophilia A, n (%)	5 (23.8)	19 (23.2)	0.951	
Use of the reference care unit for treatment, n (%)	1 (4.8)	39 (47.6)	<0.001	0.018
Residence in the Federal District, n (%)	15 (71.4)	58 (70.7)	0.950	–
Prophylactic treatment, n (%)	19 (90.5)	74 (90.2)	0.974	–
Use of recombinant factor in disagreement with protocol, n (%)	8 (38.1)	5 (6.1)	<0.001	0.014

SD: standard deviation; 95%CI: 95% confidence interval.

ratio for judicialization was 0.081 (95% confidence interval [CI] 0.010–0.055) for treatment in the reference care unit and 5.067 (95%CI 1.392–18.446) for recombinant FVIII not in accordance with the protocol.

Table 3 compares the results of serologies for blood-borne diseases and antibodies that inhibit coagulation factors during treatment between judicial and non-judicial patients. Patients receiving judicial treatment had a higher incidence of antibodies that inhibited coagulation factors (33.3 vs. 4.9%, $p<0.001$). Regarding serology, no significant differences were observed between groups.

DISCUSSION

Judicialization of coagulation factors has become a persistent phenomenon even after the adoption of the care protocol in the FD. This phenomenon is associated with the use of recombinant factors in disagreement with the protocol, which becomes, in particular, a problem for managers because it is a product with high costs. Treatment at the referral care unit was associated with reduced judicialization, which shows the importance of monitoring at a trained center to deal with care for people with hemophilia[14]. More inhibitory antibodies in judicialized patients were found with no significant difference in relation to serologies for infectious diseases, and it can be inferred that judicialization did not benefit this set of patients with respect to any of these aspects. As already observed in a previous study, a higher consumption of coagulation factors in the FD when compared with other Brazilian states was demonstrated[12].

SUS is a universal health system that requires strategies for guaranteeing equity and quality. From this perspective, clinical treatment protocols aim to promote safety, efficacy, and cost-effectiveness in treatment[15]. In healthcare for patients with hemophilia, these requirements are important, and monitoring of pharmacological treatment, bleeding, and development of inhibitors is relevant[2,16]. Most of the studied patients used prophylaxis as they were young, productive people who would benefit from this monitoring in the perspective of longevity with quality of life. In relation to hemophilia A, in 2013, the Ministry of Health started to make recombinant FVIII available to patients at ages <30 in order to guarantee treatment as blood products are dependent on blood donors and more vulnerable to fluctuations in availability[8]. The disadvantage of recombinant FVIII is the cost, which was 2.6–3.2 times higher than that of plasma during the research period[17].

Approximately half of the patients used recombinant factors, and a quarter of them had prescriptions in disagreement with the protocol, which was associated with the increased judicialization. It is noteworthy that the judicial demand was granted even with a prescription different from the protocol, thus demonstrating the need for mechanisms for consultation between the judiciary and SUS managers. Furthermore, as the coagulation factors have been supplied to the FD by the Ministry of Health in quantities greater than other units of the federation, there is no justification for this judicialization[18].

Hemophilia is a rare disease with complex treatment. Healthcare professionals must have knowledge and experience to deal with its peculiarities. Studies point out the importance of reference centers in which several services are offered with a multidisciplinary team. In addition to health-related aspects, the establishment of referral centers can reduce costs and improve the long-term results. Greater judicialization by unaccompanied users in the reference center indicates to managers the

Table 3. Inhibitors of coagulation factors and serologies for blood-borne infectious diseases among judicial and non-judicial patients in adult patients with severe hemophilia (n=103).

	Judicialized (n=21)	Not judicialized (n=82)	p-value
Coagulation factor inhibitor, n (%)	7 (33.3)	4 (4.9)	<0.001
Anti-HCV positive, n (%)	12 (57.2)	44 (53.7)	0.775
Anti-HIV positive, n (%)*	2 (9.5)	3 (3.7)	0.271
Anti-HTLV 1/2 positive, n (%)	0 (0.0)	2 (2.4)	0.470
Anti-HBc positive, n (%)	3 (14.3)	19 (23.2)	0.375
HBsAg positive, n (%)	0 (0.0)	1 (1.2)	0.611
Anti-HBc e HBsAg positive, n (%)	0 (0.0)	1 (1.2)	0.611
Serology for positive Chagas disease, n (%)	0 (0.0)	4 (4.9)	0.302

HCV: hepatitis C vírus; HIV: human immunodeficiency vírus; HTLV 1/2: human T-cell lymphotropic viruses 1 and 2; HBc: hepatitis B virus core antigen; HBsAg: hepatitis B virus surface antigen; *One patient did not undergo HIV serological tests.

need to reinforce the dissemination of this service for other health services[19–22].

It is worth noting that no evidence of greater safety for recombinant factors in relation to plasma can be found[23,24]. In the present study, a greater development of inhibitors in judicialized patients with no difference in serology for blood-borne diseases was observed. These findings show the safety of blood-derived factors in relation to the transmission of infectious diseases after the introduction of donor serological screening and methods of viral elimination and inactivation in the products derivate of blood[4,22,25].

Limitations existed in our study. Since hemophilia is a rare disease, it is difficult to conduct a study with larger populations. Furthermore, as this was a retrospective study, it was not possible to obtain other variables, such as quality of life, as no record of this parameter and other parameters exists in the medical record.

CONCLUSIONS

The effectiveness of judicialization should be questioned, especially regarding the use of recombinant factors that are not in accordance with the assistance protocol. The expense resulting from judicialization has shown no benefit even with greater development of antibodies that inhibit coagulation factors in judicialized patients; this expense represents an unnecessary cost that could be applied to other needs of patients with hemophilia in addition to other health conditions. It is imperative to establish a relationship with organized civil society, district, and federal bodies, including the judiciary, in the search for a trusting relationship, in defense of the SUS, and for the quality and safety of patient healthcare.

AUTHORS' CONTRIBUTIONS

BMDS: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **KJQA:** Conceptualization, Resources, Writing – Review & Editing. **AMC:** Conceptualization, Data Curation, Writing – Review & Editing. **FFA:** Conceptualization, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MSB:** Data Curation, Resources, Writing – Review & Editing. **ARAP:** Data Curation, Resources, Writing – Review & Editing. **JCLC:** Data Curation, Resources, Writing – Review & Editing. **LAS:** Formal Analysis, Resources, Writing – Original Draft, Writing – Review & Editing. **JLS:** Data Curation, Resources, Writing – Review & Editing. **LBB:** Data Curation, Resources, Writing – Review & Editing.

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Smoking prevalence and effects on treatment outcomes in patients with tuberculosis

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SUMMARY

OBJECTIVE: More than 20% of tuberculosis (TB) cases worldwide are attributable to smoking, and it is associated with an increased risk of latent and active TB, recurrence, and mortality. The aim of this study is to assess the smoking prevalence and the effects on treatment outcomes in TB patients.

METHODS: A prospective cohort study was conducted in patients with a recent TB diagnosis. The smoking status was defined, in addition to the patients' knowledge and attitudes toward smoking. The patients were followed up until the end of the treatment, and the treatment result was recorded.

RESULTS: Ninety-two patients were included in this study. The prevalence of active smoking was 31.5%. Active smokers had less chance for cure (62.1% versus 82.5%; p=0.032) and more treatment dropout (31.0% versus 12.7%; p=0.035) than non-active smokers. Patients demonstrated positive attitudes and good knowledge about smoking.

CONCLUSIONS: Active smokers had less chance for cure and more abandonment than non-active smokers. These results can be useful for the proper planning of actions that impact TB control, especially in the treatment results, such as cognitive-behavioral approaches to smoking cessation.

KEYWORDS: Tuberculosis. Smoking. Knowledge. Prevalence. Smoking cessation.

INTRODUCTION

Tuberculosis (TB) is an important public health problem worldwide, particularly in low- and middle-income countries. Brazil is among the 30 countries with the highest TB burden, which is responsible for 87% of TB cases globally, with a cumulative incidence of 44 cases/100,000 inhabitants in 2018[1].

Among the various risk factors for TB, smoking was identified as a serious aggravating factor, especially in developing countries. Both active and passive smoking considerably increase the risk of falling ill and dying from TB. It is estimated that more than 20% of TB cases worldwide are attributable to smoking[1]. The influence of smoking on TB is explained by the dysfunction of ciliary mechanics, a decrease in the immune response of an individual, the number of macrophages, and a decrease in the levels of CD4 and CD8 cells, thus increasing susceptibility to infection by *Mycobacterium tuberculosis*[2].

Tobacco use is one of the most important public health issues worldwide. Currently, almost 6 million people consume

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tobacco each year, both for direct use of the product and for secondhand smoke. By 2020, the number of tobacco deaths will increase to 7.5 million, representing 10% of all deaths. In addition, smoking is associated with a significant increase in the risk of latent TB infection, active TB, TB recurrence, and TB mortality[3].

Therefore, considering that Porto Alegre is the Brazilian capital with the highest number of smokers (24.6% of males and 20.9% of females)[4], which is the fourth capital city with the highest number of TB cases in Brazil[5], the aim of this study is to assess the prevalence of smoking and the effects on treatment outcomes in TB patients.

METHODS

Study design and location

A prospective cohort study was conducted to assess the prevalence of smoking and its effects on treatment outcomes for patients diagnosed with TB treated at the Tuberculosis Reference Center of the District Management Glória-Cruzeiro-Cristal in the city of Porto Alegre, RS, Brazil. The study was approved by the Ethics Committee of the Municipality of Porto Alegre on January 30, 2018 (number: CAAE 81741418.7.0000.5338). All patients signed a written informed consent form before participating in this study.

Population and data collection

The study population consisted of patients with a recent diagnosis (i.e., maximum 30 days) of pulmonary TB, who were evaluated at the Tuberculosis Reference Center of the District Management Glória-Cruzeiro-Cristal. This study included patients aged 18 years or above, who were diagnosed as pulmonary TB cases according to consensus criteria[6]. Patients who refused to sign the written informed consent form were excluded.

A standardized form was filled out for each patient, with the demographic data, symptoms, smoking, alcohol and drug use, comorbidities, and TB diagnostic tests. The treatment outcome (e.g., cure, dropout, failure, and death) was also recorded.

Smoking status was determined according to the definitions of the Centers for Disease Control and Prevention (CDC)[7]. An active smoker was defined as one who smoked at least 100 cigarettes in his lifetime, and at the time of the survey he was smoking at least 1 day a week. An ex-smoker was defined as one who smoked at least 100 cigarettes in his lifetime, but who at the time of the study did not smoke anymore. That patient who smoked less than 100 cigarettes in his lifetime was considered a nonsmoker.

In addition to the smoking history, the phase in the cessation process in which the patient was found was identified, according to the stages of behavioral change described by Prochaska and Di Clemente (e.g., pre-contemplation, contemplation, preparation, action, maintenance, or relapse)[8].

The level of nicotine dependence was also assessed by using the Fagerström scale. This scale classifies the degree of dependence on smoking as follows: very low, low, medium, high, and very high. Patients' knowledge and attitudes toward smoking were also assessed. For this, a questionnaire was developed based on the earlier studies[9-11], in which the first part contains 10 questions (true/false) on knowledge about smoking and the tobacco–tuberculosis relationship and the second part contains 10 questions (e.g., the Likert scale) on attitudes toward smoking. The first part of the questionnaire was answered by all patients included in this study, and the second part was answered only by active smokers and ex-smokers. The questionnaire was pretested with 20 patients before the start of this study, and the results are described in Tables 1 and 2 (see also "Results" section).

Statistical analysis

The data analysis was performed using SPSS 18.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). The data were presented as number of cases, mean ±standard deviation (SD), and median with interquartile range (IQR). Categorical comparisons were performed by the chi-squared test using Yates's correction if indicated or by the Fisher's exact test. Continuous variables were compared using the *t*-test or Wilcoxon test. A two-sided $p<0.05$ was considered significant for all the analyses.

Considering the prevalence of active smokers among TB patients in an earlier study of approximately 40%[9], with a 95% confidence interval (CI) and a CI amplitude of 0.20, it will be necessary to include 92 patients.

RESULTS

During this study period, 92 patients were included. The prevalence values of active smokers, ex-smokers, and nonsmokers were 31.5% (n=29), 22.8% (n=21), and 45.7% (n=42), respectively. Table 3 describes the characteristics of active smokers compared with those of non-active smokers (ex-smokers and never smokers). Active smoking patients were more often males (75.9% versus 49.2%; p=0.0016) and drug users (62.1% versus 11.1%; p<0.0001) compared with non-active smoking patients. The positive sputum smear microscopy was more frequent in active smoking

Table 1. Knowledge of patients regarding smoking.

Affirmative	True (%)	False (%)
Smoking is addictive	90 (97.8)	2 (2.2)
Smoking is a disease	78 (84.8)	14 (15.2)
Smoking has the greatest negative effect on the vascular system	86 (93.5)	6 (6.5)
"Smoker's cough," a type of chronic bronchitis, is caused by irritation of the lungs and bronchi and due to chemicals in the cigarette	92 (100.0)	0
Dangers from cigarette smoking increase with dose (number of cigarettes smoked, number of years a person smoked, and amount of smoke inhaled)	89 (96.7)	3 (3.3)
Smoking affected your health	85 (92.4)	7 (7.6)
Smokers are at increased risk of tuberculosis	85 (92.4)	7 (7.6)
Smokers are at higher risk of having tuberculosis more than once	84 (91.3)	8 (8.7)
Smokers with tuberculosis are more likely to spread the tuberculosis bacillus than nonsmokers with tuberculosis	86 (93.5)	6 (6.5)
Smokers with tuberculosis are at higher risk of death than nonsmokers	86 (93.5)	6 (6.5)

Table 2. Attitudes of patients toward smoking.

Affirmative	Totally agree	Agree	Not sure	Disagree	Totally disagree
Smoking is fun	0	22 (44.0)	2 (4.0)	26 (52.0)	0
People smoke just to show off	0	27 (54.0)	3 (6.0)	20 (40.0)	0
Smoking calms your nerves	1 (2.0)	43 (86.0)	0	6 (12.0)	0
Smoking makes you smelly	2 (4.0)	46 (92.0)	0	2 (4.0)	0
Smoking is a waste of money	2 (4.0)	45 (90.0)	0	3 (6.0)	0
Smoking makes you relieve all life stresses	1 (2.0)	30 (60.0)	0	19 (38.0)	0
Smoking keeps your weight down	0	36 (9.2)	0	14 (28.0)	0
Smoking gives you confidence	0	21 (42.0)	0	29 (58.0)	0
Smoking should be allowed at fewer places than it is now	1 (2.0)	42 (84.0)	2 (4.0)	5 (10.0)	0
Sales of cigarettes should be outlawed	2 (4.0)	39 (78.0)	0	9 (18.0)	0

patients (89.7 versus 66.7%; p=0.020). Regarding treatment outcomes, active smoking patients were less cured (62.1 versus 82.5%; p=0.032) and had more treatment dropout (31.0 versus 12.7%; p=0.035) than non-active smoking patients.

Among smokers, the degree of dependence measured by using the Fagerström scale was as follows: very low (n=2; 6.9%), low (n=6; 20.7%), medium (n=5; 17.2 %), high (n=11; 37.9%), and very high (n=5; 17.2%). With regard to the stages of behavioral change, smoking patients were distributed as follows: pre-contemplation (n=8; 27.6%), contemplation (n=16; 55.2%), and preparation (n=5; 17.2%). Table 1 shows the results for the patients' knowledge regarding smoking, and Table 2 shows the results for the patients' attitudes toward smoking.

DISCUSSION

In this cohort study, we found a prevalence of active smoking of 31.5% in TB patients. In addition, active smoking patients had less chance for cure and had more treatment dropout than non-active smoking patients.

There are several studies showing that smoking is strongly linked to TB, and a considerable proportion of the global TB burden can be attributed to smoking. A large proportion of TB patients can be active smokers or be exposed to other people's tobacco smoke[12-15]. In this study, we found that a prevalence of active smoking was 31.5% in TB patients. In a study conducted in Malaysia[9], the prevalence of active smoking was 40.27% among TB patients. Wang et al.[12] reported in a case–control study an even higher prevalence in China (54.6%). In a

Table 3. Characteristics of active smokers and non-active smokers.

Characteristics	Active smokers (n=29)	Non-active smokers (n=63)	p-value
Demographic data			
Age			
Male sex	22 (75.9)	31 (49.2)	0.016
White race	19 (65.5)	34 (54.0)	0.298
Symptoms			
Cough	28 (96.6)	54 (85.7)	0.162
Fever	15 (51.7)	31 (49.2)	0.822
Weight loss	25 (86.2)	52 (82.5)	0.768
Alcohol abuse	5 (17.2)	6 (9.5)	0.313
Drug use	18 (62.1)	7 (11.1)	<0.0001
HIV	14 (48.3)	20 (31.7)	0.127
Smear-positive sputum	26 (89.7)	42 (66.7)	0.020
Positive culture	20 (69.0)	44 (69.8)	0.932
Treatment outcomes			
Cure	18 (62.1)	52 (82.5)	0.032
Dropout	9 (31.0)	8 (12.7)	0.035
Death	2 (6.9)	3 (4.8)	0.649

study conducted in Iran[16], with patients with a recent diagnosis of TB, the authors demonstrated that 20.2% of the patients were daily smokers, 1.8% were occasional smokers, and 8.9% had quit smoking before TB diagnosis.

Increasing evidence suggests that smoking is significantly associated with treatment failure, dropout, and death[17-19]. In this study, smoking patients had less chance for cure and had more treatment dropout when compared to non-active smoking patients. A similar study that evaluated 183 smokers and 151 nonsmokers showed that the cure rates were higher in nonsmoking patients and in those who stopped smoking in the first 2 months of TB treatment, compared to smoking patients[20]. Dujaili et al.[21] performed a logistic regression analysis in a retrospective cohort study on the effects of tobacco on TB treatment outcomes and reported better results in nonsmokers than in smokers (odds ratio [OR] 0.312, 95%CI 0.17–0.57). El Sony et al.[22] also found a significant difference between treatment outcomes in the group who stopped smoking compared to the group of smokers.

In a cross-sectional study, more than 30% of smoking patients with TB revealed that they had never been asked about their smoking habits or were advised to stop smoking[23]. This approach to smoking in TB patients has been strongly recommended[24]. Likewise, understanding the knowledge and attitudes of TB patients about smoking is important to guide the development of effective educational interventions. In general, in this study, patients demonstrated good knowledge about smoking and positive attitudes against tobacco use. However, 88% of patients reported that "smoking calms your nerves" and more than 60% stated that "smoking relieves all life stresses." These findings alert to the need for cognitive-behavioral assessment and investigation of psychiatric comorbidities, such as anxiety and depression.

This study has some limitations. First, it was carried out in a single Health Unit. However, we believed that the results found in this study are applicable to places with similar characteristics. In addition, smoking status was self-reported and was not confirmed by biological measurements, such as the determination of carbon monoxide in exhaled air. Although the self-report of smoking status is strongly correlated with biochemical confirmation in the observational studies[25], underreporting of tobacco use may occur.

CONCLUSIONS

More than 30% of TB patients were active smokers in this study. In addition, active smoking patients were less cured and had more treatment dropout than non-active smoking patients. These results can be useful for the proper planning of actions that have an impact on TB control, especially on treatment outcomes, such as cognitive-behavioral approaches to smoking cessation.

AUTHORS' CONTRIBUTIONS

KRV: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing the original draft. **AAF:** Conceptualization, Investigation, Methodology, Writing – editing and review. **ACVA:** Conceptualization, Investigation, Methodology, Writing – editing and review. **DRS:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

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The importance of inflammation markers in polycystic ovary syndrome

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SUMMARY

OBJECTIVE: This study aimed to examine inflammation markers in patients with polycystic ovary syndrome (PCOS) and to compare them with healthy women.

METHODS: This prospective study was conducted by examining patients who applied to the Near East University Gynecology and Obstetrics Outpatient Clinic between January 2019 and January 2020. A total of 110 PCOS patients with 135 control groups were compared in terms of metabolism, hormonal factors, and inflammation markers.

RESULTS: The neutrophil count, neutrophil–lymphocyte ratio (NLR), platelet, platelet–lymphocyte ratio (PLR), platelecrit (PCT), erythrocyte cell distribution width, platelet distribution width, mean platelet volume, and C-reactive protein (CRP) values were found to be statistically significantly higher in patients with PCOS. There was a positive correlation between inflammation markers and serum androgens. Also, a positive correlation was observed between inflammation markers and cardiovascular risk parameters. In receiver operating characteristic curve analysis, the most valuable parameter in distinguishing PCOS patients from healthy controls was serum CRP levels [areas under the curve (AUC)=0.928, 95%CI 0.894–0.963, p<0.001, 92.6% sensitivity, and 82.7% specificity].

CONCLUSIONS: Serum CRP, neutrophil count, and PCT and NLR levels are valuable markers that show the inflammatory process in PCOS patients.

KEYWORDS: Polycystic ovary syndrome. C-reactive protein. Neutrophil-lymphocyte. Inflammation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy with 4–21% of women in the reproductive period[1]. Since, it was first defined by Stein-Leventhal as a syndrome in 1935, many factors have been suggested in the etiopathogenesis of the disease, which are not yet clearly known[2,3]. In 1990, according to the National Institute of Health, the diagnosis of PCOS was made with menstrual irregularity and clinical or biochemical hyperandrogenism findings after excluding other androgen elevations. According to the Rotterdam decisions taken in 2003, the diagnosis of PCOS is made if at least two of the symptoms (i.e., oligo-amenorrhea, clinical and/or laboratory findings of hyperandrogenism, and polycystic ovary appearance in ultrasonography) are present after excluding other endocrine diseases[4]. In the diagnosis of PCOS, the criteria set forth by the Androgen Excess Society (2006–2009) include hyperandrogenism (hirsutism and/or hyperandrogenemia), ovulatory dysfunction (oligo-anovulation and/or polycystic ovary), and

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the exclusion of other endocrinopathies that cause androgen elevation[5,6]. Although the diagnostic criteria are as stated, the effects of PCOS on women's life are not just these symptoms, and the disease has long-term effects through the life span of women. Many parameters, such as fasting blood glucose, fasting insulin values, and androgen levels, are affected and vary with age in PCOS patients, and it is recommended to determine the age-specific cut-off values for androgen levels[7].

PCOS is a complex disease and reproductive system disorders, such as hyperandrogenism, anovulation, and infertility, and serious metabolic system disorders, such as hyperinsulinemia, abnormal lipid levels, and obesity, are observed[8,9]. For example, infertility is common in PCOS, and this situation is also explained by a decrease in endometrial receptivity due to affected endometrial receptivity markers apart from ovarian causes[10,11]. Furthermore, all phenotypes of PCOS have been shown to be associated with metabolic disorders[12]. Besides these factors, chronic inflammation is also one of the components of PCOS, and in recent studies, it has been suggested that inflammatory markers, such as C-reactive protein (CRP), leukocytes/white blood cells (WBCs), some interleukins, and tumor-necrosis factor-α (TNF-α), are increased in patients with PCOS[13-15]. Chronic low-grade inflammation has been identified as a risk factor for endothelial dysfunction, atherosclerosis, and coronary heart disease, and it is linked with insulin resistance and obesity[16,17]. The cause of this chronic inflammation process seen in PCOS has not yet been clarified, but it is suggested that the risk of insulin resistance, obesity, and cardiovascular diseases is higher in patients who have started the inflammatory process.

Since PCOS is an endocrinopathy that affects many organs and systems and involves a chronic inflammatory process, we hypothesized that inflammation markers would be higher in PCOS patients than in healthy women. Therefore, this study was aimed to examine systemic inflammation markers like CRP and the markers that can be detected in complete blood count like neutrophil, neutrophil–lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in patients with PCOS and to compare them with healthy women. In addition, it was planned to investigate the relationship of these inflammation markers with body mass index (BMI), insulin resistance, and cardiovascular risk parameters in patients with PCOS.

METHODS

This prospective study was conducted by examining patients who applied to the Near East University Gynecology and Obstetrics Outpatient Clinic between January 2019 and January 2020. The study protocol was approved by our ethics review board, and the ethical approval form number is YDU/2019/69-825. Informed consent was obtained from all patients. A total of 245 participants were included in this study, in which 110 of them were PCOS patients (Group 1) and 135 of them were healthy women (Group 2). A detailed medical and gynecological history was obtained for all women in this study. All healthy women in Group 2 had regular menstrual cycles, and normal findings in transvaginal ultrasound PCOS diagnosis were determined according to Rotterdam criteria[4]. Exclusion criteria were as follows: age between 18 and 35, hyperprolactinemia, thyroid dysfunction, pregnancy status, congenital adrenal hyperplasia, use of drugs that affect the hypothalamic–ovarian axis, hormones or lipid parameters, history of ovarian surgery, use of any hormones including combined oral contraceptives in the past 6 months, presence of any active infection, smoking, and alcohol use. The presence of follicles larger than 10 mm in the ovary or the detection of ovarian cysts were also evaluated in the exclusion criteria.

BMI and Ferriman-Gallwey score (FGS) were calculated. Weight (kg)/height^2 (m^2) formula was used for the calculation of BMI. Blood pressure was measured, and waist–hip ratios (WHRs) were recorded. Mean arterial blood pressure (MABP) was calculated with the following formula: diastolic blood pressure+(systolic blood pressure-diastolic blood pressure)/3. To prevent bias, all the anthropometric measurements were made by a single clinician (Ö.E.Ö). Hirsutism was diagnosed in patients with FGS above 8.

Complete blood count, serum CRP, fasting plasma glucose, fasting insulin, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenodione, sex hormone binding globulin (SHBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured. Insulin sensitivity was defined by the homeostatic model of insulin resistance (HOMA-IR). The following formula was used to calculate HOMA-IR: fasting plasma glucose (mg/dL)×fasting plasma insulin (µU/mL)/405. The free androgen index (FAI) was calculated with the following formula: 100×(total testosterone/SHBG). All peripheral blood samples were taken within the first 5 days of menstruation after an 8 h night fast. In amenorrheic patients after exclusion of pregnancy, 5 mg/day medroxyprogesterone acetate (TARLUSAL; Deva Holding AS. Istanbul, Turkey) was given for 5 days, and progesterone withdrawal bleeding was created. Neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT), erythrocyte cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), and platelecrit (PCT) were analyzed from the complete blood count of patients. NLR and PLR were calculated. The NLR was calculated by dividing the absolute NEU by the absolute

number of lymphocytes. PLR was calculated by dividing the PLT by the LYM.

The Social Sciences Statistics Program (SPSS) version 16 was used for statistical analysis. The Kolmogorov-Smirnov test was performed to show the distribution of data. The Mann-Whitney *U* test was used for continuous variables not showing normal distribution. The data were expressed as median (minimum-maximum) and p-values. Correlations were made using the Spearman correlation test. The data are presented as correlation coefficient and p-values. The cut-off values were calculated using receiver operating characteristic (ROC) curve analysis for parameters that differ significantly in PCOS and healthy control group comparisons. The $p<0.05$ were considered statistically significant.

RESULTS

The demographic characteristics of participants were compared as shown in Table 1. BMI, WHR, and MABP values were found to be significantly higher in women with PCOS ($p<0.001$).

When the control group and women with PCOS were compared in terms of laboratory findings, the LH–FSH ratio, free testosterone, DHEAS, androstenedione, FAI, HOMA-IR, NEU, NLR, PLT, PLR, PCT, RDW, PDW, MPV, and CRP

Table 1. Comparison of the demographic characteristics and laboratory findings of polycystic ovary syndrome and healthy women.

	PCOS (n=110)	Control (n=135)	p
Age (years)	22 (18–31)	22 (18–33)	0.127
BMI (kg/m^2)	23.40 (16.7–40.9)	20.96 (16.53–34.38)	<0.001
WHR	0.83 (0.58–1.61)	0.66 (0.54–0.94)	<0.001
MABP (mmHg)	90.00 (66.0–106.0)	78.3 (63.3–98.6)	<0.001
LH/FSH	1.73 (0.31–3.44)	0.88 (0.23–1.92)	<0.001
Estradiol (pg/mL)	28.00 (1.90–87.00)	26.00 (12.00–104.00)	0.051
Free testosterone (pg/mL)	2.05 (0.65–3.70)	0.84 (0.36–2.07)	<0.001
DHEAS (µg/dL)	486.95 (130.50–703.90)	203.10 (98.40–373.30)	<0.001
Androstenodione (ng/dL)	140.25 (67.40–214.80)	75.30 (47.20–181.73)	<0.001
FAI	3.50 (0.79–10.20)	0.83 (0.39–3.46)	<0.001
HOMA-IR	1.78 (0.78–5.40)	1.09 (0.50–2.90)	<0.001
Neutrophil (mm^3/10^3)	4.99 (2.30–9.28)	3.75 (2.02–7.30)	<0.001
Lymphocyte (mm^3/10^3)	2.17 (1.09–3.72)	2.09 (0.90–3.30)	0.093
NLR	2.31 (0.89–4.20)	1.86 (0.74–3.32)	<0.001
Platelet (mm^3/10^3)	277.50 (153.0–448.0)	243.0 (147.0–431.0)	<0.001
PLR	129.54 (71.83–282.27)	115.79 (59.62–252.50)	0.003
Platelecrit (%)	0.21 (0.20–0.50)	0.20 (0.10–0.30)	<0.001
RDW (%)	12.50 (10.10–19.60)	11.70 (8.90–17.50)	<0.001
PDW (fL)	19.30 (9.80–23.10)	18.60 (9.90–22.30)	<0.001
MPV (fL)	9.05 (6.10–13.40)	7.70 (5.90–12.80)	<0.001
CRP (mg/dL)	1.02 (0.02–10.56)	0.08 (0.01–3.20)	<0.001
TC (mg/dL)	179.50 (97.0–266.0)	172.00 (116.0–268.0)	0.015
LDL (mg/dL)	98.50 (35.0–162.0)	88.00 (48.0–165.0)	<0.001
TG (mg/dL)	90.50 (34.0–220.0)	66.00 (38.0–249.0)	<0.001
HDL (mg/dL)	54.50 (32.0–96.0)	63.00 (43.0–81.0)	<0.001

PCOS: polycystic ovary syndrome; BMI: body mass index; WHR: waist-hip ratio; MABP: mean arterial blood pressure; LH: luteinizing hormone; FSH: follicle stimulating hormone; FAI: free androgen index; DHEAS: dehydroepiandrosterone sulfate; HOMA-IR: homeostatic model of insulin resistance; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein; TC: total cholesterol; LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein.

were found to be statistically significantly higher in PCOS group (Table 1). In addition, serum TC, LDL, and TG were increased, and HDL was decreased in PCOS group when compared with healthy controls (Table 1).

Table 2 shows the correlations between inflammation markers and androgens. A moderate positive correlation was observed between NEU versus FAI and free testosterone; PLT versus free testosterone; NLR versus androstenodione, and PLR versus free testosterone.

The correlation between inflammation and cardiovascular risk parameters are shown in Table 3. A moderate positive correlation was observed between NEU versus BMI, WHR, HOMA-IR, TC, TG and LDL; PLT versus HOMA-IR; PCT versus TC and LDL; and CRP versus WHR and LDL. In addition, a moderate negative correlation was found between NLR versus HDL.

In the ROC curve analysis, areas under the curve (AUC) of neutrophil, platelet, NLR, PLR, PCT, RDW, PDW, MPV, and

Table 2. Correlations of inflammation markers and androgens in patients with polycystic ovary syndrome.

	Androstenedione		FAI		DHEAS		Free testosterone	
	CC	p	CC	p	CC	p	CC	p
Neutrophil	0.286	0.002	0.386	<0.001	0.190	0.046	0.317	0.001
Platelet	0.024	0.800	0.278	0.003	0.191	0.046	0.424	<0.001
NLR	0.381	<0.001	0.243	0.011	0.114	0.237	0.256	0.007
PLR	0.163	0.089	0.173	0.071	0.113	0.239	0.321	0.001
Platelecrit	0.026	0.784	0.228	0.016	0.186	0.051	0.145	0.132
RDW	–0.038	0.696	0.000	0.997	0.007	0.941	0.089	0.354
PDW	–0.039	0.688	–0.007	0.940	–0.018	0.853	–0.096	0.319
MPV	0.054	0.575	0.147	0.126	0.061	0.529	0.083	0.388
CRP	0.084	0.384	0.251	0.008	0.132	0.170	0.058	0.544

PCOS: polycystic ovary syndrome; CC: correlation coefficient; FAI: free androgen index; DHEAS: dehydroepiandrosterone sulfate; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein.

Table 3. Correlations of inflammation markers and BMI, HOMA-IR, and in patients with polycystic ovary syndrome.

	BMI		WHR		HOMA-IR		TC		TG		LDL		HDL	
	CC	p	CC	p	CC	p	CC	p	CC	p	CC	p	CC	p
Neutrophil	0.318	0.001	0.300	0.001	0.329	<0.001	0.316	0.001	0.340	<0.001	0.363	<0.001	-0.272	0.004
Platelet	0.292	0.002	0.292	0.002	0.370	<0.001	0.241	0.011	0.151	0.116	0.265	0.005	-0.162	0.091
NLR	0.134	0.162	0.139	0.149	0.141	0.141	0.092	0.338	0.160	0.095	0.159	0.097	-0.313	0.001
PLR	0.121	0.208	0.142	0.140	0.158	0.098	0.102	0.287	0.069	0.472	0.149	0.120	-0.232	0.015
PCT	0.218	0.022	0.268	0.005	0.253	0.008	0.336	<0.001	0.220	0.021	0.407	<0.001	-0.249	0.009
RDW	-0.016	0.866	0.014	0.884	0.033	0.731	0.083	0.381	-0.079	0.415	0.105	0.275	-0.018	0.851
PDW	0.088	0.358	0.087	0.366	-0.078	0.417	0.019	0.847	0.016	0.871	0.003	0.979	-0.069	0.475
MPV	-0.106	0.269	0.057	0.552	-0.164	0.087	–0.006	0.948	0.004	0.967	0.029	0.763	-0.157	0.101
CRP	0.152	0.102	0.307	0.001	0.216	0.023	0.272	0.004	0.217	0.023	0.319	0.001	-0.232	0.015

PCOS: polycystic ovary syndrome; CC: correlation coefficient; BMI: body mass index; WHR: waist–hip ratio; HOMA-IR: homeostatic model of insulin resistance; TC: total cholesterol; LDL: low-density lipoprotein; TG: triglyceride; HDL: high-density lipoprotein; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; PCT: platelecrit; RDW: erythrocyte cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; CRP: C-reactive protein.

CRP were 0.772, 0.696, 0.693, 0.609, 0.760, 0.690, 0.657, 0.677, and 0.928, respectively. Among these parameters, CRP showed the highest discriminative power in distinguishing between PCOS patients and healthy controls (AUC=0.928, 95%CI 0.894–0.963, p<0.001, 92.6% sensitivity, and 82.7% specificity). The comparison of the ROC curves of parameters is shown in Figure 1.

DISCUSSION

In this study, we compared the inflammation markers in patients with PCOS and healthy women. We found that these inflammatory markers were significantly higher in patients with PCOS. In light of these data, it can be suggested that there is an inflammatory process in PCOS patients. In recent studies, it has been shown that in patients with PCOS the low-grade inflammation process progresses with increased CRP levels[18]. However, some studies suggest that this inflammatory process seen in patients with PCOS is nonspecific and is not associated with hyperandrogenism and neuroendocrine dysfunctions[19,20]. Similar to the findings of this study, Ruan et al. compared 74 PCOS patients with 51 healthy controls in terms of inflammation parameters, and they found that WBC and CRP levels were significantly higher in patients with PCOS[21]. They found that CRP levels were even higher especially in patients with PCOS with insulin resistance and obesity, and they suggested that these patients were in a chronic inflammation process and had more risks in terms of cardiovascular diseases[21]. According to our data, inflammation markers are higher in patients with high BMI, high androgen levels, and insulin resistance. These patients with chronic low-grade inflammation need close monitoring for endothelial damage, atherosclerosis, and cardiovascular diseases.

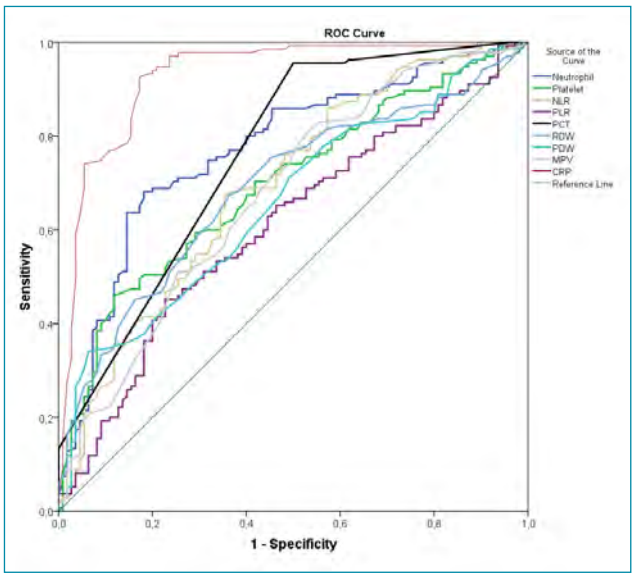

Figure 1. Receiver operating characteristic curves of the inflammation markers for differentiating polycystic ovary syndrome patients from healthy women.

Complete blood count, which is a frequently used laboratory test in clinical practice, gives us information in terms of inflammation markers as well as many other data. In addition to the information provided by each of the value in this analysis, the use of some data by comparing them has also become popular in recent years. In this context, neutrophils, lymphocytes, PCT, NLR, and PLR are used as valuable markers of inflammation. In the study of Yilmaz et al.[22], NLR and NEU were found to be significantly higher in patients with PCOS, supporting the results of this study. Yilmaz et al. also found that insulin resistance increased in obese and PCOS patients and there was a positive correlation between increased BMI and CRP[22]. The mechanism underlying increased CRP levels in PCOS patients has not yet been elucidated. It is still unclear whether increased CRP levels are a result of PCOS by its pathophysiology or concomitant obesity. Kurt et al. compared the NLR, CRP, neutrophil levels, and leukocyte levels of the patients with PCOS (n=62) and control (n=60) groups and found that all these parameters were higher in the PCOS group[23]. According to the recommendation of Kurt et al., this significant increase in inflammation markers is independent of obesity[23]. From these parameters, PCT has been relatively less studied in PCOS than other inflammation markers. Similar to our study results, Isik et al. found that PCT values were statistically higher in PCOS patients, but they did not find a significant difference in terms of NLR[24].

According to the findings of this study, it is claimed that there is a correlation between inflammation markers and hyperandrogenism in PCOS. Pergialiotis et al. examined 266 PCOS patients in terms of inflammation markers[25]. According to the results of this study, a significant positive correlation was found between androgen levels, NLR, and PLR, and this correlation continues to be significantly independent of the BMI of the patients[25]. In this study, PLR had a significant positive correlation with only free testosterone among androgens. When the NLR was examined, a positive correlation was observed with androgen levels, while a significant negative correlation was observed only with HDL among cardiovascular risk parameters. Also, this study showed a significant correlation between NEU and cardiovascular risk factors such as BMI, WHR, and lipid parameters as well as androgens in PCOS patients. However, to date, it is unclear whether inflammation increases androgen production from theca cells leading to hyperandrogenism or hyperandrogenism initiates the inflammatory process. Gonzalez et al., in two studies on PCOS patients with normal weight,

suggested that androgens trigger inflammatory cells and initiate the inflammatory process[26,27]. In a study conducted by Nehir et al. in 2016, it was shown that FAI was positively correlated with CRP, tumor necrosis factor-α, and α-1 glycoprotein[28]. It is not clear whether the increased androgen levels in PCOS cause a proinflammatory state or whether inflammation triggers androgen production. There are limited studies in the literature which examine the relationship between PCT and PCOS. In this study, PCT values showed a significant positive correlation with only FAI among androgen parameters, and significant correlations were observed with BMI, HOMA-IR, and serum lipid levels in cardiovascular risk factors. In the study by Isik et al., it was determined that there is a correlation between PCT and xanthine oxidase and superoxide dismutase activities, which are oxidative stress markers; however, the relationship between PCT and androgens or cardiovascular risk parameters was not investigated in this study[24].

This study is based on prospectively obtained results of healthy women with PCOS. The patients' results were compared in order to predict potential comorbidities such as cardiovascular diseases that may develop with hormonal, metabolic, and complete blood count measurements. The use of single center data and the use of only BMI to evaluate body fat ratio can be considered as limitations for this study. The strength of this study can be increased by evaluating tumor necrosis factor, interleukins, and more specific biochemical parameters showing body fat ratio.

CONCLUSIONS

Serum CRP and the inflammation marker that are detectable in complete blood count, such as NEU, NLR, and PCT, are higher in patients with PCOS. In addition, this study revealed that increased inflammation markers in PCOS patients are associated with obesity, androgens, insulin resistance, and lipid parameters. The positive correlation between inflammation markers and these hormonal and metabolic indices in PCOS patients may help to explain the chronic inflammation metabolism in this disease.

AUTHORS' CONTRIBUTIONS

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

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Preliminary study: myocardial T1 relaxation time in patients with ischemic findings and normal findings on coronary angiography

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SUMMARY

OBJECTIVE: The aim of this study is to evaluate the myocardium structure in patients with chest pain who were determined to have moderate and/or high risk for cardiac ischemic heart disease (IHD) but who had normal findings on conventional coronary angiography by using native cardiac magnetic resonance imaging (CMRI) T1 mapping and comparing with healthy volunteers.

METHODS: A total of 50 patients and 30 healthy volunteers who underwent CMRI were included in our prospective study. Patients whose clinical findings were compatible with stable angina pectoris, with moderate and/or high risk for IHD, but whose conventional coronary angiography was normal, were our patient group. Native T1 values were measured for 17 myocardial segments (segmented based on American Heart Association recommendations) by two radiologists independently. The data obtained were statistically compared with the sample *t*-test.

RESULTS: Myocardial native T1 values were found to be significantly prolonged in the patient group compared with the control group ($p<0.05$). Inter-observer reliability for native T1 value measurements of groups was high for both patient and control groups ($\alpha = 0.92$ for the patient group and 0.96 for the control group).

CONCLUSION: Findings suggestive of ischemia were detected by T1 mapping in the myocardium of our patients. For this reason, it is recommended that this patient group should be included in early diagnosis and close follow-up assessments for IHD.

KEYWORDS: Ischemic heart disease. Magnetic resonance imaging. T1 mapping.

INTRODUCTION

Chest pain is an important indicator of underlying ischemic heart disease (IHD). Differential diagnoses include other diseases of the mediastinum and/or thorax, as well as the upper abdomen[1,2]. After clinical risk assessment, patients presenting with chest pain who are determined to be at moderate to high risk for IHD are advised to undergo functional tests [e.g., exercise electrocardiography (ECG), effort echocardiography (ECHO), single-photon emission computed tomography (SPECT), and scintigraphy) followed by coronary angiography[1,2].

The presence of either ischemia or infarction on a stress imaging study is consistent with the diagnosis of IHD in a patient

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with angina symptoms. This is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, which is typically aggravated by exertion or emotional stress and relieved promptly with rest or by taking nitroglycerin[1,2].

The American College of Cardiology (ACC) and the American Heart Association (AHA) devised a new score to estimate the 10-year risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event, which was defined as non-fatal myocardial infarction (MI), coronary heart disease (CHD) death, or fatal or non-fatal stroke, in individuals who were initially free from ASCVD[3].

Angina usually occurs in patients with CHD but also it can occur in individuals with valvular disease, hypertrophic cardiomyopathy, and uncontrolled hypertension[3,4]. Infrequently, patients with normal coronary arteries may experience angina related to coronary spasm or endothelial dysfunction[4].

A subset of patients will have no findings of coronary artery pathology on conventional coronary angiography despite having MI[5].

Coronary heart disease (CHD) also includes a microvascular component. This process includes impaired endothelial function, inflammation, neovascularization, apoptosis, and the hypercoagulable state[4,5].

Cardiac microvascular dysfunction (CMD) is the impaired ability of microcirculation of the heart to adapt blood flow to meet oxygen demand. Microvascular disease should be suspected when chest pain persists after physical effort and shows slow or no response to short-acting nitrates[4,5].

The increasing number of both basic research and clinical studies, particularly those that develop novel imaging techniques, are promising for detection of early microvascular functional changes and early changes in the myocardium[5].

Over the past decades, new magnetic resonance imaging (MRI) sequences have been developed, which allow pixel-wise longitudinal relaxation time (T1) mapping of the myocardium. Native T1 mapping is emerging as an important tool for characterizing myocardial tissue with higher accuracy than nonspecific functional parameters[6,7].

Cardiovascular magnetic resonance research in animals and humans has shown that native T1 values (i.e., pre-contrast T1) are prolonged in pathologies, such as edema, infarction, amyloid infiltration, and fibrosis, and shortened in the presence of fat and iron accumulation[7-10]. The native T1 signal from the left ventricular myocardium has shown a particular promise for non-invasively differentiating diseased from normal regions[11,12].

In acute MI, T1 increases are more pronounced in myocardium that will become infarcted than in myocardium which will be salvaged by reperfusion. Following reperfusion, T1 increases further in infarcted tissue, but remains unchanged in salvaged myocardium[12].

In this study, we aimed to evaluate the myocardium structure by applying the Saturation Method Using Adaptive Recovery Times for Cardiac T1 Mapping ($SMART_1Map$) technique (1.5 T, Optima MR450w, GE Healthcare, Waukesha, WI, USA) in patients who underwent cardiac assessment and cardiac function tests (i.e., effort test and cardiac scintigraphy) and were determined to have moderate to high risk for IHD who had normal findings on conventional coronary angiography. We compared our findings on these patients with that of healthy controls.

METHODS

This prospective study was approved by the ethical committee at our hospital. The verbal and written informed consent was obtained from all participants.

Patient population

Between December 2016 and March 2019, we included a total of 50 patients (27 female and 23 male patients) with chest pain who had moderate and/or high risk for IHD but who had normal conventional coronary angiography findings.

Patient evaluation before magnetic resonance scan

Risk assessment of ASCVD was made according to the guidelines[5].

Trained staff measured height, weight, and supine blood pressure using a standard mercury sphygmomanometer and serum total cholesterol ratio (TCR). The serum TCR was calculated by dividing the total cholesterol number by high-density lipoprotein (HDL) number from a non-fasting blood sample. This ratio was between 4 and 1. Higher ratios mean a higher risk for heart disease.

Participants completed a questionnaire about their demographic characteristics, smoking history (i.e., never, former, or current smoking), medical diagnoses, and treatments (including hypertension and diabetes).

Typical angina pectoris criteria were as follows: substernal chest pain or a feeling of discomfort, increased pain with activity or emotional stress, and reduced pain with rest or nitroglycerin.

Those patients with typical angina complaints were included in this study.

Patients with evidence of acute coronary artery disease (CAD) detected in the laboratory analysis (e.g., troponin elevation) and with pathology and/or disease (e.g., diabetes mellitus, valve diseases, hypertension, cardiomyopathies, amyloidosis, systemic diseases, acute-chronic MI, myocarditis, etc.)

that could cause changes in the myocardial native T1 time were excluded. In addition, patients with a contraindication to MRI (e.g., pacemaker, stent in coronary arteries, pregnancy, and claustrophobia) or who had intravenous (IV) stents and similar equipment that could affect image quality were excluded.

Evaluation of patients' resting electrocardiograms

Resting ECGs were classified as showing major, minor, or no abnormalities.

Minor ECG abnormalities for our patient group are as follows: first- and second-degree atrioventricular block, borderline prolonged ventricular excitation, frequent atrial or ventricular premature beats, and fascicular blocks.

Major ECG abnormalities for our patient group are as follows: atrial fibrillation or atrial flutter, high-degree atrioventricular dissociation, left bundle-branch block, right bundle-branch block, indeterminate conduction delay, Q-wave MI, and isolated ischemic abnormalities.

The 12-lead ECG recordings were obtained in all cases. Stress ECGs were evaluated as non-ischemic, ischemic, and non-diagnostic. Horizontal or down sloping depression of ≥1 mm in patients without ST depression at rest and 1-mm additional collapse in patients with ST depression at rest were considered ischemia. If additional collapse was <1 mm in patients with ST depression at rest, it was considered non-diagnostic.

Evaluation of patients' echocardiography

After clinical and laboratory evaluation, echocardiography was performed on patients for ventricular functions. Patients with impaired cardiac wall movements and with left ventricular ejection fraction (EF) below 50% were excluded from this study.

Coronary angiography

Coronary angiography was planned for artery evaluation in patients with ischemia findings after stress tests. Normal coronary angiography was considered as smooth vessel lumen wall and absence of obstructive lesions.

Patients with normal coronary angiography findings and abnormal stress test findings were included in this study.

The mean time between coronary angiography and cardiac magnetic resonance imaging (CMRI) was 1 week.

Control group

In our control group, there were 30 healthy volunteers (18 female and 12 male patients) without any cardiac or systemic disease.

Echocardiography and ECGs were normal in our control group.

No conventional coronary angiography was performed in the patients in our control group.

Cardiac magnetic resonance imaging

All patients and control volunteers underwent MRI in the supine position on a 1.5-T MR scanner (Optima MR450w, GE Healthcare) with a 32-channel cardiac coil.

Image protocol of cardiac magnetic resonance examination

The routine CMRI sequences of our institution were as follows: trans-axial (8–10 mm) set of T2-weighted fast spin echo images through the chest. Steady-state free precession (SSFP) cine imaging with short-axis plane from the mitral valve plane through the apex of the heart (with slice thickness of 6–8 mm, 2–4 mm inter-slice gaps to equal 10 mm, and temporal resolution of ≤45 ms between phases) and SSFP cine imaging with long-axis plane in vertical and horizontal long-axis planes were obtained through the apex and center of the mitral and tricuspid valves (i.e., a set of four more rotational long-axis views were obtained).

After routine CMRI, all patients and control volunteers underwent pre-contrast short-axis $SMART_1Map$ imaging of the left ventricle for this study.

The $SMART_1Map$ imaging involved the acquisition of three slices (i.e., basal, mid-ventricular, and apical of heart) at five saturation delay times over a scan time of nine heartbeats (i.e., requiring 1, 1, 1, 2, and 4 heartbeats, respectively). Short saturation recovery times (TSs<RR interval) were acquired within a single heartbeat and were automatically distributed between TS min and trigger delay. Longer TSs (free relaxation up to 4×RR) were performed across multiple heartbeats. An additional image corresponding to an infinite delay time (TS=∞) was acquired without saturation. $SMART_1Map$ imaging (repetition time/echo time, TR/TE=2.8/1.2 ms; TS=100–4000 ms; flip angle, FA=45; field-of-view, FOV=38×30 cm; slice thickness/spacing=8/5 mm; bandwidth, BW=125 kHz; matrix=160×128) was performed under breath hold.

Cardiac magnetic resonance (CMR) scan of patient group was performed by the IV contrast agent administration in 0.2 mL/kg dose (gadoteric acid, 0.5 mmol/mL, Guerbet®) for myocardial delayed enhancement (MDE) imaging.

Cardiomyopathies, amyloidosis, systemic diseases, acute-chronic MI, myocarditis, etc. could cause abnormal myocardial contrast enhancement in late phase in CMR. Therefore, patients with pathological myocardial contrast enhancement typical for these disorders in late phase MDE images were excluded from the study.

There was no IV contrast agent administration in our control group.

Image analysis and post processing

The cardiac magnetic resonance (CMR) analysis was performed independently by two radiologists (with experience in CMR for 10 and 8 years, respectively) in two sessions.

Morphological and functional evaluation of the heart was performed in the first session. Cardiac function analysis was done automatically in workstation (CardiacVX, GE Healthcare).

All short-axis SMART$_1$Map images and 2D color maps were evaluated with computer-aided analysis packages for planimetry of endocardial and epicardial borders at end-diastole in the second session. Myocardial native T1 values were measured.

Short-axis SMART$_1$Map images of the left ventricle were obtained at apical, mid-ventricular, and basal levels. Segmentation of the left ventricle was done as recommended by the AHA. Region of interest (ROI) placement was performed on native SMART$_1$Map, which was automatically reconstructed and superimposed on the 17-Segment Model of the AHA's standard left ventricular anatomy and was performed by drawing the endocardial and epicardial contours of the left ventricular myocardium. Myocardial native T1 values for a total of 16 segments (excluding the apex) were measured after ensuring that the ROI was within the limits of myocardium (Figure 1a–c).

According to the measurement results, if prominent prolongation in native T1 value was detected (considered statistically outlier), they were excluded (Figures 1a and 1c).

In addition, both radiologists also evaluated T1 mapping image quality. Scoring of this category is as follows:

1=unable to see;
2=blurry but visualized;
3=acceptable;
4=good; and
5=excellent.

Statistical analysis

The distribution of outcome categories was assessed using the Shapiro-Wilk test. The data were presented as average±standard deviation, based on the normality of the data. In the statistical analysis, outlier values were excluded so that they do not affect the average value of native T1. The categorical variables were reported as counts and percentages. The paired sample *t*-test was performed to compare the differences between groups. The Cronbach's alpha value was used to assess inter-observer reliability for myocardial native T1 measurements. The statistically significant *p*-value was accepted as <0.05. All assessments were performed using the Statistical Package for the Social Sciences (SPSS) software (version 22.0; SPSS Inc., Chicago, IL, USA).

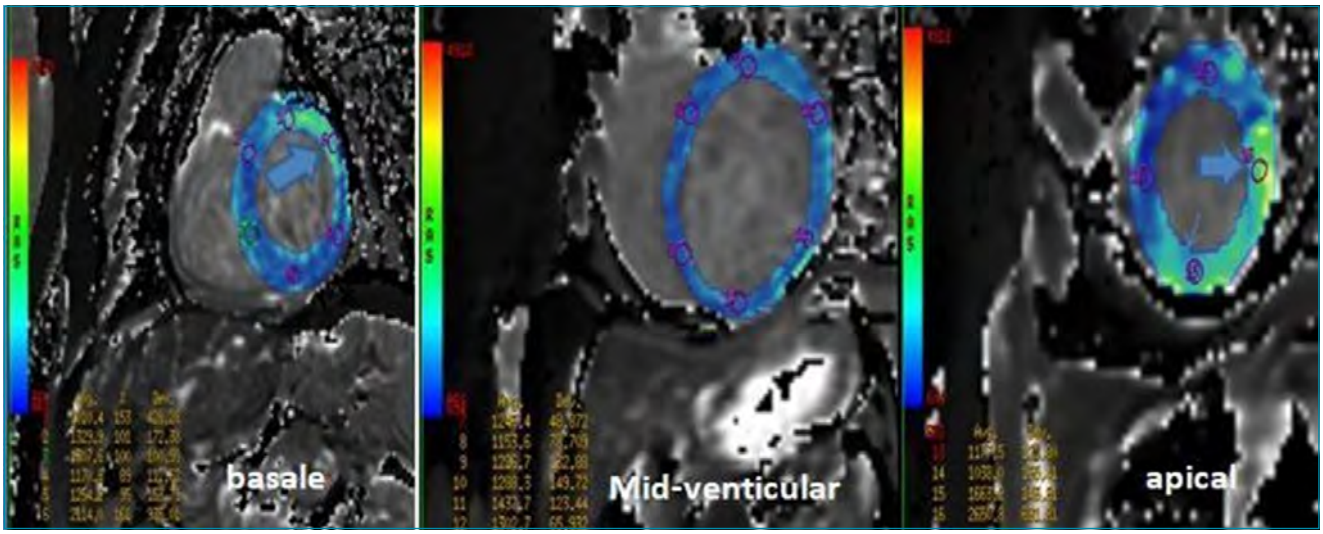

Figure 1. Images obtained from the study of a 46-year old male patient with chest pain and active smoker (i.e., average 1.5 packs/day) with a total cholesterol ratio value of 3. The native T1 value measurements were made from short-axis sections obtained from (A) the basal, (B) midventricular, and (C) apical levels of the heart. Myocardium is shown in blue color after the endocontour (i.e., blue-colored thin arrow on the apical segment) and epicontour are drawn. The native T1 values corresponding to each segment according to the American Heart Association classification of automatic segmentation are measured for circular region of interest in the myocardium. The obtained values can be seen in the left lower corner of the pictures (i.e., average 1094.8 ms). Prominent prolongations in native T1 values (2914 and 2500 ms) were detected that were considered statistically outlier, and so they were excluded (blue-colored thick arrows).

RESULTS

A total of 50 patients (27 female and 23 male patients) with ischemic findings but normal conventional coronary angiography and 30 healthy volunteers (18 female and 12 male patients) were included in this study.

The age range of the patient group was between 35 and 62 years (mean age=45). The heart rate measured during the CMR examination was between 60 and 84 heartbeats/minute (HB/min). The mean BMI was 27 kg/m^2.

The age range of the control group was between 30 and 55 years (mean age=48) without any cardiac or systemic disease. The heart rate measured during this study was between 75 and 82 HB/min. The mean BMI was 24 kg/m^2.

Total cholesterol ratio assessment of our patient group was as follows: ratio 1=16 patients, ratio 2=14 patients, ratio 3=17 patients, and ratio 4=3 patients. Twenty-one patients in our group were active smokers (i.e., average 2 packs/day). After familial history evaluation, 15 patients revealed to have diabetes mellitus and 19 patients have hypertension in their relatives. No abnormality was present in 16 patients during ECG examination but 4 patients had minor changes. Those changes were frequent atrial or ventricular premature beats.

The mean EF values for both patient (left ventricle average EF 62% and right ventricle average EF 52%) and control volunteer (left ventricle average EF 65% and right ventricle average EF 54%) groups were within normal limits.

Digital subtraction angiography (DSA) coronary angiography was normal in the patient group. There was no evidence of stenosis in the coronary arteries. There were smooth vessel lumen walls.

Heart muscle contractions were natural on functional evaluation, in both patients and volunteers. Cusp functions were normal and no evidence of insufficiency and/or stenosis was detected.

Figures 2 and 3 show the native T1 values in the patient group and control group as performed by the first and second radiologists, respectively.

Average native T1 values were significantly longer in the patient group than in the control group ($p<0.05$). This difference was less pronounced in segments 3, 9, 13, and 14 (AHA) ($p=0.04$, $p=0.045$, $p=0.042$, and $p=0.038$, respectively) while other segments were more prominent ($p<0.001$).

When T1 mapping was evaluated in terms of image quality, both observers evaluated the image quality as good (score=4) with high compliance (alpha=0.87).

DISCUSSION

In this study, we aimed to evaluate the myocardial structure using the SMART$_1$Map technique in patients who underwent cardiologic assessment due to chest pain and who were found to have moderate to high risk for IHD in stress tests, but who had normal conventional coronary angiography. We compared our findings with that of healthy participants.

Coronary artery disease (CAD) also includes a microvascular component. CMD is the impaired ability of microcirculation of the heart to adapt blood flow to meet oxygen demand[13].

Microvascular disease should be suspected when chest pain persists after physical effort and shows slow or no response to short-acting nitrates[13]. This was the case in our patient group.

Transthoracic Doppler echocardiography (TTDE) is an initial screening method to detect significant microcirculation impairment. It allows the measurement of coronary blood flow

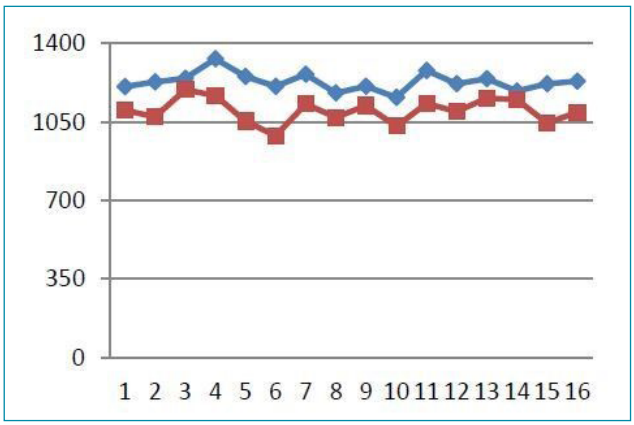

Figure 2. The graph shows the native T1 values as measured by the first observer for the patient group (blue curve) and the control group (red curve). The native T1 values of the patient group were significantly longer ($p<0.001$). The values along the *x*-axis show the native T1 signal values and the measured cardiac segments along the *y*-axis.

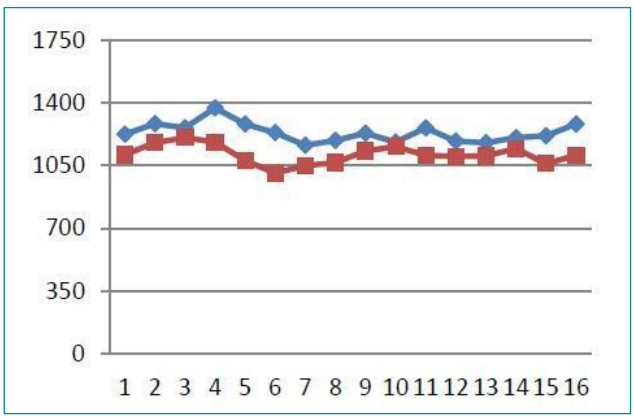

Figure 3. The graph shows the native T1 values as measured by the second observer for the patient group (blue-colored curve) and the control group (red-colored curve). The native T1 values in the patient group were significantly longer ($p<0.001$). The values along the *x*-axis show the native T1 signal values and the measured cardiac segments along the *y*-axis.

(CBF) velocity in the left anterior descending artery. With this method, coronary microvascular dilatator function is calculated as the ratio of diastolic CBF velocity at peak vasodilatation to CBF velocity at rest[13,14].

Mild coronary microvascular dysfunction may not be identified earlier by TTDE, and microvascular dysfunction can be assessed only in the left anterior descending artery perfusion area, because other coronary arteries are not well visualized[14].

In addition, diastolic left ventricular dysfunction is a first sign of myocardial changes even in younger patients with normal systolic function detected by transthoracic echocardiography (TTE)[14]. In our patients, we found that TTE showed early signs of diastolic dysfunction.

The endothelium is a central regulator of vascular homeostasis. This includes hormone transport and distribution, metabolic waste product disposal and regulation of regional blood flow by synthesis, and release of different mediators with opposing vascular properties[13,14].

Metabolic abnormalities (i.e., hyperglycemia, hyperlipidemia, insulin resistance, and insulin deficiency) are lead to myocardial fibrosis and/or myocardial hypertrophy directly or indirectly. Several processes are responsible for these adverse changes including impaired calcium cycling, myocardial insulin resistance, increased lipid uptake, glucotoxicity, and activation of the renin-angiotensin-aldosterone system observed in mouse models of dilated cardiomyopathy[13,14].

Increased activation of the renin-angiotensin-aldosterone pathway leads to the fibrosis formation. These processes lead to altered myocardial relaxation and manifest as diastolic dysfunction. Systolic dysfunction is a later manifestation, usually occurring after diastolic dysfunction develops[14,15].

Neurogenic, hormonal, metabolic, myogenic, and flow (shear stress-induced) endothelial mechanisms control coronary vascular resistance at specific microvascular sites. Integration of multiple mechanisms could hypothetically form a system matching CBF to myocardial metabolic demands[13-15].

A unique feature of CMR is its ability to characterize myocardium. Proton relaxation times, T1, T2, and T2*, are a reflection of the composition of individual tissues and change in the presence of disease[16,17]. Research into T1 mapping has largely been focused on the study of cardiomyopathies, but T1 mapping also shows huge potential in the study of IHD[18].

Systemic disorders that affect the heart, such as sarcoidosis, systemic lupus erythematosus, and systemic sclerosis, are known to induce tissue edema at the acute stage and exhibit elevated T2 (and T1) values. Thus, T1 mapping may be a useful clinical tool for identifying cardiac involvement with implications for therapy and for assisting in determination of prognosis[15-17].

Beyond focal lesions that are well depicted by late gadolinium enhancement sequences, T1 mapping has made it possible to discriminate diffuse myocardial alterations, previously not accessible by other non-invasive means. The strengths of T1 mapping are high reproducibility and immediate clinical applicability, even without the use of contrast media injection (i.e., native T1)[15,16].

T1 mapping is allowed for the non-invasive quantitative assessment of cardiac remodeling. Native T1 mapping has shown pathology with high accuracy in cases of IHD, acute MI, and myocardial edema, even demonstrating a higher sensitivity than T2-weighted short-tau inversion recovery (IR) imaging[16,18].

Cardiac T1 mapping methods are performed either by IR or saturation recovery (SR) technique, followed by pre-pulse sequences applied on this basis, resulting in raw images generated by different degrees of recovery along the z-axis. Then, two-dimensional color T1 maps are created automatically[19].

The most common T1 mapping strategy involves an IR pulse sequence, in which the application of a non-section selective 180° pulse inverts the magnetization. As longitudinal magnetization recovers, at a time defined as the inversion time (TI), a section-selective 90° excitation pulse is applied and rotates the magnetization into the transverse plane. This is repeated again and again, each time with the TI changed. This method, which is very sensitive to many patient-related factors (i.e., heart rate, obesity, and blood hematocrit value), especially the changes that may occur in R–R intervals, has been modified in various ways[18-20].

The Modified Look-Locker Inversion Recovery (MOLLI) method, which was first developed as a Look-Locker technique, was developed with a single-shot balanced SSFP to reduce scan time and artifact sensitivity.

There are IR pulse sequences, such as shortened MOLLI (shMOLLI), which are developed for signal collection, differences in breathing techniques, and breathless patients. With these methods, the apparent T1 value of the myocardium can be calculated[10-12].

However, in this study, we used the $SMART_1Map$ technique, which uses the SR preparation instead of the IR technique, and is similar to the saturation recovery single shot acquisition technique. Dephasing the whole imaging volume leads to depletion of the entire magnetization, alleviating the need for any rest periods[19,20]. In this way, we could measure the true T1 value of the myocardium by the $SMART_1Map$ technique, regardless of the patient-related or device-related effects[20]. When we evaluated the studies performed in the literature, we found that there were not enough *in vivo* studies with the $SMART_1Map$ technique for myocardium[11-20].

The normal natural myocardial T1 values measured at 1.5 T with MOLLI in the literature are between 900 and 1100 ms, but as we have already mentioned, it depends on several technical and physiological parameters[20]. In this study, the mean native T1 value of myocardium was 1101±89 according to the measurements in the control group and was in concordance with the literature.

We believed that the prolongation we have detected in the myocardial native T1 value with the SMART$_1$Map method in our group is caused by ischemic damage. This finding can be deemed reversible since no heart contraction dysfunction accompanies this segmental or diffuse myocardial native T1 prolongation in our patient group[18-20]. We believed that the native T1 prolongation we have detected in our study is caused by transient myocardial edema and inflammation[16,18].

Limitations

There are some limitations of this study. First, the fact that native T1 value difference between patient and control groups in segment 3, 9, 13, and 14 in accordance with AHA classification (i.e., basal inferoseptal, mid-inferoseptal, apical anterior, and apical septal, respectively) is thought to be related to secondary to the artifact caused by the actuality that these segments are much more mobile compared to the other parts of the heart (e.g., closer proximity to diaphragm). Perhaps to prevent this, operators must aim to minimize partial volume effects by optimal slice orientation relative to the tissue, which is preferably orthogonal to the imaging plane to minimize obliquity[10,17,18].

Second, we did not make extracellular volume fraction measurements. The normal myocardium consists of two parts: the intracellular compartment (including myocytes, fibroblasts, and other blood cells such as red cells) and the extracellular compartment (dominant water associated with the extracellular matrix, but also including the intracapillary plasma volume). The native T1 value notifies us about both compartments. Extracellular volume fraction measurements may show changes in the extracellular compartment by allowing hematocrit correction, which may allow the origin of the pathology to be elucidated[21].

In addition, as a preliminary study, the number of patients and healthy people in the control group was small, and more extensive work will be needed to verify our findings.

CONCLUSIONS

This study shows that in the patients with clinical findings as stable angina with abnormal stress test results, the prolonged myocardial native T1 value was observed even if conventional coronary angiography was normal. When evaluated together with clinical findings, this should be considered significant in terms of microvascular dysfunction and should be included in early diagnosis and follow-up assessments for IHD.

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ETHICAL APPROVAL

This article does not contain any studies with animals performed by any of the authors. This study had an ethical committee approval from the local institution (no. 15718). Informed consent was obtained from all individual participants included in this study.

AUTHORS' CONTRIBUTIONS

SSDB: Conceptualization, Data curation, Formal analysis, Writing – original draft. **FN:** Data curation, Formal analysis, Writing – original draft. **BO:** Data curation, Formal analysis. ZS: Data curation, Formal analysis. **YB:** Writing – review & editing. **OA:** Writing – review & editing.

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Technique to reduce blood loss during open abdominal myomectomy: transverse or vertical incision?

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SUMMARY

OBJECTIVE: To determine if there is a difference between uterine incision techniques (vertical vs. transversal) in terms of clinical results.

METHODS: All women with leiomyomas who underwent open abdominal myomectomy (n=61) between March and August 2016 at the Gynecology and Obstetrics Clinic at the Women's Health Research and Training Hospital Zekai Tahir Burak were included, and the clinical results were included and prospectively reviewed.

RESULTS: The estimated blood loss during myomectomy increased in the transversal group compared with the vertical group (809.33±483.34 *versus* 405.32±180.95 mL, p<0.001). The average operation duration was 60 min, and the patients got discharged on the second day after surgery. No intergroup statistical differences were observed in the surgical procedure.

CONCLUSIONS: Surgeons should give preference to the most viable incision depending on the size and location of the leiomyoma.

KEYWORDS: Gynecologic surgical procedures. Uterine myomectomy. Safety. Ergonomics.

INTRODUCTION

Uterine leiomyomas are common conditions characterized by the estrogen-dependent benign tumors in women of reproductive age[1]. The leiomyomas may be asymptomatic or may cause bleeding, pain, pelvic pressure, or infertility. The standard treatment for symptomatic leiomyomas is surgical treatment, which is either hysterectomy in women whose age is above the childbearing age or myomectomy in women who wish to preserve fertility and their uterus[2]. Open abdominal myomectomy was described for the first time by Dr. Victor Bonney in 1931 for the women who want to preserve the uterus whether she desires for future fertility or not[3]. Myomectomy is reported to cause more blood loss and to have longer operating hours compared with hysterectomy[4].

In myomectomy, Pfannenstiel transverse incision is commonly used for the abdominal wall. The next step of the procedure is to make the uterine incision. In a normal uterus, arcuate blood vessels run horizontally and radial vessels penetrate deeply into the myometrium[5]. However, leiomyomas distort normal vascular anatomy and also the vessel structures. The traditional teaching advocates vertical incision during myomectomy to prevent transection of the vascular architecture of the

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uterus. However, there is no consensus on the optimal direction of myomectomy incisions.

We designed a randomized prospective study to determine if there is a difference in clinical outcomes regarding the blood loss, operation duration, and hospitalization duration between the vertical and transverse uterine incision techniques. In this prospective analysis of patients who desired future fertility and underwent open abdominal myomectomy, we compared the estimated blood loss during myomectomy, operation duration, and complications of both types of uterine incisions.

METHODS

This randomized case–control study was conducted in a tertiary care center in Ankara, Turkey between March and August 2016. This study was approved by the institutional review board of the University of Health Sciences, Zekai Tahir Burak Women's Health Care, Education, and Research Hospital (26/06/2014 #18). All participants gave written informed consent, and the principles of the Declaration of Helsinki were followed.

During the study period, myomectomy procedures were performed to a total of 61 women aged 25–45 years. The exclusion criteria were infertility, prior myomectomy, leiomyomas localized in submucosa, cervix or broad ligament, women with adnexal masses, congenital uterine abnormality, and women with malignant tumors due to risks of complication and prolonged operation duration. Clinical characteristics and sociodemographic data of the women were recorded. The women were examined and operated by the same operator (OU). Before the surgery, the uterine size was examined by OU in terms of gestational weeks. The researcher (MCI) attended all cases in order to analyze the operation duration and to calculate blood loss. Surgical sponges and laparotomy packs were weighed dry before surgery and wet immediately after use. Blood loss in surgical sponges was calculated by the following formula: [wet sponge weight (g) – dry sponge weight (g)] divided by 1.06 g/mL (the density of blood)[6]. The total blood loss was calculated according to the total number of surgical sponges (10 mL), laparotomy packs (100 mL), and the blood in the vacuum aspirator.

All women were operated under general endotracheal anesthesia, and a Foley catheter was placed inside the bladder. The Pfannenstiel transverse incision was used for all abdominal wall incisions. The abdominal fascia and peritoneal membrane were cut longitudinally and then uterus was visualized. Bistoury and scalpels were used for all incisions. A simple random sampling method was used for choosing control and study groups. In this sampling method, each member of the population had an exactly equal chance of being selected. After randomization, the transverse or vertical uterine incision groups were performed, extending through the myometrium and entire fibroid pseudocapsule. Allis clamps were put on the myometrial edges to expose the leiomyomas, and then leiomyomas were extirpated by grasping them with a single tooth tenaculum. The location, number, and direction of uterine incisions in the cases of multiple leiomyomata depended on their locations and sizes. An effort was made to remove as many fibroids as possible through each uterine incision to minimize the total number of uterine incisions. Multiple incisions were often necessary but the number and size were minimized and performed anteriorly when possible. Towel clamps were used on the leiomyoma for traction as required. All visible and palpable fibroids were removed. The endometrial cavity was stained with diluted methylene blue dye transcervically after the anesthetic induction, immediately preceding the operation to facilitate recognition of cavity entry during surgery and to aid in carefully layered closure of uterine defects. If the uterine cavity was entered, the endometrium was reapproximated with a running 3–0 vicryl suture on a small tapered needle. Myometrial defects were closed with interrupted number 0 vicryl suture before the subsequent uterine incision was carried out. The serosa was reapproximated with a running imbricating suture of 3–0 vicryl, and then the peritoneum, fascia, and skin were closed. Each subject received the routine postoperative care, which included monitoring of the patient's hemodynamic and fluid status, pain control, and reintroducing normal diet and activity.

Statistical analysis

The statistical analyses were performed by using IBM SPSS Statistics 21 (IBM, Armonk, NY USA). For continuous variables, results were presented as mean±standard deviation in parametric data and as median (minimum, maximum) in nonparametric data, and for categorical variables, the results are summarized as frequency and percentages. The normality of the continuous variables was evaluated with the Shapiro–Wilk test. A comparison of continuous variables for the two groups was performed using the Mann–Whitney U test for nonparametric data and independent sample *t*-test for parametric data. Comparisons between two categorical variables were performed using the chi-square analysis. Repeated measures of ANOVA were used to evaluate group differences over three time points (baseline, second hour, and sixth hour). All tests were two-sided, and a $p<0.05$ was considered to be statistically significant.

RESULTS

Among the 61 myomectomy operations, 31 women were operated with a vertical uterine incision, and 30 women were operated with a transverse uterine incision in this study.

The demographic variables (e.g., median age and number of parity) of patients were considered because of their impact on the operation. The size, number, and location of leiomyomas were also identified. The characteristics of the participants and the leiomyomas are presented in Table 1. The two groups were similar regarding the median age, parity, mean leiomyoma diameter, and uterine size. There was one dominant myoma in two groups, but the number of leiomyomas was significantly different from each other. There were significantly more leiomyomas in the transverse incision group than vertical incision group. The most common symptoms were chronic pelvic pain and abnormal uterine bleeding, and no statistically significant differences were observed between the two groups.

The intraoperative blood loss was higher in the transverse incision group compared with the vertical incision group (809.33±483.34 mL *versus* 405.32±180.95 mL, p< 0.001). Table 2 summarizes the operation duration (min), hospitalization duration (days), and total blood loss (mL) during operation. The median operation duration was 60 min, and the patients were discharged on postoperative second day.

The hemoglobin levels are compared in detail in Table 3. In Table 2, no difference was observed between preoperative and postoperative second- and sixth-hour hemoglobin values

Table 1. Demographic and general characteristics of groups.

	Vertical incision group (n=31)	Transverse incision group (n=30)	p-value
Age, years (median, range)	39 (26–45)	37.5 (25–44)	0.058
Parity (median, range)	2 (0–3)	2 (0–5)	0.887
Mean myoma diameter, cm (median, range)	8 (5–15)	8 (4–13)	0.351
Number of leiomyomas (median, range)	1 (1–4)	1 (1–6)	0.010
Uterine size, cm (median, range)	12 (8–18)	12 (8–20)	0.485
Chronic pelvic pain	17 (54.8)	15 (50)	0.903
Menorrhagia	22 (71)	18 (60)	0.528
Location of myomas (n, %)			
Anterior	12 (38.7)	16 (53.3)	0.374
Posterior	16 (51.6)	14 (46.7)	0.896
Fundal	5 (16.1)	6 (20)	0.952
Operation duration (min)	60 (45–180)	60 (40–200)	0.344
Blood loss (mL)	400 (170–850)	745 (170–2200)	<0.001
Hospital stay duration (days)	2 (2–4)	2 (1–7)	0.329

Table 2. Comparison of the two groups in terms of operation duration (min), length of hospital stay (days), and estimated total blood loss (mL) during surgery, pre- and postoperative hemoglobin values.

		Vertical incision group (mean±standard deviation)	Transverse incision group (mean±standard deviation)	p-value
Hemoglobin levels (g/dL)	Preoperative	11.95±1.62	11.65±1.32	0.434
	Postoperative 2nd hour	11.13±1.54	10.36±1.54	0.056
	Postoperative 6th hour	10.98±1.60	10.49±1.43	0.211
Operation duration (min)		60 (45–180)	60 (40–200)	0.344
Blood loss (mL)		405.32 (170–850)	809.33 (170–2200)	<0.001
Hospital stay duration (days)		2 (2–4)	2 (1–7)	0.329

Table 3. Comparison of the two groups in terms of difference between second and sixth hours of postoperative hemoglobin levels.

		Vertical incision group (mean±standard deviation)	p-value	Transverse incision group (mean±standard deviation)	p-value
Hemoglobin Levels (g/dL)	Difference between preoperative and postoperative 2nd hour	0.82±1.25	<0.001	1.29±0.81	<0.001
	Difference between preoperative and postoperative 6th hour	0.97±1.26	<0.001	1.16±0.86	<0.001
	Difference between postoperative 2nd hour and 6th hour	0.15±0.57	0.249	-0.12±0.88	0.365

when the vertical and transverse incision groups were compared. It was found that in the transverse incision group, higher level of blood loss was observed when compared with the vertical incision group. No intraoperative and postoperative complications were reported with transverse or vertical incisions.

DISCUSSION

The treatment option of leiomyomas depends on the patients' age, future expectation of fertility, symptoms, and size[2,7]. A standard operative technique has not been established in open abdominal myomectomy for the uterine incision.

It has been revealed that the Pfannenstiel incision was preferred three times over multiple laparoscopic incision sites[8]. Mini-laparotomy myomectomy with skin incision <8 cm is an alternative surgical method for symptomatic myomas. This surgical technique significantly reduces the operation duration and may even reduce blood loss[9]. In addition, the operators working in rural areas prefer laparotomy because of the circumstances in which laparoscopic operations may not be performed due to the lack of qualified personnel and the lack of blood transfusion centers and equipment[10]. Robotic myomectomy is feasible for managing large uterine myoma, such as those larger than 10 cm in diameter, but it takes a reasonable longer operation duration[11]. Therefore, we chose to analyze the open abdominal myomectomy technique.

The myomectomy incision could injure the arterial blood vessels on the leiomyoma surface. The optimal direction of myomectomy incision according to the direction of the blood vessels is unclear. The results of the studies may be contradictory as they are based on the anatomy of the blood vessels in the normal uterus. Most gynecologic surgeons prefer a vertical incision in myomectomy operations, while some surgeons may prefer a transverse incision to protect the horizontal curved arcuate vessels[12]. In a retrospective analysis of the course of arteries in angiography, in patients with symptomatic uterine leiomyomas undergoing uterine artery embolization, it was reported that arterial blood vessels were mostly crossed on the surface of the anterior and posterior fibroids, whereas no dominant pattern was observed in the arterial course of fundal fibroids. It was concluded that the vertical incision would not protect the vascular injuries since approximately 40% of the vessels cross the middle line[5]. In this context, it can be concluded that the type of uterine incision does not affect the amount of blood loss. Earlier studies have recommended the use of hemostatic procedures during myomectomy to reduce blood loss[13]. Several pharmacological agents (e.g., injection of vasoconstrictors into the incision site, uterotonics, and tranexamic acid) and tourniquets and clamps that occlude the uterine vascular supply are used to decrease the blood loss.

The surgeons often chose their familiar hemostatic technique. There is no consensus on the preferred uterine incision techniques to reduce the blood loss. Blood loss during myomectomy is also correlated with the number, size, and location of leiomyomas. In this prospective study, we found no difference in demographic variables. Although it was shown in the literature that surgical technique affected blood loss during myomectomy, it was found that the uterine size did not affect the blood loss during hysterectomy. Given that myomectomy incisions do not affect the amount of blood loss, the choice of the incision type should depend primarily on the preference of the surgeon. In this study, we studied different incision techniques by randomizing fibroids of similar character.

In this study in which myoma was accessed through two separate incisions made in laparotomic myomectomy, we aimed to compare parameters such as loss of blood, length of stay, and operation duration. However, it was revealed during this study that difficult-to-access myomas such as the posterior and lower segment or cervical leiomyomas can be accessed more easily through transverse incisions. As transverse myomectomy incision makes it easier to approach the fibroids that are difficult to reach, this incision contributes to the shortening of the

operation duration and the associated risk of anesthesia complications. It also offers individual solutions in the approach to specific cases in training and education hospitals where resident training is provided. But these data are not evidential; rather, it is a fact that we observed at the end of the study. As a secondary outcome, knowing that no intraoperative or early postoperative complications were reported with the two incisions, we may also comment that both incisions are safe and the surgeon should decide the appropriate incision type depending on the size and location of the leiomyoma.

The limitation of this study is that more number of leiomyomas were present in transverse incision groups. The standardization of techniques in this type of study is always a challenge because of the patient-dependent factors. Also, further studies evaluating the outcomes of the type of incision in terms of obstetric outcomes and risk of uterine rupture may be valuable.

CONCLUSIONS

Both vertical and transverse incision techniques were safe and effective in terms of operation duration and intraoperative blood loss. The surgeons should prefer the most feasible incision depending on the leiomyoma size and localization.

AUTHORS' CONTRIBUTION

OU: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **MCI:** Data Curation, Formal Analysis, Writing – Original Draft. **AK:** Formal Analysis, Writing – Original Draft.

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The value of C-reactive protein/albumin, fibrinogen/albumin, and neutrophil/lymphocyte ratios in predicting the severity of COVID-19

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SUMMARY

OBJECTIVE: This retrospective study aimed to determine the predictive values of the C-reactive protein (CRP)/albumin ratio (CAR), fibrinogen/albumin ratio (FAR), and neutrophil/lymphocyte ratio (NLR) parameters, which reflect the systemic inflammatory status, for the severity of COVID-19.

METHODS: A total of 188 patients diagnosed with COVID-19 were enrolled in this study. Among them, 118 were in the severe group, and 70 were in the non-severe group. Levels of albumin, CRP, D-dimer, procalcitonin, fibrinogen, and hemoglobin; leukocyte, neutrophil, lymphocyte, and monocyte counts; and the FAR, CAR, and NLR were compared between the two groups.

RESULTS: The CAR, FAR, and NLR values were significantly higher in the severe group compared to the non-severe group. CAR, FAR, and NLR were positively correlated with leukocyte and neutrophil counts and CRP, procalcitonin, and fibrinogen levels. On the other hand, they were inversely correlated with monocyte (except for NLR) and lymphocyte counts. Receiver operator characteristic analysis showed that the area under the curve (AUC) for CAR, FAR, and NLR was 0.841, 0.737, and 0.802, respectively.

CONCLUSIONS: Our investigation revealed that the CAR, FAR, and NLR indices can be used to predict the severity of COVID-19, among which CAR was the best predictor of severe COVID-19.

KEYWORDS: COVID-19. C-reactive protein. Fibrinogen. Neutrophils.

INTRODUCTION

The COVID-19 pandemic started in China in December 2019 and is still ongoing worldwide. This highly contagious disease, which is a priority public health problem in countries affected by the pandemic, is transmitted among humans via close contact and respiratory droplets. The patients present with a wide clinical spectrum ranging from asymptomatic infection to mild or severe viral pneumonia, or respiratory failure leading to death[1,2]. The course of the disease was reported to be more severe in frail patients, that is, elderly persons and patients with preexisting chronic illnesses[3,4]. Early diagnosis and discriminating the critical cases to administer timely therapy is very important to slow down or prevent the progression of the disease. Thus, for rapid clinical decision-making, easy-to-access, quick, and low-cost markers are needed. Among several laboratory parameters assessed in many studies, lymphocyte,

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platelet, albumin, C-reactive protein (CRP), fibrinogen, procalcitonin, D-dimer, interleukin-6, and their derived neutrophil/lymphocyte ratio (NLR) and fibrinogen/albumin ratio (FAR) have been proposed as predictive markers for the severity of COVID-19[5-9]. The CRP/albumin ratio (CAR) is a novel index calculated by dividing the CRP to albumin level, and many studies have shown that CAR can be used to predict the activity, severity, and prognosis of various conditions[10-13]. However, whether CAR is an efficient indicator in determining the severity of COVID-19 has not been investigated so far. Therefore, in this retrospective study, we aimed to determine the predictive values of the CAR, FAR, and NLR indices for the severity of COVID-19.

METHODS

A total of 188 patients diagnosed with COVID-19 at the Sanliurfa Training and Research Hospital from April to July 2020 were included in this retrospective study. The COVID-19 diagnosis was confirmed by a positive PCR result from nasopharyngeal swab specimens. The patients were categorized into two groups, including the non-severe (mild/moderate cases) and severe (severe/critical cases) groups, according to the disease severity[14]. Non-severe cases had either mild clinical symptoms without signs of pneumonia on imaging (mild type) or fever and respiratory symptoms, with signs of pneumonia on imaging (moderate type). Cases in the severe group met at least one of the following criteria:

1. Respiratory rate ≥30/min;
2. Oxygen saturation ≤93%;
3. The ratio of arterial partial oxygen pressure to inspiratory oxygen fraction (PaO_2/FiO_2) ≤300 mmHg;
4. Respiratory failure and requiring mechanical ventilation;
5. Shock;
6. Other organ failure requiring intensive care support.

Among the 188 included patients, 118 were in the severe group and 70 were in the non-severe group. Patients with connective tissue disorders, hematologic diseases, kidney or liver dysfunction, thyroid diseases, cancers, age less than 18 years, who were pregnant, and those receiving albumin transfusion before treatment were not included in the study. This retrospective study was approved by the Harran University Ethics Committee.

The age, gender, comorbidities, and laboratory results of the participants on admission were obtained from the database of the hospital information system. Complete blood count parameters (leukocyte, neutrophil, lymphocyte, monocyte, and hemoglobin) were determined using a Sysmex XN-1000 analyzer (Sysmex, Japan). Albumin, CRP, D-dimer, and procalcitonin levels were analyzed using the classical methods in a Cobas 8000 analyzer (Roche Diagnostics, Germany); the fibrinogen level was measured using a Sysmex CS-2000i analyzer (Sysmex, Japan). The FAR, CAR, and NLR values were calculated as follows: FAR=(fibrinogen/albumin ratio), CAR=(CRP/albumin ratio), and NLR=(neutrophil/lymphocyte ratio).

Statistical analysis

Data analysis was done using SPSS version 20 (IBM Corp, Armonk, NY) and a $p<0.05$ was considered significant. Demographic and laboratory data were compared between the severe and non-severe groups using the independent sample t-test, Mann-Whitney U-test, or χ^2. Correlations between CAR, FAR, and NLR and inflammatory markers in the COVID-19 patients were determined using the Spearman test. The predictive value of FAR, CAR and NLR in distinguishing severe from non-severe COVID-19 patients was determined by receiver operator characteristic (ROC) analysis.

RESULTS

A total of 188 patients with COVID-19 were included in this study. Of these patients, 112 were in the non-severe group while 70 were in the severe group. As shown in Table 1, the severe group had higher leukocyte and neutrophil counts; CRP, D-dimer, procalcitonin, and fibrinogen levels; and CAR, FAR, and NLR; and lower lymphocyte and monocyte counts and albumin levels than those in the non-severe group ($p<0.05$). The two groups did not differ in terms of age, male/female ratio, incidences of comorbidities, and hemoglobin level ($p>0.05$).

Correlations between CAR, FAR, and NLR and the inflammatory markers studied in COVID-19 patients are shown in Table 2. CAR and FAR were positively associated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen levels and negatively associated with monocyte and lymphocyte counts. NLR was positively associated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen levels and negatively associated with lymphocyte count.

ROC analysis results of the CAR, FAR, and NLR are shown in Table 3. The area under the ROC curve (AUC) was 0.841 (95%CI 0.784–0.899, $p<0.001$) for CAR, 0.737 (95%CI 0.663–0.811, $p<0.001$) for FAR, and 0.802 (95%CI 0.735–0.869, $p<0.001$) for NLR (Figure 1).

DISCUSSION

In this study, we found that the severe COVID-19 group had higher CAR, FAR, and NLR compared to the non-severe

Table 1. Demographics and laboratory characteristics of patients with COVID-19 on admission.

	Non-severe group (n=118)	Severe group (n=70)	p-value
Age, years	59.6±12.2	62.3±12.7	0.146
Gender, male/female	55/63	38/32	0.309
Comorbidities, n (%)			
Diabetes	43 (36.4)	21 (30.0)	0.368
Hypertension	65 (55.1)	37 (52.9)	0.767
Cardiovascular disease	33 (28.0)	20 (28.6)	0.929
Dyslipidemia	31 (26.3)	21 (30.0)	0.581
Pulmonary disease	18 (15.3)	8 (11.4)	0.463
Laboratory Parameter			
Leukocyte, x10^3/µL	6.28 (2.15–15.28)	9.33 (2.10–25.92)	<0.001
Neutrophil, x10^3/µL	3.98 (1.18–14.22)	8.11 (1.42–23.25)	<0.001
Lymphocyte, x10^3/µL	1.58 (0.49–5.05)	1.10 (0.27–6.35)	<0.001
Monocyte, x10^3/µL	0.60 (0.12–1.79)	0.45 (0.11–11.06)	0.017
Hemoglobin, g/dL	13.52±1.52	13.73±1.69	0.381
Albumin, g/dL	4.18±0.43	3.65±0.42	<0.001
D-dimer, ug/mL	0.28 (0.11–3.92)	0.58 (0.15–26.87)	<0.001
CRP, mg/L	13.2 (0.7–267.5)	91.9 (4.63–408.1)	<0.001
Procalcitonin, ng/mL	0.07 (0.02–0.39)	0.15 (0.03–87.63)	<0.001
Fibrinogen, mg/dL	374.9 (102.8–888.9)	516.6 (101.6–900)	<0.001
CAR	3.18 (0.16–84.12)	25.62 (1.08–126.35)	<0.001
FAR	94.8 (25.1–279.6)	138.5 (23.6–262)	<0.001
NLR	2.56 (0.51–26.33)	6.25 (1.19–52.44)	<0.001

CRP: C-reactive protein; CAR: C-reactive protein (CRP)/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

Table 2. Correlations of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio with the inflammatory markers in COVID-19 patients.

	CAR		FAR		NLR	
	r	p	r	p	r	p
Leukocyte	0.336	<0.001	0.289	<0.001	0.606	<0.001
Neutrophil	0.504	<0.001	0.414	<0.001	0.818	<0.001
Lymphocyte	-0.532	<0.001	-0.348	<0.001	-0.722	<0.001
Monocyte	-0.229	0.002	-0.175	0.018	-0.089	0.224
CRP	0.998	<0.001	0.713	<0.001	0.635	<0.001
Fibrinogen	0.611	<0.001	0.970	<0.001	0.391	<0.001
Procalcitonin	0.671	<0.001	0.438	<0.001	0.560	<0.001

CRP: C-reactive protein; CAR: C-reactive protein (CRP)/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

COVID-19 group. In addition, the values of these 3 parameters were positively correlated with the leukocyte and neutrophil counts and CRP, procalcitonin, and fibrinogen levels and negatively correlated with monocyte (except for NLR) and lymphocyte counts. ROC analysis illustrated that CAR had the highest AUC value, thus demonstrating that it was more efficient than FAR and NLR in predicting the severity of COVID 19. To our knowledge, this is the first study

Table 3. Receiver operator characteristic analysis results of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio.

	AUC (95%CI)	Cut-off level	Sensitivity (%)	Specificity (%)	p-value
CAR	0.841 (0.784–0.899)	7.54	82.6	66.7	<0.001
FAR	0.737 (0.663–0.811)	113.5	69.6	65.8	<0.001
NLR	0.802 (0.735–0.869)	3.16	78.3	68.4	<0.001

AUC: area under the curve; CAR: C-reactive protein/albumin ratio; FAR: Fibrinogen/albumin ratio; NLR: Neutrophil/lymphocyte ratio.

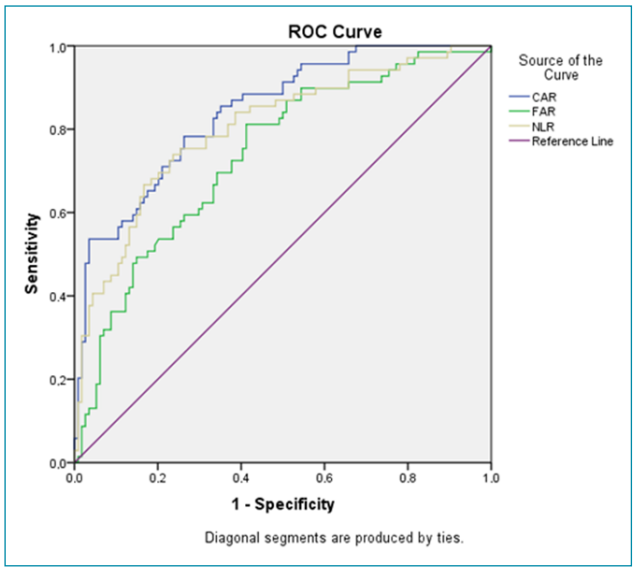

Figure 1. Receiver operator characteristic curves of C-reactive protein/albumin ratio, fibrinogen/albumin ratio and neutrophil/lymphocyte ratio in predicting severe COVID-19 on admission.

that explores the predictive values of CAR for the COVID-19 severity.

COVID-19 infection has a wide clinical spectrum ranging from asymptomatic infection to severe/critical disease. Patients with severe COVID-19 can progress rapidly to develop worse clinical outcomes such as acute respiratory distress syndrome, multiple organ failure, and eventually death, while non-severe patients have a good prognosis[15]. Therefore, efficient indicators are needed to distinguish between severe and non-severe patients for timely treatment. In this context, the researchers focused on the predictive value of various laboratory parameters like lymphocyte count, NLR, CRP, albumin, and fibrinogen in severe COVID-19 disease[5-9].

Lymphopenia and neutrophilia are commonly observed hematological abnormalities in COVID-19 patients and have been proposed as effective indicators of disease severity and poor prognosis in COVID-19[16-18]. Recently, Nalbant et al.[19] found that the NLR index, which can be easily calculated by dividing the neutrophil count by the lymphocyte count, is an independent predictor for COVID-19 diagnosis. Moreover, some studies have reported that the NLR index is closely related to the progression of COVID-19[20,21]. Concordant with these studies, we observed that the NLR was higher in the severe than the non-severe COVID-19 patients and that it was positively associated with the inflammatory markers (leukocyte count, CRP, procalcitonin, and fibrinogen), suggesting that the NLR might be a potential predictor of severe COVID-19.

Albumin is a negative acute-phase reactant that tends to decrease in response to acute conditions such as inflammation, trauma, surgery, and burns[22]. The albumin level was found to be lower in COVID-19 patients, and the hypoalbuminemia was more severe in critically ill patients[9,23]. On the other hand, fibrinogen is one of the positive acute phase response proteins that increase during inflammation[24]. Recent studies have shown that fibrinogen levels are significantly increased in severe COVID-19 patients compared to non-severe patients[5,6]. In addition, Bi et al.[7] reported that FAR, simply calculated by the ratio of fibrinogen to albumin, could be a new marker for estimating the severity of COVID-19, which is consistent with our results.

CRP, another positive acute phase reactant, increases in response to infections, inflammation, and tissue damage[25]. It has been shown that in COVID-19 patients, CRP reaches high levels and the magnitude of the increase correlates with the severity of the illness[8]. On the other hand, the role of the CAR index, the ratio of CRP to albumin, in predicting the severity of COVID-19 is unknown. Therefore, this study investigated the ability of CAR, as well as NLR and FAR, to differentiate between patients with and without severe COVID-19. We found that the CAR value was higher in severe patients compared to non-severe patients and that it was positively correlated with leukocyte, neutrophil, CRP, procalcitonin, and fibrinogen and negatively correlated with monocyte and lymphocyte counts. In addition, in our ROC curve analysis, the AUC value of CAR was greater than that of FAR and NLR. These results showed that CAR was more efficient than FAR and NLR in predicting the severity of COVID 19.

The main limitation of our study is its retrospective design and it was conducted at a single center. Another limitation was the lack of data on smoking, alcohol use, and body mass index affecting laboratory results.

CONCLUSIONS

In conclusion, we found that the CAR, FAR, and NLR indices could be used as new potential parameters to distinguish severe COVID-19 patients from non-severe patients. Of these, CAR was the best predictor of severe COVID-19.

AUTHORS' CONTRIBUTIONS

AT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **TDÇ:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **GÇ:** Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review & editing. **RDP:** Investigation, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

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Mean serum D-dimer level to predict in-hospital mortality in COVID-19

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SUMMARY

OBJECTIVE: The prognostic effect of the mean serum D-dimer levels, which was calculated from the first five days of hospitalization of the patients, has not been elucidated. This study aimed to evaluate the effect of mean D-dimer level about in-hospital mortality in patients hospitalized due to coronavirus disease-2019 (COVID-19) infection.

METHODS: In this observational retrospective study, we examined the in-hospital prognostic value of mean D-dimer [D-dimer$^{first\ day}$ +D-dimer$^{third\ day}$ +D-dimer$^{fifth\ day}$)/3 on 240 consecutive adult patients with COVID-19. Patients were stratified into tertiles according to their mean D-dimer starting from the lowest one. In-hospital mortality rates were compared between tertiles and the power of the mean D-dimer level was also presented by a receiver operating curve analysis.

RESULTS: After adjustment for confounding baseline variables, mean D-dimer in tertile 3 was associated with 4.2-fold hazard ratio of in-hospital mortality (odds ratio [OR] 4.2; 95% confidence interval [CI] 1.8–20.1, p<0.001). A receiver-operating curve analysis revealed that the optimal cutoff value of the mean D-dimer to predict in-hospital mortality was 779 µg/L with 77% sensitivity and 83% specificity (area under the curve [AUC] 0.87; 95%CI 0.81–0.94; p<0.001).

CONCLUSION: Patients with a higher mean D-dimer level should be followed-up more closely as they may be a candidate for a more aggressive treatment modality, such as biologic agents or convalescent plasma.

KEYWORDS: COVID-19. D-dimer. In-hospital mortality.

INTRODUCTION

A newly defined 2019 coronavirus (SARS-CoV-2) has been declared as a pandemic by the World Health Organization (WHO) on March 2020[1]. Although there is no standard therapy worldwide in terms of anticoagulation following the diagnosis of SARS-CoV-2 infection, it has been already illustrated to activate procoagulation cascades especially in critically ill patients. As the pandemic becomes widespread over time, routinizing the treatment options and the prognostic factors to detect critically ill patients as early as possible becomes vital.

D-dimer has been presented as one of the most frequent and promptly elevated laboratory findings associated with coagulopathy in coronavirus disease 2019 (COVID-19) patients[2]. A strong synergy between SARS-CoV-2 infection and venous thromboembolism is a remarkable relation representative of the predictive value of D-dimer in these patients. The prevalence of venous thromboembolism has been reported to be 25% in patients with severe pneumonia due to SARS-CoV-2 infection[3]. On the contrary, high serum levels of D-dimer are not disease specific and are usually related to several medical circumstances such as infection, inflammation, and pregnancy[4].

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Despite the high level of D-dimer which appears as a nonspecific marker, more than half of the patients who have serum D-dimer levels >3.0 μg/mL have a thrombotic complication necessitating imaging modalities for the etiologic investigation[5]. In COVID-19 era, D-dimer >0.5 μg/mL has been first reported as a prognostic indicator in a retrospective analysis with a large cohort from China[6]. Moreover, D-dimer levels were compared between the intensive care unit (ICU) and non-ICU patients showing a remarkable highness in the ICU patients[1,2]. However, there is very little evidence about the prognostic effect of D-dimer level follow-up during the index hospitalization period in COVID-19 patients.

Therefore, we hypothesized a new score calculated from the first-, third-, and fifth-day level of D-dimer to predict in-hospital prognosis. The purpose of this study was both to test the in-hospital mortality predictive value of mean D-dimer level and to draw the attention toward the anticoagulation treatment strategies in COVID-19 patients.

METHODS

The consecutive 240 patients, who were either diagnosed with COVID-19 in our emergency department or referred to our hospital with the COVID-19 diagnosis, were included in our study retrospectively following their index hospitalization period. All of the patients enrolled in this study were hospitalized in the Sultan Abdulhamid Han Training and Research Hospital between March 2019 and May 2019. Patients were involved in the study if their D-dimer serum levels of first, third, and fifth days were obtained from the hospital database. If one of the D-dimer levels was missing among the first, third, or fifth day in their hospitalization period, the patients were excluded. The patients were also excluded if they were under anticoagulation treatment. The baseline characteristics, presenting symptoms, laboratory and computed tomography findings were attained from the hospital database. The treatment approach of the patients was determined according to the consensus between the attending physicians and the specialist of infectious and clinical microbiology in compliance with national ministry of health COVID-19 guidelines. The diagnosis of COVID-19 had two steps: (1) specific signs and symptoms or imaging findings in computed tomography consistent with COVID-19 and (2) the confirmation of active COVID-19 infection was provided with the real-time polymerase chain reaction (RT-PCR) test. The investigators first obtained approval of the study from the Turkish Ministry of Health Scientific Research Committee. The investigation was later approved by the Local Ethics Committee (approval number 2020/KK/132). Our study was conducted in compliance with the "Good Clinical Practice" guidelines of the Declaration of Helsinki as revised in 2008. There was no need for an informed consent as the study had an observational and retrospective design. Blood samples were gathered from the patients within 24 h of their admission to the hospital. The Sysmex XN 9000 hematology analyzers (Sysmex Corporation, Kobe, Japan) were used to analyze the complete blood count parameters. Beckman Coulter, Inc. kits and calibrators were used to perform biochemical measurements. Serum D-dimer levels were calculated via particle-enhanced immunoturbidimetric methods by using Roche Cobas 6000 c501 analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland). The reference range of D-dimer in our hospital is 0–500 μg/L. The mean serum D-dimer levels were calculated as follows: $(\text{D-dimer}^{\text{first day}} + \text{D-dimer}^{\text{third day}} + \text{D-dimer}^{\text{fifth day}})/3$. According to our hospital's approach to patients with COVID-19, patients with D-dimer levels >1000 μg/L were administered enoxaparin at anticoagulation doses. A single value >1000 μg/L was defined as the level for the start of anticoagulation.

In our study, in-hospital mortality was defined as the primary outcome. A trained physician evaluated the medical data of the patients and notified the patients with in-hospital mortality.

Statistical analysis

In a first step, our study group was divided into tertiles according to their mean serum D-dimer levels calculated according to the definition in the method section. All of the tertiles included 80 patients. In a second step, baseline characteristics, admission symptoms, laboratory parameters, and pneumonia regions in the lungs were compared between these tertiles. Quantitative variables were presented as mean value ± standard deviation. Kolmogorov–Smirnov test was used for evaluation of normality. All continuous variables showed skewed distributions and these are compared using Kruskal–Wallis test. Categorical variables were presented as numbers and percentages. Analyses of categorical variables were performed by Pearson's chi-square test. Univariable and multivariable logistic regression analyses were performed to determine the independent predictors of in-hospital mortality other than serum D-dimer levels. Variables that could be a predictor of in-hospital mortality and with a significant p-value in Table 1 were entered into univariable analysis. Variables with a $p<0.05$ in univariable regression were included into binary logistic regression analysis. The results of regression analysis were presented as odds ratio (OR) with 95% confidence interval (CI). Two multivariable models were used: model I (unadjusted) and model II (adjusted). The variables covaried in model II were age, white blood cells, lactate dehydrogenase and lymphocytes,

Table 1. Baseline clinical characteristics, laboratory parameters, and pneumonia regions in the lungs of all patients.

	Mean D-dimer level through index hospitalization period			
	T1, n=80	T2, n=80	T3, n=80	p-value
Baseline characteristics				
Age, years	50.1±14.8	53.8±14.6	59.6±15.1	0.001
Male gender, n (%)	42 (52.5)	43 (53.8)	43 (53.8)	0.983
Hypertension, n (%)	25 (31.3)	30 (37.5)	39 (48.8)	0.071
Diabetes mellitus, n (%)	20 (25.0)	15 (18.8)	26 (32.5)	0.135
Insulin dependency, n (%)	3 (3.8)	2 (2.5)	7 (8.8)	0.158
Hyperlipidemia, n (%)	1 (1.3)	3 (3.8)	8 (10.0)	0.033
COPD, n (%)	5 (6.3)	8 (10.0)	13 (16.3)	0.121
Coronary artery disease, n (%)	3 (3.8)	5 (6.3)	14 (17.5)	0.007
Chronic renal failure, n (%)	2 (2.5)	3 (3.8)	7 (8.8)	0.158
Atrial fibrillation, n (%)	1 (1.3)	1 (1.3)	1 (1.3)	1.000
Cerebrovascular disease, n (%)	0 (0.0)	2 (2.5)	2 (2.5)	0.362
Dementia, n (%)	1 (1.3)	1 (1.3)	1 (1.3)	1.000
Cancer, n (%)	0 (0.0)	2 (2.5)	5 (6.3)	0.061
Congestive heart failure, n (%)	0 (0.0)	2 (2.6)	6 (7.5)	0.028
Smoking, n (%)	10 (12.8)	11 (13.8)	6 (7.5)	0.406
Alcohol, n (%)	12 (15.0)	16 (20.0)	13 (16.3)	0.682
Admission symptoms n (%)				
Fever	27 (33.8)	45 (56.3)	47 (58.8)	0.002
Cough	46 (57.5)	45 (56.3)	44 (55.7)	0.973
Dyspnea	10 (12.5)	18 (22.5)	22 (27.5)	0.059
Diarrhea	3 (3.8)	3 (3.8)	6 (7.5)	0.454
Myalgia	25 (31.6)	27 (33.8)	26 (32.5)	0.960
Weakness	28 (35.0)	25 (31.3)	21 (26.3)	0.485
Asymptomatic	13 (16.3)	5 (6.3)	3 (3.8)	0.012
Laboratory parameters				
White blood cells, cells/µL	6.0±2.4	5.8±2.7	7.4±4.3	0.070
Lymphocytes	1.5±0.7	1.5±0.7	1.1±0.7	<0.001
Platelets, cells/µL	204.6±62.1	190.8±54.9	207.2±73.8	0.408
Hemoglobin, g/dL	13.4±1.7	13.2±1.8	13.0±1.6	0.192
Glucose, mg/dL	106.6±28.2	117.3±41.9	126.2±62.9	0.169
Lactate dehydrogenase, U/L	449.8±261.0	452.1±137.3	634.3±594.7	<0.001
Alanine aminotransferase, U/L	36.3±27.0	35.7±27.2	39.1±45.0	0.298
Aspartate aminotransferase, U/L	28.4±15.8	26.6±13.5	32.0±30.7	0.729
Creatinine, mg/dL	0.9±0.2	0.9±0.2	1.0±0.4	0.074
Potassium, mEq/L	4.2±0.3	4.1±0.3	4.2±0.5	0.264
Sodium, mEq/L	137.1±3.8	136.8±3.7	136.3±3.9	0.317
D-dimer, µg/L$^{\text{first day}}$	213.0±72.3	372.9±184.3	1630.1±1682.0	<0.001
D-dimer, µg/L$^{\text{third day}}$	213.0±71.5	383.8±114.5	1127.7±963.0	<0.001
D-dimer, µg/L$^{\text{fifth day}}$	279.9±61.3	390.5±137.9	1405.2±1020.3	<0.001
Mean D-dimer, µg/mL	247.4±28.3	382.4±86.4	1387.6±957.1	<0.001
C-reactive protein, mg/dL	35.3±46.5	50.0±68.5	75.8±74.8	<0.001
Albumin, g/L	42.2±6.0	40.3±5.5	37.0±6.3	<0.001
Troponin, ng/L	10.9±15.4	11.3±17.8	93.7±535.4	<0.001
Pneumonia region in the lungs				
Bilateral	57 (71.3)	64 (80.0)	60 (75.0)	0.435
Left	16 (20.0)	12 (15.0)	9 (11.3)	0.307
Right	7 (8.8)	4 (5.0)	11 (13.8)	0.157

Continuous variables were presented as mean ± Standard Deviation; COPD: chronic obstructive pulmonary disease.

and troponin. The cutoff values of mean serum D-dimer levels and in-hospital mortality with the highest sensitivity and specificity were calculated by nonparametric receiver-operating characteristics (ROC) curve analysis. Data were analyzed by using the Statistical Package for Social Sciences (SPSS) software program, version 24.0 (IBM, Armonk, New York).

RESULTS

Table 1 presents the baseline features, laboratory parameters, and pneumonia region in the lungs stratified by tertiles. This retrospective study included 240 patients (mean age 54.5±15.3; 53.3% male). The patients in tertile 1 had a mean D-dimer level 181–284 µg/L, tertile 2 286–559 µg/L, and tertile 3 570–4380 µg/L through their index hospitalization period. Tertile 3 had notably older, and had a higher frequency of hyperlipidemia, coronary artery disease, and congestive heart failure compared to other tertiles. According to their admission symptoms, patients stratified in tertile 1 had a higher frequency of fever and were more frequently hospitalized in an asymptomatic manner compared to other tertiles. Total lymphocyte count and the serum level of albumin on admission were remarkably lower in tertile 3. The levels of lactate dehydrogenase, D-dimer$^{\text{first day}}$, D-dimer$^{\text{third day}}$, D-dimer$^{\text{fifth day}}$, mean D-dimer, C-reactive protein, and troponin were statistically higher in tertile 3. The prevalence of pneumonia region in the lungs did not differ between the tertiles. Univariable analysis excepting D-dimer levels was implemented and revealed that hypertension, coronary artery disease, age, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, white blood cells, lymphocytes, lactate dehydrogenase, troponin, albumin, and C-reactive protein as predictors of in-hospital mortality. In the multivariable analysis, white blood cells (OR 1.605; 95%CI 1.287–2.001), age (OR 1.091; 95%CI 1.010–1.179), lymphocytes (OR 0.437; 95%CI 0.195–0.978), lactate dehydrogenase (OR 1.003; 95%CI 1.001–1.006), and troponin (OR 1.045; 95%CI 1.002–1.093) were appeared as the independent indicators to have an effect on in-hospital mortality (Table 2). The logistic regression models for in-hospital mortality by mean D-dimer level through index hospitalization period tertile are presented in Table 3. In-hospital mortality has the higher rates at tertile 3 and that had 6.9 times higher than tertile 1, which was determined as the reference group. The relevancy slightly decreased after the adjustment for the confounders revealed to predict in-hospital mortality; tertile 3 had 4.2 times higher rates of in-hospital mortality compared to tertile 1. There were no major bleeding complications among our study population during hospitalization period.

A ROC analysis revealed that the optimal cutoff value of the mean D-dimer to predict in-hospital mortality was 779 µg/L with 77% sensitivity and 83% specificity (AUC 0.87; 95%CI 0.81–0.94; p<0.001) (Figure 1).

Table 2. Univariable predictors and multivariable model for in-hospital mortality.

	Univariable analysis			Multivariable analysis		
	p-value	OR	95%CI	p-value	OR	95%CI
Age	<0.001	1.098	1.055–1.142	0.027	1.091	1.010–1.179
Hypertension	0.017	3.019	1.214–7.509	–	–	–
Diabetes mellitus	0.028	2.729	1.114–6.684	–	–	–
COPD	<0.001	6.349	2.351–17.148	–	–	–
Coronary artery disease	<0.001	8.327	2.992–23.175	–	–	–
Chronic renal failure	0.001	8.866	2.541–30.928	–	–	–
Congestive heart failure	0.014	6.663	1.477–30.053	–	–	–
White blood cells	<0.001	1.475	1.296–1.679	<0.001	1.605	1.287–2.001
Lymphocytes	0.009	0.282	0.110–0.725	0.044	0.437	0.195–0.978
Lactate dehydrogenase	0.002	1.002	1.001–1.004	0.012	1.003	1.001–1.006
Troponin	<0.001	1.052	1.029–1.076	0.048	1.045	1.002–1.093
Albumin	<0.001	0.844	0.780–0.913	–	–	–
C-reactive protein	<0.001	1.011	1.006–1.016	–	–	–

CI: confidence interval; OR: odds ratio, COPD: chronic obstructive pulmonary disease. All clinical relevant parameters were included in the model. Only parameters that reached statistical significance at univariable analysis were given in the leftmost column.

Table 3 Logistic regression models for in-hospital mortality by mean D-dimer level through index hospitalization period tertile.

	Mean D-dimer level through index hospitalization period		
	T1, n=80	T2, n=80	T3, n=80
In-hospital mortality			
Number of patients	0	3	19
Case rate, %	0.0	3.8	23.8
In-hospital mortality, OR (95% CI)			
Model 1: unadjusted	1[Reference]	4.7 (1.5–8.1)	7.9 (2.2–28.2)
Model 2: adjusted for all covariate[s]a	1[Reference]	2.8 (1.2–6.9)	5.2 (1.8–20.1)

CI: confidence interval; OR: odds ratio. [a]Only parameters that reached statistical significance at multivariable analysis were age, white blood cells, lactate dehydrogenase and lymphocytes and troponin.

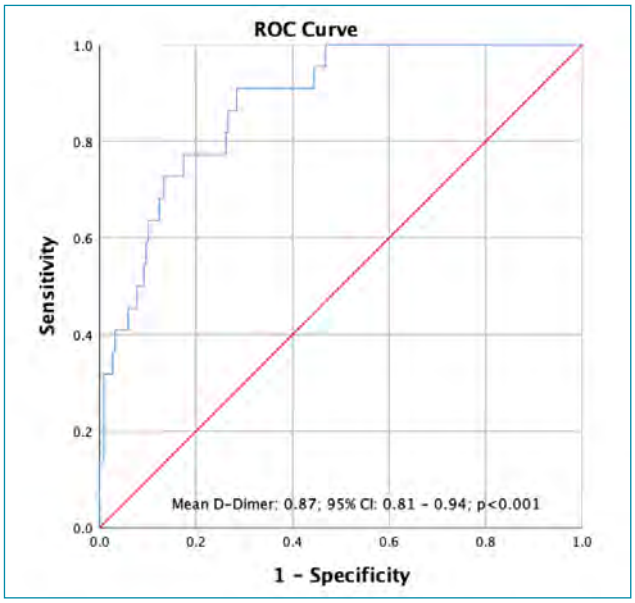

Figure 1. Receiver-operating characteristic curve analysis of mean D-dimer levels for in-hospital mortality.

DISCUSSION

This investigation is the pilot study representing the mean serum D-dimer level to estimate in-hospital mortality in hospitalized patients with COVID-19 infection. Mean serum D-dimer level, which is easily attainable from the first five days data of hospitalization due to COVID-19, was proved to have both high sensitivity and specificity to predict in-hospital mortality remarking the high procoagulant nature of SARS-CoV-2 infection.

D-dimer is identified as the soluble plasmin-mediated breakdown product of fibrin which is triggered following the initiation of coagulation and fibrinolysis cascade[1]. D-dimer has been already appeared as one of the criteria of disseminated intravascular coagulation in addition to its use for excluding thrombotic events[2]. Before the pandemic of COVID-19, D-dimer within the normal range has been already shown to have a higher sensitivity but remarkably lower specificity to predict thromboembolic circumstances. However, clinicians are accustomed to experience higher levels of serum D-dimer in hospitalized patients in the COVID-19 era, thereby bringing into prominence the follow-up serum D-dimer levels. Admission serum D-dimer level has been demonstrated to be notably higher in non-survivors compared to survivors in several investigations with different cohorts with COVID-19[1,7,9-11]. Moreover, D-dimer has been associated with COVID-19 disease severity as higher levels of serum D-dimer have been defined as an indicator of acute respiratory distress syndrome[9]. As long as COVID-19 has been strongly associated with procoagulation cascades which have been repeatedly confirmed, the follow-up serum D-dimer levels gain serious importance regarding in-hospital outcomes[12]. Therefore, it is extremely reasonable that higher mean serum D-dimer level has been linked to an increase in in-hospital mortality in hospitalized patients due to COVID-19.

Anticoagulation medical preferences and doses are still the question of debate in the COVID-19 era. Heparin treatment has been found to be related to lower mortality in severe SARS-CoV-2 infection[13]. Even though heparin treatment also has an additional anti-inflammatory effect, the main benefit in the aforementioned investigation is considered to be secondary to the anti-coagulation properties of the heparin. The main worth of notice is the beneficiary effects of heparin occurs if the serum D-dimer levels exceed sixfold of the upper limit of normal[13]. High levels of serum D-dimer and fibrinogen have been indicated as signs of the initiation of the procoagulation cascade; the disease severity may be manifested by the increase

in serum D-dimer level as clearly presented in our study. In the pandemics such as COVID-19, it is invaluable to determine prognostic factors in order to specify the disease severity before the occurrence of complications. The beginning treatment strategies such as biologic agents, anticoagulation, or convalescent plasma may dependently change to a patient-based approach, which may have a role to minimize disease-associated vital complications. As a result, the mean D-dimer level appears to have a substantial role to predict in-hospital mortality in hospitalized patients with COVID-19.

STUDY LIMITATIONS

This study has several limitations. The investigation was a single-center, retrospective, and observational study; therefore, our study has a slight limitation for generalizability. There may be a possible presence of unmentioned residual confounding factors, which may have an effect on the outcomes of the investigation.

CONCLUSION

The present investigation showed that mean D-dimer level obtained during the first five days of hospitalization was an independent predictor of in-hospital mortality in COVID-19 patients.

AUTHORS' CONTRIBUTION

MİH: Conception, Formal Analysis, Writing – Review & Editing. **TÇ**: Supervision, Writing – Review & Editing. **VÇ**: Data Curation Funding Acquisition, Resources. **ŞK**: Data Curation, Funding Acquisition, Resources.

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The ATRIA score is superior to the m-CHA_2DS_2-Vasc score in predicting in-hospital mortality in COVID-19

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SUMMARY

OBJECTIVE: Coronavirus disease 2019 (COVID-19) has become a health and social problem all over the world. Most of the deaths occur from embolism and thrombus formation. We aimed to compare the predictive value of the anticoagulation and risk factors in atrial fibrillation (ATRIA) and m-CHA_2DS_2-Vasc scores in in-hospital mortality in COVID-19.

METHODS: Three-hundred and ninety-four patients who were hospitalized due to COVID-19 between 10 June 2020 and 10 September 2020 were included. Three-hundred and sixty patients who survived were defined as the non-mortality group and the remaining 34 whose hospitalizations resulted in death were defined as the mortality group. The anticoagulation and risk factors in atrial fibrillation and m-CHA_2DS_2-Vasc scores of the patients were calculated.

RESULTS: A total of 394 patients, mean age 66.2±9.7 (221 male [56.1%]) were included in this retrospective study. The median values of the anticoagulation and risk factors in atrial fibrillation and m-CHA_2DS_2-Vasc scores were different between the groups (p<0.000 for both). The multivariate logistic regression analysis showed that both the m-CHA_2DS_2-Vasc and anticoagulation and risk factors in atrial fibrillation scores were independent predictors of in-hospital mortality (p=0.024, 95%CI 1.039–1.704 for anticoagulation and risk factors in atrial fibrillation and p=0.043, 95%CI 1.012–2.088 for m-CHA_2DS_2-Vasc). In the receiver operating characteristic curve analysis, the anticoagulation and risk factors in atrial fibrillation score was superior to the m-CHA_2DS_2-Vasc score with an AUC 0.774 and SE:0.037, and p<0.001.

CONCLUSIONS: In our study, we showed that the anticoagulation and risk factors in atrial fibrillation and m-CHA_2DS_2-Vasc scores can be used as predictors of thrombosis and mortality in COVID-19 patients. In addition, the predictive value of the anticoagulation and risk factors in atrial fibrillation score was higher than that of m-CHA_2DS_2-Vasc. The use of the anticoagulation and risk factors in atrial fibrillation score to assess high-risk patients in COVID-19 may be recommended.

KEYWORDS: Anticoagulants. Risk score. Coronavirus.

INTRODUCTION

The mortality rate of COVID-19, which emerged in Wuhan, China in the last quarter of 2019, varies between 2–3%[1-2]. This rate can go up to 50% in those who are hospitalized in intensive care units[3]. Possible complications of COVID-19, a viral infection, can be listed as septic shock, acute cardiac injury, arrhythmia, cardiovascular collapse, ARDS, and multiple organ failure[4]. Although most of the fatal cases included patients who died due to respiratory failure, in addition to this outcome, myocardial damage or heart failure findings were observed in some cases[5,6]. In COVID-19 patients, it is stated that the risk for coagulopathy increases especially in the elderly, or those

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with comorbid diseases, due to endothelial damage caused by the virus that binds to ACE_2, endothelial damage due to sepsis, activation of inflammatory and microthrombotic mechanisms, and stasis due to prolonged hospitalization[7,8]. Considering that thromboembolism increases mortality, the importance of determining which patients are at a greater risk for thromboembolism can be clearly justified. Congestive heart failure-Hypertension-Age ≥75 years-Diabetes Mellitus-Stroke ($CHADS_2$), Congestive heart failure-Hypertension-Age ≥75 years-Diabetes Mellitus-Stroke-Vascular disease-age 65–74 years- female sex (CHA_2DS_2-Vasc), modified-Congestive heart failure-Hypertension-Age ≥75 years-Diabetes Mellitus-Stroke-Vascular disease-age 65–74 years- male sex (m-CHA_2DS_2-Vasc) and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) scores are the most common scoring systems used to determine the risk of these patients[9,10]. In a study conducted by Kılıc et al., it was emphasized that the CHA_2DS_2-Vasc score was a predictor of unsuccessful response in STEMI patients receiving thrombolytic therapy[11]. Studies have shown that the ATRIA score is superior to $CHADS_2$ and CHA_2DS_2-Vasc in predicting the risk for thromboembolism[12,13]. Cetinkal et al. showed in their recently published studies that mortality increases in COVID-19 patients with higher m-CHA_2DS_2-Vasc scores[14]. The aim of this study was to compare the ATRIA and m-CHA_2DS_2-Vasc scores in patients with COVID-19 who were followed in intensive care units.

METHODS

This retrospective study consisted of 394 patients who were hospitalized with COVID-19 symptoms and laboratory or radiological findings between 10 June 2020 and 10 September 2020. Additionally, all patients over the age of 18 who had a confirmed diagnosis of HT, DM, and other comorbid conditions and received ongoing treatment were included in the study. Patients with end-stage heart failure, malignity, chronic inflammatory disease, and known coagulopathy were excluded. In the study of Ai et al., published in August, chest CT findings were more sensitive than PCR positivity[15]. Considering that, PCR positivity status was not imposed for the patients included in our study. A detailed medical history was recorded for each patient, and the baseline clinical characteristics at study entry, along with information on follow-up, were carefully collected. Systolic heart failure was defined as left ventricular ejection fraction <40%. Hypertension was defined as systolic and diastolic blood pressures >140/90 mmHg or if the patient was taking any anti-hypertensive medication. Diabetes mellitus (Type 2 DM) was defined as having a previous diagnosis of DM or using an anti-diabetic medication, or fasting blood glucose ≥126 mg/dL or HbA1c >6.5%. Patients with a history of thromboembolic stroke originating from carotid or vertebral arteries were defined as "presence of stroke". m-CHA_2DS_2-Vasc score was calculated by adding 2 points for age ≥75 years; 2 points for prior stroke or transient ischemic attack (TIA); and 1 point for each of the following factors: congestive heart failure or left ventricular ejection fraction ≤40%, hypertension, diabetes mellitus, vascular disease, age 65–74, and male gender, with a maximum score of 9 points[14]. The ATRIA risk score was calculated by adding 1 point for each of the following factors: female gender, diabetes mellitus, congestive heart failure, hypertension, proteinuria, and renal dysfunction (i.e. eGFR <45 mL/min/1.73 m^2 or end-stage renal disease), and by adding 0–9 points depending on the specific score weight of patient's age according to the presence or absence of prior ischemic stroke[16]. We did not have data about proteinuria, so the maximum score of the ATRIA risk score will be 14 points. Patients with ≤5 points were defined as low risk, patients with 6 points were at intermediate risk, while patients with ≥7 points were defined as high risk[17].

eGFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD-4) equation[18].

The study was approved by the Clinical Research Ethics Committee of the Ministry of Health of our country and the local Clinical Research Ethics Committee of our hospital (No. 1081, date: September 23, 2020). The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the approval previously obtained by the institution's human research committee.

Statistical analysis

All statistical analyses were performed with SPSS 17 (SPSS, Inc., Chicago, Illinois, USA) and MedCalc for Windows. The minimum number of subjects required in both groups for a significant difference between the two groups was 40 for the ATRIA score and 41 for the m-CHA_2DS_2-Vasc score (type 1 error: 0.01, test power: 0.9). Continuous variables were expressed as mean ± standard deviation (mean ± SD) or median (interquartile range), and categorical variables as numbers and percentages. Comparisons of the continuous variables between groups were performed using the independent samples t-test and Mann-Whitney U test. For appropriate and categorical variables, the χ^2 test or Fisher's exact test was used. We analyzed whether continuous variables had normal distribution using the Kolmogorov-Smirnov test. Univariate and multivariable logistic regression analyses were performed to assess the relationship between the ATRIA and m-CHA_2DS_2-Vasc scores. Variables with a $p \leq 0.05$ in univariate analysis were included in the multivariate analysis. The receiver operating characteristic

(ROC) curve analysis was performed to demonstrate the cut-off values, and sensitivity and specificity of the ATRIA and m-CHA_2DS_2-Vasc scores in showing COVID-19 mortality. The results are expressed as relative risk and 95% confidence interval (CI). A p value lower than 0.05 was considered statistically significant.

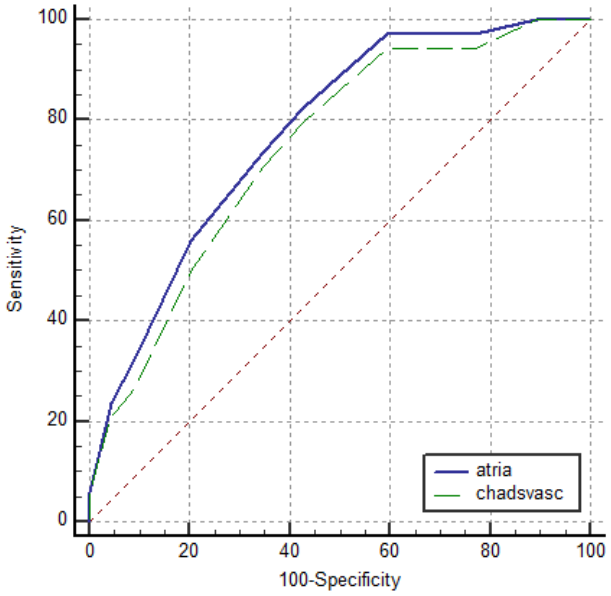
RESULTS

Three-hundred and ninety-four patients with a mean age of 66.2±9.7 years were included in the study (56.1%, n=221, male). Three-hundred and two patients (n=15, mortality group) were in the low-risk category, 49 (n=8, mortality group) were in the intermediate-risk category, and 43 (n=11, mortality group) were in the high-risk category according to the ATRIA score. One-hundred and ninety-six (n=5, mortality group) patients had a m-CHA_2DS_2-Vasc score of <3 and the remaining 198 (n=29, mortality group) had a score of ≥3. The median ATRIA and m-CHA_2DS_2-Vasc scores, with which patient-based cumulative risk was calculated and total comorbidity was evaluated, were different between the groups (Table 1).

A multivariate logistic regression analysis showed the ATRIA and m-CHA_2DS_2-Vasc scores were independent predictors of mortality in COVID-19 patients. Moreover, in the ROC analysis, the ATRIA score performed better than the m-CHA_2DS_2-Vasc score at predicting mortality with an AUC 0.774, 95%CI 0.729–0.814 and SE:0.037, and p<0.001 (Figure 1). The results of univariate and multivariate logistic regression analyses are shown in Table 2.

DISCUSSION

COVID-19 has become a health problem with deaths worldwide. It is known that mortality is higher in the elderly and those with comorbidity and widespread pulmonary involvement[19]. Around



	Area under the curve	Standard error	95%CI
ATRIA	0.774	0.0371	0.729–0.814
m-CHA_2DS_2Vasc	0.744	0.0404	0.698–0.787

Figure 1. Receiver operating characteristic curve analysis of the ATRIA and m-CHA_2DS_2Vasc scores.

Table 1. Baseline characteristics of non-mortality and mortality groups.

	Non-mortality group (n=360)	Mortality group (n=34)	p
Age, years	65.8±9.9	70.3±6.3	0.009*
Gender, male, n(%)	202 (56.1)	19 (55.8)	0.980
HT, n (%)	228 (63.3)	27 (79.4)	0.063
DM, n (%)	129 (35.8)	17 (50)	0.136
CAD, n (%)	117 (32.5)	16 (47)	0.091
HF, n (%)	31 (8.6)	6 (17.6)	0.115
CVD, n (%)	6 (1.6)	2 (5.8)	0.146
ESRD or GFR<45, n (%)	9 (2.5)	0 (0)	1.000
AF, n (%)	16 (4.4)	1 (2.9)	1.000
m-CHA_2DS_2-VASc, median (IQR)	2 (0–6)	5 (1–7)	<0.001
ATRIA, median (IQR)	3 (0–8)	6 (1–10)	<0.001

AF: atrial fibrillation; ATRIA: the anticoagulation and risk factors in atrial fibrillation; CAD: coronary artery disease; CVD: history of cerebrovascular disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GFR: glomerular filtration rate; HF: heart failure; HT: hypertension; m-CHA_2DS_2Vasc: modified-congestive heart failure-hypertension-age ≥75 years-diabetes mellitus-stroke-vascular disease-age 65–74 years-sex category;
*Although p-value was statistically significant, lowest and highest age values were in the same score for both scoring systems.

Table 2. Univariate and multivariate regression analyses of the ATRIA and m-CHA_2DS_2-VASc scores, and other variables.

	Univariate analysis OR (95%CI)	p	Multivariate analysis OR (95%CI)	p
ATRIA score	1.603 (1.339–1.920)	<0.001	1.331 (1.039–1.704)	0.024
m-CHA_2DS_2-VASc score	1.976 (1.529–2.554)	<0.001	1.453 (1.012–2.088)	0.043
Age	1.012 (1.052–1.093)	0.010	–	–

ATRIA: the anticoagulation and risk factors in atrial fibrillation; m-CHA_2DS_2Vasc: modified-congestive heart failure-hypertension-age ≥75 years-diabetes mellitus-stroke-vascular disease-age 65-74 years-sex category.

5–10% of the patients who have the disease become severely ill and need intensive care[20]. While the mortality rate in intensive care hospitalizations reaches 60% when the disease was first detected, it is now around 20%. The course of the disease is more serious and mortality rates are higher in those who are intubated[21].

Increased vasoconstrictor angiotensin II, decreased vasodilator angiotensin, and sepsis-induced release of cytokines can trigger a coagulopathy in COVID-19[22]. It is known that approximately 50% of patients hospitalized due to COVID-19 develop thrombosis and, despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 followed in intensive care unit developed life-threatening thrombotic complications[23].

Determining the thrombosis risk of the patients who are followed in intensive care units due to COVID-19 is important to both improve disease prognosis and guide treatment. Coagulation tests, such as prothrombin time, fibrinogen, activated partial thromboplastin time and fibrin degradation product, and d-dimer, are the laboratory tests that could determine patients' coagulation status[24,25]. Zhang et al. showed that elevated d-dimer levels on admission could predict in-hospital mortality in patients with COVID-19[26]. In another study by Tang et al., longer prothrombin time and higher levels of d-dimer and fibrin degradation product were determined in non-survivors[27]. Similar to these results, we determined higher levels of d-dimer and longer prothrombin time in patients with COVID-19 who did not survive.

The CHA_2DS_2-Vasc score, which is one of the most widely used scoring systems to determine thrombosis risk without the need for laboratory tests, has been evaluated in recent studies in patients with COVID-19. Çetinkal et al. demonstrated that higher CHA_2DS_2-Vasc scores are associated with adverse clinical events in patients with COVID-19, and they also showed that the m-CHA_2DS_2-Vasc score was superior to the CHA_2DS_2-Vasc score in predicting in-hospital mortality. The ATRIA score is another score used for thrombosis risk and some studies have indicated it performs better at determining risk compared to the CHA_2DS_2-Vasc score. In our study, where we compared the ATRIA and m-CHA_2DS_2-Vasc scores, we found that both scores were higher in non-survivors. Also, we believe both scores can be used as independent predictors of thrombosis and mortality in patients hospitalized in intensive care units due to COVID-19. In addition, the predictive value of the ATRIA score was higher than that of the m-CHA_2DS_2-Vasc score. A relationship between COVID mortality and CHA_2DS_2-Vasc has been shown in previous studies[28]. ATRIA may have a better performance than m-CHA_2DS_2-Vasc as it categorizes age more effectively and is calculated using GFR.

Acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction, and systemic arterial embolism are responsible for the majority of deaths in COVID-19 patients. Although the treatment protocol of these patients includes anticoagulants, there is no definite consensus on dosage. Identifying patients at risk of thromboembolism could offer the possibility of more careful treatment in the form of thromboprophylaxis. The ATRIA score could be a guide in determining whether anticoagulants can be used in prophylactic or therapeutic doses in this group.

We think that the low number of patients in our study is a limitation that can be overcome with a longer study period and prospective studies. The fact that the laboratory parameters affecting the prognosis of COVID-19 infection were not obtained is not a great obstacle to our study, as it will only play a role in proteinuria evaluation in the ATRIA score, which we already mentioned in the protocol and did not add to the study.

Limitations

Our study has more than one limitation. The most significant one is the retrospective and single-centered design of the study. Furthermore, since there were no data for proteinuria, it was evaluated as 0 in all patients included in the study. The laboratory parameters that could have an effect on the primary outcome were not included in the study, and this is another limitation.

CONCLUSIONS

The ATRIA and CHA_2DS_2-Vasc scores are scoring systems that can be used to determine the risk of thromboembolism in

COVID-19 patients and can be evaluated quickly at bedside. Moreover, the ATRIA score may give a better result than the CHA_2DS_2-Vasc score. It can be recommended for the evaluation of high-risk COVID-19 patients.

AUTHORS' CONTRIBUTIONS

OOA: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft. **AY:** Data curation, Formal analysis, Supervision.

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REVIEW ARTICLE
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Triggering receptor expressed on myeloid cells-1 as pediatric sepsis biomarker

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SUMMARY

OBJECTIVE: Triggering receptor expressed on myeloid cells-1 concentration can be used as a predictive, diagnostic, and prognostic marker in patients with sepsis. The objective of this study was to determine the validity of triggering receptor expressed on myeloid cells-1 levels as a biomarker of sepsis in pediatric patients.

METHODS: This was an integrative literature review. PubMed, ScienceDirect, LILACS, MEDLINE, and VHL databases were searched for papers published between 2015 and 2020, using the keywords triggering receptor expressed on myeloid cells-1, sepsis, and child.

RESULTS: The review included ten studies, of which four used triggering receptor expressed on myeloid cells-1 as a predictive biomarker; four, as a diagnostic biomarker; and two, as a prognostic biomarker. A total of 1,409 and 1,628 patients were included in primary and review studies, respectively. There was a predominance of significant results for the validity of triggering receptor expressed on myeloid cells-1 levels in the prediction, diagnosis, and prognosis of sepsis in pediatric patients.

CONCLUSIONS: Triggering receptor expressed on myeloid cells-1 is a valid predictive, diagnostic, and prognostic biomarker of sepsis with good sensitivity and specificity in the pediatric population.

KEYWORDS: TREM-1 Protein. Sepsis. Child.

INTRODUCTION

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a member of the immunoglobulin superfamily expressed on the surface of neutrophils, monocytes, and macrophages that plays a regulatory role in signaling pathways. TREM-1 activation leads to the production of pro-inflammatory cytokines and chemokines, increases the expression of co-stimulatory molecules, and induces neutrophil degranulation and phagocytic activity. Concomitantly, the enzymatic cleavage of TREM-1 results in increased plasma levels of the soluble form of TREM-1 (sTREM-1)[1].

Recently, serum sTREM-1 concentrations were found to be promising in the diagnosis of sepsis, pneumonia, meningitis, and fungal infections. However, results from different studies are inconsistent, especially in the pediatric population[2]. Sepsis is a common cause of morbidity and mortality in children. Clinical and laboratory signs of systemic inflammation are neither sensitive nor specific enough to be used in the diagnosis of sepsis[3].

Infectious/inflammatory stimuli lead to an increase in the production of this receptor, so it can be a valuable diagnostic parameter when monitoring such conditions. Rios-Toro et al.[4] showed that it is possible to consider sTREM-1 as a biomarker of sepsis severity, considering the Sepsis-related Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Disease Classification System II (APACHE II) scores.

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This aspect is of great interest since many biomarkers are described in the literature for the diagnosis and prediction of sepsis outcome, but due to their unspecific characteristics and insufficient predictive value, their use in clinical practice is still a source of disagreement. Given the predictive, diagnostic, and prognostic value of TREM-1 levels in patients with sepsis, the implementation of routine TREM-1 measurements should be considered[5], especially in cases of patients with bacterial infections[6]. The objective of this study was to determine the validity of TREM-1 as a biomarker of sepsis in pediatric patients.

METHODS

This was an integrative literature review conducted in six stages: theme identification and research question selection, establishment of inclusion and exclusion criteria, study search and result extraction, study evaluation, result interpretation, and synthesis of knowledge[7].

The theme of the research question was based on the PICO strategy (P – population: pediatric patients; I – interest: TREM-1 as a biomarker; CO – co-context: patients with sepsis), which resulted in the following question: Is TREM-1 a valid biomarker of sepsis in the pediatric population?

The inclusion criteria were as follows: papers on the use of TREM-1 as a biomarker of sepsis in a pediatric population, clinical and observational studies or systematic reviews, and studies published between 2015 and 2020. Papers on adult and/or older populations, books, monographs, theses, dissertations, and editorials were excluded. The following databases were used: PubMed, ScienceDirect, *Literatura Latino Americana y del Caribe em Ciências de La Salud* (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Virtual Health Library (VHL) Portal.

Sampling was conducted by surveying and analyzing publications using the descriptors selected from the Health Sciences Descriptors (DeCS), namely "TREM-1," "sepsis," and "child," and their respective Portuguese translations, crossed using the Boolean operator "and".

Initially, the titles and abstracts of the studies were read by two independent researchers and each researcher decided whether to include the evaluated study (first stage). Discordant cases were evaluated by a third researcher (second stage). Subsequently, the papers included by the three researchers were read in full to answer the review question (third stage).

The search resulted in 34 studies, which were evaluated according to the eligibility criteria, resulting in a sample of ten papers (Figure 1). The evaluation of level of evidence (LE) was guided by the determinations of the Oxford Center Evidence Based Medicine[8]. The extracted information was descriptive and directly related to the review question (Table 1).

RESULTS

Of the studies included, four used TREM-1 as a predictive biomarker[9,11,14,15], four used it for diagnosis purposes[6,10,12,13], and two, as a prognostic marker[16,17] of sepsis in pediatric patients. As for the type of study, eight were primary surveys[9-13,15-17] and two were systematic reviews[6,14]. As for the LE, five papers were classified as 2C[9,10,12,13,17], three as 3B[11,15,16], and two as 2A[6,14]. As for the number of patients involved, there were 1,409 in the primary studies[9-13,15-17] and 1,628[6,14] in the review studies.

As for the interpretative analysis of primary study results, only one[15] suggested that TREM-1 levels are not appropriate for detecting infections. The others[9-13,16,17] showed significant results that validated the use of TREM-1 levels in the prediction, diagnosis, and prognosis of sepsis in children. The reviews concluded that TREM-1 is useful for predicting[14] and diagnosing[6] sepsis.

DISCUSSION

Sepsis is defined as a multisystemic failure with a significant risk of mortality. In recent years, several studies have been conducted to determine ways in which sepsis can be diagnosed and treated, using early interventions to reduce mortality in children. Increased survival can be a result of early recognition associated with adequate and targeted treatment[18].

Biomarkers can be used to predict, diagnose, and prognose sepsis, in addition to monitoring therapeutic responses. The use of biomarkers must be based on critical analysis, and results should be interpreted according to the clinical status of the patients[18].

Cordeiro et al.[11] developed a mathematical model with 27 biomarkers for predicting adverse neonatal outcomes in premature infants. They found that TREM-1 levels was able to predict the incidence of sepsis (OR 0.99, 95%CI 0.063–1.36). In serious situations, TREM-1 levels were found to be useful. Arızaga-Ballesteros et al.[9] found that TREM-1 levels were a significant predictor of septic shock or death ($p<0.0001$), corroborating the findings of Şen et al.[17]. They showed that TREM-1 values were significantly higher in patients with septic shock (129 pg/mL; min. 9.85; max. 494.90) than in those with severe sepsis (105 pg/mL; min. 8.21; max. 289.17) ($p=0.048$).

Bellos et al.[14] showed that TREM-1 levels were a useful biomarker of neonatal sepsis; however, due to the variations found, they suggest using it with caution (sensitivity 0.95, 95%CI 0.81–0.99; specificity 0.87, 95%CI 0.56–0.97).

Pontrelli et al.[6] presented preliminary evidence on the role of TREM-1 in the diagnostic investigation of sepsis in newborns and children. However, it was not possible to obtain quantitative results due to the small number of studies, which included heterogeneous populations.

Özdemir et al.[15] found no significant difference in TREM-1 levels at days 1, 2, and 7 between patients with positive or negative blood culture results. The results suggest that TREM-1 is present at measurable levels on admission in children with febrile neutropenia, but it may not be appropriate to predict bloodstream infections. The expression of TREM-1 increased markedly in patients infected with Gram-positive and Gram-negative bacteria and fungi. Some studies in the literature showed that patients with septic shock have negative blood cultures, although they present with high TREM-1 values and progress to septic shock[9].

The use of predictive biomarkers in children with sepsis is promising but surrounded by challenges. To date, no single biomarker with predictive power in terms of patient outcome has been found. Based on the complexity of each patient's immune responses and genetic variations, it is unlikely that one biomarker alone can identify and stratify sepsis in a pediatric population[19].

Saldir et al.[10] showed that mean TREM-1 concentrations were significantly higher at the time of sepsis diagnosis in the septic group than in the non-septic group (median 985, IQR 576–1,400 pg/mL *versus* median 836.6, IQR 702.2–944.8 pg/mL, p=0.028). Receiver operating characteristic curve analyses showed that TREM-1 levels had a significant area under the curve for the early identification of septic neonates (OR 0.97, 95%CI 0.931–0.998, p<0.001). Univariate logistic regression analysis showed that increased TREM-1 levels was a strong predictor of neonatal sepsis (OR 126, 95%CI 16.26–976.27, p<0.001).

Al-Asy et al.[12], despite not studying sepsis specifically, reported that children with diarrhea due to acute bacterial infection had significantly increased levels of serum TREM-1 on admission compared to patients with diarrhea due to non-bacterial infection and controls (26.3667±16.8184 ng/mL *versus* 7.2267±6.4174 ng/mL vs. 6.7367±5.6479 ng/mL and 39.9933±22.5260 ng/mL vs. 1.8533±1.7123 *versus* 0.2840±0.1208 ng/mL, respectively, p<0.05). TREM-1

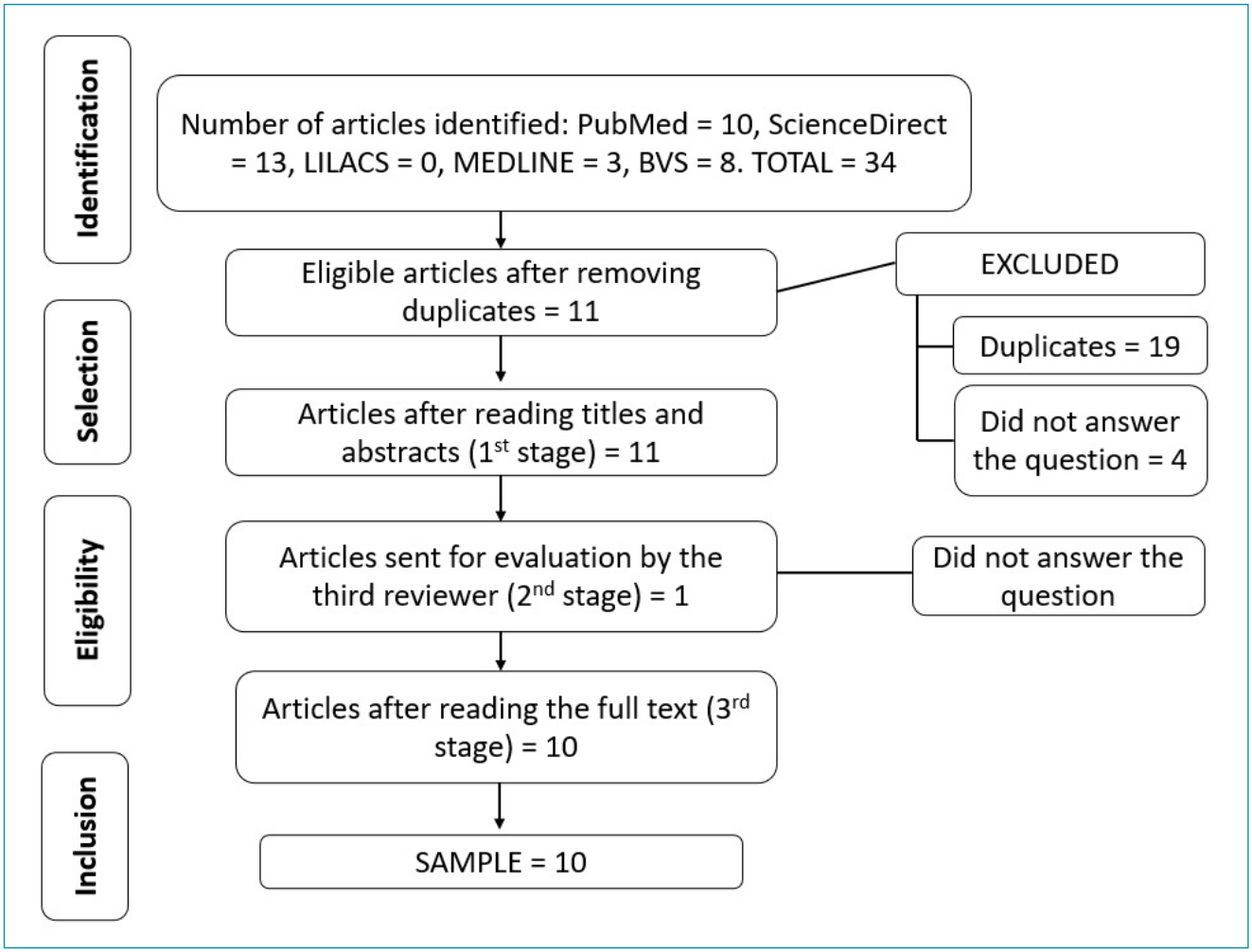

Figure 1. Flow diagram of the research strategy results and study selection.

Table 1. Summary of studies by author, year, level of evidence, number of patients, and main results.

Author and year/Level of evidence/Number of patients	Main results
Arízaga-Ballesteros et al., 2015[9]/2C/71	In neonates with late-onset sepsis, sTREM-1 showed excellent predictive value (p<0.0001) for septic shock/death, with a specificity and sensitivity of 0.97 and 0.78, respectively.
Saldir et al., 2015[10]/2C/50	sTREM-1 levels were significantly higher (p<0.001) in neonates with sepsis than in neonates who did not have sepsis.
Cordeiro et al., 2016[11]/3B/926	TREM-1 had a strong influence on building a model that showed significant predictive value (p<0.05) for sepsis.
Pontrelli et al., 2016[6]/2A/961	sTREM-1 can be used as a diagnostic tool for pediatric sepsis, but the results cannot be considered conclusive due to heterogeneity of the samples.
Al-Asy et al., 2017[12]/2C/80	Children with acute bacterial infection showed significantly increased (p<0.05) sTREM-1 levels as compared to patients who had diarrhea without bacterial infection, showing a specificity and sensitivity of 93.7 and 94.3%, respectively.
Özdemir et al., 2018[13]/2C/62	Neonates with confirmed sepsis had significantly higher urine sTREM-1 values (p<0.05) than those in the suspected sepsis group. The measurement of this marker in the urine showed a sensitivity and specificity of 0.90 and 0.78, respectively.
Bellos et al., 2018[14]/2A/667	sTREM-1 can be a useful biomarker for the prediction of neonatal sepsis, but the small number of studies and the variation in the limit values negatively impact its use in clinical practice.
Özdemir et al., 2019[15]/3B/57	There was no significant difference (p>0.05) in blood sTREM-1 levels on days 1, 2, and 7 between patients with positive and negative blood culture results, suggesting that this marker is not appropriate for predicting blood infections.
Zhang et al., 2020[16]/3B/76	The severe pneumonia group had significantly higher serum sTREM-1 levels than the non-severe pneumonia and the control groups (p<0.05).
Şen et al., 2020[17]/2C/87	TREM-1 values were significantly higher (p=0.048) in patients with septic shock than in those with severe sepsis.

levels showed significantly high sensitivity (93.7%) and specificity (94.3%, 0.84–0.99) in predicting bacterial infection as a cause of acute diarrhea in children (95%CI) at a cutoff value of 12.4 ng/mL. Acute diarrhea is an important cause of mortality in children aged under five years[20]. Although rare, abdominal sepsis in children is potentially fatal.

Özdemir et al.[13] reported that newborns in the positive culture group had significantly higher urine TREM-1 levels than those in the suspected sepsis group (sensitivity, 0.90; specificity, 0.78; positive predictive value, 0.68; negative predictive, value, 0.94).

Zhang et al.[16] showed that the severe pneumonia group had significantly higher serum TREM-1 levels, APACHE II scores, and SOFA scores than the non-severe pneumonia group and the control group (p<0.05). Regarding children with severe pneumonia, the unresponsive group had significantly increased serum TREM-1 levels and SOFA scores at day 7 after admission, while the response group showed reduction in these values, with significant differences between the two groups (p<0.05). A positive correlation was observed between TREM-1 levels and SOFA score (p<0.05).

CONCLUSIONS

Sepsis is a common condition in hospital settings that is especially severe in the pediatric population. Biomarkers can be used as important tools in the search for new management strategies. This review showed that TREM-1 levels are a valid predictive, diagnostic, and prognostic biomarker of sepsis, with good sensitivity and specificity in the pediatric population.

AUTHORS' CONTRIBUTIONS

JVBC: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **MMBMS:** Data Curation. **ATX:** Data Curation. **NA:** Data Curation. **DCSF:** Writing – Original Draft, Writing – Review & Editing. **DCO:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft.

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REVIEW ARTICLE
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Telehealth in audiology: an integrative review

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SUMMARY

We performed an integrative review on the scientific literature about the use of telehealth in audiology care. Through high criteria search of published studies on the "Biblioteca Virtual em Saúde" – Virtual Health Library, PubMed, and Scientific Electronic Library Online databases, nine articles were selected. It was possible to verify that the use of telehealth in audiology is feasible and efficient, because it could promote audiological care for patients from away places. This process reaches more patients and communities by breaking down geographic barriers, and it offers a specific service not available with less cost and more quickly when compared with traditional speech therapy care.

KEYWORDS: Telehealth. Healthcare. Telemedicine. Audiology. eHealth.

INTRODUCTION

Telehealth is defined as the provision of health care services, such as consultancy, monitoring, prevention, and treatment of diseases, through the use of information and communications technology (ICT)[1]. It is a term used interchangeably with telemedicine, eHealth, and digital health, and it can be considered as a strategy to mitigate problems related to the shortage of professionals in remote areas, as well as the need for training professionals in that regions and consequent improvement in health care provided by them[2].

In a systematic review of public investment in telehealth actions, Celes et al.[3] identified the use of this strategy in different actions, such as continuing education programs for health professionals, expansion of health care access with reduced costs in remote areas, collaboration in hospital care and palliative care, care of bedridden patients with limited mobility, strengthening primary health care, improvement of health record systems, and the planning of other relevant actions and services.

In Brazil, the use of telehealth services has been implemented since mid-2007, aiming to support Primary Care all over the country through the *Sistema Único de Saúde* (SUS) – Unified Health System. The program "Telessaúde Brasil Redes" provides teleconsulting services, telediagnostics, teleducation, and formative second opinion to SUS professionals[4].

The Brazilian Federal Council of Phonoaudiology regulates the use of telehealth strategies. The first regulation was published in 2013, with changes made in 2020 excluding some limitations to the practice. Besides core professional activities, such services can also be used in teleconsultation and telemonitoring activities. Teleconsultation may involve the speech therapist or other health professional at one side, and the patient and another speech therapist at a distance, or even a consultation with patient and speech therapist, both at a distance – introduced in 2020. Telemonitoring, on the other hand, involves the remote monitoring of previously face-to-face attended patient[5,6].

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With regard to telehealth applied to phonoaudiology, there is a greater number of publications in audiology, with focus on both educational and patient assistance. Teleaudiology is the term used to designate the provision of hearing services at a distance, and it has been a promising area in the adaptation of prostheses and guidance to cochlear implant (CI) users[7]. Audiology deals with audiological evaluation, diagnosis, and treatment of people with impaired auditory and vestibular function and the prevention of associated dysfunctions. The central focus of audiology is on hearing impairment and their relationship with communication disorders[8]. It provides therapies that involve adaptation of individual sound amplification devices (i.e., hearing aids) for people with partial hearing loss. In audiology, teleconsultation has been used in different areas ranging from diagnosis of hearing loss to rehabilitation process. The first reports of the use of teleconsultation to adapt hearing aids date from the 1990s, in a pilot program at the Mayo Clinic, Rochester, MN, USA. In this program, audiology professionals used remote controlled applications to perform the adjustments of hearing aid devices[9].

We aimed to demonstrate that the telehealth management could be a new trend on audiological clinical assistance and to show the evidences of the use of telehealth in audiology care.

METHODS

We conducted an integrative review of the scientific literature. This method was chosen to identify the scientific basis for understanding the role of telehealth in audiological care, besides providing a synthesis of published studies, and allowing general conclusions on teleaudiology and a more complete understanding of the topic.

The leading question of this study was as follows: "What is the scientific evidence for the use of telehealth in audiology?" For this research, published studies on telehealth in audiology were used. The databases consulted were "Biblioteca Virtual em Saúde" – Virtual Health Library (BVS/VHL), PubMed, and Scientific Electronic Library Online (SciELO). The research was carried out in May 2020 and limited to studies published in full text versions, without language restrictions, within the last 10 years. We used English key words that are listed in Table 1, descriptors registered in the Health Sciences Descriptors (DeCS) and/or Medical Subject Headings (MeSH). For articles not available in electronic databases or for the data not available in the articles included in this review, the authors were contacted to obtain the necessary information.

Table 1. Keywords of the search strategies.

[(Telehealth or eHealth or mobile health or telemedicine) and (audiology)]

The articles identified by the initial search strategy were evaluated according to the following inclusion criteria: addressing telehealth in audiology care regardless of age and/or sex of subjects and methodological design. Articles that used telehealth tools for the training of professionals in the field and those that addressed the topics in other areas of speech therapy, review studies, editorials, and research notes and comments were excluded. Out of 1,312 articles, 945 were found in BVS/VHL, 195 in PubMed, and 172 in SciELO. From those articles, only 18 articles were selected for addressing the researched theme. Of these, nine articles were excluded, as they addressed telehealth in the context of speech therapy generally and in professional training. Finally, nine articles were included in this review (Figure 1).

Finally, after the final selection of the studies included in the analysis, the main information was gathered, and a descriptive analysis was performed.

RESULTS

Of the nine studies selected in this integrative review, two were carried out in Canada, two in Brazil, and the other five in Australia, the United States, South Africa, Germany, and India, respectively. These articles are summarized in Chart 1 with the authors' descriptions, year of publication, country, type of study, objectives, and conclusions.

For the qualitative synthesis of this review, four cross-sectional studies[10-13], a case–control study[14], a case study[15], a validation study[16], and two accuracy studies[17,18] were analyzed. The sample size of the studies included in this review ranged from 2[15] to 42,697[14].

In 2019, Hatton et al.[10] examined telehealth-enabled auditory brain stem response (TH-ABR) in 50 babies with hearing loss, living in rural communities in a program provided by British Columbia. The authors concluded that the program is efficient when compared with the face-to-face assessments, in addition to optimizing the availability of audiology resources. The program also builds local service capacity and reduces costs for communities.

Schepers et al.[11], through an observational study, evaluated the safety and feasibility of remote programming in CI users. The sample consisted of 25 children and 21 adults, users of CIs, submitted to adjustment sessions locally and remotely. The results of these two adaptation sessions were compared in terms of safety, impedance field telemetry (IFT), maximum comfortable level (MCL), threshold level (THR), audiometry, duration of adaptation, and speech comprehension.

The authors concluded that remote follow-up adjustment is safe, feasible, and effective when compared to local adjustment for CI users of all ages.

Monica et al.[12] evaluated the feasibility of school hearing screening using telehealth technology operated by a professional located in a hospital 400 km away. The results showed no significant difference between pure tone audiometry (PTA) and distortion product otoacoustic emissions (DPOAE) performed in person or by tele-hearing screening methods. The authors indicated that synchronous hearing screening services can be provided in schools using mobile devices through hotspots or dongle connectivity in places where Internet bandwidth is limited.

Another study[14] evaluated the effectiveness of teleaudiology for hearing aid services through a retrospective case–control study

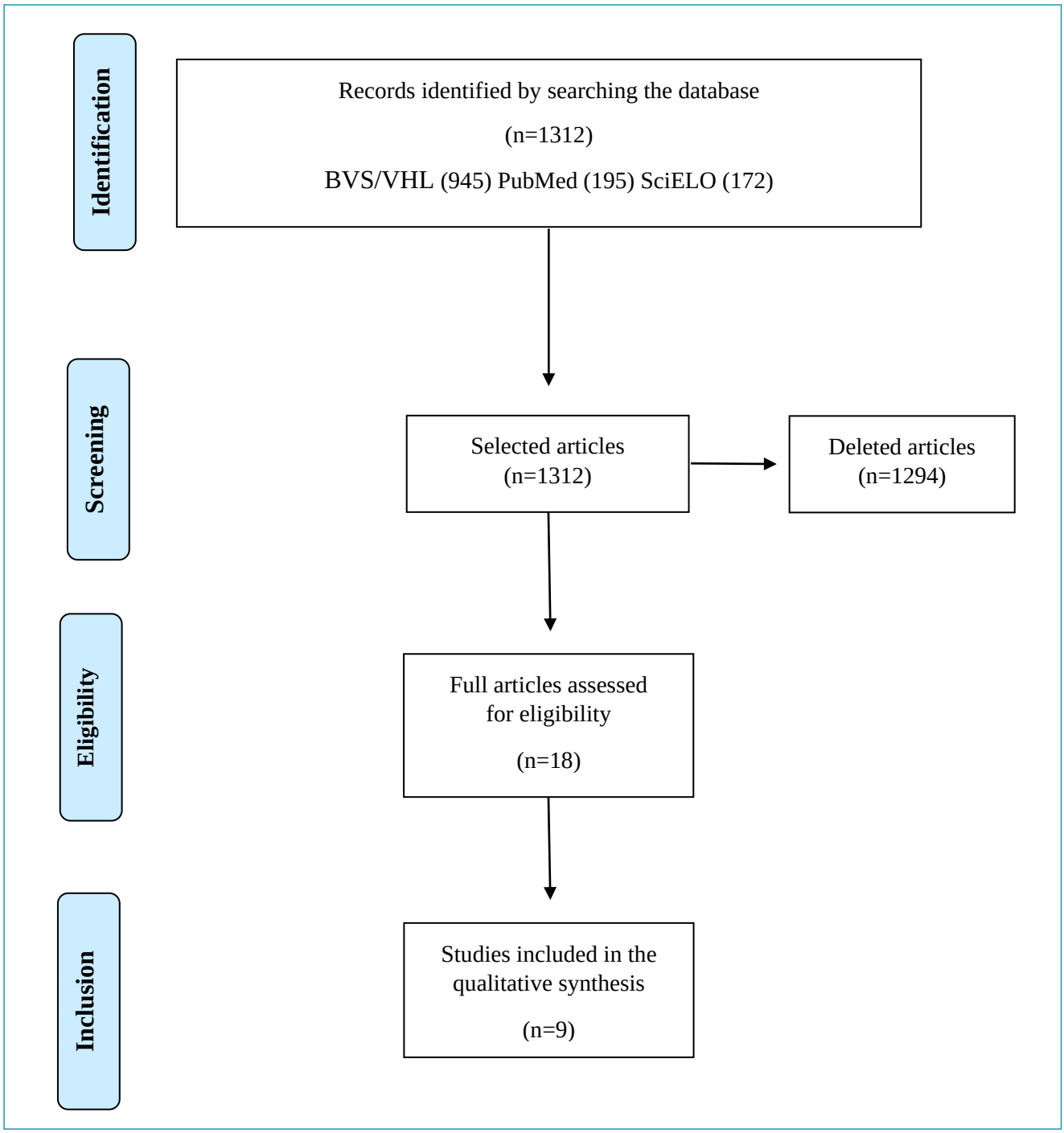

Figure 1. Flowchart of the literature search and screening process.

Chart 1. Characteristics of the included studies.

Author/Year/ Country	Study Design	Objective	Conclusion
Hatton et al.[10], 2019, Canada	Cross-sectional	To describe the design/ implementation of a telehealth-enabled auditory brain stem response (TH-ABR) program; summarize equipment/procedures; report the results of the TH-ABR program.	TH-ABR is efficient, accurate, valued by parents, optimizes the availability of audiology resources, creates local service capacity, and reduces costs for communities in Northern British Columbia.
Schepers et al.[11], 2019, Germany	Cross-sectional	To evaluate the safety and feasibility of remote programming in cochlear implant (CI) users for all ages.	Remote tracking adjustment is safe, feasible, and effective for local adjustment for CI users. A more extensive adoption of remote adjustment can allow many CI users greater access to clinics and greater benefits from the use of CI.
Samelli et al.[18], 2018, Brazil	Accuracy study	To evaluate the performance of a tablet-based teleaudiometry method for automated hearing screening of schoolchildren by comparing the results of various hearing screening approaches.	The highest diagnostic values were generally obtained by the automated method of hearing screening (including 500 Hz). The application, developed for the tablet, proved to be a valuable hearing screening tool for use in schoolchildren. Therefore, we suggest that this hearing screening protocol has the potential to improve the provision of asynchronous teleaudiology services.
Monica et al.[12], 2016, India	Cross-sectional	To evaluate the feasibility of school hearing screening using telehealth technology operated by a professional located in a hospital 400 km away.	Synchronous hearing screening can be provided in schools using mobile device hotspots or dongle connectivity in places where Internet bandwidth is restricted.
Pross et al.[14], 2016, United States	Case–control, retrospective	To evaluate the effectiveness of teleaudiology (TA) for hearing aid services.	Assistance through TA and conventional care to provide hearing aid services to veterans is comparable, as both are highly effective based on the results of the International Outcome Inventory for Hearing Aids (IOI-HA) results. The non-inferiority of TA suggests that its adoption by non-veterans can improve access and preserve high satisfaction. The financial impact of migration on TA will require future econometric analysis.
Rourke et al.[13], 2016, Canada	Cross-sectional and prospective	To determine the prevalence of hearing loss in children aged 4–11 years; test and demonstrate the use of the tablet audiometer as a portable hearing test device in children in a remote location.	A total of 14.8% children tested positive for hearing loss based on our interactive audiometer for tablets. The audiometer for tablets was time-efficient and largely language-independent. This test is valuable for providing the necessary hearing health care for high-risk populations in rural and remote areas where audiology services are not available.

Continue...

Chart 1. Continuation.

Author/Year/ Country	Study Design	Objective	Conclusion
Blamey et al.[17], 2015, Australia	Accuracy study	To evaluate the effectiveness of an online speech perception test (SPT) for measuring hearing and adjusting the hearing aid in comparison with conventional methods.	SPT is an effective tool for the detection and measurement of hearing loss and the adaptation of hearing aids. The use of SPT reduces costs and increases the effectiveness of adjusting the hearing aid, enabling a sustainable teleaudiology business model.
Penteado et al.[15], 2013, Brazil	Case study	To describe a case of remote adaptation between two cities, with a literature review.	Remote adjustment of hearing aids is possible over the Internet, in addition to providing additional technical training for a remote center on assembly procedures. This technological approach can help the government to promote public policies in hearing rehabilitation, as patients can be motivated to keep using hearing aids with the option of asking for help in the comfort of their own homes.
Swanepoel et al.[16], 2010, South Africa	Validation study	To validate remote pure tone audiometric tests performed in North America on individuals from South Africa.	It may be possible to expand the reach of hearing services in remote and underserved regions of the world.

with 42,697 veteran patients who received hearing aids. The main measures of outcomes were analyzed through a seven-item questionnaire that used to assess the effectiveness of the hearing aid (7–35 points, in which the highest scores are the most favorable). Among veterans who received hearing aids and completed the questionnaire, 1,009 received teleaudiology care and 41,688 received conventional care (in person). Although the comparison between groups showed a statistically significant difference ($p<0.0001$, *t*-test), mainly due to the large sample size, it was not clinically significant. The authors concluded that teleaudiology and conventional meetings are highly effective based on the results of the questionnaires. The non-inferiority of teleaudiology suggests that its adoption by non-veterans can improve access to other population groups and preserve high levels of satisfaction.

The prevalence of hearing loss in children aged 4–11 years was studied by Rourke et al.[13] The authors also tested and demonstrated the use of the tablet audiometer as a portable hearing test device in children in a remote location. Of the studied population, 14.8% had hearing loss based on the interactive audiometer for tablets. The authors suggested that the tablet audiometer is an efficient and valuable tool for providing the necessary hearing health care for high-risk populations in rural and remote areas where audiology services are generally unavailable.

In our review, two studies were found[17,18] addressing the accuracy of remote care in audiology. Blamey et al.[17] evaluated the effectiveness of an online speech perception test (SPT) for measuring hearing aids and adjusting hearing aids compared with conventional methods. The research provided evidence that the online SPT can be considered an effective tool to detect and measure hearing loss and to adapt hearing aids. This test also reduces costs and increases the effectiveness of adjusting the hearing aid, enabling a sustainable teleaudiology business model. Following the same reasoning, the study by Samelli et al.[18] aimed to evaluate the performance of a tablet-based teleaudiometry method for automated hearing screening in schoolchildren by comparing the results of hearing screening approaches. The authors concluded that the application developed for the tablet was proved to be a valuable hearing screening tool for use in school-aged children. Therefore, the authors suggested that this hearing screening protocol has the potential to improve the provision of teleaudiology services.

The research by Swanepoel et al.[16] evaluated the validity of PTA tests. The study was carried out in individuals from South Africa. The results suggest that the thresholds for face-to-face and remote audiometry differed by 10 dB in only 4% of cases. The limits of agreement between the two techniques were 28 – 7 dB, respectively, with a 90% confidence interval

of 25 – 5 dB, respectively. The authors concluded that it is necessary to use strategies to expand the scope of audiological services in remote and underserved regions of the world.

Penteado et al.[15] described three patients who had their hearing aids adapted remotely with procedures being made between two different cities. The study points out that remote installation of hearing aids may be possible over the Internet. This technological approach can help the government to promote public policies in hearing rehabilitation, as patients can be motivated to keep using hearing aids with the option of asking for help from the professional from their own homes.

DISCUSSION

This integrative review analyses the following aspects: the accessibility to audiological assistance and the comparison between traditional strategies and the remote form of assistance, both in terms of effectiveness and cost.

The expansion of the scope of audiological services and the consequent improvement of access to audiological care through the use of telehealth are the factors highlighted by all authors listed in this review.

Hatton et al.[10], Pross et al.[14], and Blamey et al.[17] emphasized the cost reduction for communities that receive remote services and the convenience it brings to patients similar to services located closer to their homes. According to Penteado et al.[15], this contributes to better treatment success rates. It is important to note that most hearing aid users are elderly people with mobility issues or the need for a companion or caregiver during clinical assessments. These facts have potential impacts on therapeutic adherence.

Despite the benefits resulting from care assisted by communication technology, Pross et al.[14] pointed out the loss of physical interaction between health care professional and patient as a possible negative impact of this model on health service delivery. In fact, the concern with the efficiency of the dialogue between these actors permeates remote evaluations where non-verbal aspects of communication, such as touch and body expression, can make the patient feel "robotic" and "artificial"[19].

Among the studies comparing face-to-face care and remote assistance, there was an agreement about the safety, feasibility, and efficacy of remote CI programming activities[11], hearing screening[10,12,16], and adaptation/monitoring of hearing implants[14,17].

The use of a portable device (tablet) for audiometric tests was carried out in two studies[13,18], both reporting efficiency and feasibility in hearing screening tests. In the study by Samelli et al.[18], 244 Brazilian children were included, and in the study by Rourke et al.[13], 218 Canadian children were included. Despite dealing with different countries and methodologies, the two studies proved that the use of portable devices is a valuable tool for screening of school-aged children, with practical and efficient uses. It is of great value to highlight the importance of screening in early detection and intervention to minimize the impact of hearing loss on the development and educational achievements of children.

Still, with regard to hearing screening, the study by Monica et al.[12], carried out on Indian children aged between 5 and 8 years, showed that face-to-face screening compared with videoconference in the school environment had a concordance of 87–97%, which confirms the feasibility of applying teleaudition for screening.

Schepers et al.[11] concluded that remote CI programming and its adjustments are safe and effective when compared to local care, with no significant differences. Zumpano et al.[20] studied the benefits and limitations for the implementation of remote CI programming and concluded that teleaudiology provides the decentralization of health services and cost reduction, being a viable practice. Although there is a 10-year difference between the two studies, their results reinforce possible benefits, showing that remote CI programming is feasible. Nowadays, the greater accessibility to technologies, the global Internet revolution, and the growing implementation of cellular networks make the practice of teleaudiology increasingly possible. In addition, it is worth noting that during the current coronavirus disease 2019 (COVID-19) pandemic, in which the safest approach requires social distancing, the teleaudiology is an effective tool for providing care to patients with CI.

Hatton et al.[10] studied the TH-ABR for the pediatric population in a remote location and concluded that the TH-ABR program was adequate, sustainable, and scalable. In a similar study, Ramkumar et al.[21] compared a pediatric hearing screening program, integrating an ABR diagnostic test using a telemedicine and a face-to-face approaches. The authors concluded that this telehealth model has improved follow-up of patients compared with the face-to-face model, making it possible to provide care to people living in remote locations. This type of service reduces disparities between urban and rural populations, frequently with limited access to health care resources.

Regarding the audiological evaluation through the audiometry exam, Swanepoel et al.[16] stated that there were no clinically significant differences between remote audiometric testing and conventional face-to-face testing results, and they concluded that it may be possible to expand audiological services to remote and underserved regions in the world. Visagie et al.[22] obtained hearing thresholds from 20 adults living in a rural community, with no significant difference in hearing threshold results determined in the conventional scenario and in the telemedicine strategy. Innovative ways of bringing hearing health services to people who live in places far from urban centers, often in need, should be encouraged.

CONCLUSION

This review highlights successful experiences in teleaudiology in programming CIs and adapting hearing aids, as well as in screening hearing disorders and validating instruments for this purpose. Despite the small number of studies, we identified that telehealth in audiology is a viable and efficient strategy, facilitating access to audiological services, with potential for cost reduction when compared to traditional care strategies. The changes in the Brazilian legal framework for the use of telehealth with the COVID-19 pandemic, in addition to cost effectiveness, showed that the use of telehealth is a new trend.

We emphasize the urgency in the adoption and development of new strategies, given the potential of telehealth in audiology and its consequent benefits, especially in countries with large territorial extension such as Brazil.

AUTHORS' CONTRIBUTIONS

TRCML: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **LMS:** Data Curation, Writing – Review & Editing. **MCHM:** Data Curation, Writing – Review & Editing. **BCLA:** Data Curation, Writing – Review & Editing. **MAS:** Writing – Review & Editing. **AAO:** Conceptualization, Supervision, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **SMS:** Conceptualization, Supervision, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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REVIEW ARTICLE
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Depression and dry eye: a narrative review

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SUMMARY

Dry eye disease (DED) is a multifactorial disease affecting tear quality and/or production and eye surface and is one of the most common eye disorders found in clinical practice. The association between psychiatric disorders and dry eye has been the subject of several studies since patients with this syndrome present a tendency toward a depressive mood. This narrative review aims to demonstrate the relationship between depression and DED, which is due to the side effects of psychotropic drugs or the tendency of the low pain threshold of the depressive patient. The work was produced from the analysis of 13 articles published during the last decade on this subject and demonstrated that the depressive state is linked to the appearance or worsening of DED resulting from chronic eye pain. Also, the treatment of depression with selective inhibitors of serotonin receptors causes inflammatory cytokine secretion with subsequent inflammation and apoptosis of cells on the ocular surface. The need for new studies on optimization of psychiatric treatment in patients with ophthalmic diseases, such as DED, was verified, aiming at the relief of symptoms and the reduction of psychological and eye damage caused by them.
KEYWORDS: Dry eye. Depression. Ophthalmology. Psychiatry.

INTRODUCTION

Dry eye disease/syndrome (DED) is a multifactorial disease that affects tear quality and/or production and the surface of the eye[1]. It is one of the most common eye disorders and is characterized by symptoms of eye discomfort, such as pain, dryness, foreign body sensation, visual disorders, and tear film instability[2]. The discomfort caused by this disease diminishes the quality of life not only concerning vision but also about daily activities in general, which tend to become impaired[3].

The association of DED with psychiatric disorders has already been the subject of several studies[4]. It has been reported that individuals with this syndrome present an increased risk for psychological stress, severe anxiety, and depression[4]. It has been suggested that a predisposition of DED patients to depression exists since their symptoms, such as visual blur induced by tear film instability, can worsen depressive moods[5].

In addition, previous studies have indicated that drugs prescribed for psychiatric conditions can precipitate DED[6-8].

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Most antidepressant drugs have antagonistic effects on muscle receptors, which can cause adverse effects, including DED[9,10].

In this sense, this study aimed to explain the relationship between the depressive state and DED either through the psychological stress generated by the eye picture or by psychotropic drugs used for the treatment of depression.

METHODOLOGY

This study was formatted as a literature review concerning the association between depression and signs of suicide (SOS). Articles written from 2010 to 2020 were selected from the LILACS, SCIELO, and MEDLINE databases, both in Portuguese and English, using the keywords "dry eyes syndrome", "xerophthalmia", and "depression" in addition to their corresponding English terms, "dry eyes syndromes", "xerophthalmia", and "depression" using AND/OR as operators. we established the relationship: "dry eyes syndromes OR xerophthalmia AND depression".

Adding all of the databases, we found 254 articles, 15 of which were used after reading their abstracts. The inclusion criteria consisted of several parameters:

(1) articles available in full on the internet;
(2) articles published in English and Portuguese;
(3) those that demonstrate a direct relationship between DED and depression;

The exclusion criteria included several parameters:

(1) thesis;
(2) monograph;
(3) non-scientific resources;
(4) articles whose full texts were not available;
(5) texts that did not present significant content on the proposed theme based on reading the abstracts.

RESULTS

Depression and DED are distinct disorders that are related in their pathophysiology and treatment (Table 1). Thus, the analyzed studies state that chronic eye pain is associated with the development of anxiety, depression, and loss of sleep quality in patients.

In addition, the treatment of depression with selective serotonin receptor inhibitors results in DED due to activation of the nuclear factor kappa beta (NF-kB) pathway that leads to inflammation and apoptosis of cells on the ocular surface. In this scenario, a study showed the participation of inflammatory cytokines, interleukin-7, and tumor necrosis factor alpha (IL-7 and TNF- α, respectively) in the instability of tear film.

Furthermore, the neurotrophic factor levels derived from the brain may be altered in patients with depression since this is the factor responsible for alterations in the secretion of the lacrimal gland and the appearance of DED.

DISCUSSION

Relationship between dry eye syndrome and depression

DED causes numerous unpleasant symptoms and directly affects the quality of life of individuals who have it[3]. As a result of DED, patients with this syndrome present themselves with the most depressed mood in relation to those with depression[4,11]. In addition, it is important to emphasize that in major depression, it is common to have a relationship between these psychic conflicts and organ disorders (somatization), one example being depression and DED[10,11].

A study by Galor et al.[6] with patients who were seen in an ophthalmology clinic aimed to evaluate the relationship between dry eye symptoms, non-ocular conditions, and lacrimal film parameters from standardized questionnaires and tests for measuring the lacrimal film[6]. As a result, it was concluded that non-ocular conditions, such as post-traumatic stress disorder and non-ocular pain, are more significantly associated with dry eye symptoms than the parameters of the tear film, which is one of the signs for the diagnosis of this syndrome[6].

Another study performed by Hallak et al[7] in which cases of patients with DED and control individuals were compared aimed at determining the association between depressive symptoms and DED[7]. The data for this weighting were obtained from the evaluation of depressive symptoms using the Beck Depression Inventory[7]. As a result of this research, it was determined that DED symptom scores and depression scores were significantly different between cases and controls[6,7]. The established chance ratio was 2.79 in a 95% confidence interval[7]. Thus, this study provides further evidence on the association between DED and depression[7].

In addition, research by Tiskaoglu et al.[3] also aimed to evaluate the association between depression and DED[3]. However, this time, patients diagnosed with depression had their data compared to the control group[3]. The following parameters were considered for the index of eye surface diseases:

(1) visual function questionnaires;
(2) tear break time;
(3) vital eye surface staining; and
(4) Schirmer's test, which evaluates whether the eye produces enough tears to remain lubricated[3].

Table 1. Analysis of studies that signaled the influence of depression in patients with dry eye syndrome (DED).

Author	Study summary
Tiskauglu N.S. et al. 2017[3]	The study shows the association between depression and dry eye syndrome (DED).
Nepp J. 2016[4]	Patients with dry eye that is resistant to drug therapy often have symptoms of anxiety and depression.
Han S.B. et al. 2017[5]	The study reviews the main pathological and neurological conditions related to dry eyes, such as anxiety, depression, post-traumatic stress, chronic pain, and peripheral neuropathy.
Galor A. et al. 2015[6]	Dry eye symptoms in patients are more related to non-ocular pain and depression than to alterations in the tear film.
Hallak J.A. 2015[7]	The study consisting of 53 patients with dry eye showed the association between dry eye pathology and the appearance of depressive symptoms.
Koçer E. et al. 2015[8]	A study with 57 control subjects using antidepressants proved the relationship between the use of selective serotonin receptor inhibitors and a higher risk of dry eye development in these patients.
Zhang X. et al. 2019[9]	Selective serotonin reuptake inhibitors cause dry eye via activation of the NF-kB pathway, which is associated with inflammation and apoptosis of cells on the ocular surface.
Wen W. et al. 2012[10]	DED is common in patients with depression and anxiety, especially in the elderly, with longer diagnostic times and in use of selective serotonin receptor inhibitors.
Weatherby T.J.M. et al. 2019[11]	A metanalysis with 22 studies showed a direct relationship between the severity of dry eye and the development of depression and anxiety.
Acan D. et al. 2016[12]	A study of 72 patients showed a possible relationship between selective serotonin receptor inhibitors and tear film instability.
Mrugacz et al. 2017[13]	Lacrimal secretion samples were collected from 32 controls with depression using psychotropics that showed the participation of inflammatory cytokines, interleukin-7, and tumor necrosis alpha (IL-7 and TNF- α, respectively) in the development of dry eye in these patients.
Sano K. et al. 2019[14]	The neurotrophic factor levels derived from the brain can be altered in patients with depression since this factor is responsible for alterations in lacrimal gland secretions.
Wu M. et al. 2019[15]	Poor sleep quality, anxiety, and depression are conditions associated with decreased secretion of the tear gland and instability of the tear film.

Author: Cunha, CEX. (2020) The pathophysiological processes illustrated above were described by Zhang X. et al.[9]; Acan D. et al.[12]; Mrugacz et al.[13]; Sano K. et al.[14], (Adapted).

Comparison of cases and controls revealed significantly lower scores for Schirmer's test and tear breakage time in the depressive group[3]. This finding indicates a higher propensity of this group of patients to develop DED[3].

Selective serotonin reuptake inhibitor treatment causes increased levels of lacrimal serotonin, severe inflammatory response, and cell apoptosis on the ocular surface

To explore the performance of the selective serotonin reuptake inhibitors (SSRI) in DED associated with depression, serotonin and inflammatory cytokine levels in tears were analyzed[8,9].

An enzyme-linked immunosorbent assay (ELISA) results showed that patients undergoing SSRI treatment had higher levels of lacrimal serotonin than controls (2.66±0.63 ng/mL versus 1.18±0.33 ng/mL, $p<0.01$)[9].

Analysis of the protein chip revealed even more cytokines after the use of SSRI, based on the examination of 507 proteins, including Toll-like receptor 4 and interleukins-6 and 10 (TLR4, IL-6, and IL-10, respectively) were found[9]. TLR4 was detected exclusively in patients treated with SSRI as confirmed by qRT-PCR ($p<0.01$)[9].

The qRT-PCR assay demonstrated that the inflammatory cytokine genes for TNFa, IL1b, and IL10 and the pro-apoptotic gene AIF, BAD, and BAX levels increased in the SSRI group, while the levels of the anti-apoptotic gene BCL2 and XIAP decreased in this same group ($p<0.01$)[9].

Serotonin induces inflammation and cellular apoptosis by activating the NF-jB pathway, thus indicating that this pathway is closely related to serotonin and regulatory effects on inflammation and cellular apoptosis[9]. (Figure 1) To understand whether NF-jB was actually involved, a specific NF-jB

signaling inhibitor (JSH-23) was used in cells treated with SSRI[12]. The Western Blot assay demonstrated changes in the level of expression of P-p65, IjBa, the pro-inflammatory response element TLR4, and the inflammatory cytokine IL-1b. Western blotting also demonstrated that the pro-apoptotic proteins BAX, BAD, and AIF were all reversed in the corneal epithelial cells treated with JSH-23[9].

The ELISA assay showed that the IL-1b and IL-10 levels increased and TNFα content in the cell supernatant was reversed by the NF-jB signaling inhibitor ($p<0.01$)[9].

In addition, a decrease in cell apoptosis was observed after cells were treated with JSH-23 of cells along with a concurrent increase in serotonin levels ($p<0.01$)[13].

These data suggest that the use of SSRI aggravates DED associated with depression and causes intensification of the response to inflammation in addition to cellular apoptosis on the ocular surface, revealing that a higher level of lacrimal serotonin is the main cause of inflammation and apoptosis of corneal epithelial cells[8,9,13]. (Figure 1) These results showed that serotonin regulated the inflammatory response and cellular apoptosis through the activation of NF-jB signaling thus corroborating that there is more evidence about the serotonin/nuclear factor (HT/NF-jB) axis in DED that is associated with depression[3,9]. This finding provides a new strategy for clinical treatment in the face of this clinical condition[9].

Two major challenges in the management of dry eye exist:

(1) diagnosis, whose exams often do not correlate with clinical results;

(2) treatment, mainly because conventional therapy with artificial tears is not sufficient in moderate to severe cases of dry eye[7,3,9].

Selective serotonin reuptake inhibitors aggravate dry eye associated with depression

In the study, to verify the behavior of the SSRI in the DED associated with depression, an SSRI was offered to the cases of depressive rats over a period of 3 or 6 weeks[9]. It was observed that the corneal staining scores gradually increased along with the levels of lacrimal serotonin in the SSRI group ($p<0.01$), while no difference in lacrimal secretion was found between the two groups ($p>0.05$)[9].

Corneal staining also showed that the staining was diffuse and progressively intense in the SSRI group[7,9]. qRT-PCR, immunohistochemical staining, and ELISA results showed that the levels of IL-1b, TNFα, and TLR4 increased significantly in the SSRI group ($p<0.01$)[9]. In addition, normal rats were subject to SSRI for a period of 3 or 6 weeks, and it was found that the content of 5-HT, IL-1b, and TNF- in tears increased similarly ($p<0.01$)[11].

These data demonstrate that SSRI cause progressive damage to the corneal epithelium and DED, as they increase lacrimal serotonin levels[9,7,8]. The findings showed that depression could cause a decrease in lacrimal secretion and an increase in production of IL-1b and TNFα in rats with a close association between DED and depressive symptoms[9].

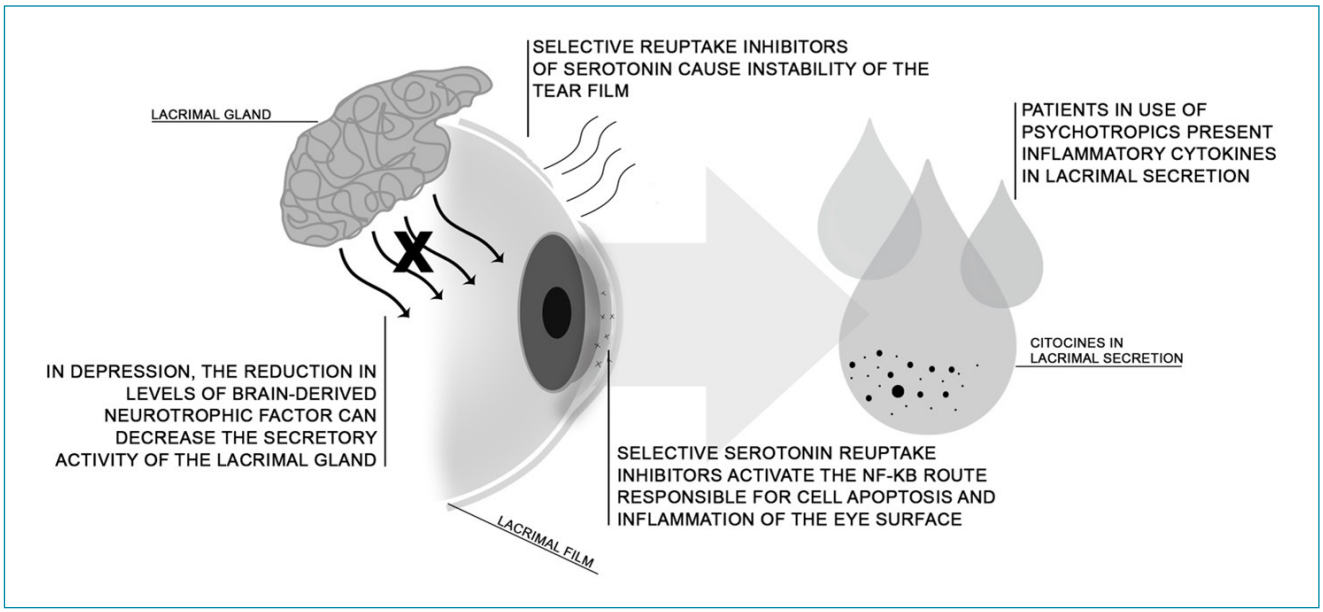

Figure 1. Relation between depression and dry eye disease (DED).

Prospects of therapy for dry eye syndrome in patients with depression

The participation of ophthalmologists and psychiatrists in the treatment of people with Dry Eye Syndrome can be highly favorable[11]. DED intervention can help reduce manifestations of depression, and in addition to providing appropriate therapy for depressive symptoms can cooperate in reducing DED symptoms since these symptoms are closely linked and interfere with people's quality of life[4,5,11].

Treatment goals that may serve as a principle in the study of therapies for DED correlating to depression in human beings in the future have been suggested[11,14]. The idea exists that psychological and physical stress causes a decrease in the secretion of tears, and to evaluate this association, a reference of stress DED mice was instituted[14]. In the research study, the enriched environment (EE), which presents additional cognitive, sensory, and social stimuli, was an influence to act to alleviate the stress-induced decline in the amount of tears[14].

EE succeeded in increasing the expression of the brain-derived neurotrophic factor (BDNF) in rats; in contrast, the stress load caused a decrease in the expression of this factor[9]. An animal model was employed, but the intervention can also relieve symptoms in humans[9]. (Figure 1) The results indicate that BDNF is correlated with DED disease[9]. Therapy consists of relieving the symptom of dry eye using supplementary eye drops; however, a treatment that acts on the underlying pathology is necessary[7,9]. Two conditions that help in the success of the treatment are the practice of physical exercise in addition to a sense of well-being[14,15].

The most common reports from patients with DED are dryness (45%), foreign body sensation (24%), and tired eyes (15%)[15]. More than half of the patients had obtained inadequate quality sleep when compared to the control group, and the group with DED had a shorter duration of sleep and a higher depression score[9,15]. The study indicated that mood and sleep are closely related to DED and an improvement in these two aspects could be linked to good therapy[15].

CONCLUSION

It is observed that the depressive state is linked to the appearance or worsening of DED resulting from chronic eye pain in the patient resulting. Given the above findings, the need to search for new ways to optimize the psychiatric treatment of patients with ophthalmic diseases, such as DED, to relieve symptoms and the reducing damage with broad therapeutic success.

AUTHORS' CONTRIBUTIONS

MVMRR: Supervision. GCFV: Writing – Review & Editing. **LHRMF:** Writing – Review & Editing. **CEXC:** Writing – Review & Editing. **GBM:** Writing – Review & Editing. **BROR:** Writing – Review & Editing.

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REVIEW ARTICLE
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Polycystic ovary syndrome in adolescents with obesity

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SUMMARY

INTRODUCTION: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age with the prevalence from 5% to 15%, and the prevalence of PCOS in adolescents with obesity seems even higher. The weight status is significantly associated with the quality of life in adolescents with PCOS.

OBJECTIVE: This review aims to summarize the latest findings of pathogenesis, diagnosis, comorbidity, and management in PCOS adolescents with obesity.

METHODS: This is a narrative review of articles published in PubMed from June 2013 to June 2020 Data were searched using the key words of "polycystic ovary syndrome" AND "adolescent" AND "obesity."

RESULTS: Pubertal obesity, particularly central obesity, could have a negative impact on the pathophysiology of PCOS. In adolescents with obesity, a review of medical history and a long-term follow-up for PCOS symptoms are essential to avoid misdiagnosis. There is a link between obesity and comorbidities of PCOS in adolescents. Holistic treatment and concern for related comorbidities should ideally begin as early as possible in obese adolescents once the diagnosis of PCOS is confirmed.

CONCLUSION: Adolescents with PCOS and obesity need more attention from physicians and researchers, and the effective interventions in the early stage are critical to improve their life quality.

KEYWORDS: Polycystic ovary syndrome. Adolescent. Obesity.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age with the prevalence from 5% to 15%, and the primary cause of anovulatory female infertility.[1-2] It was reported that many manifestations and biomarkers of PCOS changed with the advancing age, involving androgen concentrations, fat distribution, and menstrual irregularity.[3]

Obesity, especially visceral obesity, is common among adolescences and adults with PCOS.[4] A recent study indicating that the prevalence of PCOS among overweight or obese pubertal patients seemed to be higher than in adult patients,[5] and its prevalence seemed to be associated with the state of obesity in adolescent girls.[6] In addition, it was shown that weight status was closely associated with the relationship between PCOS and health-related quality of life in those girls with PCOS,[7] and the

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risk factors related to metabolic syndrome were also found in obese adolescents with PCOS.[8-9]

Treatments of PCOS include not only improvement of menstrual cycles and hirsutism but also reducing risk factors of metabolic syndrome and cardiovascular events, such as insulin resistance, dyslipidemia, and obesity.[10] Considering the impact of obesity on adolescents, the early-stage interventions should play an important role in this population. Therefore, the aim of this article was to conduct a narrative review of PCOS in obese adolescents, including the pathogenesis, diagnosis, comorbidity, and management. This review might also contribute to improving the quality of life in obese girls with PCOS.

METHODS

In this narrative review, we searched the PubMed database using the following key words: "polycystic ovary syndrome" AND "obesity" AND "adolescent." The inclusion criteria for selection were as follows: articles in the English language and articles published during the period of 7 years (June 2013—June 2020), with studies related to obese adolescents with PCOS. We excluded studies that did not specify which populations were probably involved, either adults or nonobese people.

RESULTS

First, we found 455 studies related to this subject, of which 30 were included for this review after further exclusion. Then we summarized the results and divided them into four aspects, including pathogenesis, diagnosis, comorbidity, and management in PCOS adolescent with obesity.

Pathogenesis

Adolescent PCOS was the outcome of a mismatch between energy saving and obesogenic environment.[6] The hypothesis of adipose tissue expandability speculated that hyperinsulinemic androgen excess in PCOS was usually caused by depletion of the capacity to expand subcutaneous adipose tissue in a metabolically safe way. If prenatal weight gain was less than postnatal weight gain, more fat would be stored in central tissues than in subcutaneous adipose, which induced central obesity.[11] However, young girls might increase the speed of their growth and/or maturation to avoid such central obesity.[12] At adolescence and adulthood, this homeostatic mechanism could be out of balance and PCOS might ensue.[13] It was reported that high body mass index (BMI) during childhood was associated with menstrual irregularity, and weight gain during adolescence to adulthood was also related to PCOS.[14-15] In addition, omentin-1, an adipokine secreted essentially by visceral adipose tissue, was negatively correlated with free testosterone level in obese girls with PCOS as compared with obese girls without PCOS, suggesting that virilization of adipose tissue might have a role in the pathogenesis of PCOS *via* alternating adipokine profile.[16] In addition, S100A4, a marker of subcutaneous adipose tissue dysfunction, might become a circulating marker of hepato-visceral fat excess in adolescents with PCOS.[17]

Pubertal obesity was one of the adverse factors underlying the pathophysiology of PCOS in adolescents. First, considering the role of mitochondrial dysfunction and systemic inflammation played in the pathogenesis of PCOS in adult patients, it was investigated that manifestations of oxidative stress and systemic inflammation also performed in overweight adolescents with PCOS, but less obvious in PCOS adolescents with normal weight due to the homeostasis control system and adaptive compensative mechanism of antioxidant defense in adolescence.[18] In addition, obesity could exacerbate the insulin-resistant (IR) and hyperinsulinemia to aggravate hyperandrogenism indirectly,[19] and peripubertal obesity was a potential factor of hyperandrogenism, which was especially prominent in early puberty.[20] It was found that obese adolescents with PCOS had significantly lower sex hormone-binding globulin (SHBG) and significantly higher free testosterone levels as compared with normal-weight girls with PCOS.[21] Furthermore, the free testosterone levels were significantly higher in obese adolescents with PCOS than those without PCOS.[21]

In summary, pubertal obesity, including central obesity, is associated with PCOS, which reminds physicians to perceive the appearance of PCOS. Early interventions need to put on PCOS adolescents with increased BMI to restrict weight as obesity could have a negatively multifactor impact on the pathophysiology of PCOS in the pubertal time.

Diagnosis

The diagnosis of PCOS in adolescents was challenging, because of the overlap of the normal puberty with manifestations of PCOS, such as menstrual irregularity, acne, and hirsutism, and now mainly determined by the coexisting of menstrual irregularity and hyperandrogenism according to different published guidelines.[22]

Obesity in puberty might be an important marker for the diagnosis of PCOS in the early stage. A prospective study indicated that early adiposity rebound, the second rise in BMI following a nadir occurring before 5 years old, was correlative with the diagnosis of PCOS. It was crucial for adolescents with adiposity rebound and continuous obesity to screen for PCOS manifestations, such as persistently menstrual irregularities and hirsutism.[23] In addition, adolescents "at risk" of PCOS are those who only have a single condition of PCOS

diagnostic criteria, that is, irregular menstrual cycles or clinical hyperandrogenism. These adolescents needed reassessment in menstrual cycle irregularity at 3-year post-menarche and polycystic ovarian morphology at 8 years post menarche, which was particularly important for those with persisting PCOS features and significant weight gain.[24] In addition, the cutoff of hirsutism score with Ferriman–Gallwey index was associated with ethnic background, and the diagnosis of hirsutism might create psychological pressure for women, and even more for adolescents. Thus, accurate cutoff of diagnostic criteria of hyperandrogenism needs more studies to verify in order to avoid overdiagnosis.[25]

The serum level of anti-Müllerian hormone (AMH) is correlated to the antral follicular count or the excessive number of follicles per ovary.[26] The serum AMH levels in adolescents and adults with PCOS were mostly higher than in those without PCOS, but they were not recommended for PCOS diagnosis due to insufficient studies and inaccurate standard for different populations.[24] Considering the difficulties of performing vaginal ultrasound in obese adolescent girls and distinguishing PCOS-related hyperandrogenic manifestations from obesity-related alterations, a study reported that the AMH of 6.26 ng/mL seemed to be an optimal cutoff value in obese girls for predicting PCOS; addition of SHBG and total testosterone to AMH increased the predictive power to 93.4% for diagnosing PCOS.[27]

In conclusion, a review of medical history and a long-term follow-up of symptoms related to PCOS were important for adolescents with obesity to avoid misdiagnosis. In addition, obese adolescents, especially "at risk" of PCOS, with high serum levels of AMH need more attention to detect the alterations of manifestations associated with PCOS.

Comorbidity

The presence of obesity seems to be clearly associated with metabolic syndromes and psychological issues in adolescents with PCOS. The prevalence of abnormal glucose metabolism in adolescent patients with PCOS was reported at 17.2%, who were mostly overweight or obese.[8] In obese girls with PCOS, more markers of cardiovascular disease (CVD) risk were found as compared with those without PCOS.[9] Furthermore, it was found that nonalcoholic fatty liver was connected with increasing abdominal adiposity in adolescents with PCOS.[28] The emotional depress partly was also connected with some certain symptoms of PCOS such as obesity and hirsutism in adolescents with PCOS.[29] The depression scores were definitely higher with elevated BMI, which meant potentially important interaction between obesity and depression in adolescents with PCOS.[30]

Increasing clinical and laboratory data emerge as early evidence of metabolic disorders in obese adolescents with PCOS. It was reported that elevated fasting and postprandial plasma triglyceride and apolipoprotein (Apo)B-lipoprotein remnants could provide evidence of early subclinical CVD risk in obese girls with PCOS, which were highly associated with impaired insulin metabolism and hyperandrogenaemia.[31] Moreover, increased pulse wave velocity, vascular cell adhesion molecule-1, and high-sensitivity C-reactive protein might be the earliest subclinical atherosclerosis biomarkers in obese girls with PCOS.[32] The oral glucose tolerance test (OGTT, using a dose of 1.75 g/kg to a maximum of 75 g) was a superior diagnostic test to assess abnormal glucose levels in obese girls with PCOS.[8] In addition, estimate of insulin sensitivity (e-IS), an index without an OGTT derived from waist circumference, fasting triglyceride concentrations, and HbA1c, could predict server IR in girls with PCOS.[33]

In a word, there is also a link between obesity and comorbidities of PCOS in adolescents. Special biomarkers or clinical tests could provide evidences of metabolic disorders in obese adolescents with PCOS, periodical tests for the condition of the liver and emotional counseling are also necessary for those girls.

Management

The long-term management for reproductive, metabolic, and mental health was suggested once a pubertal girl was diagnosed with PCOS.[34] It was reported that both lifestyle interventions and pharmacological strategies for weight management were beneficial to obese women with PCOS.[35] Considering the influence of obesity in PCOS, weight management is important for obese adolescents with PCOS, even for those "at risk" of PCOS.

Lifestyle interventions, with an objective of weight loss, were recommended as a first-line treatment for adolescent PCOS girls with overweight or obesity.[36] Evidences indicated that successful weight loss in obese PCOS girls was associated with improvement in the menstrual cycle, reduction in androgens, and cardiovascular risk factors.[37-39] In order to get rid of the side effects of medicine, lifestyle interventions could also be recommended to the obese girls "at risk" of PCOS. Comprehensive lifestyle interventions, including a balanced diet, exercise, behavioral education and psychotherapy, were significantly achieved weight loss.[39] As we know, women with PCOS had increased appetite and calorie input; therefore, the general management rule of diet was calorie restriction (500–1000 kcal per day) and reduced amount of carbohydrate (not exceeding 200 g or no more than 30% of total energy).[40] It was also shown that low-glycemic load (45% carbohydrate, 35% fat, 20% protein) or low-fat ((55% carbohydrate, 25%

fat, 20% protein)) diet over 6 months were both efficacious for promoting weight loss and reductions in body fat among overweight and obese adolescents with PCOS.[41] Exercise with at least 60 min of moderate-to-vigorous intensity physical activity per day, including those that strengthen muscle and bone, at least three times weekly was recommended for adolescents.[42] However, the optimal exercise dose for promoting weight loss in adolescents with overweight–obesity was still uncertain.[43] In addition, it was found that poor sleep behaviors were associated with metabolic dysfunction and metabolic symptoms among obese adolescents with PCOS, so sleep health should be included in the assessment of adolescents with PCOS and obesity.[44]

Pharmacological treatments of the combined oral contraceptive pill (COCP) and/or metformin were recommended in adolescents clearly diagnosed with PCOS or in adolescents deemed "at risk" of PCOS for the management of symptoms. In obese adolescents with PCOS, COCP combined with metformin could be considered when COCP and lifestyle changes could not achieve desired targets.[24] A study reported that treatment with metformin or oral contraceptives in obese adolescents with PCOS could lead to reduction in androgen levels, weight loss, and increased insulin and sensitivity.[45] In addition, lifestyle interventions combined with oral contraceptives and metformin could reduce central adiposity and total testosterone and increase high-density lipoprotein, but could not enhance overall weight reduction.[46] However, there was no exact recommendation for special types and doses of COCP due to insufficient data in adolescents.[24] Local therapies like photoepilation were recommended as first-line therapies to treat localized hirsutism in adolescents with PCOS.[47] Antiandrogens were advised to consider after the use of the COCP alone with cosmetic therapy for at least 6 months, and antiandrogens should only be used when contraceptive measures are guaranteed in those sexually active adolescents.[24] The use of anti-obesity medications in children and adolescents was not approved.[48] However, it was found early low-dose combination of spironolactone 50 mg/day, pioglitazone 7.5 mg/day, and metformin 850 mg/day (SPIOMET) treatment for PCOS in adolescent girls normalized posttreatment ovulation rates more than oral contraceptive, with normalizing visceral fat and insulinemia but no significant change on body weight. Thus, the intervention on early reduction of hepato-visceral fat in adolescents with PCOS could be an important strategy.[49]

In summary, weight management is crucial for obese adolescents with PCOS. Holistic treatments should ideally begin at early time once obese adolescents get diagnosed with PCOS in case situations get worse in adults, and weight loss is significantly important in obese adolescents with PCOS or in obese girls "at risk" of PCOS. In addition, treatments of PCOS-related symptoms could be considered for obese girls "at risk" of PCOS.

DISCUSSION

Polycystic ovary syndrome is one of the most common endocrine disorders in women of reproductive age, and its manifestations could start at pubertal period and change with advancing age.[1-3] According to our narrative review, pubertal obesity, particularly central obesity, could have an impact on the pathophysiology of PCOS. The diagnosis of PCOS in adolescents with obesity requires a review of medical history and a long-term follow-up of PCOS symptoms to avoid misdiagnosis. There is a link between obesity and comorbidities of PCOS in adolescents. The holistic treatment for obese adolescents with PCOS, involving diet, exercise, emotion, sleep, and concern for comorbidities associated with PCOS should ideally begin at early time once they get diagnosed with PCOS, in case that situation would get worse in adults. This narrative review provides a comprehensive summary of studies about obese adolescents with PCOS in recent years, which might facilitate physicians in clinical practice and arise their awareness to take management in early stage in order to improve long-term health in adults.

However, this review has several limitations. One is that the selection of articles was restricted to one database with one language, which might reduce the number of relevant publications. Another limitation is that the samples involved in most of the included studies were from South America and Europe; this might bias the conclusion about the association between obesity and PCOS toward the above ethnic populations.

CONCLUSIONS

The pubertal obesity is related to the pathogenesis of PCOS. Obese adolescents with PCOS or "at risk" of PCOS need more attention of physicians to undertake holistic management in time to avoid the deteriorating scenario with advancing age. The exact mechanism underlying the relationship between obesity and PCOS in adolescence is still not fully understood; future work is required to explore its etiology. More studies with a large sample size are needed on the diagnosis criteria, comorbidities supervision, and treatments in obese adolescents with PCOS.

AUTHORS' CONTRIBUTIONS

LF: Writing – Review and Editing. **FQ:** Supervision, Writing – Review and Editing. JP: Writing – Review and Editing. **TW:** Writing – Review and Editing. **FW:** Supervision, Writing – Review and Editing.

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REVIEW ARTICLE
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Efficacy and landscape of Covid-19 vaccines: a review article

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SUMMARY

INTRODUCTION: The rapid advance of Coronavirus disease 2019 (Covid-19) has led to the incessant search for therapeutic and prophylactic measures to fight the pandemic. Because it is a viral infection, the safest long-term prophylactic form, in addition to social distance and hygiene, is the vaccine.

OBJECTIVE: Thus, this study aimed at conducting a review of the efficacy and landscape of Covid-19 vaccines.

METHODS: The following electronic databases were used MEDLINE via PubMed, SCIELO, LILACS, NEJM, and Clinical Trials. Our study includes the 7 vaccines (phase 3) that reported an efficacy rate for Covid-19, including characteristics inherent to each one of them.

RESULTS: Preliminary studies have shown that, although an efficacy ≥70% is necessary to eliminate the infection, a prophylactic vaccine with efficacy <70% will still have an important impact and can contribute to the elimination of the virus, provided that appropriate measures of social distancing remain.

CONCLUSIONS: The effectiveness of the vaccines obtained in this study varied between 50.38 and 95%, data that may represent a reduction in serious cases, hospitalizations, sequels, and deaths caused by Covid-19, respecting the panorama presented in this article.

KEYWORDS: Covid-19. Vaccines. Efficacy.

INTRODUCTION

The imminent need for effective solutions and the rapid advance of Coronavirus disease 2019 (Covid-19) has led to the relentless search for therapeutic and prophylactic measures to fight the pandemic. Because it is a viral infection, the safest long-term prophylactic form, in addition to social distance and hygiene, is the vaccine. Several teams around the world are working on developing effective and safe vaccines for human beings[1].

A total of 93,956,883 cases of Covid-19 have been confirmed including 2,029,084 deaths, reported to World Health Organization (WHO) and 223 countries, areas, or territories with cases as of 19 January 2021[2]. Hence, a race against time is being established for

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months so that fewer people will be affected by this devastating virus. Given the urgent need, vaccine development and production are being fast-tracked to hopefully make a safe and effective vaccine available for the more vulnerable group of the population, to minimize the impacts of the pandemic worldwide[3].

Although the production capacity may not be able to meet the global demand for vaccines in the very near future, it would be beneficial to have a limited number of vaccines available for emergency use and the more vulnerable population as soon as possible with the ultimate aim of distributing vaccines globally to the rest of the population by the end of 2021[4]. Thus, this study aimed at conducting a review of the efficacy and landscape of Covid-19 vaccines.

METHODS

Our study includes the 7 vaccines (phase 3) that reported an efficacy rate until 19 Janeiro 2021 for Covid-19, including relevant information about vaccine name, countries, developers, type, vaccine platforms, number of doses, the interval between doses, storage, mechanisms of action and efficacy of Covid-19 vaccines as well as characteristics inherent to each one of them. The search used in this review article was carried out using the following electronic databases: Medline via Pubmed, SCIELO, LILACS, NEJM, and Clinical Trials.

The landscape of Covid-19 vaccines

Vaccines generally require many years of detailed research and testing before reaching the clinical stage. Due to the great current need, researchers are working hard to make effective vaccines available to society. To develop a safe and effective vaccine, pre-clinical and clinical trials must be done with vigilance to avoid severe adverse effects[5]. Various platforms are being looked at for the development of Covid-19 vaccines. These include RNA-based vaccine, DNA-based vaccine, viral vector (non-replicating), inactivated vaccine, protein subunit, and virus-like particle[6].

There were 64 vaccines in clinical development and 173 vaccines in pre-clinical development, totaling 237 potential vaccines to act as prophylaxis for the new coronavirus infection. Of the vaccines under clinical development, there were 15 in phase 3 of the clinical study, 6 using the inactivated virus, 4 with viral vector without replication, 2 with protein subunit, 1 using DNA, and 2 using viral RNA to induce the production of antibodies against the SARS-CoV-2[2]. Table 1 shows some relevant characteristics about the vaccines.

Table 1. Inherent characteristics of the 7 different vaccines (phase 3) for Covid-19.

ID	Vaccine name	Country	Developers	Type	Vaccine plataform	Phase	Doses	Interval between doses	*Storage*
1	Coronavac	China	Sinovac Research and Development Co., Ltd	SARS-CoV-2 vaccine (inactivated)	Inactivated virus	3	2	14 days	2–8°C
2	BBIBP-CorV	China	Sinopharm+Wuhan Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Verocell)	Inactivated virus	3	2	21 days	2–8°C
3	BBIBP-CorV	China	Sinopharm+Beijing Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Verocell)	Inactivated virus	3	2	21 days	2–8°C
4	Astrazeneca	England	AstraZeneca + University of Oxford	ChAdOx1-S-AZD1222 (Covishield)	Viral vector (Non-replicating)	3	1-2	0+28 days	2–8°C
5	Sputinik V	Russia	Gamaleya Research Institute; Health Ministry of the Russian Federation	Gam-COVID-Vac Adeno-Based (rAd26-S+rAd5-S)	Viral vector (Non-replicating)	3	2	0+21 days	2–8°C
6	BTN162b2	USA and Germany	Pfizer/BioNTech+ Fosun Pharma	BTN162 (3 LPN–mRNAs)	RNA-based vaccine	3	2	21 days	-70°C
7	mRNA-1273	USA	Moderna+National Institute of Allergy and Infectious Diseases (NIAID)	mMRNA	RNA-based vaccine	3	2	28 days	-20°C

Source: World Health Organization, 2021. Some information was collected from the respective clinical studies.

Genetic vaccines (DNA and RNA vaccines)

Genetic vaccines, in contrast to vaccines that employ recombinant bacteria or viruses, consist only of DNA or RNA, which is taken up by cells and translated into protein. Genetic vaccines are a group of vaccines that deliver one or more of the coronavirus's own genes into our cells to provoke an immune response. Among those that are part of phase 3, we can mention The Cominarty (Tozinameran or BNT162b2) — Pfizer BioNTech, The mRNA-1273 — Moderna, and The CVnCoV — Curevac[7].

The mRNA-1273, for example, is a vaccine composed of synthetic mRNA encapsulated in Lipid nanoparticle which codes for the full-length, pre-fusion stabilized spike protein S of SARS-CoV-2[8], while the BNT162b1 is a codon-optimized mRNA vaccine that encodes for the trimerized SARS-CoV-2 RBD, a critical target of the virus nAb[9].

Viral vector vaccines

The viral vector vaccines contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make a viral protein while other viral vectors slowly replicate, carrying coronavirus proteins on their surface. Among those that are part of phase 3, we can mention the Sputnik V (previously Gam-Covid-Vac), the AZD1222, AstraZeneca, the Convidecia (also known as Ad5-nCoV) — CanSinoBIO, and the Ad26.COV2.S — Johnson&Johnson[7].

Protein-based vaccines (subunit)

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them of which[7]. A protein-based vaccine is based on synthetic peptides or recombinant antigenic proteins, which are necessary for invigorating long-lasting protective and/or therapeutic immune response, however, the aid of an adjuvant is necessary[10].

Inactivated virus vaccines

Inactivated or attenuated coronavirus vaccines are created from weakened coronaviruses or coronaviruses that have been killed with chemicals. We can mention the BBIBP-CorV — Sinopharm and the CoronaVac (previously PicCoVacc) — Sinovac Biotech[7]. Among the advantages presented by inactivated virus vaccines, there are: it has the pre-existing technology and infrastructure required for its development; It can be used along with adjuvants to increase their immunogenicity; has already been tested for SARS-CoV and various other diseases[11].

Efficacy of vaccines

Experts are currently trying to do what is necessary to convince the population of the benefits of a Covid-19 vaccine, which is apparent by the number of vaccines under clinical trials and the funding being directed toward vaccines to obtain one before 2021, however, there is a concern about rushing vaccines and producing one with limited effectiveness. One of the main current concerns is that the vaccine is ready for use but does not show results as effective as expected in the population, this could lead to loss of trust in vaccines. In consequence, when an effective vaccine is introduced fewer people may be willing to accept it resulting in a worsening of the pandemic and further reduce the confidence in already approved and effective vaccines for other diseases[12].

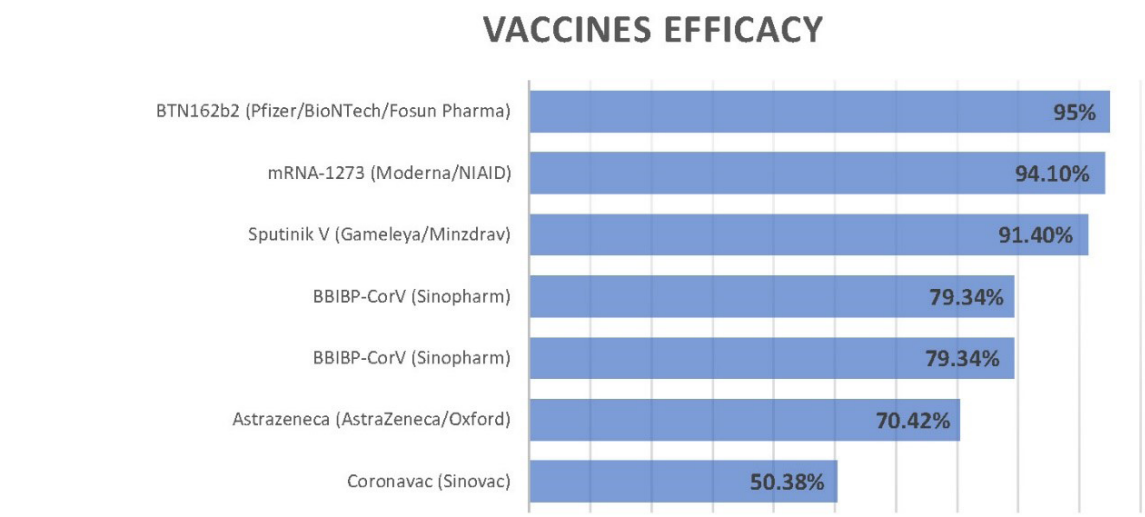
Because of the rapid development of vaccines and clinical trials underway, questions arise as to how much efficacy is needed for the vaccine to be immunogenic. Preliminary studies have shown that, although an efficacy ≥70% is necessary to eliminate the infection, a prophylactic vaccine with efficacy <70% will still have an important impact and can contribute to the elimination of the virus, provided that appropriate measures of social distancing. Vaccines with efficacy below 70% can also contribute to reducing the duration of infection in people infected with the virus[13]. Figure 1 shows the 7 vaccines that have defined efficacy until this article publication.

Belonging to the vector viral group vaccines the Sputnik V vaccine was the first registered vaccine in the world on a well-studied human adenoviral vector-based platform and is between the top 10 candidate vaccines approaching the end of clinical trials have reached the efficacy of 91,4% on data analysis at the end of it and starting the mass production by the WHO list. AstraZeneca showed significant vaccine efficacy of 70.4% after two doses and protection of 64.1% after at least one standard dose, against symptomatic disease, with no safety concerns[14,15].

On 2020 December 8 the FDA released their independent analysis of the clinical trials. They determined that the BTN162b2 has an efficacy rate of 95 percent. Less than two weeks after the first dose[7]. Moderna showed vaccine efficacy of 94.1% based on 196 covid-19 cases, of which 185 were in the placebo group[16]. Both vaccines BTN162b2 and mRNA-1273 are RNA-based vaccines.

In the group of inactivated vaccines, the Coronavac was studied in Turkey, in phase 3 clinical tests, concluded that the efficacy of 78% in the prevention of mild cases of Covid-19 and 100% in the prevention of severe and moderate cases were concluded. At this point, it was not clear how the researchers came to the conclusion of efficacy, and further details were not officially demonstrated in the studies. The confusion is justified by Turkey and Indonesia who provided different results in the effectiveness of doses. However, in Brazil, the Butantan Institute approved the vaccine with 50.39% efficacy[17,18].

A Covid-19 vaccine developed by a Beijing firm linked to Sinopharm has a protection rate of 79.34 percent against the disease, the firm said in a statement on December 2020. The 79%



Source: The information was collected from the respective clinical studies.

Figure 1. Efficacy of the 7 different vaccines (phase 3) for Covid-19.

figure by Sinopharm is lower than the 86% that was reported by the United Arab Emirates on December 9 for the same vaccine[19].

Challenges and future perspectives

It is known that the process of immunization of the world population is not easy, mainly because it is a pandemic that has been devastating the world since the end of 2019. In addition to issues of production itself, respect protocols, phases, to develop a safe and effective product, there are a whole logistics of transport, storage, ethical and political issues involved.

Therefore, some of the main questions that remain for the future are how long these current vaccines will be able to maintain human immunity to the new coronavirus and whether such vaccines that are being developed and applied to the population will be useful in combating possible mutations viruses that may occur.

CONCLUSIONS

The effectiveness of the vaccines obtained in this study varied between 50.38% and 95%, data that may represent a reduction in serious cases, hospitalizations, sequels, and deaths caused by Covid-19, respecting the panorama presented in this article.

AUTHORS' CONTRIBUTIONS

TCPA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing –original draft. **PVF:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **PHPC:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **EAPM:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **TJMR:** Formal analysis, Supervision, Validation, Writing – review and editing. **FTB:** Formal analysis, Supervision, Validation, Writing – review and editing. **CFSR:** Formal analysis, Supervision, Validation, Writing – review and editing. **FWSR:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – review and editing. All authors have reviewed and approved the final text of the article and are responsible for its content.

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COMMENTARY
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The relationship between intermittent fasting and weight loss

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Dear Editor,

I have reviewed the article by Lima et al.[1] entitled "Impact of intermittent fasting on body weight in overweight and obese individuals". In recent decades, intermittent fasting (IF) is currently a popular strategy for weight loss. Therefore, it is of great evidence-based practice to verify the relationship of IF in the body weight of overweight and obese individuals. The study of Lima et al.[1] makes some valuable contributions. However, I'd like to confirm the details of this article. The authors indicate that table 1 shows 4 papers related to the impact of vitamin D in the glucose profile of pre-diabetic individuals in the headline. In fact, four studies were considered enrolled all assessed the effect of IF in overweight or obese individuals comparing IF groups with calorie-restrictive diet (CRD) groups but not mentioned the impact of vitamin D in the glucose profile.

In addition, a review of the published literature reported improvements in cardiovascular and metabolic parameters (triglycerides, LDL-cholesterol particle size, blood pressure, fat mass, and C-reactive protein), mood/depression status, and quality of life, even longevity genes expression or DNA damage[2]. Observational studies expanded on the fasting benefited with CAD and diabetes. IF with a high-protein diet is effective for weight loss were reported in few studies but not included vitamin D[3]. The description of the impact of vitamin D in the glucose profile of pre-diabetic individuals should be addressed in detail or revised.

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