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Editors-in-Chief: Renato Delásio Lopes and Jose Maria Soares Jr.
Managing Editor: Cesar Teixeira
E-mail: ramb@amb.org.br
Website: www.ramb.org.br

ADDRESS: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal Code: 01333-903
Phone no.: (+55 11) 3178-6800 Ext. 177
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Editorial Production

EDITORIAL
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The influence of essential fatty acids on the female health

Ceci Mendes Carvalho Lopes[1], Lucia de Fatima Cahino da Costa Hime[1], Edmund Chada Baracat[1], Jose Maria Soares-Júnior[1]*

INTRODUCTION

Essential fatty acids are polyunsaturated fatty acids (PUFAs) that are not synthesized in the organisms. Therefore, PUFAs are needed to be supplied through the diet for proper functioning of the metabolic processes. There are several sources of PUFAs, such as some oils (soybeans and canola), some seeds (pumpkin, chia, and sunflower), leafy vegetables, nuts, fish, and shellfish[1]. The essentiality of these acids was defined in 1930, when rats fed with a deficiency of PUFAs developed dermatological, renal, and visual problems and fertility disorders, and that the reintroduction of these acids reversed the symptoms[1-3]. PUFAs are considered essential because they are the precursors of important substances, such as prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), denominate eicosanoids[2], and act in various functions of the organisms.

The nutritional supply is generally ample, and PUFAs may find in various types of food. Basically, there are two types of PUFAs, namely, omega-3 and omega-6, defined by the location of the first double bond in the initial molecule of the carbon atom in relation to the methyl end of the chain[2,3]. The three types of omega-3 fatty acids involved in human physiology are alpha-linolenic acid (ALA), found in plant oils, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Linolenic acid (LA), the shortest chain of the common omega-6 fatty acids in the human diet, is categorized as an essential fatty acid because the human body cannot synthesize it[2,3].

The omega-6 fatty acids are precursors to endocannabinoids, lipoxins, and specific eicosanoids. LA converts to gamma-linolenic acid (GLA), while GLA converts to EPA. GLA is a precursor to prostaglandins and leukotrienes. EPA is a precursor of anti-inflammatory factors (lipoxins, resolvins, and protectins)[3,4]. In some situations, such as aging, insulin resistance, autoimmune diseases, obesity, a diet with a predominance of saturated fats, and alcohol intake, there is a tendency for the activity of enzymes involved in PUFA metabolism to decrease, requiring the introduction of supplementary diet consumption[5].

The balance between the intake of omega-3 and omega-6 fatty acids prevents the appearance of chronic inflammatory diseases, cardiovascular diseases, and some cancers. The "Western diet" has more LA than ALA. There are controversies about the ideal ratio, but it is considered ideal when the ratio between omega-3 and omega-6 is 1:4, respectively, to avoid the risk of developing cardiovascular diseases[6].

The action of polyunsaturated fatty acids on immunity

Although immunity and resistance to infection are dependent on several factors, and therefore very different between people, nutrition can significantly influence it not only as a factor but also as interacting with others (genetics, environment, and lifestyle). Among the nutrients, there is a prominent place for essential fatty acids[6,7].

Omega-3s have been well studied and shown to play a significant role in cellular immune function. Omega-6s have not seemed to perform that preponderantly. In many studies, they are used as controls for omega-3s. This potent activity of omega-3s is due to their high capacity to inhibit the production of inflammatory mediators. Among these eicosanoids, everything indicates that they also participate in a process of gene activation, prostaglandin E2, and some leukotrienes. There are also pro-inflammatory cytokines, adhesive molecules, platelet-activating factors, and reactive oxygen and nitrogen species[7].

An extensive and detailed review addresses the metabolic and genetic mechanisms of PUFA action on immunity and inflammation. They demonstrate that this process is, in many respects,

[1]Universidade de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Departamento de Obstetrícia e Ginecologia – São Paulo (SP), Brazil.
*Corresponding author: jsoares415@hotmail.com
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quite paradoxical, as, in similar situations, it sometimes leads to even opposite effects. The conclusion they reach is that there are many individual variables, both metabolic and even genetic, and that, therefore, there is no way to establish a dose or a therapeutic scheme with them, as this has to be established individually[8].

Asthma and allergic rhinitis

Based on the prior knowledge, leukotrienes are very important in triggering asthma. In fact, leukotrienes come from the metabolism of arachidonic acid (AA), via the 5-lipoxygenase pathway, and that they also have numerous pro-inflammatory properties, which also significantly contribute to the onset of asthma and allergic rhinitis. Some authors decided to study the activity of a mixture of borage oil and echium oil, i.e., another borage, which are rich in omega-6 fatty acids (and therefore do not produce AA in their metabolic cascade) and its impact on the inflammatory mechanism[9]. Specifically, they selected 37 asthmatic participants and divided them into four groups. Each group received capsules of a mixture of oil from the two plants (1,000 mg of echium and 1,300 mg of borage), respectively, in increasing doses for each group, for three weeks. The authors found a decrease in the PUFA levels and an attenuation of the production of leukotrienes in patients with asthma[9].

Several studies since the 1980s have shown that oils rich in GLA can promote improvements in various inflammatory diseases, such as asthma, atopic dermatitis, and rheumatoid arthritis. Some of the studies evaluated the combination of omega-6 and omega-3 and demonstrated a reduction in cytokines and leukocyte contribution, including in patients with severe lung injury, requiring intensive care. However, these studies did not have uniformity, and the number of participants was low. Therefore, further studies are necessary for a consistent framework of conclusions[8].

Studies show that populations who use the "Mediterranean diet" present fewer cases of asthma than those who eat the "Western diet." The Mediterranean diet, rich in vegetables and fish, is a great source of essential fatty acids. The "Western diet" tends to be pro-inflammatory. In addition, this diet favors obesity, another triggering factor for asthma[10].

Rheumatoid arthritis

Rheumatoid arthritis occupies a prominent place among autoimmune diseases. Pathogenesis is associated with the inflammatory agents that infiltrate the joints, producing swelling and pain. Several studies have proven the action of omega-3 fatty acids in improving the clinical picture of this disease. Some omega-6s exert this benefit, especially GLA, found in borage, evening primrose, and black currant, because this substance may be converted to dihomo-gamma-linolenic acid (DHLA), which has a potent anti-inflammatory[11].

A double-blind study was carried out dividing 60 patients into three groups of 20, in which all participants received the recommended traditional treatment. The first group of patients also received a daily postprandial dose of five fish oil capsules (300 mg of DHA, 200 mg EPA, and 100 mg of other PUFAs); the second group received a daily postprandial dose double capsules of the first group and two capsules of evening primrose oil (each containing 1,300 mg–949 mg LA and 117 mg GLA); and the third group received only placebo. Clinical improvement was observed in both the first and second groups[11].

Action on cardiovascular health

Myocardial infarction and stroke

About one-third of deaths around the world may be attributed to atherosclerosis that causes cardiovascular disease and stroke[12].

PUFAs are the potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase that is essential in cholesterol metabolism. Statins act on this enzyme, known as potent lipidemia reducers, so significantly involved in atherosclerosis and, consequently, in infarction and strokes. There are strong indications that PUFAs act as mediators of statin action. If administered together, as a medicine, they can potentiate its action on the protection. PUFAs act as antiplatelet agents which is considered an important action in both the treatment and prevention of myocardial infarction[13].

Based on the knowledge that PUFAs, especially omega-3s, play a major role in atherosclerosis, although omega-6s are considered antagonists (due to their pro-inflammatory action), some omega-6s also play a beneficial role. Significant in this process, a group of British and Israeli researchers sought to investigate the mechanisms. Their studies led to the determination of several cellular mechanisms. In addition, the authors demonstrated that DHLA, derived from GLA, may play an important role in this process[12,13].

DHLA has an antithrombotic activity, which is important for decreasing arterial thrombotic events that lead to circulatory obstruction and serious damage. Although statins promote an obvious improvement in the prognosis of cardiovascular, they present side effects, which decrease the treatment adherence. PUFAs have been referred to as having great therapeutic and adjuvant possibilities for a long period of treatment. As inflammation is closely linked to the action of cytokines, in triggering atherosclerosis, DHLA has been proven to decrease the release of these cytokines. However, further studies are necessary[12].

Systemic arterial hypertension

Following the data recorded in the National Health and Nutrition Examination Survey (NHANES) 2007–2014, the adequate

balance between omega-6 and omega-3 intake is associated with a lower incidence of hypertension[14].

A study carried out with postmenopausal hypertensive patients with 2 g of GLA per day for six months proves the effect on blood pressure without the appearance of side effects[15].

PUFAs influence the action of the renin-angiotensin system, acting in the reduction of hypertensive processes. Its action is known to improve renal plasma flow, reduce renal vascular resistance, and favor glomerular filtration. This effect may act protectively and preserve kidney function[13-17].

Dry eye syndrome

Dry eye is a problem that can interfere a lot in people's daily lives, especially affecting activities that require the use of vision, such as reading, driving at night, using the computer, and so on, both professionally and for dilettantism. Some factors seem to influence its appearance, such as aging, female gender, inflammatory and immune processes as well as hypoestrogenism and hyperprolactinemia[17,18].

PUFAs, especially omega-3 and omega-6, seem to ameliorate the prevalence of dry eye. In fact, the authors suggested that effect after systematic review[1]. After three generations of rats were fed with the omega-3 deficit, there was no difference in the severity of the condition (dry eye) in the group with and without deficiency. However, several clinical studies, using both topically and by ingestion, diets or supplements balanced with omega-3 and omega-6 have shown an improvement in the syndrome. The explanation lies in the anti-inflammatory action of these fatty acids and leads to the obvious suggestion of prescribing them to the affected people. However, further study is necessary for adjusting the dose for the routine therapeutic protocol[1].

Obesity and colorectal cancer

It is well known that obesity is an inflammatory disease and plays an important role in the development of colorectal cancer. In fact, adipocytes release immunosuppressive signals, associated with a pro-inflammatory state, and omega-6s seem to be of importance in this process. The nutritional diet with the imbalance between omega-3 and omega-6 may participate in the pathogenesis of colorectal cancer, although increasing inflammation, acting on lymphocytes, and interfering with the release of cytokines and chemokines[16].

Action in menopause

Although the use of essential fatty acids is not usually highlighted among the various treatment options, some authors have administered them to climacteric patients, including studies in Brazil. Although, in some of them, there was no difference between treated cases and controls, some described benefits such as improved well-being and quality of life, improvement in symptoms such as memory capacity and depressive states and irritability, and even symptoms, i.e., vasomotor, with the use of omega-6 capsules with $^{3}2$ g per day. Improvements were also found in processes associated with the climacteric patients, such as high blood pressure and even the distribution of body fat (a risk factor for heart disease and the leading cause of lethality worldwide)[15,17].

Action during pregnancy

Discussing the importance of the Mediterranean diet, rich in vegetables and fish, that this diet therefore promotes the administration of essential fatty acids and that people who are nourished with this type of food are less prone to asthma, it is also reported that the administration of fatty acids, such as GLA, during pregnancy promotes the birth of children with a lower incidence of allergic problems, such as asthma[10].

A Cochrane review addressing studies with the administration of omega-3 supplements during pregnancy (covering a total of almost 20,000 patients) suggested that these substances may reduce the preterm births, despite a certain increase in prolonged pregnancies beyond 42 weeks, which increased the need for interventions. The authors suggest that therefore the administration of supplements with omega-3 to pregnant women may be an option for pregnancy[19]. They also confirm the beneficial action of DHA during pregnancy and breastfeeding for at least 6 months with a positive response in cognitive abilities[20].

CONCLUSION

PUFAs participate in several metabolic processes acting not only in the prevention but also in the treatment of several diseases. Corroborating the aforementioned authors, we indicate a nutritional diet with PUFAs for improving female health.

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LETTER TO THE EDITOR
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Revisiting optimal needle size for thyroid fine-needle aspiration cytology: not much finer, less non-diagnostic?

Ilker Sengul[1], Demet Sengul[2]*, Eduardo Carvalho de Arruda Veiga[3]

Optimal needle size for thyroid fine-needle aspiration (FNA) cytology has not been established distinctly and conclusively in thyroidology to-date. The literature on the subject is scarce. We read with respect the research article, entitled: "Optimal needle size for thyroid fine-needle aspiration cytology[1]." Tanaka et al.[1] declared to utilize two different sizes, 22- and 25-gauges, of needles for the FNA procedures. The authors reported the nondiagnostic/unsatisfactory rates of 22- and 25-gauge needles were being as 18.5% and 21.0%, respectively. Nevertheless, we currently reported the possible efficacy of nodule size of 10- and 15-mm in the greatest dimension, as the cutoff points, on three diagnostic tools; (i) strain elastography (SE), (ii) ultrasonography-guided FNA (US-FNA) cytology, and (iii) histopathology[2]. We had utilized just 27-gauge fine-needle (Hayat, 2 ml 3P 27-G, 0.40×50 mm, Istanbul, Turkey) by performing US-FNA for a total of 425 cases with 500 thyroid nodules by the surgeon-performed ultrasonography (SUS), based on the revised American Thyroid Association (ATA) management guidelines for patients with thyroid nodules and differentiated thyroid cancer [i.e. low, intermediate, and high suspicion nodules; 2015 ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer] for the duration of 3 years and 2 months[2,3]. This is a considerable and novel 'SUS-based' US-FNA thyroid study for the specific and also 'well-accepted crucial' size cutoffs of 10- and 15-mm in endocrine surgery, endocrine pathology, and thyroidology, to-date[2]. To this end, the cytopathologic evaluation of the cases had been performed based on The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), 1st ed.[4] and our FNA cytology outcomes for non-diagnostic/unsatisfactory cytology were revealed as 9.0%[2]. Moss et al.[5] reported in a systematic review and meta-analysis that the regular and coordinated thyroid FNA should be performed with smaller needle gauges, 24–27-gauges, without aspiration, routinely. In addition, we very recently introduced and suggested a novel terminology, in this sense, termed as "minimally invasive FNA; MIFNA" and "minimally invasive thyroid FNA; Thy MIFNA" involving 27-gauge fine-needle with topical and local anesthetic agents administration with the reasonable rates of nondiagnostic cytology, TBSRTC[6,7].

Of note, we recommend opting for Thy MIFNA with 27-gauge fine-needle to practice US-FNA procedure for indicated suspicious thyroid nodules with reasonable low rates of Category I (TBSRTC, 1st and 2nd eds.) and probably low severity of pain. To this end, we also recommend wielding facilitating pre- or periprocedural local, even topical anesthetic agents toward US-FNA for the thyroid nodules[2,6,7]. As a matter of fact, this issue merits further investigation.

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AUTHORS' CONTRIBUTIONS

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

[1]Giresun University, Faculty of Medicine, Division of Endocrine Surgery, Department of General Surgery – Giresun, Turkey.
[2]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
[3]Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Obstetricia e Ginecologia – São Paulo (SP), Brazil.
*Corresponding author: demet.sengul.52@gmail.com
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LETTER TO THE EDITOR
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Abdominal ultrasound, physical examination, and intraabdominal fluid

Steven Howard Yale[1]*, Halil Tekiner[2], Eileen Scott Yale[3]

To the Editor,

We read with interest the paper by Toledo et al. titled "Abdominal ultrasound augments the medical students' ability to identify free intraabdominal fluid[1]." Identifying a way to teach medical students' bedside abdominal ultrasound is paramount because of its known role in augmenting the physical examination. It has been estimated that at least 500 mL of intraperitoneal fluid is required for shifting dullness to be detected on physical examination[2]. Presumably, the accuracy for detecting fluid within the abdominal cavity is better when higher volumes are present. However, both ultrasound and computed tomography scans of the abdomen have the ability to detect as little as 100 mL of intraperitoneal fluid, and thus the physical examination will always be limited for this reason[3]. The questions are whether the physical examination can be taught to improve the examiner's performance and how these bedside maneuvers can be used in combination in order to further enhance the accuracy and reliability in detecting intraperitoneal fluid. The authors identified higher sensitivity, specificity, and accuracy of bedside ultrasound compared with the physical examination in diagnosing intraperitoneal fluid[1]. A prior study comparing these two modalities in first-year medical students found no differences in sensitivity, specificity, and accuracy between these two modalities[4]. We identified several methodological limitations from Toledo et al.'s[1] study and thus believe that they affected their findings, interpretation, and conclusion.

Free abdominal fluid refers to readably moveable fluid within the intraperitoneal cavity. A small volume may be normally present in otherwise healthy males and females[5]. Thus, the fluid may or may not be pathological, and if the latter is so, it is referred to as ascites. The free intraperitoneal fluid typically follows the contours of intraabdominal organs and conforms to the peritoneal folds. It usually accumulates in dependent regions, and when assuming the supine position it is found in the hepatorenal fossa (Morrison pouch), recto-uterine pouch (pouch of Douglas), and right and left paracolic gutters[6]. Instillation of 2,000 ml of dialysate in the supine position found on a computed tomography abdominal scan confirmed that the majority (30–55%) of fluid was identified in the pelvis, 15–30% in the paracolic gutters, 10–20% in the perisplenic and perihepatic spaces, and 1–3% in the lesser sac[7].

Studies performed by advanced practitioners compared the abdominal physical examination with the abdominal ultrasound and reported wide sensitivities and specificities for flank dullness (57–94%; 39–69%), shifting dullness (60–88%; 56–90%), and fluid wave (20–80%; 82–100%)[8-11]. These findings suggest that no single sign has sufficient sensitivity or specificity to be used alone and would be more useful if used in combination. The best indicators of ascites on physical examination are the presence of a positive fluid wave and shifting dullness. Ascites is unlikely to be found if bulging flanks, flank dullness, and shifting dullness are absent on physical examination.

In Toledo et al.'s study, medical students conducted a physical examination (flank dullness, percussion shifting dullness, and a fluid thrill or wave) and an ultrasound of the abdomen in the right and left upper abdominal quadrants and pelvic cavity[1]. Although the students received didactic and hands-on formal training using abdominal ultrasound, there is no mention of whether this occurred for the physical examination. Furthermore, no information was provided regarding performance on each of these physical examination tests. Shifting dullness is performed by moving the patients to the right or left lateral recumbent position. In doing so, it shifts free intrabdominal fluid to the most dependent position. If the physical

[1]University of Central Florida College of Medicine – Orlando, United States of America.
[2]Erciyes University, Faculty Of Medicine, Department of the History of Medicine and Ethics – Talas, Turkey.
[3]University of Florida, Division of General Internal Medicine – Gainesville, United States of America.
*Corresponding author: steven.yale.md@gmail.com
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examination is performed before the ultrasound examination or if the same patient is examined sequentially by different examiners, movement of the patient will affect the location of the fluid making comparison between examiners unreliable. Thus, the interobserver reliability of the test would be completely nullified.

One study in medical students found high interobserver reliability suggesting high concordance in test performance[3]. Toledo et al.'s study adds to the growing body of literature regarding the relative ease of teaching and performing bedside ultrasound[1]. However, further studies are needed to assess the utility of the physical examination using a combination of tests and a more uniformed methodological approach when examining patients with variable amounts of ascites.

AUTHORS' CONTRIBUTIONS

SHY: Writing – original draft, Writing – review & editing. **HT:** Writing – original draft, Writing – review & editing. **ESY:** Writing – original draft, Writing – review & editing.

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SHORT COMMUNICATION
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Burnout, engagement & leadership

Sónia Chan[1]*

INTRODUCTION

Burnout has been the subject of research, as it has been considered a public health problem[1,2] of great relevance owing to its costs[1]. American studies from 2013 reported that burnout in over 40% of physicians, with a tendency to increase in the following years[3] and with physicians in specialties working in the first-line care, being those with the highest risk of burnout[3,4]. Stress is considered inherent to health care professions owing to a number of factors such as long working hours, time-related pressure to perform, sleep deprivation, high expectations, and low tolerance for errors[5].

A 2002 study by the European Commission revealed that 10% of occupational diseases resulted from occupational stress and that the costs associated with these pathologies amounted to 20 million euros annually. In addition to the social costs, occupational stress also incurs costs for organizations through increased absenteeism and turnover, accompanied by a decrease in productivity and performance. A 2009 British study indicates that 25% of absences from the national health system are related to stress, anxiety, and depression. Also of note is presenteeism – where the professional chooses to continue working, but performs worse as a result of health problems; the costs associated with presenteeism are several times higher than the costs of absenteeism[6].

Initially, burnout and engagement at work were considered to be opposite poles of the relationship of well-being at work, in which burnout represented the negative and engagement the positive[1,7]. However, the fact that a person is not in burnout does not necessarily mean that he is engaged[7]. and for this reason, burnout and engagement are defined as two distinct concepts[7].

BURNOUT

Burnout is defined as a reaction to occupational stress and the link between an adverse psychosocial environment at work and psychiatric disorders[7]. The inability to cope with sources of pressure at work can generate physical and mental problems, as well as dissatisfaction at work[2,8], and can even put the patient at risk[2,3].

The sources of occupational stress in the health area that can contribute to burnout are a lack of resources at work[2,7,8], work overload[7,8,10], team conflicts[7,8], shift problems[8], death of patients[8], excessive responsibility[8], exposure to biological risk[8], contractual status[8], and the work environment itself (such as temperature)[7,8].

Burnout can be conceptualized as the final stage of chronic job stress that is characterized by emotional exhaustion, depersonalization (distancing behaviors, coldness), and decreased personal accomplishment at work (feeling of professional inefficacy) that result in dysfunctional behaviors at work associated with reduced motivation and effectiveness[1,3,8,11].

The development of burnout depends not only on individual factors (personality, work expectations)[1,8] but also on organizational aspects (bureaucracy, frequent organizational changes)[1,8] and social aspects (lack of social and family support, cultural values, and norms)[1]. When the organization does not recognize the human side of work and there are major mismatches between the nature of the work and the people, there is a higher risk of burnout[1].

Social support plays an important role in moderating the effects of stress. Social support is the ability of the individuals to perceive themselves as a part of a group where they have emotional support (feeling of esteem, protection, and safety), information (easy access to information, advice and help from others to solve problems), and confirmation (perception of feelings, recognition of skills and abilities). Good social support tends to increase self-esteem, optimism, and positive mood and decreases anxiety, feelings of failure, and isolation[9].

Burnout can be considered a syndrome that manifests itself in different ways, affecting the quality of life of an individual[1], and can have psychosomatic symptoms (asthenia, headache,

[1]Centro Hospitalar Universitário do Porto, Department of Medicine – Porto, Portugal.
*Corresponding author: sonialittlehouse@gmail.com
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gastrointestinal disorders, muscle pain), behavioral (work delays and absenteeism, substance dependence, family conflicts), emotional (affective withdrawal, irritability, depression), and defensive symptoms (denial and suppression of the presence of other symptoms)[1,2,9,11]. In more severe cases, it can lead to suicide[2,4].

ENGAGEMENT

Engagement is one of the emerging concepts of positive psychology that is characterized by motivation, enthusiasm, and commitment at work[8]. Work engagement is defined as a positive, fulfilling, work-related state of mind that is characterized by vigor, dedication, and absorption[1,4,7,10,12]. Vigor is characterized by high levels of energy and mental resilience while working, a willingness to invest in work, and persistence in difficult situations. Dedication refers to being strongly involved in work and experiencing a sense of significance, enthusiasm, inspiration, pride, and challenge. Absorption is characterized by being completely focused and involved in work with time passing quickly and the individual having difficulty letting go of work[1,7].

Engagement is not only an individual phenomenon but also occurs on a collective level. The more engagement in a team, the more engagement in the team members[7]. Engagement also offers a competitive advantage to the organizations in which individuals work[1,8]. The possible consequences of work engagement are described as positive attitudes toward the organization, such as having initiative and motivation to learn[7], a willingness to work overtime[7], proactive behavior[7], higher productivity[12], increased organizational commitment[7], and low turnover[7,12]. Work engagement is positively related to work performance[7,13] and is also associated with low levels of depression, stress, and psychosomatic complaints[7].

Engaged individuals are more able to cope with the challenges they encounter and recover from stress, which may be a burnout prevention strategy[1]. Motivation and job satisfaction are influenced by working conditions, opportunities for personal development and advancement, remuneration and other benefits, recognition by supervisors and peers, physical working conditions, and existing resources[7,9,12]. Factors associated with increased work engagement include the presence of work resources[7,8], motivational or energizing resources[7], social support from colleagues[7], feedback from superiors[7], performance feedback[7], coaching[7,14], work autonomy[7], task variety and training facilities[7], and stable family environment[7].

On an individual level, personal resources such as high self-esteem, self-efficacy, optimism, and resilience are factors that enhance work engagement. From an organizational perspective, engagement should be seen as an agent of human capital development, an essential element for the health, well-being, and performance of the organization's employees, as it constitutes a positive link between individual and organizational results and is consequently a fundamental factor for organizational success[8].

LEADERSHIP

In an organization, we can have leadership in different work groups and at different institutional levels[15]; however, the qualities needed, in a leader, to build a positive work environment and an engaged team are transversal: operational efficiency, clarity in outlining objectives, inspiring confidence and integrity, humility, and empathy[16].

People are a key factor for organizational success, and the organization should aim to attract, develop, and retain human capital essential to the pursuit of organizational objectives[17,18]. Leadership should apply policies, practices, and systems that influence the behavior, attitudes, and performance of organizational members to increase competitiveness and learning capacity, to sustainably improve the organization over time[18].

In transformational leadership, leaders influence their subordinates by emphasizing the opportunities and challenges that the environment presents to them, stimulating individual intellect and consideration, and not simply reacting to problems as they are presented to them, but by asking how they can collaborate in building a common purpose[19]. The focus of transformational leadership is on developing a vision, building trust and engagement of employees, and ultimately facilitating learning[19]. Positive and safe work environments facilitate learning and skill acquisition[13,15] and work-family balance[17] and are associated with better indicators such as mortality rate[15] and patient satisfaction[13,15].

It is known that the constant presence of conflict has harmful consequences for the functioning of teams, in terms of both performance and job satisfaction. This highlights the importance of leadership in finding points of convergence, agreement, and tolerance among members to dilute the differences between them[20].

DISCUSSION

Early studies of burnout focused primarily on it as a predictor of health impairment, whereas work engagement has been seen as a predictor of job performance and employee turnover. The focus of this study on engagement has changed, with current research that focuses on aspects related to employee health[10]. In addition to mental health consequences, psychosocial risks associated with work can also bring cardiovascular, musculoskeletal, and metabolic diseases[6]. However, engaged professionals

have a healthier diet, lower risk of health problems, and lower level of inflammation[10].

The main challenge of any organization providing health care is its capacity for constant improvement in a sustainable way, ensuring high-quality health care with safety and empathy[15]. Knowing that leadership effectiveness increases with training[18] and considering the relationship between leadership, engagement, and burnout, there should be an effort at the organizational level to prevent burnout, promote engagement, and invest in leadership training. The first step would be for the organization to recognize burnout as an organizational problem and prioritize the well-being of its employees[4,18].

Individual and organizational preventive strategies are crucial to combat or minimize the effects of burnout[1] and improve the quality of life of professionals[11]. Some strategies that organizations can use are having flexible schedules to facilitate work–family balance, letting professionals dedicate more time to their areas of interest, allowing social gatherings to improve camaraderie and solidarity among colleagues, or promoting healthy lifestyles by introducing healthy eating, meditation, and physical exercise programs[3,4,18].

Yoga and meditation are scientifically recognized as effective methods to promote empathy, reduce stress, and improve work-related physical and emotional problems in health care professionals[21]. Meditation is a protective strategy for controlling emotions, increasing resilience, and reducing stress, anxiety, and depression[21]. The therapeutic approach of Traditional Chinese Medicine may include the combined or stand-alone use of acupuncture, moxibustion, Chinese herbal medicine, Tuina, Qigong, and Tai Chi[22]. The use of QiGong is shown to be an effective practice in the promotion, prevention, and rehabilitation of certain disorders in adults, such as burnout and depression[23]. It is shown to be a mind-body exercise modality that can easily be practiced by adults[23,24], at work or elsewhere[24]. Interventions with physical exercise such as stretching have also shown efficacy in reducing anxiety and symptoms of exhaustion associated with improved physical and mental well-being for health professionals[25].

CONCLUSION

This review shows that burnout in health care professionals is a widespread issue; however, there are few studies assessing the state of engagement of health care professionals. Studies in this area should be a priority to raise awareness among health professionals about occupational stress and its associated adverse effects, without forgetting that it is the organization's responsibility to provide working condition and a healthy working environment to its employees.

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SHORT COMMUNICATION
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Urban mobility and COVID-19 in Brazil: Comparison between 2020 and 2021

Anderson da Costa Armstrong[1], Carlos Dornels Freire de Souza[2]*, Márcio Bezerra Santos[3], Lucas Gomes Santos[2], Rodrigo Feliciano do Carmo[1]

SUMMARY

OBJECTIVE: The aim of this study was to analyze and compare the indicators of urban mobility and the number of new cases of COVID-19 recorded daily between 2020 and 2021.

METHODS: An observational study was carried out involving new cases of COVID-19 registered daily in the state of Pernambuco, Brazil between March 12, 2020 and March 28, 2021 and six indicators of urban mobility. For analysis, the study was divided into two periods: the first was composed of 295 days and represents the year 2020 and the second was composed of 86 days and represents the year 2021. Spearman's non-parametric correlation was used.

RESULTS: In 2021, the greatest reductions in relation to the baseline were observed in parks (-29.0) and in retail and recreation areas (-28.7). However, these reductions were smaller than those observed in the previous year, indicating a greater circulation of people in 2021 when compared with mobility in 2020. In contrast, in residential areas, there was a reduction in the percentage change in relation to the previous year (11.2 in 2019 and 7.6 in 2021). In grocery and pharmacy, there was an increase 1.8 times greater than that observed in 2020 (9.1 in 2020 and 17.0 in 2021). It is also noteworthy that the daily average of new cases almost doubled in value (753.4 in 2020 and 1409.1 in 2021).

CONCLUSION: More vigorous measures must be taken to adequately control the pandemic.

KEYWORDS: SARS-CoV-2. Coronavirus Disease-19. Urban health. Epidemiology.

INTRODUCTION

In late 2019, the city of Wuhan in China recorded an outbreak of a rapidly progressing pneumonia. On January 7, 2020, the disease was named coronavirus disease 2019 (COVID-19), and its causative agent was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 pandemic[2]. At that time, there were already more than 118,000 cases in 114 countries and more than 4,000 deaths[3].

In Brazil, the first case of COVID-19 was confirmed on February 26, 2020 in the state of São Paulo[4]. Until March 5, national transmission appeared to be sporadic, with 85.3% (n=29/34 cases) of confirmed cases being of imported origin[5]. However, on March 20, 2020, community transmission was evidenced[4]. On April 26, 2021, 14 months after the confirmation of the first case, Brazil ranks third in the world in the number of cases (14.3 million cases) and second in the number of deaths (392,200 deaths)[3].

[1]Universidade Federal do Vale do São Francisco, Program in Health and Biological Sciences – Petrolina (PE), Brazil.
[2]Universidade Federal de Alagoas, Program in Health Family, Department of Medicine – Arapiraca (AL), Brazil.
[3]Universidade Federal de Sergipe, Program in Health Sciences – Aracaju (SE), Brazil.
*Corresponding author: carlos.freire@arapiraca.ufal.br
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In Pernambuco, northeastern Brazil, the first cases were registered on March 12, initially individuals with a history of travel to Italy[6]. The large flow of individuals, the circulation between neighboring cities, and the urban agglomeration observed in the metropolitan region of Recife and in the *Zona da Mata* region may have been decisive factors for the acceleration of the pandemic in the state of Pernambuco[7]. As of April 30, 2021, the state recorded 406,500 cases and 14,000 deaths from COVID-19[4].

In the absence of proven effective drugs against COVID-19, non-pharmacological measures have been implemented as alternative behavioral pathways with the aim of slowing down the spread of the virus[8]. Among the set of measures implemented is the restriction of urban mobility, which is pointed out as a viable alternative since the transmission of coronavirus is highly dependent on the spatial behavior of individuals. Therefore, this study aimed to analyze and compare the indicators of urban mobility and the number of new cases of COVID-19 recorded daily between 2020 and 2021.

METHODS

An observational study was carried out involving new cases of COVID-19 registered daily in the state of Pernambuco, Brazil between March 12, 2020 and March 28, 2021 and six indicators of urban mobility as follows:

i. mobility trends in retail and recreation (restaurants, cafes, shopping centers, theme parks, museums, libraries, and movie theaters),
ii. mobility trends in grocery and pharmacy (grocery markets, food warehouses, farmer markets, specialty food shops, drug stores, and pharmacies),
iii. mobility trends in parks (national parks, public beaches, marinas, dog parks, plazas, and public gardens),
iv. mobility trends in transit stations (public transport hubs such as subway, bus, and train stations),
v. mobility trends in workplaces, and
vi. mobility trends in residential areas. Data regarding new cases of COVID-19 were obtained from consolidated records from the Ministry of Health and State Health Departments (https://covid19br.wcota.me/), and mobility data were obtained from Google community mobility report (https://www.google.com.br/covid19/mobility/).

The mobility indicators consider the daily percentage change in relation to a baseline. The baseline value is defined by the median of the corresponding weekday over the 5-week period (from January 3 to February 6, 2020). This means that this baseline concerns an urban mobility pattern before the entry of SARS-CoV-2 in the region. The closer to the baseline, the more the movement of people in the places approaches a pattern considered normal, that is, before the pandemic. Positive values (above the baseline) represent an increase in the circulation of people in the places, and negative values represent a reduction in circulation in relation to that same baseline.

For analysis, this study is divided into two periods: the first was composed of 296 days and represents the year 2020 (March 12, 2020 to December 31, 2020), and the second was composed of 86 days and represents the year 2021 (January 1 to March 28, 2021). The measures of central tendency (mean and standard deviation, SD) and dispersion (minimum and maximum) of the indicators studied were analyzed, and Spearman's non-parametric correlation was used to evaluate the relationship between the variations in mobility and the number of new cases of COVID-19. A 5% significance level was considered. Since we used secondary data from the public domain, we did not need the approval of the Research Ethics Committee.

RESULTS

In 2020, the largest reductions from the baseline occurred in retail and recreation areas (-36.0; SD 21.9) and in parks (-32.9; SD 18.9). Positive mean values, i.e., increased movement of people compared with baseline, were observed in grocery and pharmacy areas (9.1; SD 23.9) and residential areas (11.2; SD 4.8). It should be noted that the average number of new cases registered daily in 2020 was 753.4; SD 533. In 2020, Spearman's correlation showed that the closer to the baseline (median person circulation observed in the period before the pandemic – January 3 to February 6, 2020) in retail and recreation areas (rho 0.187; p=0.001), grocery and pharmacies (rho 0.291; p<0.001), parks (rho 0.136; p=0.019), transit stations (rho 0.149; p=0.001) and workplaces (rho 0.185; p=0.001), the greater is the number of new cases of COVID-19 registered daily. An inverse relationship was observed in mobility in residential areas (rho -0.127; p=0.030), indicating that the more people circulating in these regions, the fewer new cases were registered on a day (Table 1).

In 2021, the greatest reductions in relation to the baseline were observed in parks (-29.0; SD 13.4) and in retail and recreation areas (-28.7; SD 12.2). However, these reductions were smaller than those observed in the previous year, indicating a greater circulation of people in 2021 when compared with mobility in 2020. In contrast, in residential areas, there was a reduction in the percentage change in relation to the previous year (11.2; SD 4.5 in 2020 and 7.6; SD 2.5 in 2021). In grocery and pharmacy, there was an increase 1.8 times greater than

Table 1. Descriptive analysis and Spearman's correlation between urban mobility variation and registration of daily new cases of COVID-19. Pernambuco, Brazil, March 2020 to March 2021.

	March 12, 2020 to December 31, 2020 (296 days)			January 01, 2021 to March 28, 2021 (86 days)		
	Descriptive analysis		Spearman's rank correlation coefficient	Descriptive analysis		Spearman's rank correlation coefficient
	Min–Max	Mean (SD)	December 03, 2020 to December 31, 2021	Min–Max	Mean (SD)	January 01, 2021 to March 28, 2021
A – Retail and recreation (percentage change from baseline)	-78.0; 5.0	-36.0 (21.9)	0.187 (p=0.001)	-63.0; -16.0	-28.7 (12.2)	0.053 (p=0.626)
B – Grocery and pharmacy (percentage change from baseline)	-58.0; 83.0	9.1 (23.9)	0.291 (p<0.001)	0.0; 35.0	17.0 (7.8)	-0.038 (p=0.727)
C– Parks (percentage change from baseline)	-74.0; 23.0	-32.9 (18.9)	0.136 (p=0.019)	-63.0; 0.0	-29.0 (13.4)	-0.174 (p=0.106)
D – Transit stations (percentage change from baseline)	-67.0; 73.0	-20.9 (24.5)	0.149 (p=0.001)	-41.0; 0.0	-14.6 (8.7)	-0.029 (p=0.787)
E – Workplaces (percentage change from baseline)	-68.0; 28.0	-16.3 (18.7)	0.185 (p=0.001)	-27.0; 6.0	-6.7 (7.3)	-0.280 (p=0.009)
F – Residential (percentage change from baseline)	-1.0; 24.0	11.2 (4.8)	-0.127 (p=0.030)	5.0; 14.0	7.6 (2.5)	0.27 (p=0.805)
G – Number of new cases of COVID-19	0.0; 2512.0	753.4 (533.3)	–	215.0; 2786.0	1409.1 (597.4)	–

Min: minimum; Max: maximum; SD: standard deviation.

that observed in 2020 (9.1; SD 23.9 in 2020 and 17.0; SD 7.8 in 2021). It is also noteworthy that the daily average of new cases almost doubled in value (753.4; SD 533.3 in 2020 and 1409.1; SD 597.4 in 2021). In 2021, only the indicator of social mobility in workplaces (rho= -0.280; p=0.009) showed an inverse relationship with the number of daily new cases of COVID-19 (Table 1).

It is important to note that mobility restriction measures are implemented at peak times of the pandemic and their effects will appear in the following 2–3 weeks. For this reason, it is not possible to have a perfect synchrony between mobility restriction and daily cases of COVID-19 since the effect on case reduction will occur after the intervention. In addition, case drops are observed on weekends due to a decrease in case notifications. Details of the daily variation in the time series are shown in Figure 1.

DISCUSSION

The changes in the correlations between social mobility indicators and the number of new cases of COVID-19 observed in the first three months of 2021 may indicate the changes in the dynamics of COVID-19 transmission in the region, caused by factors such as the beginning of vaccination of risk groups, the emergence of new variants, the loosening of social distancing measures, and even signs of a possible seasonality of COVID-19.

The first dose of vaccine against COVID-19 was applied in Brazil on January 19. On that date, many other countries had already started mass vaccination of the population, such as Israel, the United Kingdom, and the USA. The slow vaccination process in Brazil places it in the 67th place in the world ranking of countries that have applied at least one dose of the vaccine against COVID-19, totaling 13.71% of the population on April 30, 2021[9]. The delay in the population's immunization may result in more new cases of COVID-19 and a greater chance of the appearance of variants, such as the one identified in the northern region of the country at the beginning of 2021[10].

Scientific evidence reveals that the strains that circulate in Brazil, despite not being more virulent, have greater infectivity[10]. This facilitated transmission, associated with the lower social distance observed in 2021, may have increased the contagion, resulting in an increase in cases in 2021[11]. This may explain why we found no statistical significance in the relationship of new cases and social mobility in the year 2021, except in workplaces (rho -0.280; p=0.009). There is no clear explanation as to the inverse relationship between mobility in workplaces in

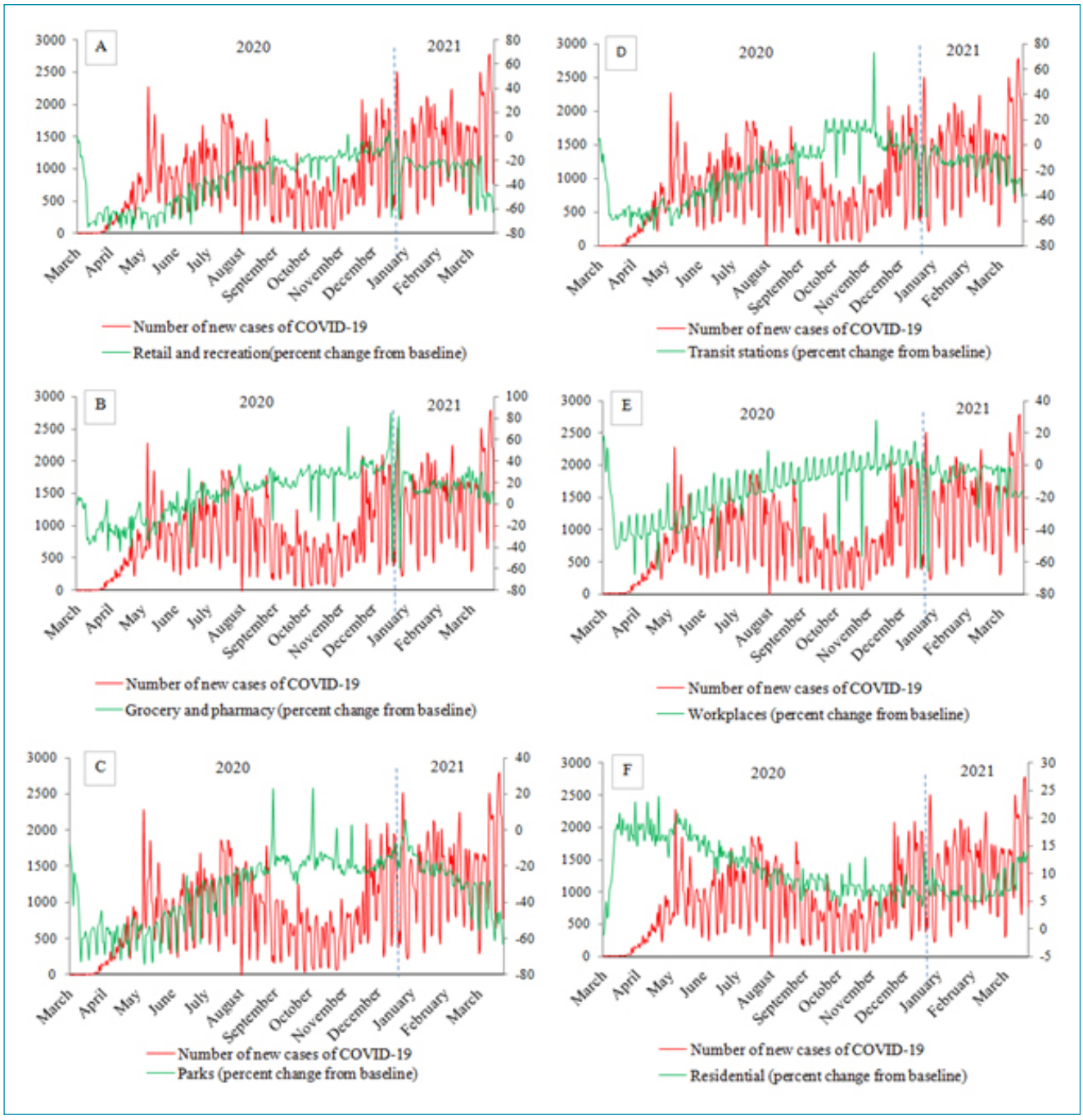

Figure 1. Temporal evolution of the daily variation of new cases of COVID-19 and urban mobility by sector. Pernambuco, Brazil, March 2020 to March 2021.

2021 with the daily number of cases. It is possible that there is a relationship with the opening of trade with health protocols and vaccination, although it is not possible to say, requiring detailed investigations in this regard.

Since the beginning of the pandemic in 2020, a series of non-pharmacological measures have been implemented to contain the transmission of the virus-remote work, school closures and remote education, reduced transportation flow, closure of nonessential services, and even more restrictive measures such as complete trade closures[12]. As a result, a greater circulation of people in residential areas and an inversion relationship with a lower number of cases was observed, given the impacts of these measures on the virus transmission chain. In contrast, in 2021, with the relaxation of the measures and the gradual return of

commercial activities, there was a reduction in the movement of people in these areas.

Another important issue that occurred at the beginning of the pandemic was the increased circulation of people in pharmacies and drugstores. Among the factors associated with this dynamic are[12-14]

i. the fear of virus contamination (*coronaphobia*),
ii. the fear of a shortage of medications for continuous use,
iii. the search for treatments and/or prophylaxis disseminated through fake news, and
iv. the increased incidence of other emotional problems, such as anxiety, depression, and compulsive disorders, among others.

In addition, the emergence of new cases of COVID-19 may also be related to a possible seasonalization process of the disease. Although this study does not provide details about this hypothesis, due to the need for a larger time series than the one available, this characteristic is known for other viruses, such as H1N1, H3N2, and influenza B[15].

CONCLUSIONS

The Brazilian epidemiological scenario – complex and dynamic – characterized by the greater circulation of people, delay in vaccination, emergence of new variants, use of clinical protocols not sanctioned by science, and the lethargy of the Brazilian government, we believe that the pandemic is still out of control and far from over. We hope that more energetic measures will be adopted in line with the scientific knowledge produced so far by scientists worldwide for adequate control of the pandemic in Brazil.

AUTHORS' CONTRIBUTIONS

ACA: Conceptualization, Writing – original draft, Writing – review & editing. **CDFS:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **MBS:** Conceptualization, Writing – review & editing. **LGS:** Writing – original draft, Writing – review & editing. **RFC:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

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SHORT COMMUNICATION
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Vitamin D levels and SARS-CoV-2 assay results in health care workers in Brazil

Aline Cavalcante de Lira[1], Alexsandro Pedro da Silva[1], Madi Veiga Diniz[1], Arione Vieira do Nascimento[1], Wagner Roberto Cirilo da Silva[2], Caroline Louise Diniz Pereira[3], Milena Lima Rodrigues[3], Evônio de Barros Campelo Júnior[3], Kledoaldo Lima[1,4]*

INTRODUCTION

A new coronavirus, which emerged in China in December 2019 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), has led to a severe acute respiratory syndrome (coronavirus disease 2019, COVID-19) whose severity of symptoms has been linked to different biological risk factors, such as diabetes, hypertension, cardiovascular diseases, cancer, and cerebrovascular diseases[1].

Although Hastie et al. did not confirm the association between lower plasma vitamin D rules and the risk of SARS-CoV-2 infection, several other studies associated vitamin D with less clinical severity and positive testing for COVID-19 (MELTZER et al., 2020)[2-4]. Moreover, vitamin D has a protective effect on the alveolar epithelium and reduces damage to the alveolar capillaries, preventing severe acute respiratory syndrome (SRAG)[5].

In addition to COVID-19 having a lower incidence in children and pregnant women, several studies have demonstrated protective effects, less inflammation and an association of higher concentrations of vitamin D, and lesser chances of infection by SARS-CoV-2[3,4,6]. To our knowledge, there are no reports of this type of study in Brazil nor of the assessment of serum levels of vitamin D in health care professionals who work with patients or clinicians diagnosed with COVID-19. This study aimed to evaluate the serum concentration of vitamin D in health care professionals who work directly with patients or their biological samples from a tertiary hospital in the Northeast region, Brazil.

METHODS

We analyzed 596 health care professionals at Hospital das Clínicas, Universidade Federal de Pernambuco (HC-UFPE). Blood samples were obtained from October to November 2020 for the measurement of serum vitamin D, which was performed using the Architect 25-OH Vitamin D Kit (Abbott Diagnostics, United States), using the chemiluminescent microparticle immunoassay methodology. Data related to participants, i.e., sex and age were obtained. In parallel with the dosage of vitamin D, we also performed tests for SARS-CoV-2 infection through qualitative immunochromatographic tests for the detection of immunoglobulin G (IgG) antibodies against the virus (COVID-19 IgG ECO test-ECO Diagnóstica, Brazil).

As recommended by the consensus of the Brazilian Society of Clinical Pathology/Laboratory Medicine and Brazilian Society of Endocrinology and Metabolism, the reference values for vitamin D were stratified according to age and clinical conditions: >20 ng/mL, a desirable value for a healthy population (up to 60 years of age); between 30 and 60 ng/mL, the recommended value for at-risk groups such as elderly people, pregnant women, breastfeeding women, patients with syndromes related levels of vitamin D; and above 100 ng/mL, the risk of toxicity and hypercalcemia[7].

Descriptive statistics were revised for the variables. A comparison was made between vitamin D levels and serological reactivity with SARS-CoV-2-IgG. The Fisher's exact test was used for qualitative variables and the Student's *t*-test

[1]Universidade Federal de Pernambuco, Hospital das Clínicas – Recife (PE), Brazil.
[2]Universidade de Pernambuco, Institute of Biological Sciences – Recife (PE), Brazil.
[3]Universidade Federal de Pernambuco, Medical Sciences Center, Postgraduation in Tropical Medicine – Recife (PE), Brazil.
[4]Faculdade Pernambucana de Saúde, Instituto de Medicina Integral Professor Fernando Figueira – Recife (PE), Brazil.
*Corresponding author: kledoaldo@gmail.com
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for continuous variables. The normal distribution of continuous variables was verified using the Shapiro-Wilk normality test. The differences were considered statistically significant when p<0.05. All statistical analyses were performed using SPSS Statistics software, version 25 for Windows (IBM Corporation, United States). This study was approved by the Ethics Committee of the Health Sciences Centre of Universidade Federal de Pernambuco on October 16, 2020 with protocol number 38060620.6.0000.5208.

RESULTS

Out of the 596 health care professionals who worked directly with patients diagnosed with COVID-19, the majority were females (n=451, 76%), and a high serological reactivity for SARS-CoV-2 IgG (n=250, 42%) was detected. The serum dosage of vitamin D was carried out in 571 health care workers, out of which 492 (86.2%) health care workers had levels considered desirable (>20 ng/mL). Our findings demonstrate an association between vitamin D insufficiency (≤20 ng/mL) in females and people under the age of 50 years (p<0.001) (Table 1). There was a statistical association between serological reactivity for SARS-CoV-2 and health care workers over 50 years old (p<0.001) (Table 2). Regarding the relationship between serum vitamin D levels and the presence of IgG antibodies to SARS-CoV-2 in the asymptomatic health care professionals evaluated, we found that there was an inverse relationship between the serological reactivity to the virus and the levels of vitamin D, that is, health care professionals who were tested positive for SARS-CoV-2 had higher serum vitamin D levels.

Table 1. Characteristics of health care professionals related to the concentration of serum levels of vitamin D.

	Vitamin D		
	≤20 ng/mL	>20 ng/mL	p-value
Sex (n=569)			
Female	58	374	<0.001
Male	21	116	
Age (years) (n=569)			
≤50	76	403	<0.001
51–64	08	82	
Point of care test IgG COVID-19 (n=571)			
Reagent	28	211	<0.001
Non-reagent	51	281	

IgG: immunoglobulin G; COVID-19: coronavirus disease 2019.

DISCUSSION

We found that there was an inverse relationship between the serological reactivity to the virus and the levels of vitamin D, that is, health care professionals who were tested positive for SARS-CoV-2 had higher serum vitamin D levels. This result is the opposite of that observed by Meltzer et al. and Kaufman et al. in individuals in the United States[4,6]. Meanwhile, Hastie et al. showed no statistical association between serum vitamin D levels and serological reactivity to SARS-CoV-2 in individuals tested in the United Kingdom[2]. In addition, Murai et al. demonstrated, in a clinical trial conducted in Brazil with patients admitted to a hospital in a moderate or severe state of COVID-19, that a single dose of 200,000 IU of vitamin D did not interfere in mortality, length of stay in the hospital, the number of admissions to the intensive care unit, or the need for mechanical ventilation when compared with placebo[8].

Our findings demonstrate an association between vitamin D insufficiency (≤20 ng/mL) in females and people under the age of 50 years. Meltzer et al. also showed an association of lower serum vitamin D levels and the age of <50 years[6]; however, the same was not evidenced for females. There was a statistical association between serological reactivity for SARS-CoV-2 and health care workers over 50 years old (p<0.001) (Table 2). This result is important, as it illustrates a greater susceptibility of older health care professionals to viral infection, which causes greater concern since it is known that older individuals may be more prone to more severe symptoms of the disease.

One of the limitations of this research was the fact that, although the individuals evaluated were asymptomatic in the period of serological diagnosis, there were no data available regarding the results of RT-PCR tests for SARS-CoV-2 in these professionals in the months before the research. Due to the less data available about the action of vitamin D in COVID-19 and some of them have conflicting results or have different study designs and populations,

Table 2. Characteristics of health care professionals related to the serological results of IgG for SARS-CoV-2.

	Rapid test IgG COVID-19		
	Reagent	Non-reagent	p-value
Sex (n=594)			
Female	190	261	1.00
Male	59	84	
Age (years) (n=578)			
≤50	195	288	<0.001
51-64	47	48	

IgG: immunoglobulin G; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019.

it is necessary to carry out studies that are better designed to evaluate the role of vitamin D in preventing viral infection.

CONCLUSIONS

Our results demonstrated an association between low serum vitamin D concentrations and nonreactive serological testing for viral infection. However, it appears that there are conflicting results in the literature on the role of vitamin D in decreasing the chances of infection or progression to more severe symptoms by SARS-CoV-2. Thus, other clinical trials are required to understand the real role of vitamin D supplementation, either in preventing infection or decreasing the progression to more severe symptoms.

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AUTHORS' CONTRIBUTIONS

ACL: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **APS:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **MVD:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **AVN:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **WRCS:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **CLDP:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **MLR:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **EBCJ:** Investigation, Methodology, Writing – review & editing. **KL:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
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Effects of the COVID-19 on the public interest in medical specialties in Brazil

Lise Queiroz Lima Verde[1]*, José de Paula Barbosa[1], Paulo Goberlânio Barros Silva[1,2], João Crispim Ribeiro[1,3]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the effects of the COVID-19 pandemic and the social isolation on the interest rates of different medical specialties in Brazil.

METHODS: The research was performed using the terms "Médico" (Doctor), "Infectologista" (Infectologist), "Cirurgião" (Surgeon), "Geriatra" (Geriatrician), "Otorrinolaringologista" (Otolaryngologist), and "Oftalmologista" (Ophthalmologist), related to several medical specialties, and "COVID-19," which represented the public interest for the disease, utilizing the Brazilian version of Google Trends, where the data were acquired. The time range of this analysis was from 29 September, 2019 to 20 September, 2020. The data were tabulated in Microsoft Excel, exported to the Statistical Package for the Social Sciences software, and correlated with searches for the term "COVID-19" using Pearson's correlation. 95% confidence interval was used for all analyses.

RESULTS: "Geriatra" (72.26±16.42) and "Cirurgião" (72.15±12.53) remained with the higher means among the evaluated specialties. In terms of standard deviation, "Oftalmologista" (64.71±16.72) and "Infectologista" (22.03±16.60) presented the most significant changes. After utilizing the Pearson's analysis to identify the correlation between each medical specialty and the term "COVID-19," all the evaluated specialties presented significant statistical correlations. "Oftalmologista" (r= -0.607) was notoriously the most negatively affected, while "Infectologista" (r=0.504) was pointed to have the highest positive correlation with the term.

CONCLUSIONS: Several changes in the interest rates of different medical specialties in Brazil were found during the time range of the COVID-19 pandemic.

KEYWORDS: Social Isolation. COVID-19. Medical specialties.

INTRODUCTION

In December 2019, a new virus, named Sars-CoV-2, was discovered in the city of Wuhan in Hubei Province, China[1]. The pathogen quickly disseminated to more than 200 countries, becoming a public health emergency of international concern. In response to the outbreak, national governments adopted many serious interventions that affected the epidemic evolution of the disease, the global economy, and the population's lifestyle[2].

The lockdown is the most radical policy to prevent the circulation of people and the spread of the virus. Vertical isolation refers to the restriction of movement of the risk group for COVID-19. In a survey that analyzed 24 countries that were most affected by the disease, it was found that 20 of them (83%) adopted a lockdown, in an attempt to flatten the transmission curve, and 3 countries (13%) opted to the vertical isolation to decelerate the increase in the number of cases. The countries that

[1]Centro Universitário Christus – Fortaleza (CE), Brazil.
[2]Centro Universitário Christus, Programa de Pós-Graduação em Ciências Odontológicas – Fortaleza (CE), Brazil.
[3]Centro Universitário Christus, Mestrado Profissional em Tecnologia Minimamente Invasiva e Simulação na Área de Saúde – Fortaleza (CE), Brazil.
*Corresponding author: lise.lqlv@gmail.com
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adopted the lockdown are South Africa, Germany, Argentina, Canada, China, Spain, the United States, France, India, Italy, the United Kingdom, Russia, and Singapore. The countries that have adopted vertical isolation are South Korea, Sweden, and Turkey[3].

In Brazil, the first case detected was a tourist who visited Italy in February and got infected by the virus[4]. The incidence of cases increased until the latest July and started to decrease in August. It has 58.9 deaths per 100,000 of its inhabitants, being the eighth nation with the highest mortality rate and the second nation in absolute number[5].

Although community quarantine reduces the spread of the disease, it also brings a relevant economic and social impact, resulting in a significant increase in unemployment, a higher rate of mental illness, and a greater difficulty in having access to medical care for other pathologies[6].

The COVID-19 pandemic altered the dynamic of medical practice, not only by raising the demand for some services and devices like intensive care units and mechanic ventilators but also by causing a decrease in ambulatory care practices, examinations, and surgical procedures, due to the suspension of elective surgeries and some primary health services and due to the increase in the unemployment rates which leads to the loss of health insurance[7-9].

Thus, the scope of this study was to evaluate the effects of the COVID-19 pandemic and the social isolation on the interest rates of different medical specialties in Brazil.

METHODS

Google Trends (GT) is a platform that works by comparing relative popularity in geographical and temporal ranges based on the sample of Google search data, varying from 0–100[10].

On September 9, 2020, a research was performed using the terms "Médico" (Doctor), "Infectologista" (Infectologist), "Cirurgião" (Surgeon), "Geriatra" (Geriatrician), "Otorrinolaringologista" (Otolaryngologist), and "Oftalmologista" (Ophthalmologist), related to several medical specialties, and "COVID-19", represented the public interest for the disease, using the Brazilian version of GT, where the data were acquired. The time range of this analysis was from September 29, 2019 to September 20, 2020.

The data were tabulated in Microsoft Excel, exported to the Statistical Package for the Social Sciences software, and correlated with searches for the term COVID-19 using Pearson's correlation. 95% confidence interval was used for all analyses.

RESULTS

During the first months of the time range, all curves remained stable, with a mild increase in all specialties. On February 26, 2020, the first case of COVID-19 occurred in Brazil, corresponding to the same time when changes in the pattern of the GT graph occurred (Figure 1).

During most of the time, the term "Médico," representing a general interest for doctors without a specific specialty in Google Search, remained with similar interest rates during all the COVID-19 pandemics and the lockdown, with a small increase during the pandemics, showing a peak of interest rate at the end of September.

In contrast, the terms "Oftalomologista," "Cirurgião," "Geriatra," and "Otorrinolaringologista" faced a severe decrease in their interest rates, achieving their minimum frequency of Google Searches during the end of March and the start of April, the same time when most of the Brazilian States adopted more strict rules of social isolation. Later, during the subsequent months, a continuous recovery happened, by the point that at the end of June, most of those specialties had around 70% of their annual interest rate, similar to their rates presented before the COVID-19 pandemic.

The term "Infectologista" presented the most notorious changes during the pandemics, presenting an abrupt increase in its Google Search Interest rates, varying from a relative frequency of 21 on March 1, 2020 to 100 on March 22, 2020, when the coronavirus started to spread through the country. Later, the curve started to drop, turning back to a pattern similar to the time range before the pandemic.

When comparing the mean of the relative frequency of research, "Geriatra" (72.26±16.42) and "Cirurgião" (72.15±12.53) remained with the higher values among the evaluated specialties. In terms of standard deviation, "Oftalmologista" (64.71±16.72) and "Infectologista" (22.03±16.60) presented the most significant changes, which could suggest that those medical specialties were the most impacted for the pandemic among the group that we analyzed (Table 1).

After utilizing the Pearson's analysis to identify the correlation between each medical specialty and the term "COVID-19," all the evaluated specialties presented significant statistical correlations.

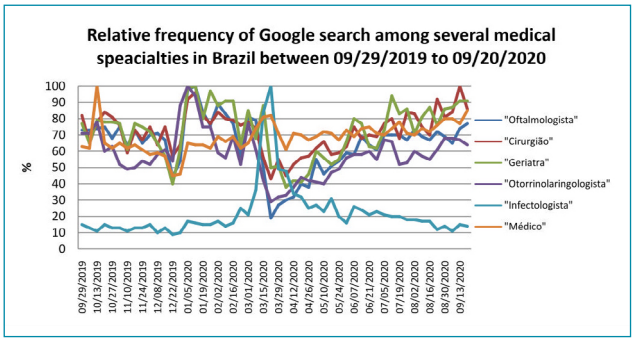

Figure 1. Relative frequency of Google search among several medical specialties in Brazil between September 29, 2019 and September 20, 2020.

"Oftalmologista" (r= -0.607) was notoriously the most negatively affected, while "Infectologista" (r=0.504) was pointed to have the highest positive correlation with the term "COVID-19." The term "Médico" (r=0.359) presented the lowest correlation (Table 2).

DISCUSSION

It is notorious that the COVID-19 pandemic has brought many challenges for several medical specialties, reflecting on their interest rates of public online searching platforms, which could be correlated to significant effects on both consultation of outpatients and elective surgeries.

One study used GT to analyze the interest rates of the term "coronavirus" worldwide, from December 31, 2019 to April 1, 2020, and it was found a small peak on January 31, a few days after the outbreak of the disease in Wuhan, corresponding to <25% of the relative frequency compared with the peak of 100% on March 12, 2020, one day after the World Health Organization declared the coronavirus pandemic[11]. In Brazil, the highest peak occurred at the time as the beginning of the quarantine in the main capital of Brazil, with a subsequent downgrade in the interest rates for "coronavirus."[12] These data fit in the time range of most of the changes that occurred in the interest rates in different medical specialties in Brazil, which points toward a major influence of the pandemic in this scenario.

Many factors associated with the pandemic could contribute to this situation, such as the mental impact of the spread of the disease or the social isolation, which can substantially increase the incidence of mental illness, for example, anxiety and depression, with the contribution of many other factors, such as changes in family functionality, in workplaces, and economic or social insecurity, which are variables hard to measure[13,14].

The economic impact of the virus has changed the consumption pattern of several people, due to general lower income during the pandemics or massive job loss, especially in the non-necessary services[15].

We believed that the sum of these factors could have contributed to the notorious decrease in the interest rates of several medical specialties. Although we were not able to explain the contrasting increase in the interest for the term "Infectologista," we believed that it is the medical specialty mostly related to the coronavirus in terms of management and researching.

Among the possible impacts of different interest rates, the pandemic can change the perspective of many students about the medical specialty they want to follow; one study pointed that about 20% of the medical students would have their future choice influenced by the effects of the COVID-19[16]. Beyond that, many residency programs had to adapt their curriculums to the new circumstances, lowering face-to-face activities and elective procedures and increasing studying hours designated to learn how to manage patients infected by the COVID-19[17].

Furthermore, many specialists from different countries are reporting a decrease in outpatient's consultation, which could lead to discontinuity in chronic disease care that can result in further mistreatment or aggravation of medical conditions[18,19]. However, there have been increased interest rates on terms related to telemedicine during March 2020, in Brazil, which could represent an alternative for many patients[19]. Although it is a promising method, we believe that it still needs several improvements, especially in countries where a significant percentage of the population does not have adequate access to the Internet.

Table 1. Mean value of Google Trends relative public interest in several medical specialties.

Medical specialty	Mean value of Google Trends relative public interest (±SD)
"Oftalmologista"	64.71 (±16.72)
"Cirurgião"	72.15 (±12.53)
"Geariatra"	72.26 (±16.42)
"Otorrinolaringologista"	58.48 (±14.49)
"Infectologista"	22.03 (±16.60)
"Médico"	68.84 (±9.06)

Table 2. Pearson's correlation between the evaluated medical specialties and "COVID-19" from September 29, 2019 to September 20, 2020.

Medical specialty	r-value when compared with the term "COVID-19"	p-value
"Oftalmologista"	r= -0.607	<0.001*
"Cirurgião"	r= -0.450	0.001*
"Geriatra"	r= -0.433	0.001*
"Otorrinolaringologista"	r= -0.573	<0.001*
"Infectologista"	r= +0.504	<0.001*
"Médico"	r= +0.359	0.009*

*p<0.05.

CONCLUSION

Several changes in the Interest rates of different medical specialties in Brazil were found during the time range of the COVID-19 pandemic, with synchronic effects of outpatients' consultations and elective procedures, representing a challenging situation for patients and for medical doctors.

AUTHORS' CONTRIBUTION

LQLV: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **JPB:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **PGBS:** Formal analysis, Software, Writing – original draft. **JCR:** Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
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Muscle mass and cellular membrane integrity assessment in patients with nonalcoholic fatty liver disease

Iasmin dos Santos Barreto[1], Raquel Oliveira dos Santos[1], Raquel Rocha[1]*, Claudineia de Souza[1], Naiade Almeida[1], Luiza Valois Vieira[1], Rafael Leiróz[2], Manoel Sarno[2], Carla Daltro[1], Helma Pinchemel Cotrim[2]

SUMMARY

OBJECTIVE: To evaluate the association between muscle mass depletion and compromising of the cell membrane integrity and clinical–anthropometric characteristics in patients with nonalcoholic fatty liver disease.

METHODS: This observational study evaluated waist circumference, body mass index, and waist-to-height ratio in patients with nonalcoholic fatty liver disease. Skeletal mass index corrected by weight and impairment of cell membrane integrity were assessed using bioelectrical impedance analysis.

RESULTS: In 56 patients, muscle mass depletion was observed in 62.5% and cell membrane impairment in 28.6%. The metabolic syndrome and elevated aspartate aminotransferase were the only clinical factors associated with mass depletion ($p<0.05$). The linear regression analysis showed association between skeletal mass index and waist-to-height ratio and waist circumference, after adjustments ($p<0.05$). The phase angle value was not different between those with and without mass depletion, and also it did not have correlation with skeletal mass index and clinical parameters ($p>0.05$).

CONCLUSIONS: The prevalence of mass depletion and cell membrane impairment was higher in patients with nonalcoholic fatty liver disease. The muscle mass depletion was associated with central obesity, aspartate aminotransferase elevated, and metabolic syndrome; however, the phase angle is not associated with clinical and anthropometric data.

KEYWORDS: Non-alcoholic fatty liver disease. Skeletal muscle. Bioelectrical impedance. Obesity. Central obesity.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases in the world, and evidence points that body composition is directly related to the pathogenesis of NAFLD[1]. Thus, visceral obesity is listed as the main factor promoting metabolic changes, since it leads to an imbalance between adipokine secretion, with an increase in inflammatory cytokines and, consequently, influencing insulin resistance (IR) and oxidative stress[2].

However, muscle mass (MM) has also gained prominence in several diseases, including NAFLD[3]. It seems that the connection between the liver, adipose tissue, and muscle occurs

[1]Universidade Federal da Bahia, Escola de Nutrição – Salvador (BA), Brazil.
[2]Universidade Federal da Bahia, Faculdade de Medicina da Bahia – Salvador (BA), Brazil.
*Corresponding author: raquelrocha2@yahoo.com.br

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through the expression of insulin receptors in these tissues, in view of the anabolic role of insulin, in the presence of IR in myocytes, protein catabolism increases, resulting in MM depletion and, consequently, in sarcopenia[4].

The integrity of the cell membrane can be assessed by bioelectrical impedance analysis (BIA) and identified with the phase angle (PA) value. PA has been studied in several clinical conditions and found that the higher the PA values, the better the integrity of the membrane and thus the better cellular function. Studies show that low PA values are correlated with prognosis of chronic obstructive pulmonary disease, peritoneal dialysis, hemodialysis, and liver cirrhosis, being used as an indicator of nutritional status and prognosis of mortality[5-8].

The aim of this study was to assess whether there is an association between MM reserve, impaired cell membrane integrity, and clinical–anthropometric characteristics in patients with NAFLD.

METHODS

Study design and sample

A cross-sectional, observational study was performed with patients followed up at a nonalcoholic steatohepatitis outpatient clinic. The sample was obtained for convenience between March 2016 and 2017. Inclusion criteria: patients of either sex above 18 years and below 60 years of age. Patients with special needs or diseases that made it difficult to perform anthropometric measurements and ethanol intake ≥140 g/week; patients with thyroid disease, hepatitis A, B, and C, autoimmune disease, Wilson's disease, or hemochromatosis and pregnant and lactating women were not included.

Clinical evaluation

Patients were screened by a team of nutritionists and previously trained students, using a semistructured questionnaire to identify demographic, clinical, and nutritional data.

Abdominal ultrasonography was used to measure intrahepatic fat, being performed by a single evaluator.

Anthropometric evaluation

Weight and height measurements were obtained with a digital scale (Leader, 200 kg capacity and 100 g precision) and coupled stadiometer[9]. The body mass index (BMI) was calculated, and overweight with BMI ≥ 25.0 kg/m² [10].

Central obesity was identified when waist circumference (WC) ≥ 80 cm for women and ≥ 94 cm for men[11] and waist-to-height ratio (WhtR) >0.5[12].

Muscle mass

MM was measured using BIA (Biodynamics 450®)[13]. The skeletal mass index (SMI) adjusted for weight was calculated[14,15].

Muscle mass depletion was defined when SMI <37% for men and <28% for women[16].

Cell membrane impairment

The cell membrane impairment was evaluated by the PA identified in the BIA, and the cutoff point ≤ the 25th percentile obtained in the statistical analysis of this sample was adopted.

Laboratory evaluation

The registered tests were alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (AF), blood glucose, insulin, and triglycerides. IR was calculated by homeostasis model assessment for insulin resistance (HOMA-IR)[17]. Metabolic syndrome was classified according to the International Diabetes Federation[11].

Statistical analysis

The statistical software SPSS version 21.0 was used for data analysis. The patients were grouped according to the MM evaluated, and to compare the means between groups by the Student's *t*-test and the proportions by Pearson's chi-square or Fisher's exact tests. Pearson's correlation was used to analyze the correlation between parametric variables and MM. Associations between MM and continuous variables were assessed by simple and multiple linear regression analyzes. For the multiple linear regression model, variables with p value <0.20, obtained in the bivariate analysis, were considered. The hierarchical selection method was used to construct the regression models and calculate the adjusted determination coefficient (R^2), with a 95% confidence interval (95% CI). The level of significance was $p<0.05$.

RESULTS

General characteristics

All eligible patients were included in the study. Fifty-six patients with NAFLD, with a mean age of 47.7 ± 8.6 years and predominantly females (67.9%), were participated. Of note, 91.1% of the patients were presented with overweight and central obesity. A higher frequency of physically inactive individuals (56.3%), hypertensive individuals (33.9%), and grades II and III steatosis (67.9%) was observed. In a subgroup of 21 patients, 38.1% had IR (Table 1).

Table 1. Clinical and demographic characteristics in a group of patients with nonalcoholic fatty liver disease treated at a referral clinic.

	Total	Muscle Mass		p**
		Depletion	Adequate	
Sex, n (%)				
Male	18 (32.1)	11 (31.4)	7 (33.3)	0.883
Female	38 (67.9)	24 (68.6)	14 (66.7)	
Age (years) $\bar{x}$ (SD)	47.7 (8.6)	47.3 (9.3)	48.6 (7.4)	0.573[a]
Race				
Whites	3 (5.4)	1 (2.9)	2 (9.5)	0.246[b]
Not whites	53 (94.6)	34 (97.1)	19 (90.5)	
Weight (kg) $\bar{x}$ (SD)	78.9 (14.7)	83.5(15.2)	71.3 (10.2)	0.002[a]
BMI (kg/m²) $\bar{x}$ (SD)	30.6 (4.8)	32.4 (4.9)	27.7 (3.1)	<0.001[a]
WHtR $\bar{x}$ (SD)	0.62 (0.07)	0.64 (0.08)	0.58 (0.05)	0.001[a]
WC (cm) $\bar{x}$ (SD)	99.1 (11.1)	103.2(10.8)	92.4 (8.1)	<0.001[a]
Phase angle $\bar{x}$ (SD)	7.3 (2.3)	7.7 (2.7)	6.8 (1.2)	0.102
Physical activity**, n (%)				
Yes	18 (56.3)	12 (57.1)	6 (54.5)	0.888
Not	14 (43.8)	9 (42.9)	5 (45.5)	
Comorbities, n (%)				
IIDM	16 (28.6)	11(68.8)	5 (31.3)	0.541
Dyslipidemia	16 (28.6)	12 (75)	4 (25)	0.360[b]
SHA	19 (33.9)	11 (64.9)	13 (35.1)	0.610
Grade steatosis, n (%)				
Grade I	18 (32.1)	11 (31.4)	7 (33.3)	0.833
Grades II–III	38 (67.9)	24 (68.6)	14 (66.7)	
ALT, n (%)				
Normal	47 (88.7)	29 (85.3)	18 (94.7)	0.402[b]
Increased	6 (11.3)	5 (14.7)	1 (5.3)	
AST, n (%)				
Normal	41 (78.8)	22 (66.7)	19 (100)	0.004[b]
Increased	11 (21.2)	11 (33.3)	0 (0.0)	
GGT, n (%)				
Normal	38 (73.0)	22 (66.7)	16 (84.2)	0.209[b]
Increased	14 (27.0)	11 (33.3)	3 (15.8)	
FA, n (%)				
Normal	38 (82.6)	23 (76.7)	15 (93.8)	0.230[b]
Increased	8 (17.4)	7 (23.3)	1 (6.3)	
TG, n (%)				
Normal	31 (59.6)	19 (57.6)	12 (63.2)	0.693
Increased	21 (37.5)	14 (42.4)	7 (36.8)	
GLICEMIA, n (%)				
Normal	36 (69.2)	21(63.6)	15 (78.9)	0.353[b]
Increased	16 (30.8)	12 (36.4)	4 (21.1)	

Continue...

Table 1. Continuation.

	Total	Muscle Mass		p**
		Depletion	Adequate	
HOMA-IR*, n (%)				
Normal	13 (61.9)	8 (57.1)	5 (71.4)	0.656[b]
Increased	8 (38.1)	6 (42.9)	2 (28.6)	
Metabolic syndrome***				
Yes	24 (46.2)	19(57.6)	5 (26.3)	0.029
No	28 (53.8)	14(42.4)	14 (73.7)	

*21 patients; ** Pearson's χ^2 test; ***52 patients; [a]Student's *t*- test; [b]Fisher's exact test. BMI: body mass index; WHtR: waist-to-height ratio; WC: waist circumference; IIDM: type 2 diabetes mellitus; SAH: systemic arterial hypertension; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; FA: alkaline phosphatase; TG: triglycerides; HOMA-IR: insulin resistance index.

Muscle mass and cell membrane impairment

MM depletion was found in 62.5% of the population patients with NAFLD and cell membrane impairment in 28.6%.

The values of BMI, WHtR, and WC were higher in the group with MM depletion when compared to the group without depletion (p<0.05). MS was present in 57.6% of patients with MM depletion (p=0.03). However, the same finding was not obtained with the HOMA-IR (Table 1). Only AST was related to MM depletion (p=0.004) (Table 1).

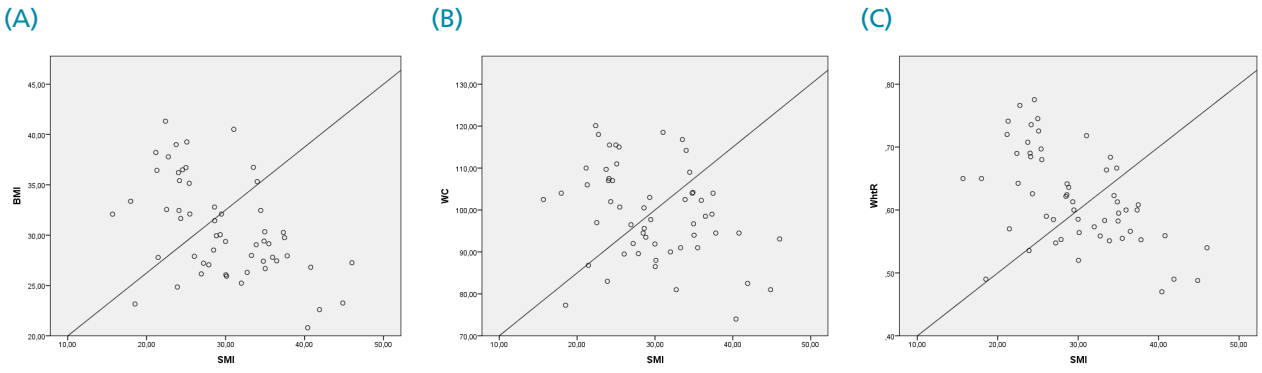
PA showed no difference in relation to MM depletion and none association or correlation with anthropometric, clinical, and biochemical data (p>0.05) (Table 1).

We observed a moderate negative linear correlation between the WHtR and the SMI, in addition to the weak negative correlation with the BMI and WC and SMI (p<0.05) (Figure 1).

Regression analysis

In the analysis of simple linear regression between SMI as independent variables, it was observed that there was a significant relation between WHtR, WC, and BMI with SMI (β= -48.74, 95%CI -69.67 – -27.81; β= -0.194, 95%CI -0.353 – -0.035; β= -0.695, 95%CI -1.029 – -0.360, respectively).

Multiple linear regression demonstrated that anthropometric parameters were associated with the dependent variable in all models. It is evident that the WHtR is a much stronger predictor in the depletion of MM. Note that the association of central obesity indicators (WHtR and WC) and total body mass improves the prediction of change in SMI, explaining 43.0% of this (Table 2).



*Pearson's correlation. BMI: body mass index; WC: waist circumference; WhtR: waist-to-height ratio; SMI: skeletal muscle mass index.

Figure 1. Correlation between: (A) BMI and SMI (r= -0.493; p<0.001); (B) WC and SMI (r= -0.312; p=0.019); (C) WhtR and SMI (r= -0.536; p≤0.001) in patients with nonalcoholic fatty liver disease.

Table 2. Linear regression selected from anthropometric variables associated with skeletal muscle mass index in a group of patients with nonalcoholic fatty liver disease treated at a referral clinic.

Skeletal muscle mass index (%)												
	Model 1				Model 2				Final model			
Variable	β adjusted	P	CI	R^2	β adjusted	P	CI	R^2	β adjusted	P	CI	R^2
WHtR	-0.54	<0.001	-69.67 – -27.81	0.29	-1.08	<0.001	-138.8 – -58.50	0.38	-0.79	0.004	-118.9 – -24.02	0.43
BMI	–	–	–		–	–	–		-0.59	0.048	-1.650 – -0.006	
WC	–	–	–		0.63	0.006	0.115– 0.657		0.90	0.001	0.241 – 0.860	

Model 1: adjusted by the BMI and WC variables; Model 2: adjusted by the BMI variable; Model 3: adjusted by BMI, WC, and WHtR. WHtR: waist-to-height ratio; BMI: body mass index; WC: waist circumference; CI: confidence interval.

DISCUSSION

More than half of the patients with NAFLD evaluated in this study had MM depletion and approximately one-third cell membrane impairment. The cell membrane impairment does not seem to be associated with the clinical and anthropometric characteristics of these patients; however, skeletal MM was associated with metabolic syndrome, elevated AST, and central obesity indicators (WHtR and WC).

The MM depletion had also a high prevalence in a study with Caucasian patients with NAFLD, using the same cutoff points adopted in the present study[18] and studies with Asian patients with NAFLD[19,20]. Koo et al.[21] observed that the occurrence of nonalcoholic steatohepatitis (NASH) may be associated with MM depletion.

In patients with NAFLD, a reduction in the MM can synergistically increase visceral fat.[22] The association of central obesity with the reduction in MM was the main finding in this study, corroborating with data from the literature[20,23].

IR has been identified as the link between MS and NAFLD[24]. Furthermore, it is also suggested as a key factor in the genesis of sarcopenia, since when there is IR in myocytes, less activation of mTOR (target of rapamycin in mammals) occurs, leading to an imbalance between the synthesis and increase of protein catabolism and, consequently, depleting to MM[4]. Although the association between IR and MS is reported[25,26], the same result was found only for MS in the present study.

Some studies observed that MM depletion affects the severity of liver disease, with worsening fibrosis[19,25]. It is noted that there is an inverse relationship between MM and ALT and AST levels in patients with NAFLD, independently of obesity[26,27]. In this study, AST was the only liver enzyme to be associated with MM and such findings were similar to the studies by Moon et al.[23]) and Petta et al.[18]

Studies that assess the correlation of PA with muscle 8 and other anthropometric and biochemical parameters are scarce. Petta et al.[18] calculated the PA in Italian patients with NAFLD and found the mean PA similar to that of the present study (6.9±1.0). This cohort adopted the cutoff point of PA<5.4 to define sarcopenia, obtaining a prevalence of 5.7%.

The main positive points of this study include the use of practical, low-cost, and easy-to-use methods in clinical practice to assess MM and central adiposity. So far, most of the studies published have been carried out on the Eastern population who have different eating habits, lifestyle, and body composition than the Western population. However, the small sample size, the absence of liver biopsy, and loss of data in variables, such as IR, are the factors, which robust statistical analyses, however, tried to minimize the limitation of this study.

In conclusion, the high prevalence of MM depletion found in the patients with NAFLD is a cause for concern, considering the association with high AST and what has already been described in the literature regarding the progression of the disease to steatohepatitis and fibrosis in the presence of MM depletion. One-third of patients with NAFLD also had impaired cell membrane integrity and it is known that this integrity is important for maintaining adequate cell function. However, further studies are needed to better assess this condition in patients with NAFLD.

The findings of this study reinforce the importance of evaluating the indicators of central adiposity and MM in patients with NAFLD, considering that the indicators of central obesity remained independently associated with MM depletion.

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ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the research ethics committee of the School of Nutrition of the Federal University of Bahia (Opinion nº 774.353 / 2014). Informed consent was obtained from all participants. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

AUTHORS' CONTRIBUTIONS

ISB: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **RR:** Conceptualization, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **ROS:** Project administration, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **CAS:** Project administration, Data curation, Writing – original draft, Writing – review & editing. **NAS:** Project administration, Resources, Data curation, Writing – original draft, Writing – review & editing. **LVV:** Project administration, Writing – original draft, Writing – review & editing. **GJS:** Project administration, Writing – original draft, Writing – review & editing. **JFO:** Project administration, Writing – original draft, Writing – review & editing. **HPC:** Resources, Writing – original draft, Writing – review & editing. **CD:** Resources, Formal analysis, Writing – original draft, Writing – review & editing. **RLPDS:** Data curation, Writing – original draft, Writing – review & editing. **MACS:** Data curation, Writing – original draft, Writing – review & editing.

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Height adjustment reduces occurrence of low bone mineral density in children and adolescents with HIV

Leonardo Bandeira de Andrade[1], Thiago Fachini Nogueira[1], Deisi Maria Vargas[2]*

SUMMARY

OBJECTIVE: The aim of this study was to quantify the reduction of bone mineral density with and without height adjustment.

METHODS: A cross-sectional study was performed with 69 Brazilian children and adolescents vertically infected by HIV. Bone mineral density was measured by dual-energy absorptiometry in the lumbar spine. Anthropometric, demographic, and clinical variables were analyzed. A specific calculator was used for height adjustment.

RESULTS: The majority of participants (52.2%) were adolescents and did not present with immunological alterations (61%). Reduced bone mineral density (*Z*-score <-1) was present in 23.2% and low bone mass (*Z*-score <-2) in 5.8%. After height adjustment, these occurrences decreased to 11.6% and 0%, respectively. Patients with reduced bone mineral density had a higher mean age and lower body mass index than patients with normal bone mineral density.

CONCLUSION: The occurrence of reduced bone mineral density decreased after adjustment for height.

KEYWORDS: Bone mineral density. HIV. Child. Adolescent. Osteoporosis.

INTRODUCTION

Chronic diseases, such as acquired immunodeficiency virus (HIV) infection, are the main causes of reduced bone mass (BM) during childhood and adolescence[1-3]. Each chronic disease may alter bone metabolism in a specific way, depending on the system affected and associated morbidities and interventions, which may affect BM in different ways and magnitudes[1]. Children and adolescents with HIV are at higher risk for BM loss[2-4].

Although the mechanisms of this loss are not fully understood, monitoring bone health is part of the care of people with HIV[5,6]. Alterations in bone metabolism, nutrient deficiency, and the use of antiviral therapy (ATV), especially protease inhibitors (PIs), have been associated with reduced BM[2,7-9]. With the improvement of ATV and greater ease of access, children with HIV have reached adolescence and adulthood with an increased risk of BM loss due to increased exposure to risk factors throughout life[10-12].

Dual-energy densitometry (DXA) is the method of choice for evaluating BM in children and adolescents by quantifying bone mineral density (BMD)[1]. Its main limitation is the quantification of areal BMD (aBMD). By not measuring volumetric BMD, BM measured by DXA is influenced by bone size, thereby underestimating BM in smaller people and generating false-positive results for low BM[13,14].

[1]Universidade de Blumenau, Centro de Ciências de Saúde, Departamento de Medicina – Blumenau (SC), Brazil.
[2]Universidade de Blumenau, Centro de Ciências de Saúde, Departamento de Medicina e Programa de Pós-graduação em Saúde Coletiva – Blumenau (SC), Brazil.
*Corresponding author: deisifurb@gmail.com
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Considering that growth deficit is a frequent situation in children and adolescents with HIV[5], the evaluation of BM by DXA may overestimate the occurrence of low BM. Despite this, most studies on the evaluation of BM by DXA in children and adolescents with HIV did not perform adjustments to minimize the impact of bone size on DXA results. One possible strategy for this purpose is to adjust for height, generating aBMD adjusted for height ($aBMD_{HAZ}$)[15]. Thus, this study aimed to evaluate BMD by DXA in pediatric patients with HIV, quantifying the occurrence of BMD reduction with and without adjustment for height and analyzing associated factors.

METHODS

Study design and participants

This is a cross-sectional study conducted on HIV carriers followed up in the Unified Health System. The inclusion criteria were children and adolescents with vertical HIV who had undergone bone densitometry in the lumbar spine. Incomplete clinical data, and age below 5 years, due to the technical limitations of height adjustment, were considered exclusion criteria. Data collection occurred between February and May 2018.

Sociodemographic variables

Age and Sex. Age was categorized into school age (5–10 years) and adolescent age (11–19 years).

Densitometric variables

Areal BMD (g/cm^2) in the lumbar spine (L1–L4) was performed with DXA Explorer model equipment (Hollogic Inc., Bedford, MA, USA) and transformed into *Z*-score for sex and age by the equipment software (Apex, version 2.1). Subsequently, using the Pediatric Bone Density Calculator tool (available at https://zscore.research.chop.edu/calcpedbonedens.php), the *Z*-score of height for age was adjusted, generating $aBMD_{HAZ}$. Low BMD was considered a *Z*-score ≤-2[16] and reduced BMD a *Z*-score <-1[17].

Anthropometric variables

Weight, height, and body mass index (BMI) were transformed into *Z*-scores for age using a calculator (available at https://www.bcm.edu/bodycomplab/Flashapps/AllDXArefsChartpage.html).

Clinical variables

These categories include viral load (CV), CD4 and CD8 counts, the use of ATV, the use of PI, and clinical category according to the Centers for Disease Control and Prevention (CDC). CD4 was categorized according to the CDC[18] in children under 12 years of age and according to the World Health Organization[19] in older patients. CD4 and CD8 were dosed by flow cytometry.

Statistical analysis

Kolmogorov–Smirnov, Student's *t*, ANOVA, chi-square, and simple and multiple linear regression tests were used. All variables were presented in terms of a parametric distribution. Variables with p≤0.2 in the simple regression were included in the multiple regression. A two-tailed sample power for the comparison of means was calculated, with an alpha error of 5%. The study was approved by the Research Ethics Committee of the University of Blumenau (opinion 020-04).

RESULTS

The study included 69 out of a total of 96 children and adolescents with vertical HIV followed up in the service. Exclusions were due to age <5 years (n=12) and incomplete data (n=15). Table 1 presents the characteristics of the participants. An occurrence of 23.2% of reduced BMD and 5.8% of low BM was observed. With the $aBMD_{HAZ}$ calculation, the occurrence of reduced BMD was 11.6%, half of that found with aBMD (chi-square=29.97; p<0.00001), and the occurrence of low BMD was 0%.

Patients with reduced BMD had higher age and lower BMI. These differences remained after adjustment for height (Table 2). Adolescents (n=36) had lower aBMD and $aBMD_{HAZ}$ than those of schoolchildren (-0.72±1.3 vs. 0.18±1.0; p<0.005 and -0.09±0.98 vs. 0.76±1.0; p<0.05; power of test >90%) and higher aBMD in g/cm^2 (0.741±0.168 vs. 0.551±0.071; p<0.0005; power of test >90%).

We observed a trend of progressive reduction of BM in association with clinical worsening that was less evident after adjustment for height, which reduced progressively throughout the clinical categories (ANOVA p<0.05; power of test <80%) (Figure 1).

Both aBMD and $aBMD_{HAZ}$ correlated negatively with BMI and age (r=-0.39, p<0.001 and r=-0.37, p<0.01 respectively) and positively with CV (r=0.32, p<0.01 and r=0.44, p<0.001), and aBMD correlated positively with height (r=0.32, p<0.01). In multiple linear regression, we observed a positive and independent correlation of aBMD with CV and BMI (R^2 adjusted 0.21; S=1.15; F=9.19; p<0.0005).

DISCUSSION

The adjustment for height minimized the occurrence of BM loss, demonstrating the impact of growth on the quantification of BM by DXA. The magnitude of this reduction is

Table 1. Characteristics of the participants.

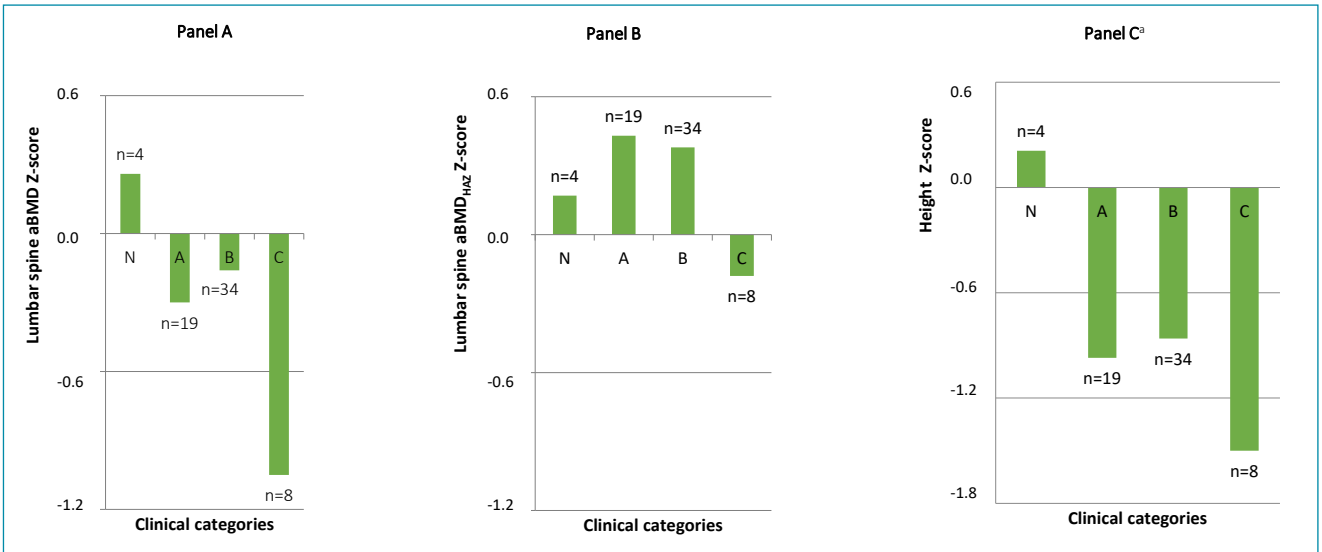
Numerical Variables	Mean±SD	95%CI	Minimum	Maximum
Age (years)	1.5±3.6	9.6 to 11.3	5.0	18.5
Use of ATV (months)	41.1±31.3	33.2 to 49.1	0.0	197.0
CD4 (cells/mm^3)	757.8±429.0	654.8 to 860.9	47.0	2,177.0
BMI (*Z*-score)	-0.4±1.1	-0.7 to -0.2	-4.4	1.6
Weight (*Z*-score)	-0.8±1.1	-1.1 to -0.6	-3.3	1.6
Height (*Z*-score)	-0.9±0.9	-1.1 to -0.7	-2.9	1.1
BMD (g)	0.6±0.2	0.6 to 0.7	0.1	1.2
BMD (*Z*-score)	-0.3±1.3	-0.6 to 0.0	-4.1	3.2
Height adjusted BMD (*Z*-score)	0.3±1.1	0.1 to 0.6	-1.8	3.5
CD8 (cells/mm^3)	1,346.7±667.3	1,181.3 to 1,521.0	317.0	3,642.0
Viral load (copies/mL)	35,196.2±74,883.0	16,179.4 to 52,212.9	0	39,000.0
Categorical Variables	**Frequency (n)**		**Relative Frequency (%)**	
Sex				
Male	33		47.8	
Female	36		52.2	
Age				
Adolescent age	36		52.2	
School age	33		47.8	
Immunologic category				
None or mild suppression	42		60.8	
Moderate suppression	23		33.4	
Severe suppression	4		5.8	
Reduced BMD (*Z*-score <-1)				
Yes	16		23.2	
No	53		76.8	
Low BMD (*Z*-score <-2)				
Yes	4		5.6	
No	65		94.4	
Clinical category[a]				
N	4		6.2	
A	19		29.2	
B	34		52.3	
C	8		12.3	
Use of ATV				
Yes	68		98.6	
No	1		1.4	
Use of protease inhibitors				
Yes	46		70.8	
No	19		29.2	

CD4: cells CD4; BMI: body mass index; BMD: bone mineral density; CD8: cells CD8; ATV: antiviral therapy; [a]Four missing data.

Table 2. Clinical characteristics of the participants according to the bone mineral density status with and without height adjustment.

Variables	Reduced aBMD (n=16)	Normal aBMD (n=53)		Reduced $aBMD_{HAZ}$ (n=8)	Normal $aBMD_{HAZ}$ (n=61)	
	Mean±SD/ n (%)	Mean±SD/ n (%)	p-value	Mean±SD/ n (%)	Mean±SD/ n (%)	p-value
Age (years)	13.5±2.9	9.5±3.5	<0.001[a]	13.4±3.7	10.1±3.6	<0.001[a]
Use of ATV (months)	51.6±28.5	37.8±31.6	NS[a]	32.5±19.9	42.5±32.5	NS[a]
CD4 (cells/mm^3)	616.8±575.8	800.3±370.2	NS[a]	569.1±514.8	779.9±416.4	NS[a]
CD8 (cells/mm^3)	1,252.7±614.4	1,374.8±685.7	NS[a]	1,247.0±802.6	1,360.6±653.2	NS[a]
BMI (*Z*-score)	-1.0±1.5	0.3±0.9	<0.05[a]	-1.0±1.6	-0.4±-1.0	<0.05[a]
Height (*Z*-score)	-0.8±0.9	-1.3±0.8	NS[a]	-1.1±0.9	-0.9±0.9	NS[a]
Use of protease inhibitor	9 (19.6)	37(80.4)	NS[b]	4 (8.7)	42 (91.3)	NS[b]

aBMD: bone mineral density without height adjustment; $aBMD_{HAZ}$: bone mineral density with height adjustment; ATV: antiviral therapy; BMI: body mass index; [a]Student's *t*-test (power of test >75% for age, body mass index, and height, and <75% for the use of antiviral therapy, cells CD4, and cells CD8); [b]Chi-square test.



[a]ANOVA p<0.05, Tukey-Kramer test p<0.02 between categories N and C.

Figure 1. Bone mineral density without and with height adjustment (Panel A and B respectively) and height (Panel C) according to clinical categories.

relevant. While one-fourth of the participants presented with reduced BMD, only one-tenth remained with this diagnosis after adjustment, showing a reduction of over 50%. The same was observed in relation to low BM, whose occurrence disappeared with the adjustment. To date, Jimenez et al.[3] were the only authors who adjusted BMD for height, showing a significant reduction in the occurrence of low BMD (from 15.3% to 4.1%). By adjusting aBMD to volumetric BMD using a mathematical formula, Sudjaritruk et al.[20] also observed a 50% reduction in the occurrence of low BMD in the lumbar spine (from 16.4% to 8.3%). Therefore, the correction for bone size from two different strategies improves the accuracy of DXA in children and adolescents with HIV.

The lower occurrence of decreased BMD generated by adjusting for height is explained by the two-dimensional nature of DXA. This characteristic of the technique underestimates

BMD in small bones, leading to a lack of diagnostic accuracy in short people by not considering bone volume[13,14]. Because of the conditions associated with HIV infection throughout the course of the disease, children and adolescents with HIV have a higher prevalence of short stature [2,9], thus adjusting for height avoids false-positive diagnoses of BM reduction.

Approximately one-fourth of the patients had reduced BMD in the lumbar spine and 5.8% had low BM. The occurrences were 21, 34, and 42%[9,21,22] for reduced BMD and 4, 11, 15%, 16%, and 32% for low BMD[2,3,9,21,23] have been reported. This variability is related to the profiles involved, especially age and clinical category. Studies with older participants[2,22] or those with a predominance of category C[2,9] showed higher rates of impaired BM. When greater age and a predominance of category C are associated, the occurrence of low BM reaches 32%[2]. The occurrences observed in this study are similar to an American study with a similar clinical profile[21].

The clinical variables that were associated with BMD were age, age group, and BMI. Although studies have shown an association between BM and the use of ATV[9,20,21] such as duration and class, this association was not evidenced in this study. PI was used with most participants, which limited the analysis of its effect on BM. BMD showed a negative correlation with age, as observed recently[20,22]. Pubertal delay and disease chronicity justify this association. Adolescents with HIV initiate puberty later, delaying the accelerated BM gain characteristic of puberty[24]; and older participants have a longer period of exposure to the disease and, therefore, are more exposed to the deleterious effects of the disease. Longitudinal data show that adolescents with vertical HIV have lower BM acquisition during puberty compared to HIV-negative adolescents[4]. Participants with reduced BMD were thinner and older, a difference that was maintained after adjustment for height. Low weight, more prevalent in children and adolescents with vertical HIV, is associated with lower BMD and related to disease chronicity[20-22]. The compromised nutritional status and the chronicity of the disease seem to negatively impact the acquisition of BM in children and adolescents with vertical HIV.

The pathophysiology of bone loss in children and adolescents with HIV is complex and multifactorial. Different mechanisms seem to act on the activity and response of bone cells depending on the clinical conditions, treatments received, and the life cycle of the affected person[8]. While some studies show an increase in bone remodeling, others show the opposite result. These studies differ in terms of the profile of the participants evaluated. Low bone remodeling is described in children under prepubertal majority, with analysis of markers of bone formation and resorption adjusted for age and sex, compared to a control group[23]. High bone remodeling is described in older, mostly pubertal participants with analyses of markers of bone formation and resorption without adjustment for sex, age, or pubertal stage[20]. Bone metabolism markers vary throughout childhood and adolescence, being highest during puberty[25]. The high bone remodeling observed in the older, mostly pubescent group, probably reflects this physiological moment. In a longitudinal evaluation, BMD increases progressively with age, but at a lower magnitude than in children and adolescents without HIV, such that by age 18, aBMD and volumetric BMD are low[20]. Considering that there is no BM loss but insufficient gain, low bone remodeling seems to be the most plausible pathophysiological mechanism. This phenomenon is observed indirectly in this study, since the adolescents had a lower BMD *Z*-score and a higher BMD g/cm^2 than the schoolchildren.

This study is the first national study and the second at the international level to demonstrate the limitation of the DXA technique in the evaluation of BMD in children and adolescents with HIV, when interpreted without adjustment for height. We recommend adjusting BMD for height in the evaluation of BM by DXA in children and adolescents with HIV to avoid the diagnostic inaccuracy inherent to this technique. In order to know more precisely the evolution of BMD assessed by DXA throughout childhood and adolescence in this clinical condition, it would be of great interest that ongoing longitudinal studies incorporate the adjustment of BMD for height in their study protocol.

The limitations of this study include data transversality, which limits the establishment of a cause-and-effect relationship; the nonprobability sample, which does not guarantee the representativeness of the population of children and adolescents with vertical HIV; and the reduced number of participants in clinical categories N and C, which limited the analysis of BMD variations between clinical categories.

CONCLUSIONS

Adjustment for height reduced the occurrence of reduced BMD and low BM in the lumbar spine of children and adolescents with vertical HIV, indicating its relevance in the evaluation of BM by DXA in order to avoid false-positive diagnoses of BM loss. Reduced BMD was associated with greater age and lower BMI.

AUTHORS' CONTRIBUTIONS

LBA, TFN: Conceptualization, Data curation, Formal analyses, Writing – original draft. **DMV:** Conceptualization, Funding acquisition, Project administration, Formal analyses, supervision, Writing – original draft, Writing – review & editing.

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Comparison of standard balloon and drug-coated balloon angioplasty in patients with the below-the-knee peripheral artery disease

Mehmet Ali Kaygin[1]*, Ümit Halici[2]

SUMMARY

OBJECTIVE: The objective of this study was to compare the interventions of percutaneous transluminal drug-coated balloon angioplasty (DCB PTA) and standard PTA in the treatment of patients with the below-the-knee peripheral artery disease (BTK PAD).

METHODS: Overall, 196 patients (113 males and 83 females; mean age: 63.56±11.94 years; 45–83 years) were treated with PTA for BTK PAD between June 2014 and March 2019.

RESULT: Standard PTA (group 1; 96 patients) and DCB PTA (group 2; 100 patients) results were analyzed and compared retrospectively. No statistically significant difference was found between the mean ages of group 1 and 2 patients (p=0.371, p>0.05). Demographic and clinical data were compared and no any statistically significant differences was found between the two groups. Comparing in terms of the iliac lesion, there was no statistically significant difference between the two groups. However, a statistically significant difference was found between the two groups in terms of frequency of popliteal lesions (p=0.001; p<0.05). There was not a statistically significant difference between the two groups in terms of other lesions. In addition, limb salvage rates were 82.0% (18 amputations) and 65.6% (33 amputations) in the drug-release balloon group and the naked balloon group, at the end of 1 year, respectively. No distal embolism, limb-threatening ischemia, and mortality were observed in any patients.

CONCLUSIONS: Based on this study, patients in the DCB group had significantly higher rates of primary patency as compared with the other patients.

KEYWORDS: Peripheral artery disease. Drug coated balloon. Angioplasty. Stenting. Percutaneous. Transluminal.

INTRODUCTION

Peripheral artery disease (PAD) is usually characterized by intermittent claudication (IC), rest pain, ischemic ulcers, or gangrene. Over a 5-year period, 5–10% of patients with asymptomatic PAD or IC will progress to critical limb ischemia (CLI)[1]. Patients with CLI are at increased risk of amputation and major cardiovascular ischemic events[2]. Therefore, revascularization treatment of these patients must be planned as soon as possible.

Revascularization is an effective treatment modality despite the benefits of pharmacological agents. Selected revascularization treatment of the patient with CLI depends upon the premorbid conditions and the extremity as well as estimating the risk of intervention based on the comorbid conditions and expected patency and durability of the vascular reconstruction[3]. Although surgical revascularization is an effective revascularization method in the treatment of PAD, the existence of the patients with high surgical risk, lack of adequate venous conduit, and poor runoff in the infrapopliteal level and foot led to

[1]University of Health Sciences, Erzurum Regional Training and Research Hospital, Cardiovascular Surgery Department – Erzurum, Turkey.
[2]University of Health Sciences, Samsun Training and Research Hospital, Cardiovascular Surgery Department – Samsun, Turkey.
*Corresponding author: malikaygin@hotmail.com
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a number of increasing percutaneous transluminal endovascular treatment (EVT) for revascularization. Nowadays, advancements in technique and technology have increased the feasibility and practicality of EVT, which now represents the preferred method of revascularization over surgical procedures in many centers across the world[4]. Unlike the open surgical technique, it can be performed under local anesthesia. Rapid application and rapid response, especially in emergency cases, enables EVT to be preferred method in patients with CLI[5]. On the other hand, the presence of long, calcific, and often occluded lesions in the infrapopliteal PAD negatively affects the patency rate after the EVT[5]. Since the optimal strategy for the management of a patient with CLI must be determined on a case-by-case basis[6]. Furthermore, patients should be informed about revascularization modalities and patients' preference should be questioned before the intervention.

It is known that drug-coated balloon (DCB) angioplasty and standard percutaneous transluminal angioplasty (PTA) (in other names are bare, naked, and old) are among EVT modalities. There is no consensus in the literature regarding the use of DCB or standard PTA in infrapopliteal lesions. This study aimed to compare the endovascular intervention techniques of DCB angioplasty and standard balloon angioplasty (PTA) in the treatment of patients with infrapopliteal PAD.

METHODS

Between June 2014 and March 2019, 196 patients (224 limb intervention) (113 males and 83 females; mean age: 63.56±11.94 years; 45–83 years) with infrapopliteal PAD who underwent endovascular revascularization operation were enrolled in this retrospective single-center study. Standard balloon angioplasty and DCB angioplasty were performed in 96 (group 1 patients' mean ages: 64.27±10.45) and 100 (group 2 patients' mean ages: 62.83±11.94) patients, respectively. Color flow Doppler ultrasound and peripheral digital subtraction or computed tomography angiography were performed after the physical examination in all patients. Control radiological imaging studies were performed during the intervention or after the procedure if needed.

Inclusion criteria were determined as lifestyle-limiting IC or CLI (Rutherford classification stages 3–6). During EVT procedure, ipsilateral or contralateral femoral artery was used for the arterial access. In case of flow-restricting dissection or ≥30% residual stenosis, the inflation time was prolonged (3 min) during the intervention. Exclusion criteria were life expectancy of less than 1 year, contraindication for dual-antiplatelet therapy, known allergy against paclitaxel, and a requirement for extensive amputation during the procedure. Also, patients with infrapopliteal vascular disease were excluded from the study if they were diagnosed with Buerger's disease. Patients received medical treatment postoperatively. Patients were called up at 1, 3, and 6 months after the procedure and followed up with ankle-brachial index (ABI) measurements and Rutherford classification. In the demographic data of patients, 6-month patency and clinical status were compared between the groups.

The primary termination variables were freedom from amputation, restenosis, and reintervention. Secondary termination variables were technical success, procedural and postoperative complications, conventional primary patency, secondary restenosis, tissue healing, limb salvage, reintervention, and patient survival. Technical success was defined as an angiographic evaluation <30% residual stenosis after the procedure and direct flow to the target site. Treatment failure was defined as any patient requiring reintervention, with/or without restenosis and/or occlusion and reintervention was performed. Also, these patients had decreasing ABI.

Following the procedure, 300 mg (75 mg×4) clopidogrel loading was given, followed by dual-antiplatelet therapy (75 mg clopidogrel and 100 mg acetylsalicylic acid daily) and cilostazol (200 mg daily) for 12 months. Also, intravenous iloprost (20 µg daily) was routinely given to all patients early postintervention term for 10 days. At the end of 6 months, clopidogrel was stopped, and patients were followed with 100 mg acetylsalicylic acid daily.

Statistical analysis

Statistical analysis was performed using SPSS mac v.20 statistical package program (IBM, Armonk, NY, USA). The suitability of the data for normal distribution was examined by the Kolmogorov-Smirnov test. Variables showing normal distribution were compared with parametric tests (Student's t-test), and mean±standard deviation values were used as descriptive statistics. The variables not normally distributed were compared with nonparametric tests (Mann-Whitney U), and median (lower quarter-upper quarter) values were given as descriptive statistics. Pearson's chi-square and Fisher's exact tests were used for the analysis of categorical data. The $p<0.05$ were considered statistically significant. Major amputation was defined as loss of limb above the metatarsal level, whereas small amputation was defined as trans-metatarsal amputation or amputation of the more distal parts of the lower limb.

RESULTS

There was not any statistically significant difference between the mean age of group 1 and 2 patients ($p=0.371$, $p>0.05$).

Demographic and clinical data were compared and found no statistically significant difference between the two groups (Table 1). Lower limb-threatening ischemia and distal embolism were not seen in any patient who enrolled in this study.

Based on the iliac lesion, there was no statistically significant difference between the two groups but iliac stent application was performed in two patients (2.1%) of group 2 (p=0.239). In all, 52 patients in group 2 and 27 patients in group 1 had popliteal lesions and there was a statistically significant difference between the two groups in terms of frequency of popliteal lesions (p=0.001; p<0.05). There was no statistically significant difference between the two groups in terms of other lesions. Lesion features are provided in detail in Table 2. Rutherford classification and ABI were used in the follow-up of the clinical recovery after the procedure. There was no significant difference between the two groups at the beginning; however, clinical improvement was significantly higher in the DCB balloon group with medication at the end of 6 months. Besides, limb salvage rates were 82.0% (18 amputations) and 65.6% (33 amputations) in the DCB balloon group and the naked balloon group, at the end of 6 months, respectively. There was statistically significant difference between the two groups (p=0.009).

DISCUSSION

The first percutaneous EVT for PAD was described by Dotter and Judkins in the mid-1960s[7]. It was reported that for selected patient population with ischemic diabetic foot and isolated infrapopliteal lesions, a successful EVT led to a high percentage of limb salvage at the long-term follow-up[8]. However, the application of standard PTA is limited due to complications associated with the endovascular procedure

Table 1. Patient demographics.

Number/percentage, n (%)	Group 1 (n=96)	Group 2 (n=100)	p-value
Gender (male/female)	55/41 (57.3/42.7)	58/42 (58.0/42.0)	0.920
Smoker	60 (62.5)	70 (70.0)	0.267
Diabetes mellitus	52 (54.2)	54 (54.0)	0.981
Hypertension (≥130/80 mmHg)	45 (46.9)	55 (55.0)	0.255
Dyslipidemia (LDL ≥200 mg/dL)	58 (60.4)	54 (54.0)	0.364
Coronary artery disease	60 (62.5)	52 (52.0)	0.138
Chronic renal failure Creatinine >2.0 mg/dL	3 (3.1)	5 (5.0)	0.721
Cerebrovascular disease	11 (11.5)	13 (13.0)	0.742

LDL: low-density lipoprotein.

Table 2. Lesion angiographic and procedural features.

	Group 2	Group 1	p-values
Lesion length, cm	12.3±7.60	13.7±8.76	0.0019
Angiography lesion length, cm	7.89±4.17	7.97±7.46	0.060
Restenotic lesions	6.7 (24/359)	3.7 (7/189)	0.176
% Diameter stenosis (before procedure)	91.2±9.8	90.71±9.29	0.065
% Diameter stenosis (after procedure)	19.8±10.1	20.2±11.7	0.068
Maximum inflation pressure, atm	6.9±3.4	11.2±4.8	0.015
Procedure complications*	9.7 (23/238)	3.4 (4/119)	0.035
Distal embolization	2.8 (9/319)	0.6 (1/169)	0.176

*Vessel rupture, vessel dissections, peripheral emboli, and hematoma.

and a relatively high restenosis rate. PTA treatment may result in residual stenosis, early elastic recoil, and flow-limiting dissection[9].

Lack of desired results caused by high restenosis with the bare metal stent and standard balloon applications in infrainguinal lesions led to the technological innovation of locally administered DCB and drug-coated stents[10]. Drug-coated stents were developed in 1999 to provide local administration of an agent without systemic side effects, which have capable of inhibiting intimal hyperplasia caused by an inflammatory reaction following stent implantation or balloon expansion[11]. In this way, the cellular mechanisms responsible for atherosclerosis and neointimal hyperplasia are inhibited.

Ipema et al. reported in their meta-analysis that no significant differences were found between DCB angioplasty and standard PTA angioplasty in patients with infrapopliteal PAD[12]. On the other hand, Schmidt et al. reported that the early restenosis rate of long-segment infrapopliteal disease is significantly lower after treatment with DCBs compared with historical data using uncoated balloons[13]. Also, Roh et al.[14] reported that treatment of the complex femoropopliteal arterial occlusive disease with DCBs showed excellent primary patency and target lesion revascularization-free survival at 1 year after the procedure. In this study, similar results were obtained in parallel with the literature.

When the disease affects infrapopliteal level, frequency of lesion increases in other parts of the limb. In this study, the incidence of superficial femoral artery lesion was 45.8 and 47% in patients with bare balloon PTA and DCB, respectively. In both groups, when the lesions complicated, this has a negative effect especially on the success of the long-term results of angioplasty.

Fernandez et al.[15] reported that tibial artery endovascular intervention is an effective treatment for CLI with acceptable limb salvage and wound healing rates, but endovascular intervention requires a high rate of reintervention. Gür et al.[5] reported that DCBs are found superior to naked balloons at 12-month patency rates and clinical follow-up. The authors also pointed out that DCB application gives successful results in the long term and have positive contributions to limb salvage in cases with BTK lesions[5]. In this study, the clinical results of the DCB group were superior to the bare balloon group in the 6-month follow-up. Also, Liistro et al.[16] reported in their study on drug-eluting balloon in peripheral intervention for below-the-knee angioplasty evaluation trial that DCBs compared with PTA strikingly reduce 1-year restenosis, target lesion revascularization, and target vessel occlusion in the treatment of BTK lesions in the diabetic patients with CLI. Similarly, lower lumen loss was detected at 6 months in the DCB group compared with standard balloon angioplasty group (0.4±1.2 mm versus 1.7±1.8 mm; p<0.001) in THUNDER trial[17].

We can conclude that increased clinical healing, walking distance, and wound healing and low amputation rates are seen after the DCB angioplasty. Accordingly, ABI rates and Rutherford levels of the patients are also improved compared with pretreatment. In this study, the improvement of the patients' status was better in current situations in the DCB group.

Interestingly, Katsanos et al.[18] reported that there seems to be an increased long-term risk of death beyond the first year after the intervention of femoropopliteal application of paclitaxel-coated balloons and stents in the lower limbs. They also mentioned that actual causes for this serious late side effect remain unknown, and further investigations with longer term follow-up are urgently warranted. On the other hand, Zeller et al.[19] reported that paclitaxel exposure was not related to increased risk for amputation or all-cause mortality at 5-year follow-up. Similarly, any patient did not develop such a complication in this study (increased death associated with paclitaxel).

There is another limitation in the literature. A long (>3 min) inflation period during balloon dilatation may prove effective as an initial angioplasty strategy to prevent severe dissection in femoropopliteal lesions[20]. Although longer inflation time did not improve primary patency within 1 year, it might result in better immediate angioplasty success[20]. Moreover, Rockley et al.[21] reported that both coronary and peripheral vascular evidence are in agreement that prolonged angioplasty balloon inflation greater than 60 seconds appears to be associated with improved immediate postinflation results. This shows that prolonged inflation time improves patency rates in DCB compared with PTA. Similarly, the inflation time was 3 min in this study.

CONCLUSIONS

In conclusion, DCB group had significantly higher rates of primary patency as compared with the PTA group, although there was no statistically significant difference between the two groups in terms of limb recovery, survival, and restenosis rates between DCB angioplasty and standard PTA. We think that it should be supported by high population, differently designed devices, and studies.

AUTHORS' CONTRIBUTIONS

MAK: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **ÜH:** Formal analysis, Software, Supervision, Writing – review & editing.

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Associations of high-mobility group box 1 and receptor for advanced glycation end products with acute lung injury in patient with acute aortic dissection

Zhaofan Zeng[1], Kun Zhang[2], Junhong Cai[3], Hongfei Wu[1], Jie Yue[4]*

SUMMARY

OBJECTIVE: To investigate the associations of high-mobility group box 1 and its specific receptor, receptor for advanced glycation end products with acute lung injury in patients with acute aortic dissection.

METHODS: A total of 96 acute aortic dissection patients were divided into acute aortic dissection with acute lung injury group (38 cases) and acute aortic dissection without acute lung injury group (58 cases), according to partial pressure of oxygen/fraction of inspired oxygen. In addition, 44 healthy individuals were selected for the control group. The blood samples were taken. The serum high-mobility group box 1 and receptor for advanced glycation end products levels were detected by enzyme-linked immunosorbent assay, and the partial pressure of oxygen/fraction of inspired oxygen was measured.

RESULTS: 24 h after admission, the high-mobility group box 1 and receptor for advanced glycation end products levels in acute aortic dissection with acute lung injury and acute aortic dissection without acute lung injury groups were significantly higher than those in the control group, respectively ($p<0.05$), and each index in acute aortic dissection with acute lung injury group was significantly higher than that in acute aortic dissection without acute lung injury group ($p<0.05$). At each time point within 96 h after admission, compared with acute aortic dissection without acute lung injury group, in acute aortic dissection with acute lung injury group, the high-mobility group box 1 and receptor for advanced glycation end products levels were increased, respectively, and the partial pressure of oxygen/fraction of inspired oxygen was decreased. The correlation analysis showed that, in acute aortic dissection patients, the high-mobility group box 1 and receptor for advanced glycation end products levels were negatively correlated with partial pressure of oxygen/fraction of inspired oxygen, respectively ($p<0.05$).

CONCLUSIONS: The serum high-mobility group box 1 and receptor for advanced glycation end products levels may be associated with the occurrence of acute lung injury in acute aortic dissection patients. Monitoring the high-mobility group box 1 and receptor for advanced glycation end products levels can evaluate the risk of acute aortic dissection with acute lung injury .

KEYWORDS: Aortic dissection. Acute lung injury. High-mobility group box 1. Receptor for advanced glycation end products.

[1]Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Department of Vascular Surgery – Haikou, China.
[2]Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Medical Care Center, Department of Geriatrics – Haikou, China.
[3]Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Molecular Laboratory Center – Haikou, China.
[4]The First Affiliated Hospital of Guangzhou Medical University, Department of Cardiovascular Surgery – Guangzhou, China.
*Corresponding author: yuejiegz2@126.com
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INTRODUCTION

Acute aortic dissection (AAD) is a serious cardiovascular disease. In AAD, the blood flows into the cystic-degenerated middle aortic layer through the avulsion of aortic intima to form a dissection hematoma that expands in the aorta driven by blood pressure[1]. Acute lung injury (ALI) is one of the common complications of AAD. It is characterized by diffuse alveolar epithelial cell injury and increased capillary permeability. The incidence of AAD complicated ALI is more than 50%[2]. AAD with ALI can prolong the time of ventilator use, prolong the length of hospital stay, increase the treatment cost, increase the mortality, and seriously affect the prognosis of patients[3,4]. Therefore, it is of great significance to study the pathogenesis of AAD with ALI for improving the prognosis of patients. The mechanism of AAD with ALI has not been fully elucidated. It is well known that the changes in cellular and biochemical regulatory pathways eventually lead to the AAD with ALI. These changes include the increased inflammatory response and oxidative stress, and matrix metalloproteinases[5,6].

High-mobility group box 1 (HMGB1) is a member of HMGB family. It is located on human chromosome 13q12 and consists of 215 amino acid residues[7]. As a nuclear nonhistone protein, HMGB1 has a strong pro-inflammatory effect and plays a key role in the initiation and maintenance of inflammatory cascade reaction[8]. When the body is in a steady state without external stimulation, HMGB1 mainly exists in the nucleus. Under stress condition, HMGB1 is secreted outside the cell through nonclassical or passive release pathway. It interacts with the specific receptor, receptor for advanced glycation end products (RAGE), to activate the mitogen-activated protein kinase pathway and nuclear factor kappa B, thus inducing the secretion of tumor necrosis factor α, interleukin 1β, interleukin 6, and other inflammatory factors that produce the inflammatory cascade reaction[9]. Therefore, the HMGB1 and RAGE may be related to AAD with ALI. This study monitored the expression levels of HMGB1 and RAGE in AAD patients complicated with ALI, analyzed the associations of HMGB1 and RAGE with oxygenation index (partial pressure of oxygen/fraction of inspired oxygen, PaO_2/FiO_2), and explore their clinical significances.

SUBJECTS AND METHODS

Subjects

A total of 96 AAD patients treated in our hospital from January 2018 to June 2020 were enrolled in this study. There were 58 males and 38 females. The age of patients was 33–82 years old, with average age of 76.32±10.34 years old. There were 59, 30, 78, and 32 cases with smoking history, diabetes history, hypertension history, and coronary heart disease history, respectively. The erythrocyte sedimentation rate was 4.47±1.27 mm/h. The serum creatinine level was 90.05±22.19 nmol/mL. The serum brain natriuretic peptide level was 102.05±25.24 pg/mL. The prothrombin time was 13.99±1.52 s and the ejection fraction was 64.12±11.05%. According to the PaO_2/FiO_2 under static oxygen inhalation, the patients were divided into AAD with ALI group (38 cases) and AAD without ALI group (58 cases). In addition, 44 healthy individuals receiving physical examination were randomly selected as the control group. This study was approved by the ethics committee of Hainan General Hospital. The signed informed consent was obtained from all subjects.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. the AAD was confirmed by computed tomography angiography or digital subtraction angiograph;
2. the patients were admitted within 24 h after AAD onset; and
3. the patients received the conservative treatment for more than 4 days after admission.

The exclusion criteria were as follows:

1. the patients were admitted after 24 h from AAD onset;
2. the patients received surgery (interventional therapy) or died within 4 days after admission;
3. the patients had malignant tumor or immune diseases;
4. the patients had taken anti-inflammatory drugs or immunosuppressants; and
5. the patients had the respiratory disease history.

Study method

After admission, the patients were immediately admitted to the intensive care unit, and were given oxygen inhalation, electrocardiogram monitoring, analgesia, antihypertension, defecation, and other symptomatic treatment. The mechanical ventilation was performed, if necessary. For all patients, the arterial blood was drawn every 4 h after admission. The PaO_2/FiO_2 was measured. At the corresponding time point, the elbow venous blood was drawn. The blood was centrifuged at 3000 r/min for 15 min. The supernatant was obtained and stored at -80°C in a refrigerator for testing. The levels of HMGB1 and RAGE were detected by enzyme-linked immunosorbent assay. The detection operations were in strict accordance with the instruction of kits. In the control group, the morning fasting elbow venous blood was drawn only once. The detection operations of HMGB1 and RAGE were the same with those in AAD patients.

Statistical analysis

All statistical analysis was carried out using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as number and rate, and the comparison between AAD with ALI and AAD without ALI groups was performed using χ^2 test. The measurement data were expressed as the mean±standard deviation. The comparison between AAD with ALI and AAD without ALI groups was performed using t-test. The comparison among AAD with ALI, AAD without ALI, and the control groups was performed using analysis of variance. The correlations of HMGB1, RAGE, and PaO_2/FiO_2 were analyzed by Spearman's rank correlation analysis. P<0.05 was considered as statistically significant.

RESULTS

General information of acute aortic dissection patients

General information of AAD patients was shown in Table 1. There was no significant difference of gender, age, smoking history, diabetes history, hypertension history, coronary heart disease history, erythrocyte sedimentation rate, serum creatinine level, serum brain natriuretic peptide level, prothrombin time, or ejection fraction between AAD with ALI group and AAD without ALI group (p>0.05).

Comparison of high-mobility group box 1 and receptor for advanced glycation end products levels among acute aortic dissection with acute lung injury, acute aortic dissection without acute lung injury, and control groups

As shown in Table 2, the levels of HMGB1 and RAGE at 24 h after admission in AAD with ALI and AAD without ALI groups were significantly higher than those in the control group, respectively (p<0.05). Compared with AAD without ALI group, the levels of HMGB1 and RAGE in AAD with ALI group were significantly increased, respectively (p<0.05).

Table 2. Comparison of high-mobility group box 1 and receptor for advanced glycation end products levels among acute aortic dissection with acute lung injury, acute aortic dissection without acute lung injury, and the control groups.

Group	n	HMGB1 (ng/mL)	RAGE (μg/L)
AAD with ALI	38	89.21±18.21[ab]	105.21±20.87[ab]
AAD without ALI	58	48.24±7.05[a]	73.75±12.33[a]
Control	44	12.95±3.29	22.78±4.40
F		521.770	385.336
t		<0.001	<0.001

AAD: acute aortic dissection; ALI: acute lung injury; HMGB1: high-mobility group box 1; RAGE: receptor for advanced glycation end products. [a]p<0.05 compared with the control group. [b]p<0.05 compared with AAD without ALI group.

Table 1. General information of acute aortic dissection patients.

Group	AAD with ALI	AAD without ALI	t/χ^2	P
n	38	58		
Gender, n (%)			0.167	0.683
Male	22 (57.89)	36 (62.07)		
Female	16 (42.11)	22 (37.93)		
Age (years)	77.58±8.05	75.04±7.44	1.583	0.117
Smoking history, n (%)	23 (60.53)	36 (62.07)	0.023	0.879
Diabetes history, n (%)	12 (31.58)	18 (31.03)	0.003	0.955
Hypertension history, n (%)	30 (78.95)	48 (82.76)	0.219	0.640
CHD history, n (%)	13 (34.21)	19 (32.76)	0.022	0.883
ESR (mm/h)	4.33±1.04	4.70±0.98	1.766	0.081
Creatinine (nmol/mL)	92.23±20.04	88.06±17.83	1.067	0.289
BNP (pg/mL)	103.27±23.04	99.36±18.27	0.924	0.358
Prothrombin time (s)	14.16±1.05	13.67±1.23	1.777	0.079
Ejection fraction (%)	65.06±9.32	63.70±8.04	0.761	0.449

AAD: acute aortic dissection; ALI: acute lung injury; CHD: coronary heart disease; ESR: erythrocyte sedimentation rate; BNP: brain natriuretic peptide.

Changes of high-mobility group box 1, receptor for advanced glycation end products, and partial pressure of oxygen/fraction of inspired oxygen in acute aortic dissection patients within 96 h after admission

The changes of HMGB1, RAGE, and PaO_2/FiO_2 in AAD patients within 96 h after admission were shown in Figure 1. After admission, in both AAD with ALI and AAD without ALI groups, the HMGB1 and RAGE levels increased gradually, and the PaO_2/FiO_2 decreased gradually. With the extension of time, the HMGB1 and RAGE levels reached the highest value, followed by gradually decreasing, and the PaO_2/FiO_2 reached the lowest value, followed by gradually increasing. At each time point, compared with AAD without ALI group, in AAD with ALI group, the HMGB1 and RAGE levels were increased, respectively, and the PaO_2/FiO_2 was decreased (Figure 1).

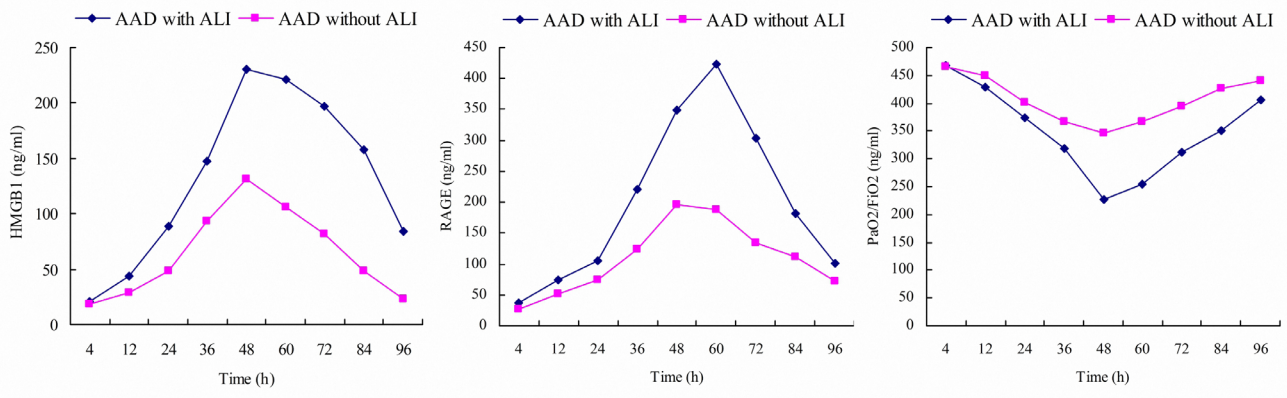
Correlations of high-mobility group box 1, receptor for advanced glycation end products, and partial pressure of oxygen/fraction of inspired oxygen in acute aortic dissection patients

The Spearman rank correlation analysis showed that, in 96 AAD patients, the HMGB1 level was negatively correlated with PaO_2/FiO_2 ($r=-0.978$, $p<0.001$). The RAGE level was negatively correlated with PaO_2/FiO_2 ($r=-0.944$, $p<0.001$). The HMGB1 level was positively correlated with RAGE ($r=0.978$, $p<0.001$).

DISCUSSION

The pathogenesis of AAD with ALI has not been fully clarified, and it is closely related to the excessive inflammatory cascade reaction. When AAD occurs, the aortic intima is avulsed. The blood flows into the aortic false lumen and contact with the extracellular matrix of aortic media. This leads to the activation of inflammatory cells and release of a large number of inflammatory mediators and pro-inflammatory factors, which then mediate the waterfall-like inflammatory cascade reaction[10,11]. There are extensive capillary beds in lung tissue, where the inflammatory cells gather. In ADD, these inflammatory cells are activated in the lung tissue. They release the inflammatory mediators that damage the pulmonary capillary endothelial cells. This leads to the increased microvascular permeability, decreased alveolar compliance, increased intrapulmonary shunt, and intractable hypoxemia[12]. Therefore, the oxygenation index PaO_2/FiO_2 is an important indicator of AAD with ALI.

HMGB1/RAGE signaling pathway exists in the constituent cells of various respiratory systems, and plays an important role in the pathogenesis of various respiratory diseases. Under stress condition, HMGB1 is released from the nucleus to the cytoplasm and further the extracellular matrix. It is internalized to the lysosome through the RAGE-mediated endocytosis, further transferring and activating the appropriate activation pathways[13,14]. It is suggested that the intervention of HMGB1/RAGE signaling pathway can inhibit the inflammatory response[15]. Zhou et al.[16] have found that inhibition of long noncoding RNA nuclear paraspeckle assembly transcript 1 can inhibit the activation of HMGB1/RAGE signaling pathway, thus antagonizing the lipopolysaccharide-induced acute injury and inflammatory response of alveolar epithelial cells. In our study, 24 h



AAD: acute aortic dissection; ALI: acute lung injury; HMGB1: high-mobility group box 1; RAGE: receptor for advanced glycation end products; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspired oxygen.

Figure 1. Changes of high-mobility group box 1, receptor for advanced glycation end products, and partial pressure of oxygen/fraction of inspired oxygen in acute aortic dissection patients within 96 h after admission.

after admission, the HMGB1 and RAGE levels in AAD with ALI and AAD without ALI groups were significantly higher than those in the control group. This indicates that, whether with or without ALI, the HMGB1 and RAGE levels in AAD patients are higher than those in healthy people.

In this study, within 96 h after admission, in both AAD with ALI and AAD without ALI groups, the HMGB1 and RAGE levels increased gradually, followed by decreasing, and the PaO_2/FiO_2 decreased gradually, followed by increasing. At each time point within 96 h after admission, compared with AAD without ALI group, in AAD with ALI group, the HMGB1 and RAGE levels were increased, and the PaO_2/FiO_2 was decreased. The correlation analysis showed that, in AAD patients, HMGB1 and RAGE levels were negatively correlated with PaO_2/FiO_2, respectively. This suggests that the activation of HMGB1/RAGE signaling pathway may be the key factor of ALI in AAD patients. The higher the HMGB1 and RAGE levels are, the more severe the inflammatory reaction is, and the more severe the lung injury is. With the decrease of HMGB1 and RAGE levels, the inflammatory reaction is decreased, and the lung injury is mitigated. They are closely related.

In conclusion, the serum HMGB1 and RAGE levels may be associated with the occurrence of ALI in AAD patients. The HMGB1/RAGE signaling pathway may play an important role in AAD with ALI. With the increase of HMGB1 and RAGE levels, the degree of ALI is gradually aggravated. Monitoring the HMGB1 and RAGE levels can evaluate the risk of AAD with ALI, which plays a good warning role in clinical practice. In-depth study of HMGB1/RAGE signaling pathway may provide potential therapeutic target for AAD patients with ALI. The limitation of this study is that the sample size is relatively small which may affect the results. In our subsequent studies, the sample size should be enlarged further for obtaining more convincing outcomes.

AUTHORS' CONTRIBUTIONS

JY: Conceptualization, Data curation, Formal analysis. **ZZ:** Funding acquisition, Investigation. **KZ:** Methodology, Project administration. **JC:** Supervision, Validation, Visualization. **HW:** Writing-original draft.

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Efficacy and safety of combined doxofylline and salbutamol in treatment of acute exacerbation of chronic obstructive pulmonary disease

Xianrong Du[1], Hongju Bao[2], Daguo Zhao[3]*

SUMMARY

OBJECTIVE: The aim of this study was to investigate the efficacy and safety of combined doxofylline and salbutamol in the treatment of acute exacerbation of chronic obstructive pulmonary disease.

METHODS: A total of 68 acute exacerbation of chronic obstructive pulmonary disease patients were randomly divided into control group (34 cases) and experimental group (34 cases), who received the doxofylline treatment and combined doxofylline and salbutamol treatment for 1 week, respectively. During the treatment, the remission time of typical respiratory manifestations was recorded, and the adverse reactions were observed. At the end of treatment, the treatment efficacy was evaluated. Before and after treatment, the pulmonary function indexes and serological indicators were detected.

RESULTS: After treatment, compared with control group, in experimental group, the effective rate of treatment was significantly increased ($p<0.05$), the remission time of typical respiratory manifestations was significantly shortened ($p<0.05$), the pulmonary function indexes were significantly improved ($p<0.05$), the serum high-sensitivity C-reactive protein and cystatin C levels were significantly decreased, respectively ($p<0.05$), and the serum prealbumin level was significantly increased ($p<0.05$). In addition, the adverse reaction rate had no significant difference between two groups ($p>0.05$).

CONCLUSIONS: In the treatment of acute exacerbation of chronic obstructive pulmonary disease, the combined use of doxofylline and salbutamol can quickly relieve the respiratory symptoms, mitigate the pulmonary dysfunction, and reduce the inflammatory response, thus promoting the outcome of patients.

KEYWORDS: Doxofylline. Salbutamol. Chronic obstructive pulmonary disease. Inflammation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a kind of airway inflammatory disease with high morbidity and mortality. It is one of the common respiratory diseases in the elderly. Acute exacerbation of COPD (AECOPD) is an important event in the clinical process of COPD. It can be caused by nonstandard treatment in stable period (e.g., discontinuation of relevant inhaled drug treatment), changes in environmental and physical and chemical factors (e.g., air pollution and smoking), respiratory tract infection, and so on[1]. The typical manifestations of AECOPD are the increased cough, increased sputum volume and/or purulent or mucinous purulent sputum, and aggravated dyspnea[2]. The onset process of AECOPD will not only accelerate the deterioration of lung function, but also increase the risk of death in the future. At present, most commonly used drugs for AECOPD include bronchodilators (e.g., β2 receptor

[1]Shanxi Provincial People's Hospital, Emergency Department – Taiyuan, China.
[2]Sozhou Ninth People's Hospital, Department of Respiratory Medicine – Suzhou, China.
[3]The First Affiliated Hospital of Soochow University, Department of Critical Care Medicine – Suzhou, China.
*Corresponding author: zhaodgsz@126.com
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agonists and theophylline), anti-inflammatory drugs (e.g., glucocorticoids), and other drugs (e.g., expectorants), among which the bronchodilators are basic drugs[3]. Doxofylline is a kind of theophylline drug that can relieve the asthma, relax the bronchial smooth muscle, and improve the respiratory muscle function. It is a commonly used bronchodilator in the treatment of AECOPD[4]. Salbutamol is a short-acting β2 receptor agonist. It can relax the airway smooth muscle, reduce the wheezing, relieve the bronchospasm, and improve the gas exchange. It is another common bronchodilator for rapid control of AECOPD symptoms[5]. In this study, the combined doxofylline and salbutamol was applied for the treatment of AECOPD, and the efficacy and safety of this strategy was observed. This study will provide a basis for further application of this treatment strategy.

METHODS

General clinical data

A total of 68 patients with AECOPD treated in our hospital from July 2018 to November 2019 were selected as the research objects. They were randomly divided into control group and experimental group, 34 cases in each group. In the control group, there were 19 males and 15 females. The age was 52–80 years, with mean age of 66.68±8.38 years. The course of disease was 6–14 years, with mean course of 9.80±2.41 years. As for pulmonary function grade in Global Initiative for Chronic Obstructive Lung Disease (GOLD), there were 5 cases of grade I, 8 cases of grade II, 14 cases of grade III, and seven cases of grade IV. In the experimental group, there were 16 males and 18 females. The age was 54–79 years, with mean age of 64.06±6.29 years. The course of disease was 5–15 years, with mean course of 7.26±3.82 years. There were 7 cases of GOLD grade I, 7 cases of grade II, 11 cases of grade III, and nine cases of grade IV. There was no significant difference of gender, age, disease course, or GOLD grade between two groups ($p>0.05$). This study was approved by the ethics committee of Shanxi Provincial People's Hospital. Written informed consent was obtained from all participants.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows:

(a) the patients met the diagnostic criteria of AECOPD;
(b) the age was less than 80 years; and
(c) the patients presented the aggravated dyspnea, fever, cough, expectoration, and other symptoms.

The exclusion criteria were as follows:

(a) the patients had allergic history to doxofylline or salbutamol;
(b) the patients were complicated with diseases not suitable for use of salbutamol;
(c) the patients were complicated with mental disorders;
(d) the patients were complicated with rheumatic immune diseases;
(e) the patients were complicated with tumor, liver or kidney dysfunction, or heart failure;
(f) the patients had respiratory surgery history;
(g) the patients were diagnosed with pneumothorax, pulmonary embolism, pneumonia, or other diseases; and
(h) the patients had contraindications of pulmonary function examination.

Treatment strategies

The patients in two groups were asked to take light diet and to avoid tobacco, wine, and sour or spicy food. They received the routine resolving phlegm and anti-infection treatment. In control group, the patients were injected with doxofylline injection (0.2 g doxofylline was dissolved in 100 ml of 0.9% sodium chloride solution) by intravenous drip, twice a day, for one week. In experimental group, based on the intravenous drip of doxofylline injection in the control group, the patients received the atomization inhalation of salbutamol (2.5 mg salbutamol sulfate was diluted into 4 ml of 0.9% sodium chloride solution), twice (morning and evening) a day, for one week.

Evaluation of total treatment efficacy

During the treatment, the remission time of typical respiratory manifestations, such as wheezing, cough, and expectoration, in two groups was recorded, and the adverse reactions were observed. At the end of treatment, the treatment efficacy was evaluated as follows:

(a) ineffective: the symptoms of wheezing, cough, expectoration, and others were not relieved, or even aggravated further;
(b) effective: the symptoms of wheezing, cough, expectoration, and others were relieved to a certain extent; and
(c) remarkably effect: the symptoms of wheezing, cough, expectoration, and others disappeared.

The effective rate was calculated as follows: effective rate (%)=([number of effective cases+number of markedly effective cases]/total case number)×100%.

Pulmonary function examination

Before and after treatment, the patients received the routine pulmonary function examination. The forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were measured. The ratio of FEVl/FVC was calculated.

Detection of serological indicators

Before and after treatment, 5 ml of fasting venous blood was drawn from the patients. The serum high-sensitivity C-reactive protein (hs-CRP) level was measured by immunoturbidimetric method. The serum cystatin C (CysC) and prealbumin levels were measured by automatic biochemical analyzer.

Statistical analysis

SPSS 20.0 statistical software was used. Measurement data were expressed as mean±standard deviation and analyzed using t-test. Enumeration data were expressed as number or rate, and analyzed using χ^2 test. $p<0.05$ presented statistically significant difference for comparison.

RESULTS

Total treatment efficacy

At the end of treatment, the number of remarkably effective, effective, and ineffective cases in control group were 16, 10, and 8, respectively, and that in experimental group were 20, 13, and 2, respectively. The effective rate in experimental group was 94.12%, which was significantly higher than 76.47% in control group ($\chi^2=4.221$; $p<0.05$).

Remission time of typical respiratory manifestations

The remission time of typical respiratory manifestations including wheezing, cough, and expectoration in the treatment process was observed. As shown in Table 1, each index in experimental group was obviously shorter than that in control group ($p<0.05$).

Pulmonary function indexes

As shown in Table 2, there was no significant difference in FEV1 or FEV1/FVC between control and experimental groups before treatment ($p>0.05$). After treatment, FEV1 and FEV1/FVC in each group were significantly higher than those before treatment, respectively ($p<0.05$), and each index in experimental group was significantly higher than that in control group ($p<0.05$).

Serological indicators

Before treatment, the serum hs-CRP, CysC, and prealbumin levels had no significant difference between control and experimental groups, respectively ($p>0.05$). After treatment, in each group the serum hs-CRP and CysC levels were significantly lower than those before treatment, respectively ($p<0.05$), and the serum prealbumin level was significantly higher than that before treatment ($p<0.05$). Compared with control group, in experimental group the serum hs-CRP and CysC levels were significantly decreased, respectively ($p<0.05$), and the serum prealbumin level was significantly increased ($p<0.05$; Table 3).

Adverse reactions

During the treatment, one case of dizziness, one case of nausea, and one case of dry mouth were found in the control group, and the adverse reaction rate was 8.82%. In the experimental group, two cases of dizziness, one case of nausea, and two cases of dry mouth were found, and the adverse reaction rate was 11.76%. The adverse reaction rate had no significant difference between two groups ($\chi^2=0.159$, $p>0.05$).

Table 1. Comparison of remission time of typical respiratory manifestations between two groups.

Group	n	Wheezing (days)	Cough (days)	Expectoration (days)
Control	34	5.05±1.04	5.77±1.23	6.45±1.38
Experimental	34	4.29±1.45	4.95±1.05	5.53±1.13
t		2.483	2.957	3.008
p		0.016	0.004	0.004

Table 2. Comparison of pulmonary function indexes between two groups.

Group	FEV1 (%)		FEV1/FVC	
	Before treatment	After treatment	Before treatment	After treatment
Control	43.62±11.65	52.10±12.44[a]	55.05±6.23	60.15±7.83[a]
Experimental	44.16±8.10	68.27±14.32[a]	56.41±8.10	68.28±5.41[a]
t	0.222	4.971	0.776	4.981
p	0.825	0.000	0.441	0.000

FEVl: forced expiratory volume in 1 s; FVC: forced vital capacity. [a]$p<0.05$ compared with before treatment.

Table 3. Comparison of serological indicators between two groups.

Group	hs-CRP (mg/L)		CysC (mg/L)		Prealbumin (mg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	42.56±6.04	28.32±4.82[a]	1.43±0.28	1.30±0.18[a]	126.21±23.62	144.93±28.12[a]
Experimental	44.18±7.26	15.62±3.90[a]	1.51±0.22	1.18±0.26[a]	119.04±19.80	172.40±31.22[a]
t	1.000	11.944	1.310	2.213	1.356	3.812
p	0.321	0.000	0.195	0.030	0.180	0.000

hs-CRP: high-sensitivity C-reactive protein; CysC: cystatin C. [a]p<0.05 compared with before treatment.

DISCUSSION

Bronchodilators are the cornerstone of drug therapy for AECOPD[6]. The combination of bronchodilators with different action mechanism and action time is an important treatment strategy for AECOPD. In this study, the combined doxofylline and salbutamol was applied to treatment of AECOPD, for improving the treatment efficacy and reduce the risk of adverse reactions. Results showed that, after 1 week of treatment, compared with single use of doxofylline, in the group using combined doxofylline and salbutamol, the effective rate of therapy was significantly increased, the remission time of typical respiratory manifestations was significantly shortened, and the pulmonary function was significantly improved. In addition, the adverse reaction rate had no significant difference between two treatment strategies. This suggests that, the combined use of doxofylline and salbutamol can play a synergistic and complementary role in treating AECOPD through their different action mechanism, while not reducing the safety of medication.

COPD is mainly caused by chronic nonspecific inflammatory response in trachea, bronchial mucosa, and surrounding tissues. AECOPD is a serious deterioration of COPD at its acute onset[7]. The severe pulmonary infection is an important factor for AECOPD. Therefore, monitoring the inflammatory biomarkers is very helpful for early diagnosis and efficacy evaluation of AECOPD[8]. hs-CRP is a common inflammatory factor. Its level usually increases significantly when the infection and trauma occur, which belongs to the instinctive response of the body. hs-CRP can be used as an important indicator to predict inflammation and infection[9]. CysC is a protein with a relative molecular weight of 13.3×10^3, which can effectively reflect the degree of inflammation[10]. Studies have shown that, the serum hs-CRP and CysC levels significantly increase in AECOPD, and they significantly decrease after the treatment. Moreover, the serum hs-CRP and CysC levels in the acute stage of COPD are significantly higher than those in the stable stage of COPD, indicating that hs-CRP and CysC are correlated with AECOPD[11,12]. Prealbumin is a kind of plasma transporter, which can remove the toxic metabolites and effectively repair the tissue cells. When the body has systemic inflammatory response, the prealbumin level will decrease rapidly[13]. It is found that the prealbumin can also be used as inflammatory indicator for early diagnosis of AECOPD. The change trend and degree of prealbumin level can be used to judge the treatment efficacy and prognosis of patients[14]. In our study, after treatment, in each group, the serum hs-CRP and CysC levels were significantly lower than those before treatment, and the serum prealbumin level was significantly higher than that before treatment. This suggests that, both single use of doxofylline and combined use of doxofylline and salbutamol can reduce the inflammatory response in AECOPD patients. Compared with control group, in experimental group, the serum hs-CRP and CysC levels were significantly decreased, and the serum prealbumin level was significantly increased. This indicates that, the combined use of doxofylline and salbutamol can further reduce the inflammatory response, compared with single use of doxofylline, which may be related with its better treatment efficacy.

CONCLUSIONS

To sum up, the application of combined doxofylline and salbutamol in the treatment of AECOPD has definite treatment efficacy. This strategy can quickly relieve the respiratory symptoms, mitigate the pulmonary dysfunction, and reduce the inflammatory response, thus promoting the outcome of patients. This study still has some limitations. First, other action mechanisms related to the therapeutic effect of combined doxofylline and salbutamol have not yet been investigated. Second, the number of patients involved in this study is relatively small. These issues should be solved in subsequent studies to obtain more credible conclusions.

AUTHORS' CONTRIBUTIONS

DZ: Conceptualization, Writing – review & editing. **XD:** Data curation, Writing – original draft. **HB:** Formal Analysis, Writing – review & editing.

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Health care professionals and end-of-life care during the COVID-19 pandemic

Esther Angélica Luiz Ferreira[1]*, Cristina Ortiz Sobrinho Valete[1], André Filipe Junqueira dos Santos[2], Juliana Nalin de Souza Passarini[3], Alexandre Ernesto Silva[4], Michelle Uchida Miwa[5]

SUMMARY

OBJECTIVE: The aim of this study was to estimate self-perception of anguish and low quality of life among health care professionals who cared for the dying patients during the COVID-19 pandemic and to determine the characteristics of health care professionals and patients and end-of-life care.

METHODS: An online survey that included health care professionals who cared for the dying patient from July 1 to October 31, 2020 was conducted. Low quality of life, anguish, characteristics of patients and health care professionals, and end-of-life care were recorded. Poisson regression was performed to assess the predictors of anguish and low quality of life.

RESULTS: A total of 102 health care professionals, including 14 males (13.7%), with a median age of 37 years, composed of 41 physicians (40.2%), 36 physiotherapists (35.3%), and 25 nurses (24.5%) were included in this study. Self-perception of anguish occurred in 69.6% and was associated with physicians and disagreement with end-of-life care offered. Low quality of life was reported in 64.7% and was associated with not having time to talk to patients' relatives. The agreement that medical care was enough reduced self-perception of low quality of life.

CONCLUSION: Self-reported anguish was more frequent in physicians and when the disagreement about end-of-life care occurred. Low quality of life was more frequent when health care professionals did not have time to talk to patients' relatives and was less frequent when health care professionals agreed that medical care was enough. Strategies should be done by health services to reduce the impact of the pandemic on health care professionals.

KEYWORDS: COVID-19. COVID-19 pandemic. Palliative care. End-of-life care. Assisted death. Grief.

INTRODUCTION

The COVID-19 pandemic represents a severe threat to public health. Aiming at reducing the infection rate, social distancing and isolation measures have been adopted. Nevertheless, they led to social and behavioral changes that considerably altered the human relationship with the environment[1].

For patients and their relatives, the coronavirus crisis has caused fear and anxiety exacerbated by the lack of information about this new disease. If the health system capacity is exhausted, these hardships may increase due to the unavailability of medical services and equipment to provide them support[2].

[1]Universidade Federal de São Carlos, Medicine Department – São Carlos (SP), Brazil.
[2]Oncological Institute of Ribeirão Preto, Oncoclínicas Group, Palliative Care Service – Riberão Preto (SP), Brazil
[3]Universidade Estadual de Campinas, Faculty of Medical Sciences, Department of Clinical Medicine – Campinas (SP), Brazil.
[4]Universidade Federal de São João del-Rei, Medical and Nursing Course – São João del Rei (MG), Brazil.
[5]Hospital de Amor de Barretos, Department of Palliative Care – Barretos (SP), Brazil.
*Corresponding author: estherferreira@ufscar.br
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In these circumstances, essential principles that orient the medical support of the ill patients, such as the attention to the needs and preferences of the ill person and their families, may be compromised. Emotional, cognitive, physical, and behavioral responses following the demise are common elements of uncomplicated grief[3]. The usual grief experiences during the COVID-19 pandemic were often interrupted, and thus it is imperative to reconsider the standard approaches and find new solutions. For many hospitalized patients, for example, visits were limited or even prohibited, regardless of having received a diagnosis of COVID-19 or not. For the grieving relatives, funerals and burials were postponed or ensued at a distance, often without the presence and warmth of their loved ones[4].

Overwhelmed hospitals demanded the transfer of patients to other health care units. These experiences can be traumatic, just as passing away in a ward or other facilities dedicated to the treatment of patients with COVID-19, which may also lead to a psychological stigma. It is known that family members of those who died at a hospital or an intensive therapy unit represent a larger risk for extended grief and depression[5]. The impossibility of a "farewell" between the family and the deceased is associated with complicated grief. Studies demonstrate that severe symptoms of anticipatory grief, lower levels of social support, lack of preparation and planning for death, and guilt are risk factors for complicated grief and depression after bereavement. These factors are relevant to the COVID-19 pandemic context[6-9].

In Brazil, the pandemic stressed the health system, which already operated at its limit in normal situations, leading to the collapse of medical groups[10]. Health care professionals handled an overwhelming flow of severely ill patients, the ailment of their medical colleagues, and the moral suffering due to their inability to provide basic care that they considered humane and necessary. Along with their workload, they also had to manage a preoccupation with their own health and that of their families[11].

In light of these data, this study aimed to estimate self-perception of anguish and low quality of life among health care professionals who cared for the dying patients during the COVID-19 pandemic. Also, it intended to determine the characteristics of health care professionals and patients and end-of-life care associated with self-perception of anguish and low quality of life.

METHODS

In this online survey, we enrolled 102 health care professionals who cared for the dying patients in their last days of life, from July 1 to October 31, 2020. This article writing followed the STROBE form for the cross-sectional studies[12].

The survey form was a short version from the international form "Care of the Dying Evaluation" (iCODE) that focused on the last 2 days of life and the grief period, asked about the quality of patient care and family support[13], and included questions about COVID-19. The translation, adaptation, and use of form were approved. The protocol proposed by Kulis et al. was used[14].

Inclusion criteria: health care professionals who took care of a patient in their last 2 days of life.

Exclusion criteria: incomplete forms.

Quality of life was registered on a scale from 1–7 and defined by the World Health Organization as "the individual perception about his life position, according to cultural context and values systems in which he lives and in relation to his objectives, expectations, patterns, and concerns"[15].

Health care professional characteristics (i.e., age, sex, and professional category) and patient characteristics (e.g., age, sex, SARS-CoV-2 infection, and if he/she felt pain always or sometimes) were registered. End-of-life care offered for the last 2 days (agreement with end-of-life care offered, a shared decision regarding limited life care support, have time to talk to patients' relatives, the agreement that medical care was enough, if visits were allowed, if emotional and spiritual support was offered to patients' relatives, the place where care was offered, and if death occurred in a COVID-19 division) was investigated.

Outcome variables were self-perception of low quality of life (≤4) and anguish (yes/no) of health care professionals. The following three hierarchical blocks of variables were analyzed: health care professional characteristics (distal variables), patient characteristics (intermediate variables), and end-of-life care (proximal variables).

Statistical analysis: All statistical analyses were done using Stata software, version 13 (https://www.stata.com/). To test if the variables were normally distributed, the Kolmogorov–Smirnov test was performed. For continuous variables, data were presented as the median and interquartile range (IQR). Categorical variables were presented as number values, percentage, and 95% confidence interval (95%CI). To determine the predictors of low quality of life and anguish, a Poisson regression (robust estimation and log link function) was used to estimate crude prevalence ratios. The variables with a significance of $p<0.20$ were included in blocks in the hierarchical multivariate analysis. The multivariate hierarchical model estimated adjusted prevalence ratios. A $p<0.05$ was considered statistically significant.

This study was approved by the São Carlos Federal University Research Ethics Committee (CAAE 31896820.1.0000.5504). Informed consent was obtained from all participants.

RESULTS

The number of health care professionals included was 102; 14 of them (13.7%) were males, with a median age of 37 years (IQR 33–42). Among health care professionals, 41 (40.2%) were physicians, 25 (24.5%) were nurses, and 36 (35.3%) were physiotherapists.

Patients' median age was 60 years (IQR 40–73), and 65 (63.7%) of them were males. Patients were taken care in 14 states, allocated in the 5 Brazilian regions. São Paulo state represented 63.8%, followed by Minas Gerais (6.9%), Bahia (5.9%), and Rio de Janeiro (5.9%). Ninety-four (92.1%) patients were taken care of in a hospital, where 52 of them (55.3%) died at a COVID-19 intensive care unit, 20 (21.2%) of them died at a COVID-19 infirmary, 16 (17.0%) of them died at a general infirmary, and 7 (7.4%) of them died at a general intensive care unit.

There was a shared decision regarding the limited life support in 59 (57.9%) patients. The most frequent decision was do-not-resuscitate in 43 of them (72.9%) followed by do-not-admit at the intensive care unit in 11 cases (18.6%). The most frequent reason to limit the life support was the clinical condition in 46 patients (77.9%). Figure 1 shows the other end-of-life care.

Self-perception of anguish was referred by 71 (69.6%) health care professionals. The predictors of anguish were identified using univariate and multivariate Poisson regression analysis as shown in Table 1. Physicians were associated with 37% more anguish (p=0.02) and disagree with end-of-life care was associated with 42% more anguish (p=0.006).

Low quality of life (≤4) was reported by 66 (64.7%) health care professionals. The predictors of low quality of life were identified using univariate and multivariate Poisson regression analysis as shown in Table 2. Low quality of life was more frequently reported in 46% where health care professionals did not have time to talk to patients' relatives (p=0.02) and 30% less frequent where health care professionals agreed that medical care was enough (p=0.01).

DISCUSSION

This study analyzed the psychosocial impact of the COVID-19 pandemic in health care professionals, exploring communication, symptom control, support, and comfort offered to relatives of end-of-life patients.

Self-perception of anguish was referred by 69.6% of health care professionals and was associated with physicians and disagreement with end-of-life care. As anguish is a condition related to negative feelings and suffering[16], we hypothesized that physicians had more anguish probably because of some factors such as the impotence feeling, as many patients died in a short time, regardless of all procedures and the responsibility of certifying death. In a multidisciplinary team, physicians usually assume a team-leader position and must take hard decisions that are extremely stressful. The high prevalence of anguish reflects moral suffering, is concerning, and may reflect harm to the work environment[16,17]. Reinforcing compassion

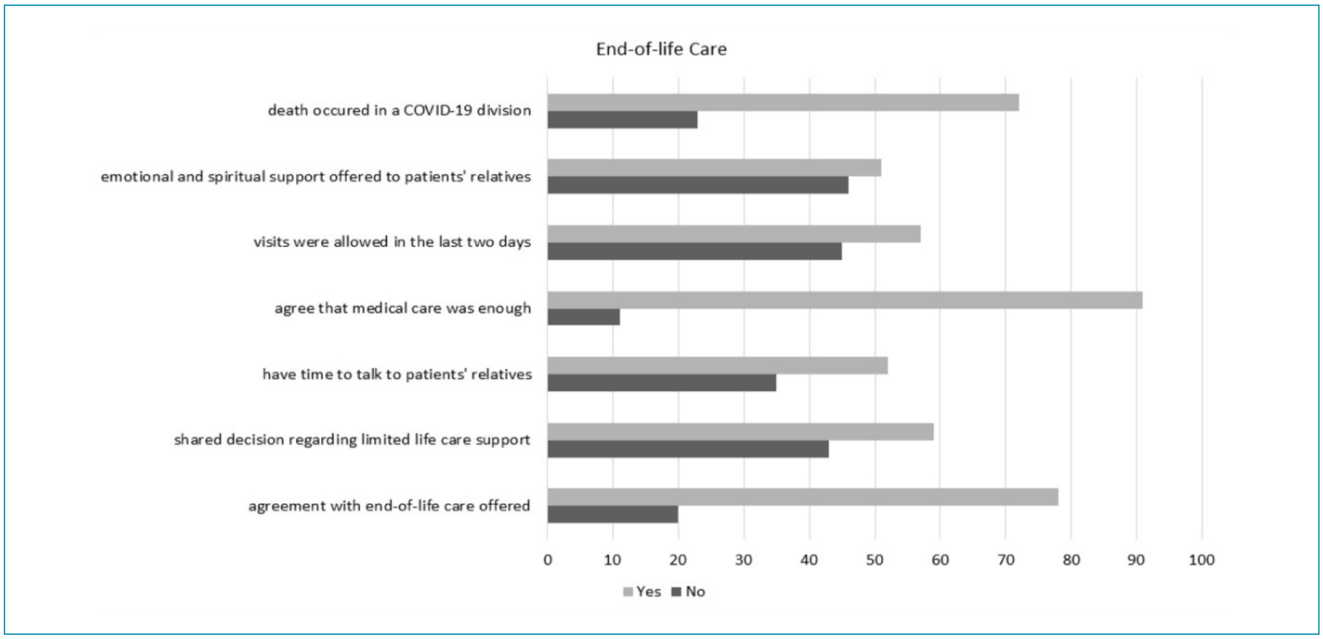

Figure 1. Health professionals and patients' characteristics and end of life care.

Table 1. Univariate and multivariate hierarchical Poisson regression for the predictors of self-perception of anguish in health care professionals.

	Anguish (%)	CPR	p-value*	APR	95%CI	p-value*
Health care professionals						
Age (years)						
>37	70.0	1.01	0,93	Not included		
≤37	69.2	1				
Sex						
Male	50.0	0.68	0.17	Not included		
Female	72.7	1				
Professional category						
Physician	78.0	1.24	0.09	1.37	1.05–1.79	0.02
Others	63.9	1				
Patients						
Age (years)						
>60	72.0	1.06	0.60	Not included		
≤60	67.3	1				
Sex						
Male	70.0	1.01	0.89	Not included		
Female	69.4	1				
SARS-CoV-2 infection						
Confirmed or probable	67.5	0.95	0.76	Not included		
No	70.8	1				
Felt pain all the time or sometimes						
Yes	64.4	0.87	0.32	Not included		
No	73.6	1				
End-of-life care						
Agreement with end-of-life care offered						
No	85.0	1.32	0.02	1.42	1.10–1.83	0.006
Others	64.1	1				
Shared decision regarding limited life care support						
Yes	71.0	1.05	0.68	Not included		
Others	67.0	1				
Have time to talk to patients' relatives						
No	80.0	1.09	0.45	Not included		
Others	73.0	1				
Agree that medical care was enough						
Yes	67.0	0.73	0.01	Not included		
Others	90.0	1				
Visits were allowed in the last 2 days						
Yes	63.1	1	0.10	Not included		
No	77.7	1.23				
Emotional and spiritual support offered to patients' relatives						
No/probably no	73.0	1	0.56	Not included		
Yes	68.0	0.92				
Place where care was offered						
Hospital	69.1	0.92	0.70	Not included		
Others	75.0	1				
Death occurred in a COVID-19 division						
Yes	69.4	0.93	0.55	Not included		
No	73.9	1				

95%CI: 95% confidence interval; CPR: crude prevalence rate for univariate analysis; APR: adjusted prevalence rate for multivariate analysis. *p-value associated with Poisson regression.

Table 2. Univariate and multivariate hierarchical Poisson regression for the predictors of self-perception of quality of life in health care professionals.

	Quality of life≤4(%)	CPR	p-value*	APR	95%CI	p-value*
Health care professionals						
Age (years)						
>37	54.0	0.72	0.03	Adjusting variable		
≤37	75.0	1				
Sex						
Male	50.0	0.74	0.29	Not included		
Female	67.0	1				
Professional category						
Physician	68.2	1.09	0.53	Not included		
Others	62.3	1				
Patients						
Age (years)						
>60	60.0	0.86	0.33	Not included		
≤60	69.2	1				
Sex						
Male	64.6	1.01	0.94	Not included		
Female	63.8	1				
SARS-CoV-2 infection						
Confirmed or probable	67.5	1.35	0.17	Not included		
No	50.0	1				
Felt pain all the time or sometimes						
Yes	66.6	1.05	0.71	Not included		
No	63.1	1				
End-of-life care						
Agreement with end-of-life care offered						
No	70.0	1.13	0.45	Not included		
Others	61.5	1				
Shared decision regarding limited life care support						
Yes	64.4	0.98	0.94	Not included		
Others	65.1	1				
Have time to talk to patients' relatives						
No	80.0	1.54	0.007	1.43	1.04–1.98	0.02
Others	51.9					
Agree that medical care was enough						
Yes	61.5	0.67	0.002	0.70	0.52–0.94	0.01
Others	90.9	1				
Visits were allowed in the last 2 days						
Yes	66.6	1	0.64	Not included		
No	62.2	0.93				
Emotional and spiritual support offered to patients' relatives						
No/probably no	68.6	1.16	0.31	Not included		
Yes	58.6	1				
Place where care was offered						
Hospital	68.0	2.72	0.10	Not included		
Others	25.0	1				
Death occurred in a COVID-19 division						
Yes	69.4	1.06	0.71	Not included		
No	65.2	1				

95%CI: 95% confidence interval; CPR: crude prevalence rate for univariate analysis; APR: adjusted prevalence rate for multivariate analysis. *p-value associated with Poisson regression.

could help health care professionals overcome anguish[18]. The disagreement with end-of-life care may reflect communication difficulties during the COVID-19 pandemic.

Low quality of life was referred by 64.7% of health care professionals and was associated with not having time to talk to patients' relatives. Effective verbal and non-verbal communication are the cornerstones of health care, provide possibilities in decision-making to the patients' relatives, and may reduce stress and disagreements with the health care team and between relatives[19]. In contrast, literature has shown that bereaved relatives who did not receive effective communication during the death and dying process of their relative demonstrate a bad understanding of the clinical aspects of the disease, resulting in wrong decisions, hassles, fear, guilt, and frustration[19]. Low quality of life was less frequent when health care professionals agreed that medical care was enough. This also reflects the importance of an adequate work environment, with the necessary resources, where physical and mental aspects are articulated[16].

In this study, shared decisions regarding limiting life support were frequent, and this was surprising as we considered that the availability of palliative care teams was estimated to be present in less than 5% of all hospitals with less than 50 beds in Brazil[20]. The most frequent decision was do-not-resuscitate. Forte et al. also reported that do-not-resuscitate was the limiting support most frequently reported by physicians who attended at an intensive care unit[21]. The decision to withdraw life support in end-of-life patients requires medical education and the recognition of unnecessary procedures[22]. This issue has been addressed in graduation courses.

Half of the health care professionals referred that visits were allowed and emotional and spiritual support to patients' relatives were offered. These attitudes contribute to prevent relatives' depression and enhance satisfaction with end-of-life care[23].

This study has some limitations. First, it was a cross-sectional study and temporal relations were not assessed. The online survey design may include selection bias. Other studies are needed to confirm our results.

CONCLUSIONS

Based on our study findings, health care professionals' self-perception of anguish and low quality of life was high. Anguish was more frequent in physicians and when the disagreement about end-of-life care occurred. Low quality of life was more frequent when health care professionals did not have time to talk to patients' relatives and was less frequent when health care professionals agreed that medical care was enough. Strategies should be developed by health services to reduce the impact of the pandemic on health care professionals.

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AUTHORS' CONTRIBUTIONS

Ealf: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **COSV:** Data curation, Formal Analysis, Writing – review & editing. **AFJS**: Conceptualization, Writing – original draft. **JNSP:** Conceptualization, Writing – review & editing. **AES:** Conceptualization, Writing – review & editing. **MUM:** Conceptualization, Writing – review & editing.

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Impact of the COVID-19 pandemic on mental health of pregnant women with diabetes mellitus and hypertension

Roberta de Pádua Borges[1]*, Angela de Azevedo Jacob Reichelt[2], Ariane de Brito[3], Gabriela Oliveira Gonçalves Molino[4], Beatriz D. Schaan[1,2]

SUMMARY

OBJECTIVE: Psychological effects of the coronavirus disease 2019 (COVID-19) pandemic on pregnant women with diabetes and hypertension are not yet studied. Besides the pregnancy, these women have additional risk factors for severe acute respiratory syndrome due to COVID-19 and are considered a particularly vulnerable, unique population. We aimed to assess their mental health during this pandemic.

METHODS: This is a cross-sectional study carried out at a Brazilian tertiary hospital. Women with pregnancies complicated by hypertension and/or diabetes were evaluated. The primary outcome was anxiety, and depressive symptoms evaluated with the State-Trait Anxiety Inventory and Patient Health Questionnaire. Perception of changing habits during quarantine was evaluated as a secondary outcome.

RESULTS: Seventy-nine patients were included. The prevalence of State-Trait Anxiety Inventory ≥40 was 79.7% and that of Patient Health Questionnaire ≥10 was 59.2%. Lower social support was correlated with higher scores on both scales. Time spent with electronic devices was perceived as greater by 62% of the women.

CONCLUSIONS: Pregnant women with diabetes and hypertension presented high levels of anxiety and depressive symptoms during the COVID-19 pandemic. Considering that these symptoms can affect both the mother's and offspring's health, it is necessary to implement tools to improve their mental health.

KEYWORDS: COVID-19. Pregnancy. Mental health. Anxiety. Diabetes mellitus. Hypertension.

INTRODUCTION

Anxiety disorders in pregnancy are frequent. Prolonged anxiety during pregnancy has been associated with premature birth, fetal growth restriction, and children's behavioral problems[1], as well as maternal postpartum depression[2].

In December 2019, a case series of respiratory syndromes caused by a new coronavirus, a disease later named COVID-19, was described in China. By May 2021, more than 150 million cases had been confirmed in the world. Since then, Brazil has recorded the second highest number of deaths in the world. To fight the pandemic, measures of hygiene care, social isolation, and use of face masks were established. Social and financial repercussion of these resolutions contributed to the pandemic negative impact on mental health, even to pregnant women. In this specific group, there was also an increase in concerns such as potential exposure to the virus during appointments with health care professionals, especially potential fetus complications in case of infections. The severity of the psychological impact of COVID-19 on pregnant women was shown in an Italian

[1]Universidade Federal do Rio Grande do Sul, Graduate program in Medical Science: Endocrinology – Porto Alegre (RS), Brazil.
[2]Hospital de Clínicas de Porto Alegre, Endocrinology division – Porto Alegre (RS), Brazil.
[3]Universidade Federal do Rio Grande do Sul, Graduate program in Psychology – Porto Alegre (RS), Brazil.
[4]Universidade Federal de Ciências da Saúde de Porto Alegre, School of Medicine – Porto Alegre (RS), Brazil.
*Corresponding author: rpborges@hcpa.edu.br
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study that evaluated 100 patients, in which about two-thirds presented exacerbation of anxiety symptoms[3].

Data suggest that people with hypertension and diabetes are more likely to develop severe clinical presentations of COVID-19[4]. Likewise, physiological changes during pregnancy can make pregnant women more vulnerable to serious infections[5]. Thus, the emotional burden of the current pandemic may be greater in pregnant women with diabetes and hypertension. In addition, treatment of these comorbidities is hampered by the need for social isolation, which can lead to changes in eating habits and an increase in sedentary lifestyle.

Considering that pregnant women with diabetes and hypertension may be particularly vulnerable to the psychological impact caused by the COVID-19 pandemic, and that there are no studies focusing on this specific population. This study aimed to evaluate the impact of adversities caused by the COVID-19 pandemic on mental health of this unique group.

METHODS

This is a cross-sectional study carried out at a public university hospital in Southern Brazil. We included pregnant women with one or more of the following diagnoses: gestational hypertension, chronic hypertension prior to pregnancy, pregestational type 1 or type 2 diabetes, and gestational diabetes, regardless of gestational age. Exclusion criteria were preeclampsia, eclampsia, or ketoacidosis, since these are serious acute complications that could be confounding factors.

Data collection was carried out by phone calls from July to October 2020. Two trained interviewers were responsible for the calls that lasted about 20 min. Anxiety symptoms were assessed by the State-Trait Anxiety Inventory, in its short version STAI-6. This questionnaire consists of two separate subscales, one measuring trait, and the other state anxiety, STAI-T and STAI-S, respectively. Each subscale consists of six items scored on a 4-point Likert scale. The scores obtained vary from 20–80, and an abnormal STAI value was considered with results ≥40[6].

The Patient Health Questionnaire-9 (PHQ-9), which consists of nine questions that assess the presence of symptoms of major depressive disorder, was also applied. The frequency of each symptom in the previous two weeks is assessed on a four-point Likert scale, ranging from 0 (never) to 3 (almost every day), with higher scores indicating greater severity of depressive symptoms (range 0–27). The recommended cutoff point for being at risk for depressive disorder is 10[7].

To evaluate the perceived social support, the Medical Outcomes Study Social Support Survey (MOS-SSS) was used. It assesses five dimensions of social support: positive social interaction, material, affective, emotional, and informational support. The STAI, PHQ-9, and MOS-SSS scales were validated for the Brazilian population and are widely used in pregnant women[6].

Issues related to the changes perceived after the beginning of the confinement period were also addressed: time spent in physical activity, exposure to electronic devices, dietary pattern, and glycemic and/or blood pressure control. Sociodemographic and clinical data were also collected through electronic medical records.

The primary outcomes were the presence of positive screening for anxiety and depression. The secondary outcome was the perception of changing habits. Women with evidence of psychological distress received a brief intervention with weekly telephone follow-up assessments and were referred to specific health services.

The Shapiro-Wilk test was used to assess the variables normality. Data are represented as frequency and percentage for categorical variables, means or medians and standard deviation, and interquartile ranges or minimum and maximum for continuous variables. Kruskal–Wallis, Pearson, and Mann–Whitney U tests were performed. The scales' internal consistencies were analyzed through the Cronbach's alpha coefficient.

Data analysis was performed using the SPSS software (version 21.0, SPSS Inc., Chicago, IL, USA). We used a significance level of $p<0.05$ for all statistical tests. The recommendations of the *STrengthening the Reporting of OBservational studies in Epidemiology* were followed for the development of this manuscript.

RESULTS

Among the 87 eligible patients, three did not answer the contact attempts, and five had no valid phone numbers on the institution's records. Thus, 79 pregnant women were included.

The median age was 32 years (minimum 16 and maximum 46). The median body mass index (BMI) was 31.6 (minimum 18.8 and maximum 48.7). The diagnosis of gestational diabetes was present in 63.3%, previous type 2 diabetes in 17.7%, and type 1 diabetes in 5.1% of the patients. Prepregnancy hypertension was present in 31.6% of patients. Regarding the presence of associated mental disorders, 58.2% had a previous or current psychiatric illness. The other demographic and clinical characteristics are summarized in Table 1.

Data from the PHQ-9 and STAI-S questionnaires are described in Table 2. PHQ-9³10 was present in 59.2% of patients, and STAI-S³40 in 79.7%. Time spent with electronic devices was perceived as greater during the pandemic by 62% of the patients, with a median exposure time of 6 h (minimum 1 h, maximum 18 h). Regarding physical activity, 64.6% of the women reported having reduced its practice and only 3.8%

Table 1. Demographic and clinical characteristics of the population.

	n=79
Age (years)	32 (16–46)
Self-declared color	White: 46 (58.2)
	Black: 18 (22.8)
	Brown: 15 (19)
Religion	Catholic: 32 (40.5)
	Evangelical: 16 (20.3)
	Others: 16 (20.3)
	No religion: 15 (19)
Education level	Illiterate/incomplete elementary school: 6 (7.6)
	Complete elementary school: 11 (13.9)
	Incomplete high school: 16 (20.3)
	Complete high school: 34 (43)
	Incomplete/complete higher education: 12 (15.2)
Unemployment	45 (57)
Body mass index (kg/m^2) n=76	31.6 (18.8–48.7)
Gestational age (weeks)*	27.7 (7.5)
Unintended pregnancy	28 (35.4)
Diabetes mellitus	Yes: 68 (86.1)
	Gestational diabetes: 50 (63.3)
	Type 1 diabetes: 4 (5.1)
	Type 2 diabetes: 14 (17.7)
Insulin use	24 (30.4)
Metformin use	19 (24.1)
Hypertensive syndromes	Yes: 30 (38)
	Gestational hypertension: 5 (6.3)
	Pregestational hypertension: 25 (31.6)
Hypertension and diabetes association	19 (24.1)
Psychiatric disorder	Yes: 46 (58.2)
	Previous: 22 (27.8)
	Current: 24 (30.4)
History of previous abortion	23 (29.1)
Previous coronavirus infection	No: 69 (87.3)
	Suspected: 8 (10.1)
	Confirmed: 2 (2.5)

Data reported as median (minimum and maximum value) or n (%). *Evaluated at the time of the questionnaire's application.

Table 2. Results from the STAI-S and PHQ-9 questionnaires.

Questionnaire	n=79
STAI-S	50 (40–60)
STAI-S ≥40	63 (79.7)
PHQ-9	11 (7–16)
PHQ-9 ≥10	47 (59.5)

STAI-S (State-Trait Anxiety Inventory, state subscale), with higher scores indicating greater severity of anxiety symptoms (range 20–80). PHQ-9 (Patient Health Questionnaire-9), with higher scores indicating greater severity of depressive symptoms (range 0–27). Data reported as median (25th and 75th percentiles) or n (%).

reported having increased it. Eating habits were described as better by 69.6% of the patients, and they attributed the concern with the fetus as a propellant for this greater care. Despite this, 53.2% of pregnant women reported the impression that blood pressure and/or glycemic control got worse during the pandemic (Figure 1).

The score distribution of the STAI-S and the PHQ-9 was similar among women with different comorbidities, age, color, education status, religion, BMI, the number of previous pregnancies, and gestational age, but differed from women with desired compared with those with unintended pregnancies. The median scores of STAI-S and PHQ-9 among women with unintended pregnancies were 58.3 (minimum 23.3 and maximum 80) and 13 (4–27), compared to 46.7 (20–80) and 9 (1–27) among women with desired pregnancies (p=0.036 and p=0.004, respectively). In addition, lower social support was correlated with higher scores on the STAI-S6 scale (Pearson's correlation -0.273, p=0.015) and with higher scores on the PHQ-9 scale (Pearson's correlation -0.519, p<0.001).

The scales' internal consistencies were analyzed through the Cronbach's alpha coefficient. It displayed satisfactory reliability with values of 0.949, 0.779, and 0.775 for the MOS-SSS, PHQ-9, and STAI-S questionnaires, respectively.

DISCUSSION

The prevalence of symptoms of depression and anxiety in women with high-risk pregnancies complicated by diabetes and hypertension was high. These symptoms were even more frequent in women with less social support and in those with unintended pregnancies. These results are aligned with what has been described in the literature[8,9]. A study comparing two cohorts, with a total of 1,754 pregnant women, one before the pandemic and other during social isolation, found that women evaluated during the pandemic had higher rates of depressive symptoms and anxiety[9].

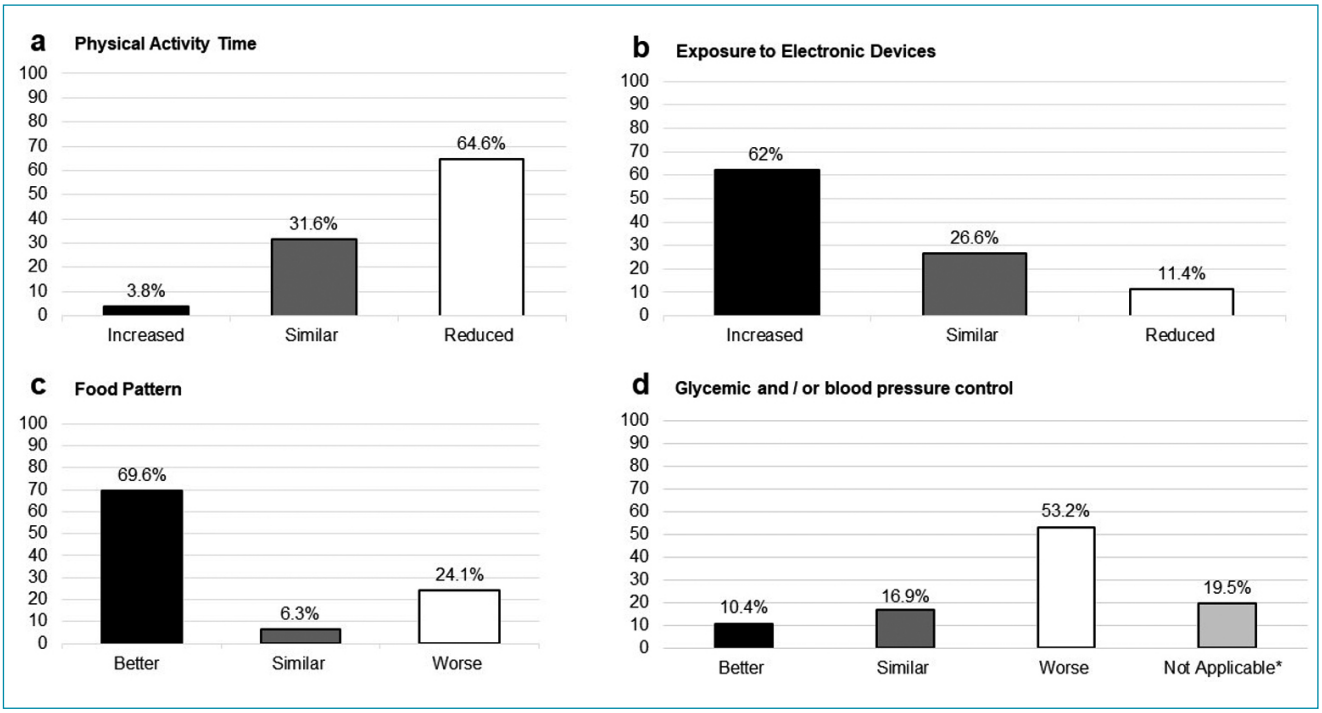

Figure 1. Perceived changes after the COVID-19 quarantine period in relation to the patient's usual routine. Different routine elements were addressed: (A) Changes in the time spent on physical activity; (B) changes in the duration of electronic devices exposure; (C) dietary pattern; and (D) alteration on the glycemic and/or blood pressure control. *Pregnant women with comorbidities diagnosed during pregnancy or who do not control them at home.

During the COVID-19 pandemic, a study by Yassa et al.[10] found a mean STAI-S score of 41.96 (SD 9.15) in women with healthy pregnancies, with 62.6% of them presenting scores ³40. In another study, women with high-risk pregnancy indicators demonstrated high levels of anxiety during the ongoing pandemic, with an average STAI-S of 52.55, close to that found in our sample[11].

Like our results, Sinaci et al.[11] also found higher levels of anxiety during the pandemic in those women with unplanned pregnancies. Furthermore, our finding of less psychological impact in those with higher perceived levels of social support, corroborates findings of several studies, in which having social support can reduce the risk of depression during pregnancy and postpartum[12].

Increasing evidence supports the idea that exercise during pregnancy is beneficial for fetal and maternal health. Among benefits for the fetus are adequacy of birth weight[13], cardiovascular benefits, and possible reduction in the risk of chronic diseases in adulthood[14]. As for the mother, it is suggested a reduction in gestational weight gain[15], decreased risk of developing pre-eclampsia[13], and decreased cesarean section rates, among others[16]. In our study, 64.6% of women reported that they have reduced the practice of physical activity. A study evaluating the lifestyle of Spanish pregnant women during the pandemic indicated, like our findings, a significant decrease in their practice of physical activity, but, in contrast, there were no changes in their dietary pattern[17]. In relation to sedentary behavior, the same study found a median of 8 h of time spent sitting per day, whereas our study showed a median daily screen time of 6 h. Excessive sitting time seems to be harmful, regardless of meeting the recommendations for physical activity[18]. In addition, sedentary maternal behavior during pregnancy seems to negatively affect the outcomes for mother and child[19].

Our study has strengths. To our knowledge, this is the first study that evaluated this specific population in Brazil, a medium income country with chronically deficient financing of its public health system. In addition to the challenges inherent to the health issues of the pandemic, the country went through a serious political crisis, with exchanges of health ministers, misinformation, and leadership vacuum, a process that reduced confidence in science and government and worsened insecurity among Brazilians[20,21].

The questionnaires application was carried out by telephone contact to avoid selection bias. According to data from the Brazilian Institute of Geography and Statistics, in 2018, the percentage of households in which there was no Internet

use exceeded 20%, while the lack of access to a telephone did not exceed 3% in the South region[22]. Data from the World Health Organization suggest that in 2019, the proportion of women using the Internet globally was 48%[23]. Despite this, most studies that assessed mental health during the pandemic used online surveys, so a large part of the population may have not been represented.

The use of questionnaires through telephone and virtual interviews has been widely used and is approved by Ethics Committees as long as privacy is guaranteed. Telephone-administered PHQ-9 has already been validated[24]. Studies that directly compare telephone and face-to-face interviewing tend to conclude that telephone administration produces data that are at least comparable in quality to those attained by the face-to-face method, with the advantage to increase accessibility[25]. Further development and evaluation are needed to support the large-scale use of online and telephone-administered assessment programs and questionaries for mental disorders, especially for moments when social distancing is imperative.

Our study differs from others that evaluated high-risk pregnancies since they also included women with unfavorable obstetric history not related to metabolic disorders, such as threat of premature labor, placenta previa, among others[11]. These complications do not appear to pose a greater risk of serious COVID-19 infection.

The small sample size is a limitation of the study. However, we included the entire population that met the inclusion criteria being assisted in our hospital during the established period, with the allowance of 10% for missing. Other limitations that may limit generalization of findings are the uncontrolled cross-sectional design and having been carried out in a single center. In addition, prior data on anxiety symptoms from each woman before the pandemic were not available. Although the STAI score makes possible to assess anxiety trait, results may not have adequately measured the real effect of the pandemic and social isolation faced by these women.

CONCLUSIONS

Periods of uncertainty, stress, and social isolation can increase the risk of depression and anxiety among vulnerable people. This study contributes by expanding the knowledge of the psychological implications of COVID-19 in pregnant women with comorbidities, such as hypertension and diabetes, known risk factors for severe coronavirus infections. Our results demonstrate high rates of anxiety and depression symptoms in this population. Considering that these symptoms can affect both the mother's and offspring's health, we highlight the importance of supporting their mental health, including the identification of risk factors for psychological distress, early recognition of these symptoms, and their treatment. Future studies are needed to rigorously assess the impact of COVID-19 on this vulnerable population in short and long term.

AUTHORS' CONTRIBUTIONS

RPB: Conceptualization, Project Administration, Writing – Review & Editing. **BDS:** Conceptualization, Project Administration, Writing – Review & Editing. **AAJR:** Project Administration, Writing – Review & Editing. **GOGM:** Project Administration, Writing – Review & Editing.

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Evolution of anthropometric data and quality of life in active bariatric individuals

Jéssica Eloá Poletto[1]*, Daniela Tezoto Rizzo[1], Ana Maria Neder de Almeida[1], Elaine Cristina Cândido[1], Everton Cazzo[1], Élinton Adami Chaim[1]

SUMMARY

Obesity is a disease characterized by the accumulation of abnormal or excessive fat that can damage health. Bariatric surgery, an effective and safe way to treat this disease, requires multidisciplinary monitoring with an educational nature to change lifestyle. Adherence to routine physical activity can be a part of adopting a healthier lifestyle and can assist in the treatment of this disease and its related comorbidities.

OBJECTIVE: Thus, the aim of this study was to analyze the correlation between the evolution of anthropometric variables and the domains of quality of life at different times, including at one year after bariatric surgery in very active and irregularly active individuals.

METHODS: This was a longitudinal, observational, prospective, and analytical study. The collected data included anamnesis, level of physical activity (International Physical Activity Questionnaire Short Form), height, weight, body mass index (BMI), average waist circumference, percentage of fat, and the World Health Organization Quality of Life Assessment Bref.

RESULTS: Seven female individuals were evaluated and divided into two groups: a very active group and an irregularly active group. In the very active individuals, significant results were found in the evolutionary variables: weight ($p<0.001$); body mass index ($p<0.001$); average waist circumference ($p<0.001$); percentage of fat ($p<0.001$); and quality of life general ($p=0.001$). In the irregularly active individuals, a significant result was found only in one evolutionary variable: body mass index ($p<0.001$).

CONCLUSION: Thus, it is evident that the improvement and maintenance of good health is more effective in bariatric individuals who maintain a routine with regular physical activity.

KEYWORDS: Anthropometry. Motor activity. Quality of life. Bariatric surgery.

INTRODUCTION

Obesity is a disease characterized by the accumulation of abnormal or excessive fat that affects health[1]. Its etiology may involve several factors, such as genetic, endocrine, behavioral, social, economic, psychological, and environmental imbalances[2].

In 2014, there were 1.9 billion overweight or obese adults worldwide. Most of the global populations live in countries where the number of deaths from obesity exceeds the number of deaths caused by low weight[3]. According to the Brazilian Association for the Study of Obesity and Metabolic Syndrome[4], about 82 million people were overweight or obese in Brazil in 2014.

The World Health Organization estimates that obesity will have involved 700 million adults and 75 million children by 2025[3].

Along with obesity, the rates of cardiovascular diseases, diabetes, musculoskeletal disorders, infertility, and endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon neoplasms have also increased[2,5].

Obesity and its related diseases are considered preventable and treatable[2]. Bariatric surgery is an effective and safe

[1]Universidade Estadual de Campinas, Hospital de Clínicas, Department Bariatric Surgery Outpatient Clinic – Campinas (SP), Brazil.
*Corresponding author: jeloap@hotmail.com
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way to treat severe and refractory forms of this disease and requires multidisciplinary follow-up with a focus on educational lifestyle changes[6].

In the long term, bariatric surgery can provide benefits such as significant and lasting body mass index (BMI) reduction[7], decreased glucose, total cholesterol (LDL-c and VLDL-c), and triglyceride indices, increased HDL-c[8], decreased prevalence of obstructive sleep apnea syndrome, dyslipidemia, and systemic arterial hypertension, increased adherence to physical activity, and improved quality-of-life (QoL) domains[9-11].

Adherence to physical activities can be a part of a healthier lifestyle and help in the treatment of this disease and its related comorbidities[12,13]. Physical activity can be defined as any movement performed by the contraction of the musculoskeletal system increasing energy expenditure, when compared to rest[14].

These activities can intensify energy expenditure, improve body composition, increase the ability to mobilize/oxidize fat, stimulate a thermogenic response, increase insulin sensitivity, decrease blood pressure, improve physical conditioning, improve psychosocial factors and self-esteem, and reduce anxiety[12], in addition to improving the recovery of patients undergoing bariatric surgery and reducing mortality and existing chronic diseases[2].

The relationship between bariatric patients and physical activity over a year after the surgical procedure is not clear in the specific literature. Thus, the objective of this study was to analyze the correlation between the progression of anthropometric variables and QoL domains at different times up to 1 year after bariatric surgery in very active and irregularly active patients treated at the bariatric surgery outpatient clinic, Hospital de Clínicas, State University of Campinas (UNICAMP).

METHODS

Study design and ethical aspects

This was a prospective and analytical, longitudinal, and observational study approved by the Research Ethics Committee of our institution, under opinion No. 2,038,341. All volunteers signed the Informed Consent Form (ICF).

Data collection

The data collection was performed at the bariatric surgery outpatient clinic, Hospital de Clínicas, UNICAMP, with grade II and III obese patients (at first participation) at four different times (i.e., first participation in the group, T0; after 10% total weight loss, T1; immediate postsurgery, T2; and 1 year after surgery, T3) in a preoperative multidisciplinary bariatric surgery group, individually.

Inclusion criteria

- Grades II and III of obesity at T0;
- Age 18–59 years;
- Female sex;
- Consent to participate in all four evaluations.

Exclusion criteria

- Physical and/or intellectual disability and/or functional limitation;
- Vulnerable groups.

Outcome measurements

Physical activity

The physical activity level of participants was assessed using the International Physical Activity Questionnaire Short Form (IPAQ SF)[15], which classifies the person as VERY ACTIVE, ACTIVE, IRREGULARLY ACTIVE A, IRREGULARLY ACTIVE B, and SEDENTARY. The classification was established by the score achieved, ranging from 0–4, with 0=sedentary and 4=very active.

Anthropometric measurements

The measurements collected were height, weight, BMI, and mean waist circumference (WC).

Fat percentage

The "Prediction Equation for Obese Individuals – Women" was used[16] at times 0, 1, and 2 to characterize the participants' fat percentage (%F). This equation uses height (in cm), weight (in kg), and WC (in cm): WC=[(W1+W2)/2], where W1 is the waist circumference in centimeters measured at the midpoint between the sternum and the umbilicus (front) and the midpoint between the last rib and the iliac crest (lateral) and W2 is the waist circumference in centimeters measured at the level of the umbilical scar.

The "Prediction Equations for Normal Weight People" were used[17] at time 3 to characterize the fat percentage (%F) of participants, using WC (in cm), hip circumference (in cm), height (in cm), and age (in years) measurements.

Quality of life

The QoL was assessed by the World Health Organization Quality of Life Assessment Bref (WHOQOL BREF) questionnaire with two general questions and 24 facets divided into four domains (i.e., Physical, Psychological, Social Relations, and Environment)[18] and determined whether the QoL was very poor=1, poor=2, fair=3, good=4, or very good=5.

Statistical analysis

The data obtained were transcribed into the BioEstat software version 5.3, and a descriptive analysis of the variables was performed. The Shapiro–Wilk test was used to verify the normality of the data. The ANOVA test (one criterion) was used to analyze the progression of the same variables at different times. The significance level was 0.1% ($p \leq 0.001$).

RESULTS

Seven women were evaluated, after being divided into two groups: a very active group and an irregularly active group. Four patients were classified as very active (because they achieved a score of 4 on the IPAQ), and three were classified as irregularly active (because they had a mean score between 1 and 2 on the IPAQ).

Table 1 presents a descriptive analysis of the data, with the mean and standard deviation of each variable.

Table 2 shows the p significance of all variables analyzed at the four times.

At T0, all patients weighed between 100 kg and 130 kg, with a median of 110 kg. The median was slightly above 100 kg at T1 and approximately 90 kg at T2. Notably, 1 year after the surgical procedure, the patients weighed between 60 kg and 70 kg, with a median in the range of 65 kg. Therefore, weight reduction between T0 and T3 was strongly significant, with $p<0.001$.

As for BMI, at T0, the values were between 41 kg/m^2 and 46 kg/m^2, and the median was close to 44 kg/m^2. The median was 40 kg/m^2 at T1 and approximately 35 kg/m^2 at T2. Of note, 1 year after the surgical procedure, the patients had BMI values below 30 kg/m^2, with a median in the range of 25 kg/m^2, which is considered normal. Therefore, BMI reduction between T0 and T3 was also strongly significant, with $p<0.001$.

The WC measurements at T0 were between 120 cm and 130 cm, as well as the median. At T1 and T2, the median was close to 110 cm and 100 cm, respectively. At 1 year after bariatric surgery, the patients had a WC between 80 cm and 90 cm, with a median in the range of 85 cm. Therefore, this variable also showed a strongly significant reduction between T0 and T3, with $p<0.001$.

The medians of %F were approximately 55, 50, 45, and 35% at T0, T1, T2, and T3, respectively. These results also presented a $p<0.001$, with a significantly decreased percentage of fat.

The general QoL (QoLG) score presented a highly significant result ($p=0.001$). At T0, QoLG was between 2 and approximately >3, with a median below 3; at T1, it was between almost 3 and approximately 3.5; at T2, it was between 4 and 5; and at T3, it was between 4.5 and 5, with a median close to 4.7 and 4.8.

Table 3 shows the p significance of all variables analyzed at the four times.

The only highly significant result in the irregularly active patients was the BMI ($p<0.001$). At T0, the BMI was between 45 kg/m^2 and 50 kg/m^2, with a median close to 50 kg/m^2. At T1, the BMI was between 40 kg/m^2 and 45 kg/m^2; at T2, it was between 38 kg/m^2 and 40 kg/m^2; and at T3, the BMI reduced to between 26 kg/m^2 and 30 kg/m^2, with a median close to 29 kg/m^2.

Table 1. Descriptive analysis of the sample of seven patients evaluated.

	T0	T1	T2	T3
Weight (kg)	121.4 (±16.1)	110.2 (±14.3)	97.3 (±11.7)	73.4 (±9.5)
BMI (kg/m^2)	45.4 (±2.7)	41.3 (±2.3)	36.4 (±2.1)	21.5 (±2.5)
WC (cm)	121.6 (±6.6)	116.6 (±9.6)	105.5 (±9.2)	85.3 (±7.4)
%F	53.1 (±1.9)	50.9 (±2)	47.9 (±1.7)	36.3 (±4.7)
QoLG	2.6 (±0.5)	3.3 (±0.6)	4.2 (±0.6)	4.8 (±0.3)
Physical QoL	3 (±0.6)	3.5 (±0.4)	3.3 (±0.5)	4.1 (±0.3)
Psychological QoL	3.2 (±0.5)	3.7 (±0.6)	3.8 (±0.3)	4.1 (±0.3)
Social relationships QoL	3.6 (±0.8)	4.1 (±0.8)	4 (±0.4)	4.3 (±0.7)
Environment QoL	3.3 (±0.6)	3.7 (±0.4)	3.7 (±0.5)	3.7 (±0.5)

WC: waist circumference; %F: percentage of fat; QoL: quality of life.

Table 2. The p-values depicting the significance of the progression analysis in very active individuals.

Weight	BMI	WC	%F	QoLG	QoLPh	QoLPs	QoLSR	QoLE
<0.001	<0.001	<0.001	<0.001	0.001	0.028	0.068	0.283	0.857

WC: mean waist circumference; %F: percentage of fat; QoLG: general quality of life; QoLPh: quality of life physical domain; QoLPs: quality of life psychological domain; QoLSR: quality of life social relationships; QoLE: quality of life environmental.

Table 3. The p-values depicting the significance of the progression analysis in irregularly active individuals.

Weight	BMI	WC	%F	QoLG	QoLPh	QoLPs	QoLSR	QoLE
0.014	<0.001	0.014	0.003	0.003	0.068	0.125	0.579	0.012

WC: waist circumference; %F: percentage of fat; QoLG: general quality of life; QoLPh: quality of life physical domain; QoLPs: quality of life psychological domain; QoLSR: quality of life social relationships; QoLE: quality of life environmental.

DISCUSSION

Bariatric surgery indicates a permanent change in the life of patients undergoing this procedure. Continuous professional follow-up and permanent changes to healthier lifestyle habits are needed[19].

Failure to follow-up on treatment after surgery can lead to numerous problems[20-22]. However, routine physical activity in association with postsurgical treatment may lead to more satisfactory long-term results than expected[12,23,24].

The results found in this study corroborate this statement, as strongly significant reductions were found in all anthropometric measures and in the QoLG in the group of very active patients[7,10,11,13,23].

These results may also be related to a lower rate of postsurgical complications and weight relapse and to a good maintenance of the respiratory system[20,21].

Physical activity can improve physical and psychosocial factors[11] as well as muscle strength and functionality in patients undergoing the Roux-en-Y gastric bypass[24], strengthening the results found in this study.

Severe malnutrition and infections can also be minimized with the combination of physical activity and a regular and balanced diet for bariatric patients, with indications and specialized professional monitoring[22].

The patients classified as irregularly active showed a significantly reduced BMI.

Despite the significant BMI reduction in the irregularly active group, these values were lower than those found in the very active group.

The lack of more significant results is possibly due to the irregular physical activity and a minimally active routine, demonstrating that the irregular physical activity can be harmful after bariatric surgery[13,20-23].

Despite the great improvement in the scores of the QoL domains assessed by the WHOQOL BREF at the four points of evaluation (Table 1), the statistical results did not show strong significance in any QoL domain (Tables 2 and 3). However, the patients report evident improvements in QoL domains 1 year after bariatric surgery[9,20,21].

CONCLUSION

This study evidenced that the long-term treatment of obesity with surgical intervention combined with routine physical activity remarkably improved the anthropometric variables and QoL of the patients undergoing this treatment. It is worth emphasizing that further studies on this subject with a larger sample are needed.

AUTHORS' CONTRIBUTIONS

JEP: Conceptualization, Formal Analysis, Data Curation, Writing – original draft, Writing – review & editing. **DTR:** Conceptualization, Data curation. Formal Analysis. **AMNA:** Data Curation. **ECC:** Data Curation. **EC:** Writing – review & editing. **ÉAC:** Writing – review & editing.

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The efficiency of a mixed exercise program on quality of life and fatigue levels in patients with breast cancer

Elif Köse[1]*, Menşure Aydin[2], Osman Köse[3], Maksut Görkem Aksu[4], Gülşah Sekban[5]

SUMMARY

OBJECTIVE: Exercise is a nonpharmacological supportive therapy which has been specifically identified to reduce postoperative complications or adverse events of cancer or treatments. Although there are few studies combining resistance and aerobic exercise in cancer survivors, exercise programs are very rare in different places in the literature. This study aims to investigate the effects of mixed-type exercise in different venues on weight, body mass index, fatigue, and quality of life in cancer survivors.

METHODS: This is a descriptive, intervention study. Participants were included in the study, and the exercise process was between January and November 2019. The exercise group consisted of 32 patients who had just completed their breast cancer treatment and did not have distant metastases, and they applied a mixed exercise program including resistance at home and aerobic exercise in the fitness center for 12 weeks. The patients with breast cancer in the control group (30 patients) did not receive any exercise program.

RESULTS: Subjective feelings of fatigue and decrease in concentration, motivation, and physical activity significantly decreased after exercise ($p<0.001$, $p<0.001$, $p=0.006$, $p=0.008$, and $p<0.001$, respectively) in the study group. The results also showed that physical health, general health status, and emotional and social health status significantly increased with the exercise program ($p<0.001$, $p<0.001$, $p=0.004$, and $p=0.003$, respectively).

CONCLUSION: Our results show that a mixed (fitness center and home) 12-week exercise program provides an improvement in general health and reduces the side effects of the treatments and fatigue in patients with breast cancer. For a good prognostic process after medical treatment, exercise can be recommended in every accessible area.

KEYWORDS: Quality of life. Fatigue. Muscle strength. Breast cancer. Exercise.

INTRODUCTION

According to the 2020 global cancer burden study prepared by the International Agency for Research on Cancer, there were 19.3 million new cancer cases, and approximately 10.0 million deaths worldwide were due to cancer. The incidence of breast cancer in women exceeded the most frequently diagnosed lung cancer, with a prevalence of 2.3 million (11.7%) newly diagnosed breast cancer appears at the top, followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers[1].

Fatigue experienced by patients with cancer can be caused by cancer or its related treatment processes[2]. This intense fatigue

[1]Sakarya University, Faculty of Medicine, Department of Public Health – Sakarya, Turkey.
[2]Halic University, Department of Physical Education and Sports Education – Istanbul, Turkey.
[3]Sakarya University, Faculty of Medicine, Gynecological Oncology clinic – Sakarya, Turkey.
[4]Kocaeli University, Faculty of Medicine, Department of Radiation Oncology – Kocaeli, Turkey.
[5]Kocaeli University, Department of Physical Education and Sports Education – Kocaeli, Turkey.
*Corresponding author: elifkose@sakarya.edu.tr
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causes patients with cancer to have difficulty in performing simple daily life activities and to decrease their ability to participate in regular exercise programs, thus causing deterioration in their general health, social interaction, and health-related quality of life (QoL)[3].

Fatigue during the cancer treatment process is defined as a clinical problem that is not related to exercise. It does not pass with rest and might even get worse[4].

Maintenance of metabolic hemostasis of the organism is possible by keeping ATP levels constant in both skeletal and cardiac muscles by continuous synthesis and degradation through anaerobic and aerobic metabolisms. With exercise, not only skeletal muscle but also all other organs are modulated. It has therapeutic effects on conditions such as autoimmune and neurodegenerative diseases, and cancer with multiple molecular events and adaptations, as well as increasing the power of oxygen use with exercise, increased attenuation corrected perfusion, changes in muscles, and functional capacity and performance[5,6].

It leads to an increase in the QoL and improvement of health[2].

However, in recent studies, exercise has been recommended as a part of an applicable, standard care to reduce cancer-related fatigue, improving physical and psychological problems, and increasing QoL[7]. Exercise is a nonpharmacological supportive therapy which has been specifically described to reduce postoperative complications or adverse effects of treatments and cancer[8].

Aerobic and resistance exercises immediately after treatment improve muscle strength, body composition, aerobic capacity, and QoL and reduce fatigue[9]. Recent scientific studies recommend exercise programs that include both resistance and aerobic exercises for patients with breast cancer[10].

This study aims to investigate the effects of a 12-week mixed exercise program, including resistance at home and aerobic exercise in the fitness center, on weight, body mass index (BMI), fatigue, and QoL in patients who had previously been treated for breast cancer.

METHODS

Subjects

Sixty-two women are included with convenience sampling voluntarily. The power of the study was found to be 0.87 in the post hoc power analysis. Participants were included in the study, and the exercise process was between January and November 2019. The study group (32/62 women) had completed breast cancer treatments (e.g., surgery, chemotherapy, and radiotherapy) without any other organ metastasis and had started routine controls (age, 52.37±5.38; height [m], 1.59±0.08; weight [kg], 63.93±5.36; BMI, 29.44±10.46). The control group consisted of remaining 30 women who did not participate in the exercise program (age, 52.6±6.15; height, 1.58±0.07; weight, 64.03±5.29; BMI, 28.85±12.12).

Inclusion criteria for the study were volunteer patients over 18 years of age, literate, not doing regular exercise in the past three years, never developing metastases, and having completed routine treatment.

Exclusion criteria were those who developed metastases and those who exercised regularly were not included in the study.

In the process of inclusion in the study group, care was taken that the breast cancer treatment process was completed and that there was no metastasis. There may be differences in the QoL during different treatment processes in individuals, but the completion of the treatment process was considered the main starting point of the study.

Two exercise programs were applied.

Aerobic exercises

Aerobic exercises were performed three days a week for 50 min under the supervision of a sports specialist in a fitness center with permission for the training program. One-on-one interviews were conducted to motivate patients. The aerobic exercise program included 10 min of warmup, 30 min of walking and cycling, and 10 min of cool-down exercises and the program was performed three days/week.

Resistance exercises

In accordance with the movements in the "exercise for oncology patients" booklet given to each patient by the researcher, the patients were asked to perform exercise at home for 1 h every day with an exercise mat, Pilates ball, and elastic band. Notably, 10 min of warmup (e.g., neck, trunk, and leg movements); 40 min of elastic band, ball, hip, and stretching movements; and 10 min of cooling activities were performed in the resistance exercises. The directions in the booklet were taught by a sports expert, who is a Pilates instructor, having the participants in the program perform them. While doing resistance exercises, the participants were warned to perform the activities that they can do comfortably among the movements in the booklet and to stop the movement if they feel pain.

The control group consists of individuals whose breast cancer treatments (e.g., surgery, chemotherapy, radiotherapy) have been completed and whose routine controls have begun but who did not perform any exercise. The control group was generally recommended to exercise within the scope of health promotion, but they were not followed up during the research

process. After the research, facilities and necessary sports materials were provided for the sports center for the control group.

Before starting the study, the required permissions were obtained from the "XXX University Faculty of Medicine Ethics Committee." Information about the study was given to participants, and consent forms were obtained for voluntary participation in the program. An expert oncologist determined the selection of the patients and their suitability for exercise. A WhatsApp group was created for communication, motivation, and follow-up purposes with the study group, and their daily programs were monitored.

Data collection materials

EORTC-QLQ-C30 includes 30 questions and three subtitles: general well-being, functional difficulties, and symptom control. The higher the score, the better the QoL in the general health status and function scales. In the symptom scales, the higher the score, the worse the QoL. Functional scales includes physical, role, cognitive, emotional, and social functions. On the symptom scales, weakness, pain, and nausea/vomiting are evaluated. In addition, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties are measured with one question each[11]. Content validity and reliability study of the scale was conducted in our country, Cronbach's alpha coefficient was α=0.9014[12].

CIS (Checklist Individual Strength or CIS) Questionnaire was used to measure the general fatigue level of individuals. It was developed by Vercoulen et al. and adapted to Turkish by Ergin and is the most widely used survey worldwide to evaluate chronic fatigue[13,14].

As a result of the reliability analyses of the CIS-T questionnaire, the Cronbach's alpha coefficient was α=0.87. According to this scale, fatigue is evaluated from four aspects: subjection perception of fatigue, decrease in concentration, decrease in motivation, and decrease in physical activity. The questionnaire consists of 20 statements that measure the exhaustion of the last two weeks, and a seven-point scale is used for the answers.

Data collection method

It was obtained through face-to-face interviews with people who met the appropriate criteria, who wanted to be included in the study, for about a year. Participation in the exercise group was voluntary. Data were collected in the same way for the second time with the same people 12 weeks after the first interview.

Statistical analysis

Data analysis was performed using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of CIS and EORTC QLQ-30 scores were normal or not normal were determined visually (by histograms and probability plots) and by analytical methods (Shapiro–Wilk tests). Descriptive analyses were presented using medians and first and third percentiles for the non-normally distributed variables. Categorical variables are specified as numbers and percentages. Mann–Whitney *U* test was used to analyze the data. Dependent variables were presented using the Wilcoxon test. The significance level for all of the statistical tests was set at $p<0.05$.

RESULTS

In this study, after 12 weeks of aerobic exercise and home-based resistance exercises, the weight, which was 63.93±5.36, became 62.37±5.60, and the BMI, which was 29.44±10.46, reduced to 28.67±10.29. In the control group, the weight within the same period changed over time from 64.03±5.29–66.23±6.26; BMI changed from 28.85±12.12–29.26±9.41.

The subjective perception of fatigue and decline in concentration, motivation, and physical activity decreased statistically significantly after exercise ($p<0.001$, $p=0.001$, $p<0.001$, and $p<0.001$, respectively, Table 1). The decrease in the scores of the scale subdimensions in the study group showed a more significant decrease than the control group. When the difference between the pre–post exercise scores in the study group and pre-post scores of the control group were compared, it was found that, except for the decrease in concentration, the difference in the subjective perception of fatigue and decline in concentration, motivation, and physical activity was statistically and significantly higher in the study group ($p<0.001$, $p=0.227$, $p=0.042$, $p=0.035$, and $p=0.002$, respectively, Table 1).

When the postexercise values of the study group and the control group were compared, it was found that the scores of the study group for the subjective fatigue and decrease in concentration, motivation, and physical activity were statistically significantly lower than the control group scores ($p<0.001$, $p<0.001$, $p=0.006$, and $p=0.008$, respectively, Table 2).

An improvement in general health status with exercise; a statistically significant increase in the physical, role, emotional, and social dimensions in the functional health status subdimension ($p<0.001$, $p=0.013$, $p<0.001$, and $p<0.001$, respectively); and a statistically significant decrease in fatigue, pain, insomnia, and financial support ($p<0.001$, $p<9.991$, $p=0.014$, and $p=0.004$, respectively, Table 3) were found.

In Table 3, comparing the study group and the control group, it was found that general health status and physical, role, emotional, and social functions were higher and statistically

Table 1. Relationship of exercise and fatigue level in the intervention and control groups.

	Intervention group Median (Q1–Q3)			Control group Median (Q1–Q3)			Difference of scale scores*
	Pre-exercise	Postexercise	p-value	First score	Second score	p-value	p-value
Subjective fatigue	34.50 (28.00–47.75)	14.00 (8.25–15.50)	<0.001	38.50 (35.00–42.00)	32.0 (30.00–34.00)	<0.001	<0.001
Concentration	20.00 (13.25–25.00)	10.50 (6.00–20.00)	0.001	21.50 (19.00–24.00)	19.00 (17.75–21.00)	0.002	0.227
Motivation	14.00 (9.50–18.00)	5.50 (4.00–11.00)	<0.001	13.50 (11.00–17.00)	10.00 (8.00–12.00)	0.001	0.042
Physical activity	12.50 (8.00–16.75)	3.50 (3.00–5.00)	<0.001	13.00 (11.00–15.00)	9.00 (8.00–11.00)	<0.001	0.035
Total	86.00 (58.75–103.50)	38.00 (26.00–59.75)	<0.001	86.50 (78.00–93.50)	69.50 (64.75–75.50)	<0.001	0.002

*Comparison of first and second measurement differences between control and study groups.

Table 2. Comparison of group measurements and control group CIS scores after exercise.

	The exercise group Median (Q1–Q3)	The control group Median (Q1–Q3)	p-value
Subjective fatigue	14.00 (8.25–15.50)	32.0 (30.00–34.00)	<0.001*
Concentration	10.50 (6.00–20.00)	19.00 (17.75–21.00)	<0.001*
Motivation	5.50 (4.00–11.00)	10.00 (8.00–12.00)	0.006*
Physical activity	3.50 (3.00–5.00)	9.00 (8.00–11.00)	0.008*
Total	38.00 (26.00–59.75)	69.50 (64.75–75.50)	<0.001*

*Mann-Whitney *U* test; CIS: checklist individual strength.

significant (p<0.001, p<0.001, p=0.028, p=0.004, and p=0.003, respectively, Table 3).

DISCUSSION

In this study, in which the effects of aerobic and home-based resistance exercises on BMI, fatigue, and QoL were examined in patients with breast cancer whose treatment was completed, it was found that training had positive effects. While BMI decreased in the exercising group in the study, Wilson et al.[15] showed that exercise reduced the BMI, body weight, and fat ratio of women with breast cancer. Statistically significant decreases were observed in BMI over time in studies in which exercise program was applied for 12 and 21 weeks[3,15].

A controlled, medium- to high-intensity, combined resistance, and aerobic exercise program is the most effective program for patients with breast cancer undergoing adjuvant chemotherapy. In a study investigating the impact of a personalized exercise intervention on body composition in patients with breast cancer undergoing treatment, significant differences were observed between exercising and not exercising groups[3]. In a study conducted on 54 people diagnosed with breast cancer, the EORTC scale applied three times a week after nine months of exercise showed a statistically significant positive change in all variables of general and functional health status. There was also an improvement in pain and fatigue in the exercise group compared with the control group[16].

In a study where home-based and aerobic exercise groups were compared with the nonexercising group, muscle strength and fatigue achieved better results in the exercising group. Kessels et al.[17] showed that aerobic exercises are more effective than combined aerobic and resistance exercises in cancer-related fatigue. In a study where training was applied to women who had received breast cancer treatment, it was found that fatigue and depressive symptoms decreased[18].

A 6-week home-based mixed aerobic and resistance exercise program increased physical activity level in colorectal cancer survivors[19]. In the study, which included 40 people

Table 3. Relationship between exercise and quality of life in the intervention group.

European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire -30	Before exercise	After exercise	p-value*	Control group 2 score	Difference of scale scores[a]
	Median (Q1–Q3)	Median (Q1–Q3)		Median (Q1–Q3)	p-value**
Global health status	50.00 (25.00–58.33)	83.33 (83.33–91.67)	<0.001	54.17 (50.00–66.67)	<0.001
Fonksiyonel					
Physical	60.00 (46.67–80.00)	86.67 (80.00–93.33)	<0.001	73.33 (66.67–80.00)	<0.001
Role	75.00 (37.50–100.00)	83.33 (66.67–100.00)	0.013	66.67 (66.67–83.33)	0.028
Cognitive	83.33 (66.67–100.00)	83.33 (66.67–100.00)	0.740	75.00 (66.67–87.50)	0.412
Emotional	75.00 (41.67–89.58)	100.00 (54.17–100.00)	<0.001	75.00 (62.50–83.33)	0.004
Social	66.67 (33.33–83.33)	100.00 (83.33–100.00)	<0.001	83.33 (66.67–100.00)	0.003
Symptoms					
Fatigue	55.56 36.11–77.78	33.33 22.22–55.56	<0.001	33.33 33.33–47.22	0.177
Nausea	16.67 0–29.17	0 0–16.67	0.100	16.67 0–33.33	0.018
Pain	50.00 16.67–83.33	33.33 16.67–50.00	<0.001	33.33 16.67–50.00	0.453
Dyspnea	0 0–33.33	0 0–33.33	0.485	33.33 0–33.33	0.299
Insomnia	33.33 8.33–66.67	33.33 0–66.67	0.014	33.33 0–41.67	0.642
Appetite loss	0 0–33.33	0 0–33.33	0.281	33.33 0–33.33	0.033
Constipation	0 0–33.33	0 0–25.00	0.135	16.67 0–33.33	0.038
Diarrhea	0 0–33.33	0 0	0.166	0 0–33.33	0.055
Financial impact	33.33 0–66.67	0 0–33.33	0.004	33.33 0–33.33	0.123

*Wilcoxon test; Q: quartile; **Mann–Whitney *U* test. [a]Comparison of measurements of the study group after exercise and European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire scale scores of the control group.

who exercised at home and in the fitness room for 10 weeks after cancer treatment, there was an improvement in physical function and body composition[20]. It is stated in the literature that cancer survivors mostly prefer physical exercise programs at home. The flexibility of the schedule at home in terms of time planning is beneficial for exercise and for individuals to organize their own work[21]. The fact that there were exercises in the fitness room in addition to home exercise in the study eliminated the possible limitations of only home exercises. While going to the fitness center provided motivation with one-to-one interaction, it contributed to supervised exercise and allowed social interaction[22].

CONCLUSIONS

It has been determined that for the women who have completed breast cancer treatment, the 12-week planned exercise program causes a decrease in BMI, an improvement in QoL, a reduction in decreased motivation, lack of concentration and fatigue, an increase in QoL, and a decrease in symptoms of insomnia and pain that may occur with the treatment.

Overall, these results hold promise for the benefit of mixed exercise to improve QoL and physical functioning in breast cancer survivors.

In interventions for cancer survivors, it is recommended to develop a standard exercise program to be applied at home and in different places, in terms of causing easy adaptation and increasing the QoL of the patients.

AUTHORS' CONTRIBUTION

EK: Conceptualization, Data curation, Formal analysis, Writing – original draft. **MA:** Conceptualization, Data Curation, Project administration, Supervision, Writing – review & editing, Writing – original draft. **OK:** Resources, Formal analysis. **GS:** Resources, Formal analysis. **MGA:** Project administration, Supervision, Writing – review & editing.

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Evaluation of factors affecting the frequency and clinical course of COVID-19 in patients using anti-TNF-alpha agents

Seyma Baslılar[1]*, Ozlem Pehlivan[2]

SUMMARY

OBJECTIVES: Patients being treated with anti-tumor necrosis factor-alpha (anti-TNF-alpha) agents were reported to have better prognosis related to COVID-19. We evaluated the factors affecting the frequency, clinical course, and outcome of COVID-19 in patients treated with anti-TNF-alpha agents.

METHODS: Patients with rheumatoid diseases and chronic inflammatory bowel diseases treated with anti-TNF-alpha agents were evaluated retrospectively. The laboratory data in routine visits, frequency of COVID-19, pneumonia, hospitalization and/or intensive care unit (ICU) follow-up and, mortality were recorded. The factors related to COVID-19 frequency and clinical outcome were evaluated.

RESULTS: A total of 324 patients (177 males [54.6%] and 147 females [45.4%], mean age: 45.3±12.16 years) was included in the study. In all, 44 (13.6%) patients had COVID-19; of these, 11 (25%) developed pneumonia, 7 (15.9%) were hospitalized, and 1 (2.3%) was followed up in ICU. There was no mortality. The patients with COVID-19 pneumonia were older (mean age: 52±11 years *versus* 41±12 years, p=0.01), had hypertension and coronary artery disease more frequently (5 cases [55.6%] *versus* 4 cases [44.4], p=0.02 and 2 cases [100%] *versus* 0 cases [0%], p=0.014, respectively), and lower eosinophil % (1.35±1.79% *versus* 2.3±1.45%, p=0.016). The diabetes mellitus was more frequent (66.7 *versus* 33.3%, p=0.013), and mean eosinophil % was lower among inpatients compared with outpatients (1.29±2.22% *versus* 2.19±1.37%, p=0.02).

CONCLUSIONS: We concluded that the patients treated with anti-TNF-alpha agents having COVID-19 might have mild clinical course and better prognosis.

KEYWORDS: Tumor necrosis factor-alpha. COVID-19. Pneumonia. Mortality. Eosinophils.

INTRODUCTION

It has been reported that patients being treated with anti–tumor necrosis factor alpha (anti-TNF–alpha) agents for rheumatoid diseases (RDs) had a lower risk of hospitalization related to coronavirus disease 2019 (COVID-19) and a better prognosis compared with those treated with other anti-rheumatoid agents especially corticosteroids (CS)[1-5]. But the factors affecting the clinical course and outcome in these specific groups of patients were not examined in detail. In this retrospective observational study, we evaluated patients treated with anti-TNF-alpha agents for RD and chronic inflammatory bowel disease (CIBD) to assess the frequency of COVID-19 and the factors affecting the clinical course and outcome.

METHODS

Adult patients with RD (rheumatoid arthritis [RA], ankylosing spondylitis [AS], psoriatic arthritis [PsA]) and CIBD (Crohn's disease and ulcerative colitis [UC]) who were treated with anti-TNF-alpha agents at least for 12 months and applied for the Umraniye Training and Research Hospital Pulmonology and Rheumatology Department between March 15, 2020 and

[1]Umraniye Training and Research Hospital, Department of Pulmonology – Istanbul, Turkey.
[2]Umraniye Training and Research Hospital, Department of Rheumatology – Istanbul, Turkey.
*Corresponding author: seymabaslilar@yahoo.com
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March 01, 2021 were evaluated retrospectively. The study was approved by the local ethics committee (Approval number B.10.TKH.4.34.H.G.p.0.01/111). The healthcare workers and patients over 65 years of age were excluded because they were included in the national vaccination schedule for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The data about demographic information, medical history, body mass index (BMI), smoking status, comorbidities such as hypertension (HT), diabetes mellitus (DM), asthma, chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD); the diagnosis of RD, anti-TNF-alpha agent, and additional pharmacological therapies used for RD and CIBD; and the duration of the anti-TNF-alpha therapy, tuberculosis skin test (TST) result, and laboratory parameters (i.e., leukocyte, neutrophil, lymphocyte and eosinophil count, and serum level of C-reactive protein) performed in the routine follow-up visit (in patients with a history of COVID-19, the laboratory tests in the last visit before the SARS-CoV-2 infection), and the history of COVID-19 was extracted from the medical files. The presence and radiological severity of pneumonia and the data for clinical course and outcome (need and duration of hospitalization and/or intensive care unit (ICU) follow-up, oxygen, CS, anti-cytokine treatment, intubation, and mortality) were also recorded in patients with COVID-19. In patients with pneumonia, the severity was degreed on thorax computerized tomography (CT) according to the scoring system offered by Bernheim A, et al[6,7].

The patients were divided into two groups, namely, COVID-19 (+) and COVID-19 (-) and compared in terms of age, sex, BMI, smoking status, comorbidities, the diagnosis of RD/CIBD, anti-TNF-alpha agent used, additional pharmacological therapies given for RD/CIBD, the duration of the anti-TNF-alpha therapy, TST result, and laboratory parameters. In the COVID-19 (+) group, the relationship of these factors with the presence and radiological severity of pneumonia, hospitalization, and ICU follow-up and clinical outcome was analyzed further.

Statistical analysis

Patient data were collected were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 package program (Statistical Package for the Social Sciences, Chicago, IL, USA). The discrete data were given as frequency and percentage. The mean±standard deviation for continuous data was given as descriptive value. The Mann-Whitney U test was used to compare the two groups. The Pearson's chi-square test and the Fisher-Freeman-Halton test were used to evaluate the relationship between the categorical features and the frequency and parameters related to the clinical course of COVID-19. The results were considered statistically significant when the $p<0.05$.

RESULTS

A total of 324 patients (177 males [54.6%] and 147 females [45.4%] with a mean age of 45.3±12.16 years) were included in this study. There were 280 patients (86.4%) in COVID-19 (-) and 44 patients (13.6%) in COVID-19 (+) group. Comparison of the data between the two groups is shown in Table 1. The mean age of the patients was 46±12 years in the COVID-19 (-) and 44±13 years in the COVID-19 (+) group (p=0.364). The both sexes were evenly distributed in COVID-19 (-) and COVID-19 (+) groups (154 males [55%] *versus* 126 females [45%], and 23 males [52.3%] *versus* 21 females [47.7%], respectively, p=0.751). AS was the most frequent disease followed by RA, Crohn's disease, PsA, and UC in COVID-19 (-) and (+) groups (129 cases *versus* 20 cases, 65 cases *versus* 14 cases, 45 cases *versus* 7 cases, 37 cases *versus* 2 cases, and 3 cases *versus* 1 case, respectively, p=0.411).

The information for BMI was available in 47 patients, and the mean BMI was similar in the COVID-19 (-) and (+) groups (27.6±4.2 and 27.24±2.64, respectively, p=0.886). There was no significant difference between the two groups in terms of smoking amount, comorbidities, anti-TNF-alpha agent, mean duration of anti-TNF-alpha treatment, and TST result (p>0.05).

Among the COVID-19 (+) group, 11 patients (25%) developed pneumonia. The information about pneumonia was lacking in 1 patient. Of note, 4 cases (36.3%) had mild, 5 cases (45.4%) had moderate, and 2 cases (18.3%) had severe pneumonia. Notably, 7 of the cases (15.9%) were hospitalized, and 1 of them (2.3%) was followed up in ICU; 2 cases (4.5%) needed nasal oxygen, 1 case (2.3%) needed high flow oxygen, 3 cases (6.8%) needed CS treatment (2 of them needed pulse steroid), and 1 case (2.3%) was treated with the anti-cytokine agent, i.e., tocilizumab. None of the cases was intubated or died. The relationship between the presence of pneumonia and the demographic, clinical, and laboratory data is shown in Table 2. The distribution of sex among cases with and without pneumonia was similar (7 *versus* 15 males and 4 *versus* 17 females, respectively, p=0.337). The patients with pneumonia were older significantly (mean age was 52±11 years *versus* 41±12 years, p=0.01). In patients with pneumonia, HT and CAD were more frequent (5 cases [55.6%] *versus* 4 cases [44.4], p=0.02; 2 cases [100%] *versus* 0 case [0%], respectively, p=0.014), and the mean percentage of eosinophil was significantly lower (1.35±1.79% vs. 2.3±1.45%, p=0.016).

Notably, 7/44 (15.9%) COVID-19 (+) cases were hospitalized. The comparison of demographic, clinical, and laboratory data in patients with and without a history of hospitalization is shown in Table 3. The frequency of DM was high, but that of CAD was low among inpatients compared with outpatients significantly (66.7% *versus* 33.3% and 15.9% *versus* 37%, p=0.013 and p=0.001, respectively). In hospitalized patients, the mean percentage of eosinophil was significantly lower (1.29±2.22% *versus* 2.19±1.37%, p=0.02).

Table 1. Comparison of demographic, clinical, and laboratory data between COVID-19 (-) and (+) groups.

		COVID-19 (-)		COVID-19 (+)		p-value
		n ormean	% or Standard deviation	n or mean	% or standard deviation	
Sex	Male	154	86.9	23	13.1	0.751
	Female	126	85.7	21	14.3	
Rheumatoid/chronic inflammatory bowel disease	Crohn's disease	45	86.5	7	13.5	0.411
	RA	65	82.3	14	17.7	
	AS	129	86.6	20	13.4	
	Ulcerative colitis	3	75.0	1	25.0	
	Psoriatic arthritis	37	94.9	2	5.1	
Anti-TNF-alpha agent	Adalimumab	101	84.9	18	15.1	0.928
	Etanercept	57	87.7	8	12.3	
	Infliximab	30	88.2	4	11.8	
	Golimumab	52	89.7	6	10.3	
	Certolizumab	35	81.4	8	18.6	
	Other	4	100.0	0	0.0	
Comorbidities	HT	40	81.6	9	18.4	0.298
	DM	31	91.2	3	8.8	0.383
	Asthma	9	75.0	3	25.0	0.242
	COPD	1	100	0	0	–
	CAD	10	83.3	2	16.7	0.754
TST result	Negative	84	85.7	14	14.3	0.830
	Positive	194	86.6	30	13.4	
Age (years)		46	12	44	13	0.364
BMI (kg/m^2)		27.6	4.2	27.24	2.64	0.886
Anti-TNF-alpha treatment duration (months)		61	29	61	30	0.708
Smoking (package/years)		4	9	1	2	0.235
CRP (mg/dL)		0.94	1.25	1.47	2.75	0.304
Number of leukocytes (×10^3/mL)		8378	4005	7855	1724	0.666
Number of neutrophils (×10^3/mL)		4745	1911	4721	1392	0.637
Number of lymphocytes (×10^3/mL)		2647	1048	2434	778	0.475
N/L ratio		2.06	1.33	2.22	1.3	0.120
Number of eosinophils (×10^3/mL)		212	159	170	118	0.137
E/L ratio		0.085	0.077	0.106	0.202	0.805
Eosinophil (%)		8.16	8.246	2.03	1.55	0.148

BMI: body mass index; CRP: C-reactive protein; TNF: tumor necrosis factor; RA: rheumatoid arthritis; AS: ankylosing spondylitis; HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; TST: tuberculin skin test.

Table 2. Comparison of demographic, clinical, and laboratory features in COVID-19 (+) patients without and with pneumonia.

		Pneumonia				p-value
		No		Yes		
		n or mean	% or SD	n or mean	% or SD	
Sex	Male	15	68.2	7	31.8	0.337
	Female	17	81.0	4	19.0	
Rheumatoid/Chronic inflammatory bowel disease	Crohn's disease	4	66.7	2	33.3	0.543
	RA	12	85.7	2	14.3	
	AS	13	65.0	7	35.0	
	Ulcerative colitis	1	100.0	0	0	
	Psoriatic arthritis	2	100.0	0	0	
Anti-TNF-alpha agent	Adalimumab	13	76.5	4	23.5	0.510
	Etanercept	6	75.0	2	25.0	
	Infliximab	4	100.0	0	0	
	Golimumab	3	50.0	3	50.0	
	Certolizumab	6	75.0	2	25.0	
Comorbidity	HT	4	44.4	5	55.6	**0.020**
	DM	1	33.3	2	66.7	0.091
	Asthma	2	66.7	1	33.3	0.750
	CAD	0	0	2	100.0	**0.014**
TST	Negative	22	75.9	7	24.1	0.755
	Positive	6	75.0	2	25.0	
Additional treatment	Mesalazine	3	100.0	0	0	0.726
	Leflunomide	1	100.0	0	0	
	MTX	2	66.7	1	33.3	
	CS	1	50.0	1	50.0	
	Sulfasalazine	0	0	1	100.0	
	Hydroxychloroquine	15	68.2	7	31.8	
Age (years)		41	12	52	11	**0.010**
CRP (mg/dl)		1.49	3.15	1.48	1.51	0.407
Number of leukocytes ($\times 10^3$/ml)		7765	1645	7968	2023	0.495
Number of neutrophils ($\times 10^3$/ml)		4594	1370	5072	1523	0.329
Number of lymphocytes ($\times 10^3$/ml)		2478	729	2203	856	0.459
N/L ratio		2.02	0.81	2.85	2.09	0.249
Number of eosinophils ($\times 10^3$/ml)		181	113	138	136	0.131
E/L ratio		0.074	0.057	0.198	0.382	0.766
Eosinophil (%)		2.30	1.45	1.35	1.79	**0.016**
Anti-TNF-alpha treatmentduration (months)		54	20	81	44	0.082

SD: standard deviation; RA: rheumatoid arthritis; AS: ankylosing spondylitis; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; TST: tuberculin skin test; MTX: methotrexate; CS: corticosteroid; CRP: C-reactive protein, TNF: tumor necrosis factor. Bold values indicate significance at $p<0.05$.

Table 3. Comparison of demographic, clinical, and laboratory features in COVID-19 (+) patients with and without hospitalization.

		Hospitalization				p-value
		No		Yes		
		n or mean	% or SD	n or mean	% or SD	
Sex	Male	19	82.6	4	17.4	0.778
	Female	18	85.7	3	14.3	
Rheumatoid disease	Crohn's disease	6	85.7	1	14.3	0.623
	RA	13	92.9	1	7.1	
	AS	15	75.0	5	25.0	
	Ulcerative colitis	1	100.0	0	0.0	
	Psoriatic arthritis	2	100.0	0	0.0	
Anti-TNF-alpha treatment	Adalimumab	16	88.9	2	11.1	0.170
	Etanercept	7	87.5	1	12.5	
	Infliximab	4	100.0	0	0.0	
	Golimumab	3	50.0	3	50.0	
	Certolizumab	7	87.5	1	12.5	
Comorbidity	HT	6	66.7	3	33.3	0.109
	DM	1	33.3	2	66.7	**0.013**
	Asthma	2	66.7	1	33.3	0.393
	CAD	37	84.1	7	15.9	**0.001**
TST	Negative	7	87.5	1	12.5	0.841 0.317
	Positive	3	100.0	0	0.0	
Additional treatment	Mesalazine	1	100	0	0	0.317
	Leflunomide	1	100	0	0	
	MTX	4	80	1	20	
	CS	0	0	1	100	
	Sulfasalazine	19	82.6	4	17.4	
Age (years)		42	12	52	14	0.072
CRP (mg/dl)		1.5	2.96	1.36	1.42	0.466
Number of leukocytes (×10³/mL)		7858	1696	7841	2005	0.895
Number of neutrophils (×10³/mL)		4642	1408	5117	1343	0.426
Number of lymphocytes (×10³/mL)		2508	716	2060	1019	0.287
N/L ratio		2.01	0.81	3.31	2.49	0.114
Number of eosinophils (×10³/mL)		176	107	145	167	0.145
E/L ratio		0.07	0.054	0.275	0.46	0.644
Eosinophil (%)		2.19	1.37	1.29	2.22	**0.020**
Anti-TNF-alpha treatmentduration (months)		59	31	67	25	0.312

SD: standard deviation; RA: rheumatoid arthritis; AS: ankylosing spondylitis; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; TST: tuberculin skin test; MTX: methotrexate; CS: corticosteroid; CRP: C-reactive protein; TNF: tumor necrosis factor. Bold values indicate significance at $p<0.05$.

DISCUSSION

The frequency of COVID-19 in cases treated with anti-TNF-alpha treatment was 13.6%. This was more than the frequency in the general population in our country reported by the Turkish Ministry of Health, which was 3.31%. It was revealed previously that COVID-19 was more frequent in RA patients compared to the general population[3]. According to the result of previous studies that anti-TNF-alpha treatment might increase the risk for infections[8], it was speculated that anti-TNF-alpha treatment might also increase the risk for SARS-CoV-2 infection and result in poor prognosis. In contrast, later, it has been reported that patients being treated with anti-TNF-alpha agents had a lower risk of hospitalization related to COVID-19 and a better prognosis compared with those treated with other anti-rheumatoid agents, especially CS[1-5]. This observation was explained with the hypothesis that the TNF-alpha is a cytokine related to the "cytokine storm" and the poor prognosis and mortality, so the blockade of this cytokine might favor the better prognosis in COVID-19.

The TST result did not differ between COVID-19 (-) and (+) groups and patients with and without a history of pneumonia or hospitalization. We evaluated the TST result to indicate immunity against tuberculosis. It was speculated that the Bacillus Calmette-Guérin (BCG) vaccine might have a cross-protective immunity on COVID-19 due to the observation that the prevalence and mortality related to COVID-19 were lower among the countries with routine BCG vaccination[9]. Several studies were conducted to investigate the relationship between COVID-19 infection and BCG vaccination[10-12]. Weng et al. reported that patients who were vaccinated with BCG required less hospital admission for COVID-19[11]. But, Aksu et al.[12] reported that older age and low income were the risk factors for developing severe COVID-19 pneumonia while BCG vaccination was not associated with disease severity. The result of our study was compatible with this study, and the patients who suffered from COVID-19 pneumonia were older.

Notably, 25% of patients suffered from pneumonia, 15.9% were hospitalized, 2.3% were followed up in ICU, and 6.8% needed oxygen treatment. In a multicenter study, the hospitalization rate for COVID-19 among rheumatic patients was reported as 85.5%, while the need for oxygen treatment was 30%, the need for the ICU follow-up was 13%, and the mortality rate was 10%[13]. In our study, there was no mortality, none of the patients was intubated, and the rate of hospitalization, the need for oxygen treatment, and the ICU follow-up were also lower.

HT and CAD were more frequent among patients with pneumonia, and DM was more frequent among inpatients compatible with the literature, while asthma and COPD were not related to pneumonia and hospitalization. Several studies reported the relationship with the negative effect of comorbidities except for asthma on the course of COVID-19[14,15]. The small sample size and presence of few cases with COPD probably caused us to fail to show the relationship between COPD and the prognosis of COVID-19. Wang et al.[16] and Serling-Boyd[17] reported that patients with RD had similar risks of poor COVID-19 outcomes with the control group. HT and lung diseases were significantly associated with the increased risk of COVID-19-related hospitalization while the use of anti-TNF-alpha drugs lowered the hospitalization risk in RA patients with COVID-19[16].

In this study, the percentage of eosinophils in routine control visits was significantly lower in patients with a history of pneumonia and hospitalization. It was reported that eosinophils have important pro-inflammatory and inflammatory functions in the antiviral response. They can recognize respiratory viruses, respond via releasing cytokines, and lead T-cell activation[18-21]. Several studies demonstrated that leukocytosis, increased number of neutrophils and neutrophil/lymphocyte ratio, and decreased number of lymphocytes and eosinophils at time of admission and follow-up of patients with COVID-19 were related to severe disease and poor prognosis. The mechanisms for eosinopenia in COVID-19 are probably multifactorial, including the decreased synthesis and inhibited migration of eosinophil from the bone marrow and direct eosinophil apoptosis[22-24]. It was suggested that eosinophils might have a protective role during SARS-CoV-2 infection. These observations depend on the blood counts of the patients following SARS-Cov-2 infection, but there was no study about the "basal" blood counts of patients before the infection, so the results of this study may be important in case supported with the results of future studies with more number of cases.

There were few limitations of the study. First, as the sample size of the COVID-19 (+) group was small, we could not determine the odds ratio for the risk factors related to clinical course and outcome of the disease because a specific group of patients was selected, so the results of this study have to be supported with multicentral clinical studies with more cases included. Second, the data about smoking status and BMI were lacking in most of the patients, so we could not discuss these factors in detail.

CONCLUSIONS

We concluded that the COVID-19 patients treated with anti-TNF-alpha agents might have a mild clinical course and a better prognosis. Older age and comorbidities such as HT and CAD may be related to developing pneumonia. The underlying RD, the anti-TNF-alpha agent used, and the duration of the treatment might not have an effect on the outcome of COVID-19.

AUTHORS' CONTRIBUTIONS

SB: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **OP:** Data Curation, Formal Analysis.

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Risk factors for radiological hip involvement in patients with ankylosing spondylitis

Shijun Chen[1], Lei Deng[1]*

SUMMARY

OBJECTIVE: Our study aimed to explore the potential risk factors for radiological hip joint involvement in patients with ankylosing spondylitis (AS).

METHODS: This cross-sectional convey collected the clinical data, laboratory indicators, and radiographic data of patients with AS. Radiographic hip joint involvement was defined as a Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip) score ≥2. Multivariate logistic regression analyses were conducted to explore the potential risk factors for radiological hip involvement in patients with AS.

RESULTS: Based on BASRI-hip score, all enrolled 386 patients with AS were classified as patients involving with radiological hip joint involvement (BASRI-hip ≥2; n=203) and those without it (BASRI-hip ≤1; n=183). Mean age of enrolled patients with AS were 36.7±11.9 years, and 320 (82.9%) patients were male. Mean course of disease was 10.7±8.3 years, and 349 (90.4%) patients were with a positive HLAB27. Multivariate analyses indicated that Juvenile onset (onset age £16 years) (odds ratio [OR]=4.159, 95% confidence interval [CI], 1.779–9.721, p<0.001), body mass index (BMI) <18.5 kg/m^2 (OR=1.986, 95%CI 1.187–3.323, p=0.009), continuous nonsteroidal anti-inflammatory drug (NSAID) use (OR=0.351, 95%CI 0.155–0.794, p=0.012), and bone mass below the expected range for age (*Z* score ≤-2) (OR=2.791, 95%CI 1.456–5.352, p=0.002) were independently associated with radiological hip joint involvement in patients with AS.

CONCLUSIONS: The potential risk factors for radiological hip joint involvement were juvenile onset, lower BMI, and bone mass below the expected range for age. Furthermore, continuous NSAID use was the protective factor for radiological hip joint involvement in these population.

KEYWORDS: Radiological hip involvement. Ankylosing spondylitis. Nonsteroidal anti-inflammatory drugs. Bone density.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that mainly damages the vertebral column and sacroiliac joints. AS has an incidence rate of 0.5–1.0% and is more common in young men. Clinical features of patients with AS include inflammatory back pain, asymmetrical peripheral oligoarthritis, enthesitis, and specific organ involvement such as anterior uveitis, psoriasis, and chronic inflammatory bowel disease[1].

Previous study reports that about 25–33% patients with AS experience hip joint involvement[2]. The hip joint is one of the most stable joints, which is also the largest weight-bearing joint in the human body and is crucial to sustain balance and body posture. Damage of hip joint is a major cause of disability in patients with AS[3]. The diagnosis of hip joint involvement in patients with AS is reliable on clinical symptoms, joint malfunctioning, and findings from X-ray and/or magnetic resonance imaging. The Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip) score based on X-ray is commonly applied in the studies of radiological hip involvement in patients with AS. Finally, almost 5% patients with AS require total hip replacement or hip arthroplasty[4].

[1]Ankang Central Hospital, Department of Hematology and Rheumatology – Shaanxi Province, China.
*Corresponding author: denglei_flower@outlook.com
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Remarkably, the factors associated with radiological hip joint involvement in patients with AS have not been extensively explored. The progression speed and severity of hip joint involvement in patients with AS are related to individual variations[5]. It is crucial to screen the potential factors that are related to the occurrence, progression, and severity of hip joint damage in these patients, and the optimal treatment and management plans could be conducted to prevent or postpone the deterioration of hip joint to the end stage. Currently, limited data are available on the factors associated with radiographic changes of hip joint damage in patients with AS. Herein, we aimed to explore the potential risk factors of radiological hip involvement in patients with AS, which could help screen the specific patients who might require a close follow-up or hip replacement surgery.

METHODS

Patients

This was a cross-sectional study of patients with AS treated at the Department of Hematology and Rheumatology of Ankang Central Hospital between May 2014 and July 2020. Inclusion criteria were (1) aged ³18 years with a diagnosis of AS according to the modified New York criteria for classification of AS developed in 1984 and (2) course of disease ³1 year. Exclusion criteria were (1) gouty arthritis, infectious arthritis, or rheumatoid arthritis; (2) cancerous bone tumors, bone metastasis, or hematological malignancies; and (3) incomplete medical records. The study was approved by the Ethics Committee of Ankang Central Hospital, and informed consent of patient was waived by the Ethics Committee due to the retrospective nature of the study design.

Data collection

Clinical data were collected from all patients, including age, sex, age of disease onset, course of disease, family AS history, smoking history, body mass index (BMI), and treatment agents (anti-tumor necrosis factor [TNF], nonsteroidal anti-inflammatory drugs [NSAIDs], sulfasalazine, methotrexate, thalidomide, and glucocorticoids). Clinical examinations were performed to record peripheral arthritis, iritis, and results of Schober's test. The Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used to assess the functional status, hip function, and disease activity. The laboratory indicators of ESR, CRP, and the HLA-B27 status were recorded and evaluated in all patients. The application of calcaneal quantitative ultrasound was conducted to determine bone mass through an Ultrasonic bone intensity meter (GE Healthcare, Waukesha, WI, USA). The Z value of -2.0 or lower is defined as the bone mass below the expected range for age.

Outcomes

The BASRI-hip (0–4 points) was used to evaluate radiographic hip joint involvement[6], which was a reliable tool for grading hip joint radiographic changes in patients with AS. It was classified as follows: 0=normal (no damage, no radiological hip joint change); 1=suspicious damage (potential focal joint space narrowing), 2=mild (obvious hip joint lesion but circumferential joint space narrowing >2 mm); 3=moderate (definite hip joint lesion, circumferential joint space narrowing £2 mm, or bone-on-bone apposition of £2 cm); and 4=severe (bone deformity or bone-on-bone apposition of <2 cm or indication for total hip replacement). Radiographic hip joint involvement was defined as a BASRI-hip score ³2.

Statistical analysis

Continuous data were expressed as mean±standard deviation or median (interquartile range [IQR]) and compared using the Student's t-test or the Mann-Whitney U test. Categorical data were presented as proportion and analyzed with the chi-square test or Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify the factors associated with radiological hip joint. Variables with $p<0.1$ in the univariable analyses were included in the multivariable analysis. SPSS version 22.0 (IBM, Armonk, NY, USA) was performed for all analyses, and a two-sided $p<0.05$ indicated statistical significance.

RESULTS

Patients' characteristics

A total of 386 patients with AS were finally analyzed. Based on BASRI-hip score, there were 203 patients with radiological hip joint involvement and 183 patients without it. The mean age was 36.7±11.9 years, and 320 (82.9%) patients were males. The mean course of disease was 10.7±8.3 years, and the mean BMI was 10.7±8.3 kg/m^2. Eighty (20.7%) patients had the juvenile onset. There were 349 (90.4%) patients with a positive HLAB27, and 35 (9.1%) patients were combined with iritis. The median value of BASDAI was 3.5 (IQR, 2.3–5.5) and that of BASFI was 3.2 (IQR, 1.1–5.6). In addition, 58 (15.0%) patients had received TNF blockers >3 months, and 70 (18.1%) patients were treated with continuous use of NSAIDs. The baseline clinical characteristics are indicated in Table 1.

Table 1. Baseline data of all enrolled patients with ankylosing spondylitis.

	All patients (n=386)
Age (years), mean±SD	36.7±11.9
Sex (male), n (%)	320 (82.9)
BMI (kg/m^2), mean±SD	23.1±4.2
Juvenile onset (onset age £16 years), n (%)	80 (20.7)
Course of disease (years), mean±SD	10.7±8.3
Smoking history, n (%)	192 (49.7)
Family AS history, n (%)	57 (14.8)
CRP (mg/dL), median (Q1–Q3)	23.0 (10.9–55.2)
ESR (mm/h), median (Q1–Q3)	42 (17–64)
HLAB27 positive, n (%)	349 (90.4)
Iritis, n (%)	35 (9.1)
Achilles tendinitis, n (%)	55 (14.2)
Peripheral arthritis, n (%)	177 (45.9)
Schober's test positive, n (%)	190 (49.2)
Bone mass below the expected range for age (Z score ≤-2), n (%)	102 (26.4)
BASDAI, median (Q1–Q3)	3.5 (2.3–5.5)
BASFI, median (Q1–Q3)	3.2 (1.1–5.6)
TNF blockers >3 months, n (%)	58 (15.0)
Continuous NSAIDs use, n (%)	70 (18.1)
SSZ >6 months, n (%)	96 (24.9)
MTX >6 months, n (%)	40 (10.4)
Thal >6 months, n (%)	31 (8.0)
Glucocorticoid >2 weeks, n (%)	38 (9.8)

SD: standard deviation; BMI: body mass index; AS: ankylosing spondylitis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASDAI: bath ankylosing spondylitis disease activity index; BASFI: bath ankylosing spondylitis functional index; TNF: tumor necrosis factor; NSAIDs: nonsteroidal anti-inflammatory drugs; SSZ: sulfasalazine; MTX: methotrexate; Thal: thalidomide.

Univariable analyses

Univariate analysis revealed that compared to patients without radiological hip joint involvement, those with radiological hip joint involvement were younger (unadjusted odds ratio [OR]=0.868, 95% confidence interval [CI]: 0.812–0.928, p<0.001), had the higher proportions of BMI < 18.5 kg/m^2 (unadjusted OR=4.387, 95%CI 1.968–9.779, p<0.001), juvenile onset (unadjusted OR=4.297, 95%CI 2.082–8.868, p<0.001), bone mass below the expected range for age (Z score ≤-2) (unadjusted OR=3.361, 95%CI 1.682–6.717, p<0.001), and TNF blockers >3 months (unadjusted OR=2.614, 95%CI 1.092–6.259, p=0.031), and the results are indicated in Table 2.

Multivariable analyses

Multivariate regression analysis of potential factors associated with radiological hip joint involvement is presented in Table 3. After adjusting for potential confounding factors (<0.1 in the univariable analyses was included in the multivariable analysis), the results indicated that juvenile onset (adjusted OR=4.159, 95%CI 1.779–9.721, p=0.001), BMI <18.5 kg/m^2 (adjusted OR=1.986, 95%CI 1.187–3.323, p=0.009), continuous NSAIDs use (adjusted OR=0.351, 95%CI 0.155–0.794, p=0.012), bone mass below the expected range for age (Z score ≤-2) (adjusted OR=2.791, 95%CI 1.456–5.352, p=0.002), and BASFI (adjusted OR=1.382, 95%CI 1.097–1.741, p=0.006) were independently associated with radiological hip joint involvement.

Table 2. Multivariate regression analysis of potential factors associated with radiological hip joint involvement (defined as a bath ankylosing spondylitis radiology hip index score ≥2).

	BASRI-hip £1 (n=183)	BASRI-hip ≥2 (n=203)	p	Unadjusted OR	95%CI
Age (years), mean±SD	39.2±11.3	31.2±10.6	<0.001	0.868	0.812–0.928
Sex (male), n (%)	145 (79.2)	175 (86.2)	0.071	1.547	0.965–2.385
BMI <18.5 kg/m^2, n (%)	13 (7.1)	51 (25.1)	<0.001	4.387	1.968–9.779
Juvenile onset (onset age £16 years), n (%)	19 (10.4)	61 (30.0)	<0.001	4.297	2.082–8.868
Course of disease (years), mean±SD	10.2±7.5	10.8±8.8	0.512	0.954	0.829–1.098
Smoking history, n (%)	84 (45.9)	108 (53.2)	0.155	1.479	0.862–2.536
Family AS history, n (%)	32 (17.5)	25 (12.3)	0.151	0.627	0.332–1.186
CRP (mg/dL), median (Q1–Q3)	20.7 (9.5–53.8)	24.9 (11.6–55.1)	0.713	1.091	0.686–1.735
ESR (mm/h), median (Q1–Q3)	36 (17–62)	42 (25–64)	0.312	1.109	0.907–1.355
HLAB27 positive, n (%)	165 (90.2)	184 (90.6)	0.871	1.071	0.468–2.451
Iritis, n (%)	11 (6.0)	24 (11.8)	0.055	2.213	0.983–4.981
Achilles tendinitis, n (%)	25 (13.7)	30 (14.8)	0.757	0.764	0.139–4.204
Peripheral arthritis, n (%)	80 (43.7)	97 (47.8)	0.427	1.197	0.768–1.865
Schober's test positive, n (%)	87 (47.5)	103 (50.7)	0.534	1.318	0.552–3.147
Bone mass below the expected range for age (Z score ≤-2), n (%)	25 (13.7)	77 (37.9)	<0.001	3.361	1.682–6.717
BASDAI, median (Q1–Q3)	3.7 (2.7–5.8)	3.6 (1.9–5.2)	0.862	0.913	0.327–2.548
BASFI, median (Q1–Q3)	2.8 (1.0–4.4)	4.2 (1.8–7.5)	0.002	1.275	1.093–1.487
TNF blockers >3 months, n (%)	16 (8.7)	42 (20.7)	0.031	2.614	1.092–6.259
Continuous NSAIDs use, n (%)	38 (20.8)	32 (15.8)	0.195	0.621	0.302–1.277
SSZ >6 months, n (%)	41 (22.4)	55 (27.1)	0.276	1.283	0.819–2.009
MTX >6 months, n (%)	14 (7.7)	26 (12.8)	0.112	1.513	0.908–2.521
Thal >6 months, n (%)	15 (8.2)	16 (7.9)	0.891	1.097	0.292–4.123
Glucocorticoid >2 weeks, n (%)	15 (8.2)	23 (11.3)	0.312	1.315	0.773–2.236

BASRI-hip: bath ankylosing spondylitis radiology hip index; OR: odds ratio; CI: confidence interval; SD: standard deviation; BMI: body mass index; AS: ankylosing spondylitis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASDAI: bath ankylosing spondylitis disease activity index; BASFI: bath ankylosing spondylitis functional index; TNF: tumor necrosis factor; NSAIDs: nonsteroidal anti-inflammatory drugs; SSZ: sulfasalazine; MTX: methotrexate; Thal: thalidomide.

Table 3. Multivariate regression analysis of potential factors associated with radiological hip joint involvement.

Variables	p	Adjusted OR*	95%CI
Juvenile onset (onset age £16 years)	0.001	4.159	1.779–9.721
BMI <18.5 kg/m^2	0.009	1.986	1.187–3.323
Continuous NSAID use	0.012	0.351	0.155–0.794
Bone mass below the expected range for age (Z score ≤-2)	0.002	2.791	1.456–5.352
BASFI	0.006	1.382	1.097–1.741

OR: odds ratio; CI: confidence interval; BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drugs; BASFI: bath ankylosing spondylitis functional index.

DISCUSSION

Our study indicated that that juvenile onset (age £16 years), bone mass below the expected range for age (*Z* score ≤-2), and BMI <18.5 kg/m^2 were independently associated with radiological hip joint involvement, with OR value of 4.159, 2.791, and 1.986, respectively.

Previous studies have already demonstrated that the juvenile onset is a risk factor for hip joint involvement in patients with AS. Patients with AS with juvenile onset might be associated with serious condition, the proportion of those with radiological hip joint damage was high, and the need for joint replacement surgery might be increased[7]. Patients with spondyloarthritis (when symptoms begin in childhood) were more likely to involve the hip joints or to induce cause attachment point inflammation, than to affect the axial bones[8]. Prior study demonstrated that the degree of radiological hip joint damage in patient with AS with juvenile onset was significantly more severe than those with adult onset, and rare patients with late-onset AS occurred with radiological hip joint damage[9,10]. These highlighted that patients with AS with juvenile onset were more prone to be involved with hip joint involvement. This patient population should be closely followed up and monitored for the progression of hip joint damage.

Patients with AS are more prone to be accompanied with low bone mass and/or osteoporosis[11]. Among all enrolled 386 patients with AS in our cross-sectional study, 102 (26.4%) patients had bone mass below the expected range for age (Z score ≤-2). The proportion of patients with bone mass below the expected range for age was 37.9% in patients with AS with radiological hip joint involvement, which was significantly higher than that (13.7%) of those without it. Multivariate regression analysis further showed that bone mass below the expected range for age was independently associated with radiological hip joint involvement in patients with AS. The lower bone density in patients with AS with radiological hip involvement may be attributed to the changes of the body biomechanical mechanism influenced by hip joint damage. Decreased exercises bring about the increasing occurrence risk of osteoporosis, while exercise could induce osteoclast differentiation, trigger bone reconstruction, and increase the bone mass[12].

Prior study indicated that high BMI and advanced hip arthritis at baseline were associated with hip joint replacement surgery in patients with AS[13]. In our study, 386 patients with AS showed a mean BMI of 22.96±4.38 kg/m^2, which was also lower than the mean value from Chinese adults (BMI=24.7±3.5 g/m^2)[14].Compared to healthy individuals, patients with AS were reported to have the fat free mass of about 3 kg lower than the mean value, and appendicular lean mass of 1 kg/m less than the mean value[15]. Multivariate regression analysis further proved that BMI <18.5 kg/m^2 was an independent risk factor for radiological hip joint involvement in patients with AS.

In our study, cumulative use of slow-acting drugs, such as SSZ, MTX, and thalidomide for no less than 6 months was not the independently protective factor for radiological hip joint damage in patients with AS. However, a few studies considered that TNF blockers could slow the progression of hip joint damage in patients with AS[16]. A prior report with small sample size even observed increased hip joint space after TNF blocker treatment in six patients with AS accompanying radiological hip joint involvement, with their baseline BASRI score (3 points) returned to 2 points[17]. Our study ruled out that the proportion of TNF blockers usage >3 months in patients with AS with radiological hip joint damage was 20.7%, which was significantly higher than that (8.7%) observed in those without it. Nevertheless, multivariate regression analysis indicated that TNF blockers >3 months is not a protective factor for radiological hip joint damage in patients with AS. Future longitudinal study might be required to explore the therapeutic effect of TNF blockers on radiological hip joint damage in patients with AS.

The encouraging efficacy of NSAIDs for the treatment of AS has been extensively verified in previous studies. The recent updated 2019 American College of Rheumatology guidelines on AS and nonradiographic axial spondyloarthritis recommended continuous applications of NSAIDs in patients with AS[18]. Treatment strategy with continuous use of NSAIDs was recommended in patients with AS without contradictions, which could help in decreasing the radiological progression of spine[19], and this was consistent with the findings observed in our study. Notably, prior studies observed that continuous treatment with NSAIDs decreased the risk of fracture in patients with AS[20].

This study also had some limitations. First, this is a single-center, cross-sectional study with small sample size. Second, although the assessment results were objected according to X-ray, only when patients with AS with hip joint damage in the advanced stage could be detected by plain radiography. Third, due to the retrospective study design, only routine laboratory indexes were available in the clinical practice.

CONCLUSIONS

Juvenile onset, lower BMI, and bone mass below the expected range for age were independently associated with radiological hip joint involvement in patients with AS. Patients with AS with these clinical characteristics should be screened and followed up for the occurrence or progression of their hip joint damage. Continuous NSAID use should be recommended if patients were without contraindications, which is considered a protective factor for radiological hip joint involvement in these population.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the manuscript.

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The effectiveness of dexamethasone on the prognosis of dialysis patients with severe COVID-19

Aysel Toçoglu[1]*, Hamad Dheir[2], Taner Demirci[3], Rumeysa Kurt[1], Salih Salihi[4], Selçuk Yaylaci[1], Gözde Çakırsoy Çakar[5], Hande Toptan[6], Oguz Karabay[7], Savas Sipahi[2]

SUMMARY

OBJECTIVE: This study aimed to investigate the effectiveness of dexamethasone in dialysis patients with COVID-19 and whether it predicts mortality.

METHODS: This is a comparative cross-sectional study of 113 consecutive patients with COVID-19 with severe pneumonia signs. The patients were divided into two groups according to the use of dexamethasone treatment: group 1 (n=45) included patients who were treated with dexamethasone and group 2 (n=68) who did not receive dexamethasone.

RESULTS: The mean age of both groups was 67.0±10.6 and 67.2±13.0 years, respectively (p=0.947). With respect to demographic and laboratory findings, there were no significant differences between the two groups (p>0.05). The hospitalization time of patients in group 1 was longer than that in group 2 (11 [7–17] days vs. 8 [5.3–14] days, p=0.093]. The 28-day survival rate was 54.2% in the group receiving dexamethasone treatment and 79.5% in the group not receiving dexamethasone treatment (p=0.440).

CONCLUSION: Dexamethasone did not reduce mortality rates and the requirement for intensive care unit in dialysis patients with COVID-19. Larger prospective randomized clinical trials are required to associate personalized medicine with the corticosteroid treatment to select suitable patients who are more likely to show a benefit.

KEYWORDS: Chronic kidney disease. COVID-19. Dexamethasone. Dialysis. Mortality.

INTRODUCTION

The new type of coronavirus (COVID-19 or SARS-CoV2) is a serious disease that causes severe acute respiratory failure and requires ward or intensive care units (ICUs)[1]. The risk of mortality increases with one or more comorbid conditions, such as advanced age, male gender, diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, and chronic kidney disease, which are independent predictors of mortality[2]. Studies have shown that patients under renal replacement therapy are also associated with increased mortality rates due to COVID-19 disease[3,4]. The transmission risk of COVID-19 is very high when patients under hemodialysis (HD) program use transfer vehicles and undergo dialysis together in the same area of the dialysis center[5]. Accordingly,

[1]Sakarya University Faculty of Medicine, Department of Internal Medicine – Sakarya, Turkey.
[2]Sakarya University Faculty of Medicine, Division of Nephrology – Sakarya, Turkey.
[3]Sakarya University Faculty of Medicine, Division of Endocrinology – Sakarya, Turkey.
[4]Sakarya University Faculty of Medicine, Department of Cardiovascular Surgery – Sakarya, Turkey.
[5]Sakarya University Faculty of Medicine, Department of Clinic Pathology – Sakarya, Turkey.
[6]Sakarya University Faculty of Medicine, Department of Microbiology – Sakarya, Turkey.
[7]Sakarya University Faculty of Medicine, Department of Infection Diseases and Microbiology – Sakarya, Turkey.
*Corresponding author: agurkan@sakarya.edu.tr
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the possibility of admission rates to the hospital wards and ICUs due to COVID-19 disease is expected to be higher in dialysis patients than in the normal population.

Many treatment approaches, such as convalescent plasma, remdesivir, and interleukin-6 inhibitors, have been suggested to treat the disease for selected patient populations, but they have controversial results[6-11]. Corticosteroid therapy has been shown as an effective treatment approach in the normal population[12,13]. A meta-analysis of the efficacy and safety of corticosteroids in non-COVID-19 patients with sepsis suggested that administration of corticosteroids was associated with reduced 28-day mortality compared with placebo use or standard supportive care[14]. Corticosteroids are commonly used as anti-inflammatory and immunosuppressive therapy in many diseases[14-17].

Corticosteroids, especially due to high doses, also have many adverse systemic effects, such as obesity, hypertension, bone disorders, and hyperglycemia, that may predispose to cardiovascular disease in future[18]. In the dialysis population with COVID-19, having more than one comorbid disease, exposure to prolonged uremia, accompanying severe atherosclerotic diseases, and hypervolemia may cause more progressive respiratory failure, making the management of the clinical course and treatment options quite complicated. Generally, the treatment options of dialysis patients may not be successful because of their anuric nature and multiorgan pathologies, compared with normal populations.

This study aims to investigate the effectiveness of dexamethasone therapy in dialysis patients with COVID-19 and whether it predicts mortality in these patients.

METHODS

This descriptive comparative cross-sectional study was conducted on 113 dialysis patients with consecutive COVID-19 disease between March 15 and December 15, 2020. The study population was only composed of patients with confirmed COVID-19 by real-time reverse transcription polymerase chain reaction (RT-PCR) taken from nasopharyngeal (NP) swab. The study was conducted in accordance with the Declaration of Helsinki and after the approval of the Ethics Committee of Sakarya University Faculty of Medicine (n° E-71522473-050.01.04-640). The inclusion criteria in the study are

1. those who have been receiving HD or peritoneal dialysis (PD) treatment for at least three months,
2. patients with consecutive positive NP RT-PCR results, and
3. those who have severe disease criteria (respiratory rate >30/min, despite more than 5 L/min of oxygen supporting, the oxygen saturation of patients is <90%, and/or PaO_2/FiO_2<300 mm Hg).

The patients who

1. underwent acute dialysis,
2. have negative NP RT-PCR,
3. have an active additional viral infection such as hepatitis B and C or human immunodeficiency virus, and
4. hospital record files inaccessible were excluded. The patients were not given steroid treatment between March 15 and July 20, 2020, because there was no evidence of successful steroid treatment as in the recovery study.

For this reason, patients were divided into two groups according to the use of dexamethasone treatment: group 1 (n=45) included patients who were treated with dexamethasone and group 2 (n=68) who did not receive dexamethasone. Demographic and laboratory results of all patients were compared. Favipiravir (FVP) treatment was given to all patients in both groups. The FVP doses were given 1600 mg twice daily and 1600 mg one time in days 2–5. All patients in group 1 received 8 mg dexamethasone for at least 10 days.

Statistical analyses were performed using SPSS version 22 software. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov). The chi-square test was used to determine whether there was any difference between the groups in terms of quality variables. Whether there is a difference between the groups in terms of numerical variables, or if parametric test conditions were fulfilled, independent groups were examined by *t*-test and, if not, Mann-Whitney U test was used. Continuous variables were expressed as means±standard deviation or medians (interquartile ranges). Categorical variables were expressed as the number of cases (percentage in brackets). The effect of dexamethasone use on the survival of dialysis patients with COVID-19 was investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 113 patients were enrolled in this study. Of these, 45 patients used dexamethasone (group 1) and 68 patients did not use dexamethasone (group 2). The mean age of both groups was 67.0±10.6 and 67.2±13.0 years, respectively (p=0.947). While 93% of the patients were HD patients, just 7% of the patients were PD patients.

There were no significant difference between patients groups with respect to symptoms of disease, comorbid conditions, basal hematologic, and basal biochemistry findings

(p>0.05) (Tables 1 and 2). The duration of the onset of symptoms to hospital admission was 3 (1.5–8) days in group 1 and 2 (1–5) days in group 2 (p=0.082). The hospitalization time of patients in group 1 was longer than that in group 2 (11 [7–17] days vs. 8 [5.3–14] days, p=0.093) (Table 1). In terms of treatment location, the patients of the two groups were followed up in the ward at a rate of 71.1 and 89.7% and in the ICU at a rate of 28.9 and 10.3%, respectively (p=0.011) (Table 2). During hospitalization, the requirement to transfer to ICU in both groups was similar (28.9 and 27.9%, respectively; p=0.913). The need for invasive mechanical ventilation in group 1 was higher than that in group 2 (31.1 *versus* 23.5%, p=0.293). The mortality rates in group 1 were higher than that in group 2 (55.6 *versus* 38.2%, p=0.070). Kaplan-Meier's survival curves according to dexamethasone treatment are shown in Figure 1. The 28-day survival rate was 54.2% in the group receiving dexamethasone treatment (group 1) and 79.5% in the group not receiving dexamethasone treatment (group 2) (p=0.440).

DISCUSSION

To our knowledge, this is the first study to investigate the effectiveness of dexamethasone on dialysis patients with severe COVID-19 disease. We did not find a significant effect of dexamethasone treatment with respect to 28-day mortality in our dialysis patients. There was no significant difference between the two groups in terms of age, gender, dialysis model, and baseline admission laboratory findings of the patients. This shows that both groups were well matched, so we can say that we correctly demonstrated the ineffectiveness of dexamethasone on mortality in equal dialysis patient groups.

Table 1. Characteristics of demographic features at the admission of dialysis patients with COVID-19.

	Group 1 (n=45)	Group 2 (n=68)	p-value
Renal replacement therapy, n (%)			
Hemodialysis	40 (88.9)	65 (95.6)	0.174
Peritoneal dialysis	5 (11.1)	3 (4.4)	
Age, years	67.0±10.6 (22–85)	67.2±13.0 (25–89)	0.947
Gender			
Female/Male (%)	25/20 (55.6/44.4)	28/40 (41.2/58.8)	0.134
Presenting symptom, n (%)			
Fever	28 (62.2)	44 (64.7)	0.788
Cough	13 (28.9)	32 (47.1)	0.053
Dyspnea	26 (57.8)	31 (45.6)	0.205
Weakness	28 (62.2)	29 (42.6)	0.042
Diarrhea	0	3 (4.4)	0.153
Nausea and vomiting	4 (8.9)	6 (8.8)	0.990
Anosmia	1 (2.2)	0	0.398
Headache	0	3 (4.5)	0.272
Chronic diseases, n (%)			
Diabetes	21 (46.7)	34 (50.0)	0.729
Hypertension	39 (86.7)	59 (86.8)	0.988
ASCVD	21 (46.7)	24 (35.3)	0.227
COPD	3 (6.7)	8 (11.8)	0.371
Malignancy	4 (8.9)	4 (5.9)	0.542
The onset of symptoms, median (IQR) days	3 (1.5– -8)	2 (1–5)	0.082
Hospitalization time, median (IQR) days	11 (7–17)	8 (5.3–14)	0.093

ASCVD: atherosclerotic cardiovascular disease; COPD: chronic obstructive pulmonary disease.

In animal experiments, it has been shown that 10 days of dexamethasone treatment has a very substantial anti-hypoxic effect on hypoxic mices[19]. Dexamethasone treatment has been shown to significantly reduce the 28-day mortality rates associated with COVID-19 disease in the normal population[12,20]. However, treatment approaches and their response rates of different disease states in dialysis patients may not be as in the normal population and the drugs must be used with caution, bearing in mind the potential development of serious side effects. In one study, COVID-19–related mortality rates in HD patients were found to be higher (25.4%, 95%CI 21.3–29.9; p<0.001) than the normal population[3]. Another study revealed that the incidence, mortality, and fatality rates in HD patients were 341/10,000 patients, 94/10,000 patients, and 27.7%, respectively[21]. In our study, we found high mortality rates in dialysis patients using dexamethasone and those did not (55.6 *versus* 38.2%). It can be said that the majority of patients as well as dialysis patients of this study was accompanied by diabetes mellitus, hypertension, and heart disease and had severe disease criteria, which lead to more mortality rates. However, in the present study, there was a greater trend of increased mortality rates in patients who used dexamethasone compared with patients who did not use it. In fact,

Table 2. Comparison of laboratory findings and clinical processes between groups according to dexamethasone use.

	Group 1 (n=45)	Group 2 (n=68)	p-value
Creatinine, mg/dL	6.0±2.7	5.9±2.6	0.765
White blood cell count, $10^3/mm^3$	6.80 (4.82–8.85)	5.6 (4.45–7.59)	0.109
Absolute lymphocyte count, $10^3/mm^3$	0.74 (0.48–1.14)	0.80 (0.47–1.07)	0.893
Neutrophil-to-lymphocyte ratio	6.57 (3.42–14.70)	5.86 (3.52–10.60)	0.395
Platelet count, $10^3/mm^3$	170±69	154±75	0.259
C-reactive protein, mg/L	113.9 (43.4–218.6)	81.6 (30.1–158.1)	0.242
Procalcitonin, ng/mL	1.17 (0.49–4.32)	1.06 (0.45–5.51)	0.826
Alanine aminotransferase, IU/L	14.0 (9.5–21.5)	14.5 (9.3–27.0)	0.647
Aspartate aminotransferase, IU/L	33.0 (22.0–43.0)	26.0 (18.0–45.0)	0.231
Fibrinojen, mg/dL	465±148	422±112	0.122
D-Dimer, ng/mL	1110 (564–2405)	931 (557–2720)	0.960
Albumin, g/L	3.0±0.5	3.1±0.6	0.519
Ferritin, ng/mL	1702 (761–3187)	1575 (661–3367)	0.946
Lactate, mEq/L	1.77±0.88	1.38±0.48	0.010
Interleukin-6, pg/mL (n=60)	81.6 (41.7–424.0)	72.3 (31.5–300.1)	0.676
Treatment location at admission, n (%)			
Ward	32 (71.1)	61 (89.7)	0.011
Intensive care unit	13 (28.9)	7 (10.3)	
Recruitment to intensive care unit, n (%)	13 (28.9)	19 (27.9)	0.913
Mechanical ventilation support, n (%)			
No	30 (66.7)	52 (76.5)	0.293
Noninvasive mechanical ventilator	1 (2.2)	–	
Invasive mechanical ventilator	14 (31.1)	16 (23.5)	
Rehospitalization after discharge, n (%)			
No	42 (93.3)	65 (95.6)	0.601
Yes	3 (6.7)	3 (4.4)	
Mortality, n (%)	25 (55.6)	26 (38.2)	0.070

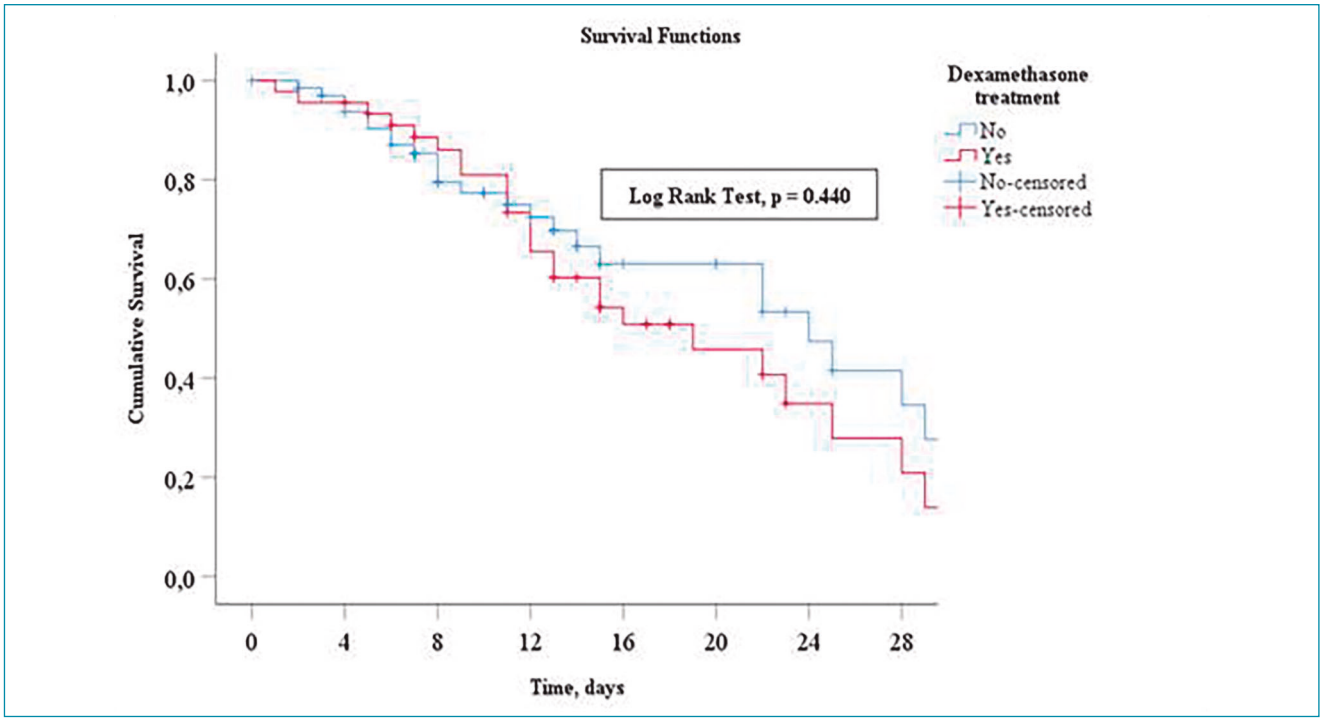

Figure 1. Overall survival according to dexamethasone use in dialysis patients with COVID-19.

compared with the other group, the dexamethasone group has more severe clinical courses, such as the fact that one-third of them were hospitalized directly in ICU from the emergency room, duration of symptom onset to hospital admission was longer, the hospitalization period was longer, and the levels of serum lactate were higher.

The hospitalization time of patients in group 1 was longer than that in group 2 (11 (7–17] days *versus* 8 [5.3–14] days, p=0.093) (Tables 1 and 2). In one descriptive study with all probable 5327 patients with SARS, the average duration of onset of symptoms to hospital admission was 3.8 days and that of admission to discharge for those who survived was 29.7 days, while admission to death for casualties was 17.4 days[22]. The duration of onset of symptoms to admission was found to be an independent variable with respect to the prognosis of disease among the nondialytic patients with COVID-19 (95%CI 1.05 [1.01–1.08], p=0.005)[23]. In the present study, the duration of onset of symptoms to hospital admission in the dexamethasone group was longer than the non-dexamethasone group. The difference between the two groups was close to significance. These outcomes need to be confirmed in future controlled studies involving more patients.

The limitations of the study are retrospective with a low number of patients in each group, not investigating acute side effects of steroids, lack of patients with mild or moderate severity illness in either group, not including normal COVID-19 patient group.

In conclusion, dexamethasone treatment did not reduce the 28-day mortality rates and need for ICUs in dialysis patients with COVID-19. This outcome may be due to the small number of study patients and the low number of patients who died. Larger prospective randomized clinical trials are required to associate personalized medicine with the corticosteroid treatment to select suitable uremic patients who are more likely to show a benefit.

AUTHORS' CONTRIBUTION

AT: Conceptualization, Methodology, Supervision, Writing – Review & Editing. **HD:** Conceptualization, Methodology, Writing – Review & Editing. **TD:** Conceptualization, Validation, Writing – Review & Editing. **RK:** Conceptualization, Validation, Writing – Review & Editing. **SS:** Conceptualization, Validation, Writing – Review & Editing. **SY:** Conceptualization, Methodology, Writing – Review & Editing. **GÇÇ:** Conceptualization, Validation, Writing – Review & Editing. **HT:** Conceptualization, Supervision, Writing – Review & Editing. **OK:** Conceptualization, Supervision, Writing – Review & Editing. **SS:** Conceptualization, Supervision, Writing – Review & Editing.

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The prognostic significance of erythrocyte sedimentation rate in COVID-19

Tezcan Kaya[1]*, Ahmet Nalbant[1], Gizem Karataş Kılıççıoğlu[1], Kübra Tuğba Çayır[1], Selçuk Yaylacı[1], Ceyhun Varım[1]

SUMMARY

OBJECTIVE: There are limited data about the significance of erythrocyte sedimentation rate as a single prognostic parameter for the prognosis and mortality of COVID-19. This study aimed to investigate the diagnostic utility of erythrocyte sedimentation rate as a prognostic factor for the disease severity and mortality in patients with COVID-19.

METHODS: A total of 148 consecutive patients with a confirmed diagnosis of COVID-19 and hospitalized at the intensive care unit or non-the intensive care unit were included in the study. The patients were allocated to groups as severe/critical disease versus nonsevere disease and survivors and nonsurvivors. The prognostic role and predictable values of erythrocyte sedimentation rate were analyzed.

RESULTS: Erythrocyte sedimentation rate was found to be higher among patients with severe/critical disease compared to those with nonsevere disease ($p<0.001$) and among nonsurvivors compared to survivors ($p<0.001$). The logistic regression analysis showed that erythrocyte sedimentation rate was an independent parameter for predicting disease severity and mortality. The role of erythrocyte sedimentation rate in the assessment of severity and mortality in patients with COVID-19 was analyzed using the receiver operating characteristic curve and was found to be significant in both. The analyses suggested that the optimum erythrocyte sedimentation rate cutoff point for disease severity and mortality were 52.5 mm/h with 65.5% sensitivity and 76.3% specificity and 56.5 mm/h with 66.7% sensitivity and 72.5% specificity.

CONCLUSION: Our results suggest that erythrocyte sedimentation rate was an independent prognostic factor for severity and mortality in patients with COVID-19.

KEYWORDS: Blood sedimentation. COVID-19. Death. Prognosis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China, and progressed to a pandemic[1]. SARS-CoV-2 can cause a large spectrum of clinical manifestations[2,3]. While COVID-19 may be asymptomatic, it may also lead to severe conditions and death[2-4].

Many laboratory data, biomarkers, prognostic indices, or scoring systems that could predict the disease severity, prognosis, poor outcomes, and mortality have been reported[5-9]. Most of these prognosis predictors make assessments by using more than one parameter. Erythrocyte sedimentation rate (ESR) is used as a marker that indicates inflammation. ESR was reported to be able to predict the disease activity and prognosis in some other disorders[10-12]. There are few studies available evaluating ESR as a single predictor of the prognosis and mortality in COVID-19 patients. This study aimed to assess the association between ESR and the disease severity and mortality in patients with COVID-19.

[1]Sakarya University Faculty of Medicine, Department of Internal Medicine – Sakarya, Turkey.
*Corresponding author: tezcankaya@gmail.com, tezcan@sakarya.edu.tr.
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METHODS

Consecutive patients above 18 years of age who had been hospitalized at the local University Training and Research Hospital between February 1, 2021, and March 31, 2021, with the diagnosis of COVID-19 were included in this retrospective cohort study. The diagnosis of COVID-19 was confirmed with a reverse transcriptase polymerase chain reaction (RT-PCR) test of the nasopharyngeal/oropharyngeal swab. Patients who had malignancy, pregnancy, sepsis, bacterial infection, chronic infection, autoimmune disorder, rheumatic disease, and hematological disorder were excluded from the study. The demographic characteristics, comorbid conditions, and clinical and laboratory data of the patients were collected from the hospital data management system.

The patients were divided into two groups as those with severe/critical disease and nonsevere disease. The diagnosis of the disease severity was made according to the World Health Organization severity definitions[4]. While patients with severe/critical disease were followed up at the intensive care unit (ICU), patients with nonsevere disease were followed up at non-ICU. In addition, patients who survived and died constituted the other two groups. ESR and other laboratory data on admission (to ICU or non-ICU) were recorded. ESR measurement (mm/h) was made using a fully automated ESR analyzer, and the other laboratory tests were carried out using routine methods. The reference value for ESR was 0–20 mm/h for males and 30 mm/h for females. The data of the groups were compared. The difference of ESR according to groups and the role in the prediction of the disease severity and mortality were assessed. This study was approved by the local University Ethics Committee (no: E-71522473-050.01.04-6064).

Statistical analysis

Descriptive analyses of the variables were expressed as mean±SD in normal distributions, categorical data were given as numbers and percentages, and parameters with abnormal distribution were expressed as the median of the 25th–75th percentile. The comparison of difference between the groups was made by chi-square test, independent samples *t*-test, and Mann–Whitney U test. Pearson correlation analysis was used for correlation between ESR and other parameters. Receiver operating curve (ROC) analysis was used to calculate ESR with the required cutoff values to distinguish disease severity and mortality with maximum sensitivity and specificity. The variables predicting disease severity and mortality were determined by binary logistic regression analysis. The significance value was accepted as $p<0.05$. The SPSS version 20.0 package program was used in the analyses.

RESULTS

Of the 148 patients, 81 were female and 67 were male, and the mean age was 63.2±16.9 years. While 67 (45.27%) had severe/critical disease, 81 (54.73%) had nonsevere disease. The mean age of the patients with severe/critical disease was higher ($p<0.001$). The median ESR was statistically significantly higher in patients with severe/critical disease (66.5 *versus* 35.5, $p<0.001$). The comparison results of the demographics and clinical characteristics between patients with severe/critical disease and nonsevere disease are provided in Table 1. In addition, white blood cell (WBC) count, neutrophil count, prothrombin time (PT), D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, and fibrinogen were also significantly higher in patients with severe/critical disease (Table 1). Forty-two (28.38%) patients had died. The mean age of nonsurvivors was significantly higher ($p<0.001$). ESR was statistically significantly higher among nonsurvivors (69.5 *versus* 39, $p<0.001$). The comparison results of the patients' demographics and the clinical characteristics between survival and death are summarized in Table 2. Furthermore, the WBC count, neutrophil count, D-dimer, ferritin, aspartate transaminase (AST), LDH, CRP, procalcitonin, troponin, and lactate were significantly higher among nonsurvivors (Table 2).

There was a significant positive correlation between ESR and the WBC count, neutrophil count, CRP, procalcitonin, ferritin, and fibrinogen (r 0.197, $p=0.021$; r 0.274, $p=0.001$; r 0.496, $p<0.001$; r 0.265, $p=0.002$; r 0.386, $p<0.001$, and r 0.38, $p<0.001$, respectively). The binary logistic regression analysis showed that ESR was an independent parameter for predicting the disease severity (OR 1.035, 95%CI 1.019–1.051, $p<0.001$) and mortality (OR 1.030, 95%CI 1.013–1.046). The role of ESR on the assessment of COVID-19 severity and mortality was analyzed using the ROC curve and was found to be significant in both (AUC 0.741; $p<0.001$, 95%CI 0.657–0.826 and AUC 0.715; $p<0.001$, 95%CI 0.715–0.047; Figure 1). Analyses suggested that the optimum ESR cutoff points for the disease severity and mortality were 52.5 mm/h with 65.5% sensitivity and 76.3% specificity and 56.5 mm/h with 66.7% sensitivity and 72.5% specificity, respectively.

DISCUSSION

The present study has revealed that ESR as a single parameter may predict the disease severity and mortality in patients with COVID-19. The optimum cutoff value of ESR by ROC analysis was 52.5 mm/h, which resulted in 65.5% sensitivity and 76.3% specificity for predicting severe/critical COVID-19.

Table 1. Comparison of demographics and clinical characteristics between patients with severe/critical disease and the nonsevere disease.

	Patients with severe/ critical disease (n=67)	Patients with nonsevere disease (n=81)	p-value
Age (years)	70.5±12.6	57.3±17.8	<0.001
Gender (male/female)	27/40	40/41	0.269
Diabetes, n (%)	25 (37.3)	19 (23.5)	0.098
Hypertension, n (%)	29 (43.3)	38 (46.9)	0.659
CHD, n (%)	10 (14.9)	3 (3.7)	0.035
COPD, n (%)	4 (6)	2 (2,5)	0.255
Asthma, n (%)	6 (9)	4 (4.9)	0.260
Heart failure, n (%)	10 (14.9)	3 (3.7)	0.017
WBC, K/µL	8150 (5940–11000)	5340 (4580–6905)	<0.001
Neutrophil, K/µL	5835 (4487–9107)	3500 (2565–4850)	<0.001
Lymphocyte, K/µL	784 (511–1212)	1300 (900–1710)	<0.001
Hemoglobin, g/dL	12.5±1.5	12.5±1.3	0.823
Platelet, K/µL	199 (147–259)	179 (146–216)	0.143
Prothrombin time, s	13.4 (12.5–14.5)	12.5 (11.5–13.5)	<0.001
D-Dimer ng/mL	1300 (826–2130)	435 (220–832)	<0.001
Ferritin, µg/L	607 (380–1438)	207 (71–390)	<0.001
AST, U/L	44 (29–66)	29 (21–37)	<0.001
Albumin, g/dL	3±0.4	3.5±0.7	<0.001
LDH, U/L	448 (368–572)	257 (205–325)	<0.001
CRP, mg/L	114 (63–172)	19 (6.4–63)	<0.001
Procalcitonin, ng/mL	0.24 (0.12–0.58)	0.05 (0.03–0.17)	<0.001
ESR, mm/h	66.5 (47–73)	35.5 (22–52)	<0.001
Fibrinogen, mg/dL	409 (343–472)	324 (302–402)	0.002
Creatine kinase, U/L	105 (68–-279)	76 (44–136)	0.012

CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; aPTT: activated partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Similarly, the suggested cutoff value of ESR by the ROC analysis was 56.5 mm/h, which resulted in 66.7% sensitivity and 72.5% specificity for predicting death in COVID-19.

Some scoring systems that include many parameters have been investigated to determine the severity and mortality rate[7,13-15]. Liang et al.[7] have reported the COVID-GRAM risk score, which is composed of 10 parameters including chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, the number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH, and direct bilirubin as a predictor of the progression to critical illness. Boero et al.[13] revealed that the COVID-19 Worsening Score (COWS), which uses the combination of COVID-GRAM score variables and lung ultrasound score, may determine the patients who need ICU care. In another study, the National Early Warning Score 2 (NEWS 2) was found to be able to predict critical COVID-19 patients[14,15]. NEWS 2 score includes respiratory rate, oxygen saturation, need for supplemental oxygen, body temperature, blood pressure, heart rate, the level of consciousness, and new confusion variables[14]. The disadvantage of these scoring systems is predicting the prognosis using many parameters. On the other hand, this study revealed that examination of

Table 2. Comparison of demographics and clinical characteristics of COVID-19 patients between survival and death.

	Survival (n=106)	Death (n=42)	p-value
Age (years)	59.8±17.6	72.1±11	<0.001
Gender (male/female)	56/50	25/17	0.579
Diabetes, n (%)	29 (27.4)	15 (35.7)	0.422
Hypertension, n (%)	50 (47.2)	17 (40.5)	0.579
CHD, n (%)	14 (13.2)	11 (26.2)	0.097
COPD, n (%)	3 (2.8)	3 (7.1)	0.223
Asthma, n (%)	7 (6.6)	3 (7.1)	0.578
Heart failure, n (%)	9 (8.5)	4 (9.5)	0.532
WBC, K/µL	6000 (4895–8000)	8510 (5627–12450)	<0.001
Neutrophil, K/µL	4100 (2725–5635)	6345 (4210–9662)	<0.001
Lymphocyte, K/µL	1220 (878–1605)	662 (469–1055)	<0.001
Hemoglobin, g/dL	12.6±1.4	12.3±1.5	0.215
Platelet, K/µL	183 (150–237)	187 (142–236)	0.990
Prothrombin time, s	13.2±6.1	13.8±1.9	0.001
D-Dimer ug FEU/L	561 (240–1252)	1515 (884–2192)	<0.001
Ferritin, µg/L	267 (90–653)	576 (328–1438)	<0.001
AST, U/L	31 (22–41)	47 (28–78)	0.002
Albumin, g/dL	3.37±0.66	2.91±0.44	<0.001
LDH, U/L	289 (223–390)	451 (357–586)	<0.001
CRP, mg/L	37 (10–92)	128 (72–174)	<0.001
Procalcitonin, ng/mL	0.06 (0.03–0.20)	0.32 (0.18–0.82)	<0.001
ESR, mm/h	39 (22.7–58.2)	69.5 (48–72.7)	<0.001
Fibrinogen, mg/dL	348 (302–426)	417 (354–472)	0.053
Creatine kinase, U/L	87 (55–142)	112 (61–295)	0.012
Troponin, ng/L	5.4 (2.9–12)	27.5 (11.4–83.9)	<0.001
Lactate, mmol/L	1.6 (1.2–2)	1.9 (1.6–2.3)	0.001

CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; APTT: activated partial thromboplastin time; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

the ESR alone is sufficient for the prediction of the prognosis of COVID-19.

There are few studies focusing on the relationship between COVID-19 and ESR. Pu et al.[16] reported in a recent COVID-19 case that ESR remained elevated for a long time and, therefore, they could not determine any other reason to explain the high ESR levels. In some studies, ESR was evaluated together with other parameters when investigating the disease severity and prognosis markers[17-20]. However, no cutoff value was reported for ESR as a predictor of disease severity and mortality until our study.

A review by Xie et al.[18], including the data of 16,526 COVID-19 patients, evaluated the characteristics that predict progression and reported elevated ESR in 72.2% of the patients. In the meta-analysis of Zeng et al.[17], CRP, procalcitonin, interleukin-6 (IL-6), ESR, and ferritin were found to be higher in severe COVID-19 patients. In a systematic review and meta-analysis of Mahat et al.[20], CRP, ESR, procalcitonin, IL-6, IL-10, IL-2R, serum amyloid A, and the neutrophil-to-lymphocyte ratio were found to be significantly higher in severe COVID-19 patients.

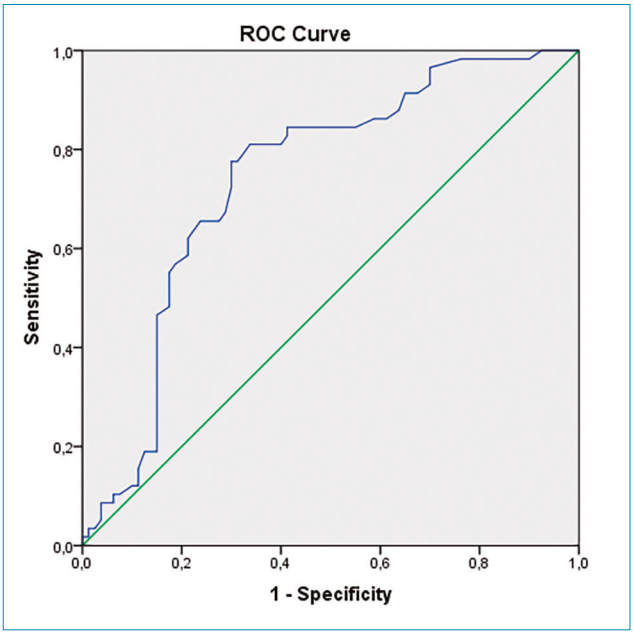

Figure 1. Receiver operating characteristic analysis showing the power of erythrocyte sedimentation rate to predict the disease severity (need for intensive care unit).

CONCLUSIONS

In this study, we observed that ESR as a single parameter is a valuable biomarker that may predict the disease severity and mortality. In addition, ESR is significantly correlated with the WBC, neutrophil, lymphocyte, CRP, procalcitonin, AST, albumin, D-dimer, and ferritin, which were shown to be significant prognostic markers for COVID-19.

AUTHORS' CONTRIBUTION

TK: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. AN: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. GKK: Conceptualization, Writing – original draft, Writing – review & editing. KTÇ: Conceptualization, Writing – original draft, Writing – review & editing. SY: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. CV: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. TK: Data curation.

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Association between fragmented QRS and postprocedural rhythm disturbances in patients who underwent transcatheter aortic valve implantation

Mustafa Duran[1]*, Murat Ziyrek[1], Yakup Alsancak[2], Hüseyin Ayhan[3]

SUMMARY

INTRODUCTION: According to recent studies, the rate of atrioventricular block requiring permanent pacing in patients following transcatheter aortic valve implantation varied between 5.7% and 42.5%. Fragmented QRS is a useful marker of myocardial scar and can predict adverse cardiac events. In this study, we examined association between fragmented QRS and postprocedural rhythm disturbances and the need for permanent pacing in patients who underwent transcatheter aortic valve implantation.

OBJECTIVE: In this study, we examined association between fragmented QRS and postprocedural rhythm disturbances and the need for permanent pacing in patients who underwent transcatheter aortic valve implantation' sentence is enough for it.

METHODS: We retrospectively analyzed standard 12-lead electrocardiographic recordings of 124 consecutive patients in whom a CoreValve prosthesis was implanted. We examined 12-lead electrocardiogram before and after procedure along with one- and six-month follow-up. We documented QRS fragmentation and postprocedural rhythm disturbances.

RESULTS: There was a significant increase in the frequency of left bundle branch block, (21.1 *versus* 0%, p<0.05) and the incidence of atrioventricular blocks requiring permanent pacing (21.1 *versus* 0%, p<0.05) following transcatheter aortic valve implantation in patients whose preprocedural electrocardiogram recordings revealed fragmented QRS compared to those without fragmented QRS. Based our collected data, the presence of QRS fragmentation in anterior derivations was the only independent factor associated with postprocedural rhythm disturbances (B-value 0.217; OR 0.805; 95%CI 0.136–4.78; p=0.004).

CONCLUSION*:* Our data showed an increased risk for the development of new-onset left bundle branch block and atrioventricular blocks following transcatheter aortic valve implantation in patients whose baseline electrocardiogram recordings demonstrated QRS fragmentation.

KEYWORDS: Aortic valve stenosis. Arrhythmias, cardiac. Transcatheter Aortic Valve Replacement.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has emerged as a novel therapeutic option for patients who are considered to be ineligible for open surgery[1]. However, postprocedural complications including rhythm disturbances and the need for permanent pacing are common[2].

[1]Konya City Hospital, Department of Cardiology – Konya, Turkey.
[2]Necmettin Erbakan University, Medicine Faculty, Department of Cardiology – Konya, Turkey.
[3]Atilim University, Medicine Faculty, Department of Cardiology – Ankara, Turkey.
*Corresponding author: drmustafaduran44@gmail.com
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Fragmented QRS complex (fQRS) is frequently seen on routine electrocardiographic (ECG) recordings with narrow or wide QRS complexes[3]. Prognostic significance of QRS fragmentation for predicting adverse cardiac events was demonstrated in previous studies[4-6].

In this study, we aimed to investigate the predictive role of fQRS in the occurrence of rhythm disturbances and the need for permanent pacing in patients undergoing TAVI.

METHODS

We retrospectively analyzed standard 12-lead electrocardiographic recordings of 124 consecutive patients in whom a CoreValve prosthesis (Medronic Inc., Minneapolis, USA) was implanted. Patients having bundle branch block, including left bundle branch block (LBBB), incomplete or complete right bundle branch block (RBBB), or QRS duration ≥120 msec in baseline ECG, and patients with permanent pacing were excluded from the study.

Demographic and clinical characteristics of patients and procedural variables were retrospectively analyzed. Preprocedural and the first and sixth months postprocedural ECG recordings were evaluated. Patients were divided into two groups based on the presence or absence of fQRS in the preprocedural ECGs. The presence of rhythm and types of rhythm disturbances were defined according to the AHA/ACCF/HRS recommendations for the standardization and interpretation of the ECG[7]. Any of the rhythm disturbances occurring within the first 48 hours after TAVI are accepted as temporary, and those persisting more than 48 hours as permanent. ECG measurements were performed by a cardiologist who was blind to the patient data and verified by a second physician to avoid errors in measurements. Definition of fQRS was made according to previous studies[8]. Informed consent was obtained from all patients in accordance with a protocol approved by the Ethics Committee of Ankara Ataturk Training and Research Hospital (approval number: 26379996-102).

Statistical analysis

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc., USA). Data were expressed as mean±SD for continuous variables and as counts and percentages for categorical variables. Differences were considered statistically significant at $p<0.05$. Fitness to the normal distribution was analyzed with the Kolmogorov–Smirnov test. Student's *t*-test and Mann–Whitney U tests were used for comparison of continuous variables, and chi-square and Fisher's exact tests were used for comparison of categorical variables. Binary logistic regression analysis was performed to explore independent factors associated with rhythm disturbances.

RESULTS

Of the 124 patients initially screened, 24 patients whose baseline ECG recordings demonstrated wide QRS (QRS>120 msec) were excluded, leaving 100 patients for analysis. According to our study, 71 patients whose baseline ECG demonstrated QRS fragmentation at least in one derivation formed fQRS(+) group and 29 patients whose baseline ECG did not demonstrate QRS fragmentation formed fQRS(-) group. A comparison of baseline clinical and demographic characteristics of both groups is provided in Table 1. Based on our data, male gender (52.1 *versus* 34.5%, $p<0.05$) and calculated Society of Thoracic Surgeons scores (7.3±1.7 *versus* 6.5±1.3, $p<0.05$) were significantly higher in fQRS(+) group compared with fQRS(-) group. In addition, there were significantly lower estimated left ventricular ejection fraction (45 *versus* 65%, $p<0.001$) and higher rates of the New York Heart Association (NYHA) classes (NYHA class III; 57.7 *versus* 41.4% and NYHA class IV; 26.8 *versus* 10.3%, $p<0.001$) in fQRS(+) group compared with fQRS(-) group. Although baseline ECG findings were comparable between the two groups, preprocedural heart rate was significantly lower in fQRS(+) group compared with fQRS(-) group (70.8±13.5 *versus* 77.4±13.3, $p<0.05$).

A comparison of procedural variables and postprocedural rhythm disturbances is given in Table 2. Both groups had similar procedural characteristics. Regarding rhythm disturbances, 39 of 71 patients with fQRS developed temporary rhythm disturbances during hospitalization. However, only 4 of 29 patients without fQRS developed temporary rhythm disturbances. Furthermore, 28 of 71 patients with fQRS and 1 of 29 patients without fQRS developed permanent rhythm disturbances. After implantation of the device, permanent pacing was required in 10 (10%) patients due to complete atrioventricular (AV) block.

Due to the loss of 10 patients, outcomes of 1- and 6-month follow-up were based on data of 90 patients: 62 patients in fQRS(+) and 28 patients in fQRS(-) group. The difference in permanent rhythm disturbances was also maintained in 1- month and 6-month follow-up (37.1 *versus* 0% and 38.7 *versus* 0%; $p<0.0001$). Binary logistic regression analysis provided that the presence of QRS fragmentation in anterior derivations was the only independent factor associated with postprocedural conduction abnormalities (Table 3).

Table 1. Comparison of baseline characteristics of fragmented QRS (+) and fragmented QRS (-) groups.

	fQRS (+) (n=71)	fQRS (-) (n=29)	p-value
Age (years)	76.5±8.6	79.1±5.2	0.078
Male gender, n (%)	37 (52.1)	10 (34.5)	0.045
Coronary artery disease, n (%)	47 (64.8)	15 (51.7)	0.254
Diabetes mellitus, n (%)	26 (36.6)	10 (34.4)	0.845
Hypertension, n (%)	54 (76.0)	21 (72.4)	0.758
COPD, n (%)	52 (73.2)	16 (55.2)	0.079
Atrial fibrillation, n (%)	29 (40.8)	10 (34.48)	0.495
β-Blocker therapy preoperative (n%)	44 (61.9)	17 (58.62)	0.678
Logistic EuroScore	29.9±9.6	28.5±9.7	0.509
STS score	7.3±1.7	6.5±1.3	0.035
NYHA class			
NYHA class II, n (%)	11 (15.5)	14 (48.3)	<0.001
NYHA class III, n (%)	41 (57.7)	12 (41.4)	0.046
NYHA class IV, n (%)	19 (26.8)	3 (10.3)	<0.001
Ejection fraction (%/ median, IQR)	45 (35–60)	65 (55–65)	<0.001
AVA (cm^2)	0.69±0.11	0.71±0.08	0.064
Aortic peak gradient (mm Hg)	77.4±26.8	79.9±23.5	0.658
Aortic mean gradient (mm Hg)	47.3.±14.9	49.1±16.4	0.861
Heart rate (bpm)	70.8±13.5	77.4±13.3	0.034
P wave duration (msec)	89.03±10.75	85.75±9.31	0.498
PR interval (msec)	142.06±17.86	139.03±15.56	0.297
QRS duration (msec)	106.44±3.14	103.16±5.87	0.382
corrected QT interval (msec)	398±13.55	387±10.85	0.078
AV block, n (%)	11 (15.49)	4 (13.79)	0.876

fQRS: fragmented QRS; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; AVA: aortic valve area, bpm: beats per minute; AV: atrioventricular. Bold values indicate statistical significance at p<0.05.

DISCUSSION

The main finding of this study is the presence of fQRS on surface ECG prior to the TAVI, which is a strong predictor for the development of rhythm disturbances and the need for permanent pacemaker implantation.

TAVI is a less invasive and safe therapeutic alternative in patients who are at very high surgical risk or in whom there are contraindications to surgical aortic valve replacement. On the other hand, life-threatening complications including stroke, paravalvular leak, and rhythm disturbances that require permanent pacing still persist[9]. In terms of postprocedural complications of TAVI, AV and intraventricular conduction disorders are still the most frequent adverse events[10].

Due to the importance of postprocedural rhythm disturbances, several studies were investigating the predictive risk factors for the development of rhythm disturbances in patients undergoing TAVI. According to those studies, septal wall thickness, noncoronary cusp thickness, preexisting RBBB, depth of valve implantation within the left ventricular outflow tract, postimplant prosthesis expansion, and the type of prosthesis were independent risk factors for this complication[11-14].

According to our study, there was a strong association between QRS fragmentation and postprocedural rhythm disturbances, including new-onset LBBB and complete AV block. In addition, the incidence of AV blocks requiring permanent pacing was higher in patients with fQRS than patients with non-fQRS (11 *versus* 0%, p<0.05). Furthermore, there was a strong relationship between the number of ECG leads with fQRS and the incidence of rhythm disturbances and this relation reached statistical

Table 2. Procedural characteristics and postprocedural rhythm disturbances of fragmented QRS (+) and fragmented QRS (-) groups.

		fQRS (+) (n=71)	fQRS (-) (n=29)	p-value
Single valve implantation, n (%)		66 (92.9)	28 (96.5)	0.014
Approach, n (%)	Transfemoral	67 (94.37)	27 (93.11)	0.684
	Transapical	4 (5.63)	2 (6.89)	0.698
İmplantation depth (mm)	LCC (mm)	6.37±2.54	6.32±2.53	0.601
	NCC (mm)	6.86±2.33	6.89±2.67	0.706
Predilatation, n (%)		53 (74.64)	20 (71.42)	0.804
Postdilatation, n (%)		10 (14.08)	4 (13.79)	0.901
Prosthesis size (mm)		27.30±2.66	26.85±2.46	0.181
Ratio of prosthesis size to annulus size		1.08±0.02	1.07±0.03	0.681
Intraoperative peak pressure gradient (mm Hg)		16.7±8.12	18.7±6.83	0.156
Intraoperative mean pressure gradient (mm Hg)		9.5±5.2	9.9±3.6	0.295
Postprocedural temporary rhythm disturbances				
		Total patients (n=100)	fQRS (+) group (n=71)	fQRS (-) group (n=29)
No rhythm disturbance (n)		57	32	25
Temporary RBBB (n)		4	2	2
Temporary LBBB (n)		27	25	2
Temporary first-degree AV block		17	15	2
Temporary second-degree AV block		0	0	0
Temporary third-degree AV block		12	12	0
Postprocedural permanent rhythm disturbances				
		Total patients (n=100)	fQRS (+) group (n=71)	fQRS (-) group (n=29)
No rhythm disturbance (n)		71	43	28
Permanent RBBB (n)		3	2	1
Permanent LBBB (n)		15	15	0
Permanent first-degree AV block		15	14	1
Permanent second-degree AV block		0	0	0
Permanent third-degree AV block		11	11	0
Postprocedural 1-month follow-up				
		Total patients (n=90)	fQRS (+) group (n=62)	fQRS (–) group (n=28)
No rhythm disturbance (n)		67	39	28
Permanent RBBB (n)		2	2	0
Permanent LBBB (n)		11	11	0
Permanent first-degree AV block		14	14	0
Permanent second-degree AV block		0	0	0
Permanent third-degree AV block		10	10	0

Continue...

Table 2. Continuation.

Postprocedural 6-month follow-up			
	Total patients (n=90)	fQRS (+) group (n=62)	fQRS (–) group (n=28)
No rhythm disturbance (n)	66	38	28
Permanent RBBB (n)	3	3	0
Permanent LBBB (n)	11	11	0
Permanent firs-degree AV block	11	11	0
Permanent second-degree AV block	0	0	0
Permanent third-degree AV block	10	10	0

fQRS: fragmented QRS; LCC: left coronary cusp; NCC: noncoronary cusp; RBBB: right bundle branch block; LBBB: left bundle branch block; AV: atrioventricular.

Table 3. Data of binary regression analysis.

	Beta value	Odds ratio	95%CI	p-value
Age	0.561	0.398	0.871–2.156	0.065
Male gender	0.231	0.167	0.451–1.542	0.483
STS Score	0.698	0.781	0.653–2.156	0.078
Preprocedural ejection fraction	0.327	0.349	0.642–2.256	0.087
AVA	0.611	0.472	0.486–1.459	0.118
Baseline heart rate	0.134	0.371	0.380–1.014	0.569
Baseline PR interval	0.498	0.287	0.135–1.816	0.603
Fragmentation in anterior leads on baseline ECG	0.217	0.805	1.036–4.78	0.004
Baseline QT_c interval	0.531	0.269	0.690–2.698	0.517
Baseline QRS interval	0.719	0.491	0.997–3.175	0.071
Prosthesis size	0.598	0.370	0.792–2.784	0.089

STS: Society of Thoracic Surgeons; AVA: aortic valve area. Bold values indicate statistical significance at p<0.05.

significance in anterior leads compared with inferior leads (84.1 *versus* 50%, p<0.05).

Although the exact mechanisms that cause the formation of fQRS are not fully understood, altered homogeneity of myocardial electrical activity as a result of myocardial fibrosis and/or ischemia is generally accepted as the underlying mechanism[15,16]. Recent studies also revealed the strong relationship between the presence of fQRS and severe aortic stenosis. According to a study conducted by Agac et al.[17], the incidence of fQRS was found to be 46% in patients with severe aortic stenosis. In our study, there was a higher rate of fQRS in patients with severe aortic stenosis compared with their study (71 *versus* 46%). The most plausible explanation was higher rates of comorbid conditions and lower rates of calculated ejection fraction in our study compared with their cohort.

In another study conducted by Ay et al.[18], there was a strong association between fQRS and long-term survival in patients undergoing TAVI. Although outcomes of our study were comparable with their study, our study group consisted of higher rates of patients with fQRS than their study (71 *versus* 30.7%). Due to exclusion of patients with a prior history of myocardial infarction, coronary bypass surgery, severe coronary lesions, and those with an ejection fraction ≤30% from their study, this difference was observed. They also investigated the relationship between the need for permanent pacing following TAVI and the existence of fQRS. According to their study, the need for permanent pacing in the long term was higher in patients with fQRS compared with patients without fQRS (8.3 *versus* 3.7%, p=0.29). Compared with our study, the rate of permanent pacing was lower (0.5 *versus* 10%) in their study and the most plausible explanation was the difference in types of devices used for the procedure. In our study, all patients (100%) underwent TAVI with the CoreValve prosthesis. However, only 26 (22.2%) of 117 patients underwent TAVI with CoreValve prosthesis in their study.

CONCLUSIONS

In conclusion, our data showed an increased risk for the development of new-onset LBBB and AV blocks in patients whose baseline ECG recordings demonstrated QRS fragmentation.

AUTHORS' CONTRIBUTIONS

MD: Conceptualization, Data curation, Formal analysis, Writing – original draft. **MZ:** Data curation, Formal analysis, Writing – review & editing. **YA:** Conceptualization, Writing – review & editing. **HA:** Conceptualization, Data curation, Formal analysis, Writing – review & editing.

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COVID-19 vaccine hesitancy among Chinese residents under the free vaccination policy

Huan Liu[1], Zhiqing Zhou[2], Xiubin Tao[2], Long Huang[3], Ergang Zhu[4], Liang Yu[5], Ming Zhang[6]*

SUMMARY

OBJECTIVE: This study aimed to assess the attitudes of Chinese residents toward COVID-19 vaccines and explore the potential drivers for Chinese residents' vaccine hesitancy.

METHODS: A cross-sectional survey was conducted from February 16 to March 16, 2021, by administering an online questionnaire to the Chinese residents.

RESULTS: Of 5240 residents who completed the survey, 464 (8.9%) participants reported to have had one shot, and 348 (6.6%) reported to have had 2 shots. At the time the questionnaire was administered, 2298 (43.9%) participants reported they wanted to get vaccinated, while 2255 (43.0%) declared that they still did not know, and 687 (13.1%) respondents declared vaccine refusal. Overall, 2255 (43%) participants were categorized as vaccine hesitancy. Female participants (p=0.000), <20 years old (p=0.000), have low risk of COVID-19 (p=0.000) infection and strong associations of vaccine hesitancy. eHealth literacy was a protective factor.

CONCLUSIONS: The results of this study show high rates of vaccine hesitancy in China. This could pose a serious threat to the preventive measures that aimed at controlling COVID-19 spread in the country. The government and different media platforms should encourage the dissemination of correct information about vaccines, the communities and medical staff to improve residents' knowledge about vaccines, and strive to improve residents' electronic health literacy.

KEYWORDS: COVID-19. Vaccine. China. Government.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) was initially reported in Wuhan, Hubei province, China, in December 2019. And due to its rapid worldwide distribution, the World Health Organization (WHO) declared it a pandemic in 2020[1]. COVID-19 pandemic has brought an unprecedented harm to human health and economic development, from all over the world. The pandemic has infected more than 160 million people and claimed more than 3.3 million lives. Vaccines have been proven to be an extremely effective way of dealing with epidemics in the past. Mathematic modeling indicates that 75% coverage is needed to reach the herd-immunity threshold to extinguish the ongoing pandemic[2]. However, the vaccine hesitancy has emerged as a major public health problem, topping the list of threats to global health.

Investigations of public attitudes during the pandemic have revealed that details about vaccine and recipient characteristics may influence eventual uptake. To our best knowledge, COVID-19 vaccination acceptance among Chinese residents

[1]Yijishan Hospital of Wannan Medical College, Department of Hemodialysis – Anhui, China.
[2]Yijishan Hospital Affiliated to Wannan Medical College, Department of Nursing – Anhui, China.
[3]Wannan Medical College, School of Humanities and Management – Anhui, China.
[4]Wannan Medical College, School of Comprehensive Foundation – Anhui, China.
[5]Wannan Medical College, School of Humanities and Management – Anhui, China.
[6]Wannan Medical College, School of Innovation and Entrepreneurship – Anhui, China.
*Corresponding author: wnyxyzhangming@foxmail.com
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has not been studied. The purpose of this study was to evaluate the vaccination acceptance of Chinese residents.

METHODS

Study design and setting

A cross-sectional survey was conducted from February 16 to March 16, 2021, by administering an online questionnaire to the Chinese residents. The participants in this study were recruited from an online survey, via a self-reported questionnaire, using Sojump (https://www.wjx.cn/). All the participants were recruited using simplified-snowball sampling technique, and the invited participants were asked to pass the invitation to their QQ and WeChat contacts. Before starting the survey, all participants had to give their informed consent, and the purpose of the study must be explained. Participants could withdraw from the survey at any time. All information and opinions provided by participants were anonymous and confidential.

Questionnaire development

The questionnaire was divided into two sections:

- Demographic information;
- eHealth Literacy Scale.

Assessment and evaluation

Demographic information

This section collects information about the general characteristics of the survey respondents, including gender, age, marital status, education level, if they had existing chronic diseases or not, risk of infection COVID-19, etc.

2.3.2. eHealth Literacy Scale (eHEALS).

The eHealth Literacy Scale (eHEALS) was compiled in 2006 by Norman and Skinner[3]. Guo Shuaijun et al. chineseized and revised the scale in 2014[4].There are a total of eight items, including application, evaluation, and decision-making. The Likert 5-level scoring method is used. From "very inconsistent" to "very consistent", 1–5 points are counted, and the total score is 8–40 points. A score of ≥32 is considered as qualified for electronic health literacy, and a score of less than 32 is considered as unqualified for electronic health. Cronbach's alpha coefficient of eHEALS was 0.975.

Statistical analysis

Information was collected from Sojump. All data were analyzed by IBM SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Frequencies and percentages were performed for categorical data. The chi-square test was used to verify the differences of categorical variables between groups. Binary logistic regression analyses were used to explore the impact factor of anti-COVID-19 vaccine hesitancy. The test level was a=0.05, that is, a p-value of less than 0.05 was considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate associations.

RESULTS

Demographic characteristics

A total of 5240 participants were included in this investigation. The average age of the 5240 participants was 25.07 years (SD=9.655; range 10–70), of which 19.8% were men; 44.2% of the participants lived in the city. Among all residents participating in the survey, 294 (5.6%) residents were high school graduate or less, 2779 (53%) residents were junior college, 1766 (33.7%) residents were college graduate, and 401 (7.7%) residents were advanced degree. Demographic data of the study samples are presented in Table 1.

The level of the COVID-19 vaccine hesitancy

A total of 464 (8.9%) participants reported to have had 1 shot, and 348(6.6%) participants reported to have had two shots. At the time the questionnaire was administered, 2298 (43.9%) participants reported they wanted to get vaccinated, while 2255 (43.0%) participants declared that they still did not know, and 687 (13.1%) participants declared vaccine refusal. Overall, 2255 (43%) participants were categorized as vaccine hesitancy.

Associated factors of COVID-19 vaccine hesitancy

When comparing the COVID-19 vaccine hesitancy and not, a significant difference was found in six items, such as gender, age, education, risk of infection COVID-19, chronic diseases, and eHealth Literacy (Table 1).

Regression analyses for COVID-19 vaccine hesitancy

To predict whether the independent variables were associated with COVID-19 Vaccine hesitancy, we used the logistic regression analyses. As shown in Table 2, four variables were found to be associated with COVID-19 Vaccine hesitancy, such as gender ($p<0.01$), age ($p<0.01$), risk of infection COVID-19 ($p<0.01$), and eHealth Literacy ($p<0.01$).

Table 1. Respondent characteristics (n=5240).

	Characteristic	Total n (%)	Hesitate n (%)		χ^2	p-value
			No	Yes		
Gender	Male	1037(19.8)	689(66.4)	348(33.6)	47.356	0.000**
	Female	4203(80.2)	2296(54.6)	1907(45.4)		
Age	<20	1994(38.1)	832(41.7)	1162(58.3)	431.112	0.000**
	20–30	1884(36)	1095(58.1)	789(41.9)		
	30–50	1196(22.7)	939(78.5)	257(21.5)		
	>50	166(3.2)	119(71.7)	47(28.3)		
Education	High school graduate or less	294(5.6)	170(57.8)	124(42.2)	173.738	0.000**
	Junior college	2779(53)	1354(48.7)	1425(51.3)		
	College graduate	1766(33.7)	1190(67.4)	576(32.6)		
	Advanced degree	401(7.7)	271(67.6)	130(32.4)		
Your risk of infection COVID-19	Low	3159(60.3)	1559(49.4)	1600(50.6)	323.685	0.000**
	General	1141(21.8)	651(57.1)	490(42.9)		
	High	940(17.9)	775(82.4)	165(17.6)		
	Other	206(3.9)	68(33)	138(67)		
Chronic diseases	No	4799(91.6)	2714(56.6)	2085(43.4)	3.952	0.047*
	Yes	441(8.4)	271(61.5)	170(38.5)		
eHealth Literacy	No	2365(45.1)	1107(46.8)	1258(53.2)	181.433	0.000**
	Yes	2875(54.9)	1878(65.3)	997(34.7)		

*p<0.05; **p<0.01.

Table 2. Logistic regression analyses for COVID-19 vaccine hesitancy (N=5240).

	B	SE	Wals	Sig.	Exp (B)	95%CI	
						Lower bound	Upper bound
Gender	0.331	0.079	17.358	0.000	1.392	1.191	1.626
Age<20			22.259	0.000			
20–30	-0.311	0.071	18.962	0.000	0.733	0.637	0.843
30–50	-0.477	0.152	9.808	0.002	0.621	0.461	0.837
>50	-0.281	0.23	1.495	0.221	0.755	0.481	1.185
Your risk of infection COVID-19 (Low)			72.398	0.000			
General	-0.132	0.077	2.974	0.085	0.876	0.754	1.018
High	-0.898	0.106	72.136	0.000	0.407	0.331	0.501
eHealth Literacy (No)	-0.353	0.065	29.732	0.000	0.702	0.618	0.797
Constant	0.631	0.095	44.244	0.000	1.88		

F=22.274; p=0.000, Cox Snell R^2=0.161, Nagelkerke R^2=0.216. *p<0.05, **p<0.01.

DISCUSSION

Key findings

This study found that three months after the vaccine was launched, among 5240 Chinese residents, only 43.9%, (n=2298) reported to be willing to accept COVID-19 vaccination. About 43% (n=2255) of the participants indicated unsure and 13.1% (n=687) indicated that they would refuse the vaccination. A total of 2255 (43%) participants were categorized as vaccine hesitancy; the overall hesitation rate was high. During the data collection period, February 16 to March 16, 2021, the total number of confirmed COVID-19 cases in China every day is almost zero, and the confirmed cases are all imported cases from abroad. On the other hand, various false information circulating on Internet and social media is also a determining factor influencing vaccine hesitancy in some groups.

It is worth noting that our data represent a high level of hesitation rate of the COVID-19 vaccine among the study population. Although China has successfully contained the epidemic, it should not underestimate the possibility of another outbreak. Previous studies have shown that high perceived susceptibility and high risk perception can be translated into better preventive measures and are related to enhanced epidemic control capabilities[5]. Therefore, sustainable prevention and control measures should be encouraged.

Differences in vaccine hesitancy

In our study, women were associated with higher rates of COVID-19 vaccine hesitancy, which is consistent with the previous results[6]. One possible explanation is that women are more likely to fear the unknown[7], and more cautious about trying new things. Some false claims about COVID-19 vaccines were believed that the vaccine is not good to female health[8]. And females are less educated, and the main source of information is social media platforms rather than medical institutions and doctors platforms.

In our study, 58.3% of the participants under 20 years old reported hesitancy to receive the COVID-19 vaccine. People under the age of 20 have the highest hesitation rate. In this study, the subjects under the age of 20 are basically college students. Because of the centralized management of the school, they feel more secure, so they show more hesitation. Young people feel healthier and, therefore, show more vaccine hesitancy[9].

Risk perception is crucial for vaccine decision-making. The present study found that perceived risk of contracting COVID-19 was negatively associated with hesitation to have a COVID-19 vaccination. Although the spread of the virus was well controlled after The Chinese government implementing a series of actions, the Chinese people experienced the earliest threats concerning COVID-19. The prevalence rates of symptoms of psychological distress were relatively high in the general population during the early stages of the COVID-19 pandemic in China[10]. These negative mood experiences will become the motivation for individuals to vaccinate against COVID-19.

These findings demonstrate that the trust in vaccines and government is key. In particular, addressing patients' concerns about the side effects through open and transparent communication may be very useful in building trust and confidence[11]. The huge amount of false/disinformation spread on social media casts a shadow on people's understanding of COVID-19 vaccine cause great confusion among the public.

The present study found that people with chronic diseases have a lower rate of vaccine hesitancy as others. Evidence suggests that patients with chronic diseases are particularly prone to serious complications and mortality than healthy individuals[12], which can lead to increased willingness to vaccinate.

Today, eHealth literacy is defined as "the ability to search, find, understand, and evaluate health information from electronic resources and apply the acquired knowledge to address or solve health problems"[13]. The internet has always been a major source of COVID-19 information, especially during the period of lockdown. However, many online information about COVID-19 lacks scientific rigor[14]. Theoretically, people with higher eHL should have the ability to efficiently process the flood of health-related information on the Internet and showed less anxiety and hesitation when faced with false information about COVID-19 vaccines on the Internet.

CONCLUSIONS

The results of this study show high rates of vaccine hesitancy in China. This could pose a serious threat to the preventive measures that aimed at controlling COVID-19 spread in the country. The government and different media platforms should encourage the dissemination of correct information about vaccines, the communities, and medical staff to improve residents' knowledge about vaccines and strive to improve residents' electronic health literacy. Our study further show that government provided timely information (such as side effects of the vaccine) by social media, and adequate protective supplies might mitigate the level of the hesitation of the COVID-19 vaccine.

AUTHORS' CONTRIBUTIONS

HL: Conceptualization, Methodology, Software, Validation, Writing–original draft preparation. **MZ:** Conceptualization, Validation, Resources, Writing–original draft preparation. **ZZ:** Software. **XT:** Validation. **LH:** Formal analysis. **EZ:** Investigation. **LY:** data curation.

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Effect of del nido cardioplegia use on kidney injury after coronary bypass operations

Ahmet Kağan AS[1]*, Mesut Engin[1], Bişar Amaç[2], Ufuk Aydın[1], Cüneyt Eriş[1], Yusuf Ata[1], Tamer Türk[1]

SUMMARY

OBJECTIVE: After cardiac surgery, acute kidney injury is observed at a rate of 5–30%, and the second most common cause of acute kidney injury in intensive care units is cardiac surgery. In this study, we aimed to investigate the effect of del Nido cardioplegia solution use on postoperative acute kidney injury development in patients who underwent coronary artery bypass grafting operation with cardiopulmonary bypass.

METHODS: Consecutive patients who underwent an elective coronary artery bypass grafting operation with cardiopulmonary bypass in our clinic between March 15, 2019, and March 15, 2020, were included in the study retrospectively. The patients were divided into two groups as those who received del Nido cardioplegia solution (Group 1) and blood cardioplegia (Group 2), and factors affecting the development of renal failure were examined.

RESULTS: A total of 350 consecutive patients were included in the study. There were 156 patients in the del Nido cardioplegia group and 194 patients in the blood cardioplegia group. Among the patient group, 74 (21.1%) patients developed acute kidney injury. The total acute kidney injury development rate was significantly higher in Group 2 (p=0.018). In multivariate logistic regression analysis, advanced age (OR 1.128; 95%CI 1.044–1.217; p=0.042), increased blood product use (OR 1.318; 95%CI 1.154–1.998; p=0.019), preoperative creatinine elevation (OR 2.434; 95%CI 1.655–4.639; p=0.005), and increased cardioplegia volume (OR 1.254; 95%CI 1.109–2.980; p=0.009) were independent predictors of acute kidney injury.

CONCLUSION: With this study, we showed that the use of del Nido cardioplegia solution can reduce the incidence of acute kidney injury.

KEYWORDS: Coronary artery bypass surgery. Cardiopulmonary bypass. Kidney. Cardioplegia.

INTRODUCTION

Among atherosclerotic cardiovascular diseases, coronary artery disease (CAD) is especially important. In its treatment, coronary artery bypass grafting (CABG) surgery can be successfully performed in conjunction with cardiopulmonary bypass (CPB) thanks to the developing extracorporeal circulation systems[1]. However, the use of these systems brings about the risk of various complications because of activated inflammatory pathways due to the contact of blood with foreign external surfaces. One of the major complications is renal failure. After cardiac surgery, acute kidney injury (AKI) is observed at a rate of 5–30%, and the second most common cause of AKI in intensive care units is cardiac surgery[2]. Many factors such as CBP duration, advanced age, the presence of preoperative renal failure, and blood transfusion play a role[3,4].

In CABG operations with cardiopulmonary bypass, the heart is usually arrested with cardioplegic solutions. Del Nido cardioplegia solution (dNCS), which was widely used in pediatric cardiac surgery in the past, has recently been used in adult cardiac surgery[5]. Various advantages of this cardioplegia method have been demonstrated over the standard intermittent blood

[1]University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Cardiovasculer Surgery – Yıldırım/Bursa, Turkey.
[2]University of Health Sciences, Mehmet Akif İnan Training and Research Hospital, Department of Perfusion – Yıldırım/Bursa, Turkey.
*Corresponding author: ahmetkagan_as@hotmail.com
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cardioplegia (BC), some of which include shortened perfusion and operation times, reduced use of blood products, and a similar level of myocardial protection[6,7].

In this study, we aimed to investigate the effect of dNCS use on postoperative AKI development in patients who underwent CABG operation with CPB.

METHODS

Consecutive patients who underwent an elective CABG operation with CPB in our clinic between March 15, 2019, and March 15, 2020, were included in the study retrospectively, which began after the approval was obtained from the local ethics committee. Emergency operations, combined surgical procedures, patients with preoperative renal insufficiency (creatinine >1.5 mg/dL), those who use platelet aggregation drugs, those who had acute myocardial infarction within the last month, those with a preoperative hemoglobin value <11 g/dL, reoperations, patients who were reoperated due to bleeding or peroperative myocardial infarction, those who needed preoperative inotropic drugs, and those who received intra-aortic balloon support were excluded from the study. As a surgical team, we started using dNCS in coronary surgery at the end of 2018. After the implementation of the exclusion criteria, 350 consecutive patients were included. The data of the patients were obtained from the hospital registry and the intensive care unit daily observation cards. Demographic data, preoperative characteristics, and operative and postoperative data were recorded. The patients were divided into two groups as those who received dNCS (Group 1) and BC (Group 2), and factors affecting the development of renal failure were examined.

Cardioplegia technique

In the BC group, cardiac arrest was achieved with an initial blood cardioplegia of approximately 1000 mL (10–15 mL/kg). Continuation of cardiac arrest was maintained with approximately 300 mL BC at 15–20-min intervals. In the del Nido cardioplegia group, cardiac arrest was achieved with 1000 mL of the dNCS. In patients whose aortic cross-clamping time would exceed 90 min, an additional 500 mL dNCS was administered 60 min after the first dose. Plasma-Lyte A (a basic solution with a pH value of 7.4 containing 140 mmol/L sodium, 5 mEq/L potassium, 3 mEq/L magnesium, 98 mEq/L chloride, 27 mEq/L acetate, and 23 mEq/L gluconate) is used in the preparation of dNCS[5]. However, balanced electrolyte solutions are used instead in many heart centers due to the difficulty of access[8]. In our center, we used Isolyte-S instead of Plasma-Lyte A.

Identification of postoperative renal failure

Hemogram and biochemical measurements were performed in all patients for three postoperative days. After these evaluations, in-hospital AKI development was defined as the primary end point of the study. Postoperative renal insufficiency was determined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Stage 1, Stage 2, and Stage 3)[9]. Development of one of the stages after surgical operations was defined as AKI.

Statistical analysis

SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program was used in the analysis of the data in our study. Continuous and ordinal data were expressed with means and standard deviations. Kolmogorov–Smirnov and Shapiro-Wilk tests were used to evaluate the distribution of normality. Student's *t*-test and the Mann-Whitney U test were used in the analysis of normally and non-normally distributed data, respectively. Frequency and percentage analyses were performed for nominal data, and the chi-square test was used for comparison. To analyze the factors affecting postoperative AKI development, univariate and multivariate logistic regression analyses were performed. $p<0.05$ was considered statistically significant.

RESULTS

A total of 350 patients were included in the study. There were 156 patients in the del Nido cardioplegia group and 194 patients in the BC group. There was no difference between the groups in terms of age, smoking, hypertension, and diabetes mellitus rates (Table 1).

Preoperative blood parameters of all patients are given in Table 1. There was no difference between the groups in terms of preoperative blood parameters such as hemoglobin, platelet counts, creatinine values, and C-reactive protein value. Operative and postoperative characteristics of the patients are presented in Table 2. The two groups were comparable in terms of total perfusion time, inotropic support needs, postoperative troponin T values, total intensive care stay, and mortality rates. Cross-clamp time, total amount of blood product used, total hospital stays, and AKI development rates were significantly higher in Group 2 ($p=0.014$, $p<0.001$, $p<0.001$, $p=0.018$, respectively).

Among the patient group, 74 (21.1%) patients developed AKI. The total AKI development rate was significantly higher in Group 2 ($p=0.018$). The rates of patients with Stage 2 and 3 renal insufficiency were similar between the groups. To analyze the factors affecting the development of AKI in the postoperative

Table 1. Preoperative features and preoperative laboratory variables of the patients.

	Group 1 (n=156)	Group 2 (n=194)	p-value
Age (years)	61.3±9.1	62.6±9.8	0.294
Male gender, n (%)	111 (71.1)	150 (77.3)	0.198
BMI (kg/m^2)	28.3±5.2	29.1±4.9	0.313
Hypertension, n (%)	75 (48)	105 (54.1)	0.237
Diabetes mellitus, n (%)	55 (35.2)	77 (39.6)	0.410
COPD, n (%)	30 (19.2)	35 (18)	0.797
Previous PCI, n (%)	51 (32.6)	69 (35.5)	0.315
EuroSCORE II	3.3±1.4	3.5±1.5	0.418
Smoking, n (%)	22(14.1)	30 (15.4)	0.710
Hiperlipidemia, n (%)	65 (41.6)	83 (42.7)	0.821
Ejection fraction (%)	51.3±9.1	50.2±9.2	0.478
ASA use, n (%)	67 (42.9)	78 (40.2)	0.613
ACEI/ARB use, n (%)	70 (44.8)	89 (45.8)	0.790
White blood cell (10^3/µL)	8.78±2.44	8.55±2.56	0.118
Hemoglobin (mg/dL)	13.3±1.2	12.9±1	0.274
Platelet (10^3/µL)	241.9±58.5	233.6±60.9	0.192
Neutrophil (10^3/µL)	5.4±1.82	5.33±1.86	0.312
Lymphocyte (10^3/µL)	2.28±0.82	2.21±0.79	0.226
Creatinine (mg/dL)	0.96±0.21	0.97±0.23	0.445
BUN (mg/dL)	19.9±6.8	20.1±5.9	0.528
CRP (mg/dL)	9.18±14.76	10.12±17.28	0.478

BMI: body mass index; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; EuroSCORE II: European system for cardiac operative risk evaluation II; ASA: acetylsalicylic acid; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BUN: blood urea nitrogen; CRP: C-reactive protein.

period, univariate logistic regression analysis was performed first. Advanced age (OR 1.224; 95%CI 1.090–1.414; p=0.003), hypertension (OR 0.878; 95%CI 0.621–0.914; p=0.022), total perfusion time (OR 0.819; 95%CI 0.499–0.916; p=0.034), need for inotropic support (OR 1.678; 95%CI 1.228–2.748; p=0.011), increased blood product use (OR 1.816; 95%CI 1.336–02.956; p=0.007), preoperative creatinine elevation (OR 3.156; 95%CI 1.874–4.614; p<0.001), and increased cardioplegia volume (OR 1.714; 95%CI 1.156–2.467, p<0.001) were correlated with the development of AKI (Table 3).

Based on the results of multivariate logistic regression analysis, advanced age (OR 1.128; 95%CI 1.044–1.217; p=0.042), increased blood product use (OR 1.318; 95%CI 1.154–1.998; p=0.019), preoperative creatinine elevation (OR 2.434; 95%CI 1.655–4.639; p=0.005), and increased cardioplegia volume (OR 1.254; 95%CI 1.109–2.980; p=0.009) were independent predictors of AKI (Table 3).

DISCUSSION

In coronary bypass operations performed with cardiac arrest, superior quality anastomoses can be achieved when excellent visibility is provided. Cardioplegia solutions are used for cardiac arrest in this technique. Previously known for its use in pediatric cardiac surgery, dNCS has become increasingly common in adult cardiac surgery in recent years. In this study, we aimed to investigate the effect of dNCS use on the development of AKI in CABG operations with CPB and found that patients receiving BC developed AKI more frequently than those receiving dNCS. Our multivariate analysis showed that besides parameters such as advanced age, increased blood product use, and preoperative creatinine height, increased cardioplegia volume was also an independent predictor of AKI (OR 1.254; p=0.009).

In recent years, various clinical studies have been published on the use of dNCS in open heart operations. Marzouk et al. compared the clinical results of dNCS and BC use in their study and

Table 2. Operative and postoperative features of the patients.

	Group 1 n=156	Group 2 n=194	p-value
Total perfusion time	90.28±25.56	93.56±24.78	0.175
Cross-clamp time	57.75±16.96	63.56±18.45	0.014
Number of distal anastomoses	3.35±0.9	3.29±0.9	0.102
Cardioplegia volume (mL)	1794.7±304.5	1090±144.6	<0.001
Packed blood products (units)	3.86±1.54	4.28±1.66	<0.001
Inotropic support, n (%)	18 (11.5)	25 (12.8)	0.184
Troponin T (ng/L)	208±32.55	215.34±34.79	0.210
Total ICU stay (days)	2.94±3.2	2.9±3.3	0.494
Total hospital stay (days)	7.34±3.12	7.7±4.14	<0.001
Development of AKI, n (%)	24 (15.3)	50 (25.7)	0.018
Stage 1 (%)	18 (11.5)	38 (19)	0.024
Stage 2 (%)	5 (3.2)	10 (5.1)	0.272
Stage 3 (%)	1 (0.6%)	2 (1)	0.794
Mortality, n (%)	6 (3.8)	9 (4.6)	0.898

ICU: intensive care unit, AKI: acute kidney injury.

Table 3. Logistic regression analysis to identify factors affecting postoperative acute kidney injury.

	Univariate analysis			Multivariate analysis		
	p-value	Exp(B) Odds Ratio	95%CI Lower–Upper	p-value	Exp(B) Odds Ratio	95%CI Lower–Upper
Age	0.003	1.224	1.090–1.414	0.042	1.128	1.044–1.217
Hypertension	0.022	0.878	0.621–0.914	0.214	1.114	0.716–1.134
Diabetes mellitus	0.056	0.768	0.448–1.278	–	–	–
Total perfusion time	0.034	0.819	0.499–0.916	0.312	0.779	0.596–1.020
Cross-clamp time	0.376	1.118	0.894–1.144	–	–	–
Inotropic support	0.011	1.678	1.228–2.748	0.118	0.986	0.657–1.295
Blood product use	0.007	1.816	1.336–2.956	0.019	1.318	1.154–1.998
Pre-creatinine	<0.001	3.156	1.874–4.614	0.005	2.434	1.655–4.639
Lymphocyte count	0.156	0.987	0.678–1.090	–	–	–
Cardioplegia volume	<0.001	1.714	1.156–2.467	0.009	1.254	1.109–2.980

found that perfusion time, operative time, and total cardioplegia volume were significantly lower in patients who received dNCS. They also demonstrated that dNCS provides similar myocardial protection with intermittent cold blood cardioplegia[7]. In another study performed by Ucak et al.[6], the administration of dNCS and intermittent warm BC during CABG surgery were compared. Similarly, the authors determined that perfusion times were shorter with dNCS. They also found that the duration of mechanical ventilation, length of stay in the intensive care unit, length of hospital stays, and 30-day mortality were significantly reduced in patients receiving dNCS[6]. In line with this information, aortic cross-clamp times and hospital stay were shorter in the dNCS group in our study as well. Our mortality rate was similar in both groups.

One of the key factors affecting postoperative AKI rates is increased blood transfusion. The key reason for increased blood transfusion in our operations is hemodilution. In a study comparing blood cardioplegia and dNCS, postoperative hemoglobin levels were higher in patients receiving dNCS[10]. In another

study, less cardioplegia volume was required in patients who were administered dNCS[11]. Increased use of blood products in these patients means increased hemolysis. Due to hemolysis, free-flowing hemoglobin consumes haptoglobin in the bloodstream. This catalyzes the production of free radicals and leads to sediment formation with Tamm-Horsfall proteins in the renal collecting system. Additionally, renal damage may occur because of increased nitric oxide consumption and consequent vasoconstriction in renal arterioles[12]. Hemolysis may cause AKI by increasing the free iron rate in the blood[13]. Increased blood product use has been shown as an independent predictor of AKI development in the study by Ramos et al.[14] In our study, we also found that increased blood product use was an independent predictor of AKI development (OR 1.224; p=0.019). We think that this may be due to decreased hemodilution because of decreased cardioplegia volume in patients receiving dNCS, because our multivariate analysis revealed that increased cardioplegia volume was also an independent predictor for AKI development (OR 1.254; p=0.009).

Total perfusion time and inotropic support were also associated with AKI development in our study. Hemolysis may occur due to extracorporeal circulation, and the renal risk increases due to atheroembolism[15]. In fact, there are publications showing that AKI development can be reduced by 40% in off-pump coronary bypass surgery[16]. Inotropic agents used in cardiac surgery practice are vasoconstrictor substances, which may also induce renal damage.

Advanced age is considered a risk in terms of mortal and morbid outcomes after surgery in all fields of medicine. With increasing age, the number of atherosclerotic foci and the risk of atheroembolism increase, especially in cardiac surgery operations performed with CPB. In addition, the vasoconstrictor response increases in the renal arteries of these patients, setting the groundwork for possible renal damage[17]. In our study, advanced age was an independent predictor of AKI. Recently, studies showing the clinical results of dNCS use in adult cardiac surgery are being published with increasing frequency. One of the key benefits of using dNCS is that cardioplegia is administered less frequently through the root needles. Frequent administration of pressurized fluid through the aortic root cannula may cause atherosclerotic embolism. Accordingly, microembolism incidence in different cardioplegia techniques was investigated in a prospective study by Mukdad et al., middle cerebral artery was visualized by transcranial Doppler ultrasonography at cross-clamp and cardioplegia times, and microembolism was scanned by monitoring. They found that single-dose dNCS strategy resulted in less cerebral microembolisms compared with conventional multi-dose cardioplegia. The authors suggested that this may be due to cardioplegia being delivered in fewer sessions[18]. Although we could not perform Doppler scans in our study, we believe that this parameter should be incorporated into further studies.

The most important limitations of our study include its single-centered, retrospective nature, and the sparse number of patients. In addition, evaluation of cystatin C, which is an important predictor of AKI, and similar blood parameters was not performed in our study. Also in our study, we found a relationship between Stage 1 AKI and cardioplegia type. More studies are needed with a larger number of patients.

CONCLUSION

In this study, we showed that the use of dNCS, which has become popular in adult cardiac surgery in recent years, can reduce the incidence of AKI. Novel studies are needed to elucidate the exact mechanism of this reduction.

AUTHORS' CONTRIBUTIONS

AKA: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **ME:** Writing – original draft, Writing – review & editing. **BA:** Writing – original draft, Writing – review & editing. **UA:** Writing – original draft, Writing – review & editing. **CE:** Writing – original draft, Writing – review & editing. **TT**: Writing – original draft, Writing – review & editing. contributed to drafting the manuscript and revising it critically for important intellectual content and made the final approval of the version to be published. **YA:** Formal analysis, Writing – original draft, Writing – review & editing.

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Incidental lung findings in coronary computed tomography angiography

Tuğba Eldeş[1], Bilge Yilmaz Kara[2]*

SUMMARY

OBJECTIVE: In coronary computed tomography angiography, a part of the lung parenchyma also enters the image area which is called the field of view. The aim of this study was to evaluate the rate of pulmonary abnormalities and document their association with demographic features in subjects undergoing multislice coronary computed tomography angiography obtained for the assessment of coronary artery disease.

METHODS: This was a retrospective observational study evaluating the coronary computed tomography angiography scans of 1,050 patients (58.5% males and 47.3% smokers) with a mean age of 52.2±11.2 years, obtained between January 2018 and March 2020. Pulmonary abnormalities were reported as nodules, focal consolidations, ground-glass opacities, consolidations, emphysema, cysts, bronchiectasis, atelectasis, and miscellaneous.

RESULTS: In total, 274 pulmonary abnormalities were detected in 266 patients (25.3%). The distribution of incidental lung findings was as follows: pulmonary nodules: 36.4%, emphysema: 15.6%, bronchiectasis: 11%, ground-glass opacities: 7.2%, atelectasis 7.2%, focal consolidations: 5%, cysts: 6%, consolidations: 2.5%, and miscellaneous: 9.1%. The patients with pulmonary pathology were older (55.5±11.4 *versus* 51.0±10.9 years), and the percentage of smokers was higher (60.1 *versus* 43.2%). The possibility of the presence of any incidental lung findings in field of view of coronary computed tomography angiography increases significantly over the age of 40.5 years (p<0.001, AUC 0.612, 95%CI 0.573–0.651).

CONCLUSION: Multislice coronary computed tomography angiography can give important clues regarding pulmonary diseases. It is essential for the reporting radiologist to review the entire scan for pulmonary pathological findings especially in patients with smoking history and over the age of 40.5 years.

KEYWORDS: Computed tomography angiography. Solitary pulmonary nodule. Incidental findings.

INTRODUCTION

Coronary artery disease (CAD) maintains its high-risk potential for morbidity and mortality in the stressful life pace of our age. Coronary computed tomography angiography (CCTA), which is a non-invasive technique that can display the anatomical structure and features of the vascular lumens of the coronary arteries along with the hilar-perihilar lung parenchyma within the FOV, is an important non-invasive tool with excellent negative predictive value (99%)[1]. Additionally, some of the risk factors for CAD, such as increasing age and smoking, are also risk factors for pulmonary pathological findings such as bronchial carcinoma[2,3].

The issue of incidental imaging findings, in patients undergoing imaging for an unrelated reason, is the subject of debate. First of all, these findings may lead to anxiety in patients. Because of the clinical uncertainty regarding their

[1]Recep Tayyip Erdoğan University, Department of Radiology – Rize, Turkey.
[2]Recep Tayyip Erdoğan University, Department of Pulmonary Medicine – Rize, Turkey.
*Corresponding author: drbilgeyilmaz@hotmail.com
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ideal management, they frequently lead potential over investigations. In addition, it is difficult for clinicians to appropriately inform patients of the chance of incidental findings because the prevalence is inconsistent and unclear[4]. Similarly, there are contradictory opinions about the benefits of scanning and reporting lung fields included in the CCTA[5]. The aim of this study was to provide information about the incidental lung findings in the FOV of patients undergoing routine CCTA and to interpret the results in a way that is more practical for medical application.

METHODS

This study was designed as an observational, retrospective, cross-sectional study, and the data were obtained from the patients' records between January 2015 and December 2019. Lesions in the lung parenchyma and the hilar–mediastinal regions that entered the FOV of routine CCTA scans were recorded. We searched for the available data related to smoking and identified the participants as smokers if they were current smokers or ex-smokers with a smoking history of more than 20 pack-years. This study was approved by the Recep Tayyip Erdogan University Clinical Researches Ethical Committee (No.: 2019/162).

Coronary CT angiography procedure

All CCTA scans were performed after oral β-adrenergic receptor blocker administration 12 h before the procedure. The blood pressure and the heart rate were monitored at 5-min intervals by an experienced cardiologist[6]. Region of interest was placed in the aorta that emerged with the bolus tracking technique[7], and scanning was started automatically when the contrast density reached 300 HU.

All patients were referred to have a radiologic assessment and have been retrospectively selected regardless of their pre-diagnosis. The CCTA scans have been run in different phases according to the electrocardiography triggering method[8] with 128 detectors (General Electric Discovery CT750 HD CT device). All CCTA images were evaluated by a radiologist with a national cardiovascular certificate of competence.

Assessment of pulmonary findings

Patients who were under the age of 18 years and who had a bronchial carcinoma history or lung surgery, such as lobectomy or pneumonectomy, and those with missing data and consecutive CCTA recordings were excluded from this study. The incidental lung findings were grouped under the following headings: solid nodule, calcified nodule, ground glass nodule, focal consolidation, ground-glass opacity (GGO), consolidation, emphysema, cyst, bronchiectasis, atelectasis, and miscellaneous (pleural effusion, pleural calcification, etc.)

Statistical analysis

SPSS 20.0 software (SPSS Inc., Chicago, USA) was used for statistical analysis. Parametric data were presented as mean±SD. The normality test was performed on all variables. The Student's *t*-test was used for parametric variables, and Mann-Whitney U test was used for the nonparametric distribution of variables. Spearman's and Pearson's tests were used for correlation analysis. Yates correction, chi-square test, and Fisher's exact test were used for the comparison of categorical data.

Receiver operating characteristic (ROC) curve analysis was used to find out the cutoff value, sensitivity, and specificity of age for predicting the presence of pulmonary pathology. Differences were considered statistically significant if the $p<0.05$.

RESULTS

The CCTA scans of 1,050 patients (58.5% males and 47.3% smokers) were retrospectively evaluated. The mean age was 52.2±11.2 (minimum–maximum: 19–89) years. A total of 274 incidental lung findings were present in 266 patients (25.3%). The rates of pathological findings were as follows: nodules: 100 (solid nodules: 85, ground-glass nodules: 10, and calcified nodules: 5), emphysema: 43, bronchiectasis: 30, miscellaneous (pleural effusion, pleural thickening, etc.): 25, atelectasis: 20, GGOs: 20, cysts: 16, focal consolidation: 13, and consolidation: 7 (Figure 1). The number of the pathological pulmonary findings according to localization was as follows: left upper lobe: 14, lingula: 34, left lower lobe: 59, right upper lobe: 23, right middle lobe: 48, right lower lobe: 25, diffuse: 70, and miscellaneous (pleura, fissures, etc.): 20 lesions. A case of bronchial carcinoma, a case of esophageal cancer, a giant sliding hernia, and a foreign body in the right lower lobe bronchus were also reported (Figure 2).

When patients with and without pulmonary pathology were compared, those with pulmonary pathology were older and the percentage of smokers was higher (Table 1).

Advanced age and smoking have been found to positively correlate with the presence of pulmonary pathology. In the ROC analysis, the cutoff value of age for predicting the presence of pulmonary pathology was 40.5 years ($p<0.001$, AUC 0.612, 95%CI 0.573–0.651, sensitivity: 91.4%, specificity: 17.1%, negative predictive value: 94%, positive predictive value: 11%, and positive and negative likelihood ratio: 1.1 and 0.53, respectively).

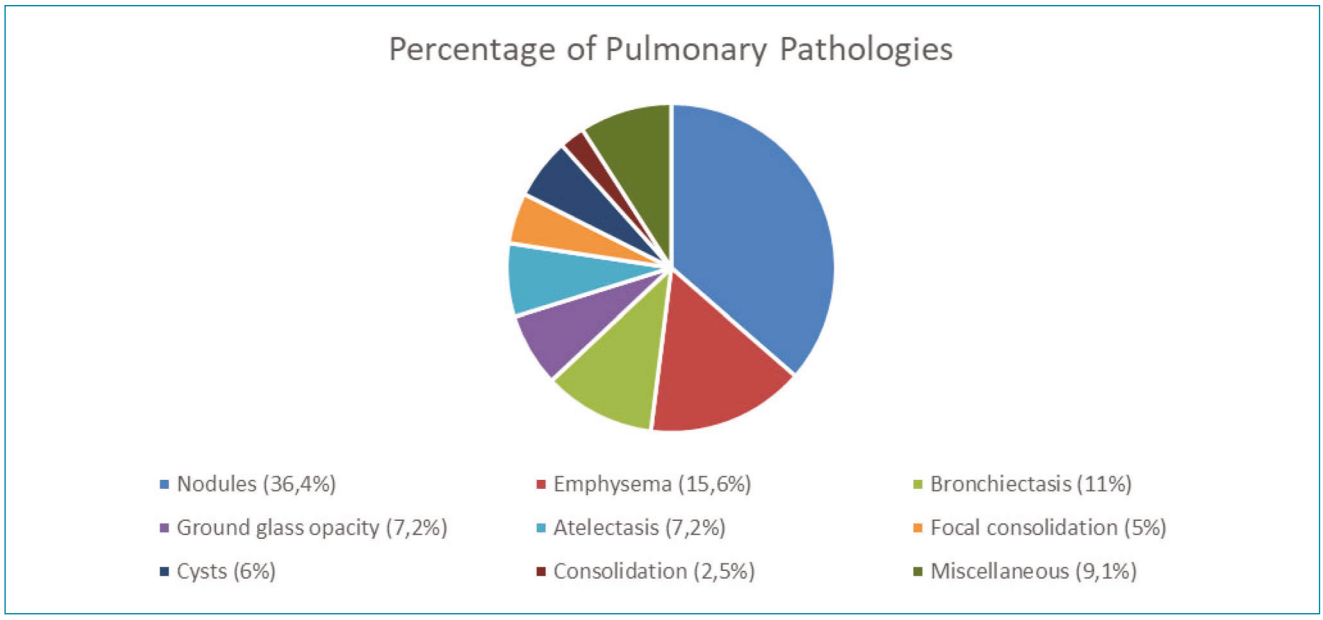

Figure 1. Types of pulmonary pathologies.

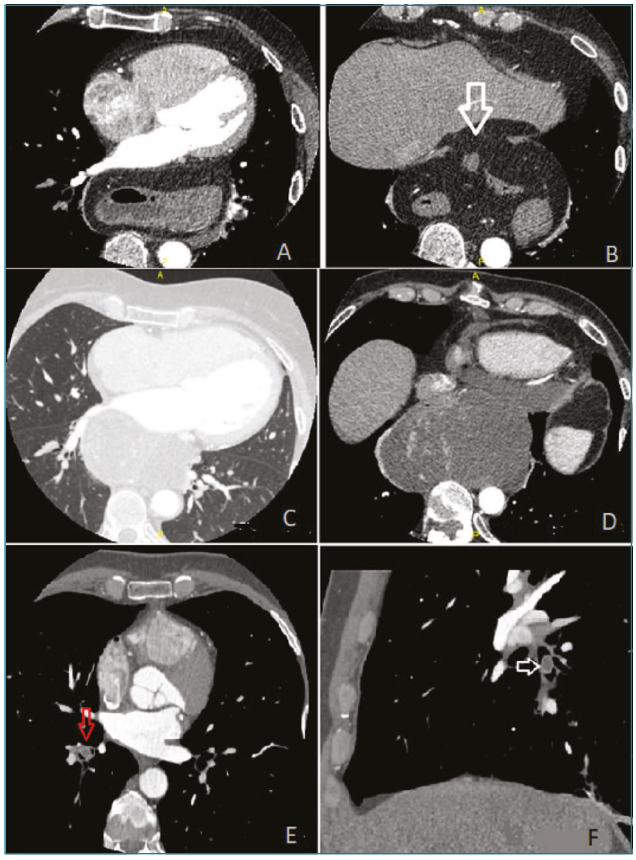

Figure 2. (A) Herniated intra-abdominal soft tissues compressing the left atrium; (B) wide diaphragmatic defect; (C) esophageal mass compressing the left atrium and right pulmonary veins; and (D) giant esophageal mass and pericardial effusion. Foreign body (cherry seed) in right lower lobe bronchus (E) axial section and (F) sagittal section.

Table 1. Comparison of patients with and without pulmonary pathology.

	Pulmonary pathology (-) (n=784)	Pulmonary pathology (+) (n=266)	p-value
Age (years)	51.0±10.9	55.5±11.4	<0.001
Gender (M/F)	467/317	148/118	0.261
Smokers (%)	43.2	60.1	<0.001

n: number; M/F: male/female. The numbers in bold represent the p-values statistically significant.

DISCUSSION

In our study, a total of 274 incidental lung findings were identified in 266 of the 1050 CCTA scans (25.3%). It was determined that the patients who have incidental lung findings were older and had a higher rate of smoking history. The most common lesion type and localization were (solid) nodules and diffuse distribution (mostly emphysema), respectively. The rate of incidental findings in our study is consistent with previous studies that reported the rate of extracardiac findings at cardiac CT as 25 and 26.6% in CCTA[9]. In the study by Yorgun et al. which includes 1,206 subjects, 186 pulmonary abnormalities were detected in 171 patients (14.1%)[10]. The mean age of the study population was 58.7 years. In this study, the mean age of the patients was 52.2±11.2 years although the possibility of pathological findings has been found to increase significantly over the age of 40.5 years. When compared, the percentage of our incidental findings is higher although the mean age of the study population is lower.

The discordance may be due to the time elapsed between the two studies and environmental, socioeconomic, and climatic differences. In recent years, with the rapid development of computed tomography technology, the radiation dose has gradually decreased, and the image quality has increased. This low-dose advantage might have paved the way for the use of CCTA for younger patients with atypical and intense subjective complaints as well as for medium-risk patients with stable angina. In addition, the higher proportion of smokers in our study (47.3 *versus* 38.9%) may explain the higher incidence of pulmonary pathologies. Since the probability of malignancy of pulmonary nodules increases after the age of 40 years, incidental findings should be more carefully followed over this age[11].

There is a positive correlation between smoking and the presence of incidental pulmonary findings (r=0.147, p<0.001), in our study population. A study that demonstrates the prevalence of incidental findings by cardiac CT scanning among patients on hemodialysis reports no correlation between the smoking status and the presence of any incidental findings or pulmonary nodules. Smoking was defined as self-reported lifetime exposure of at least 100 cigarettes, which was very few when compared with our study. This supports the idea that incidental findings are less likely to appear in those exposed to small amounts of cigarette smoke. More information is needed to specify the cutoff value for smoking regarding pulmonary abnormalities in asymptomatic smokers[12].

The most common incidental findings on CCTA scans are pulmonary nodules, which were consistent with previous studies[13]. The percentage of pulmonary nodules reported in CCTA studies ranges from 9.3–19% for nodules <1 cm and 0.6–2.4% for nodules >1 cm. In our study, the percentage of nodules was 9.5% (100/1,050) which is consistent with the literature[9]. In a study by Iribarren et al., 81 out of 459 subjects (18%) had noncalcified pulmonary nodules in cardiac computed tomography. The lesion disappeared in 35%, decreased or remained stable in 62%, and there was interval growth in 3% of the participants who were followed up for a 24-month period. This study has highlighted that reporting noncalcified pulmonary nodules resulted in substantial rescanning that overwhelmingly revealed the resolution or stability of pulmonary nodules[14]. As a limitation, because of the retrospective design of our study, we have reported the incidental findings but did not follow the consequences of the "important" findings.

The radiologists have high levels of familiarity and adherence to guidelines for pulmonary nodule evaluation, but they may overestimate the quality of evidence in support of the recommendations[15]. In addition, the incidental nodules are usually <6 mm in size and do not need further follow up[16] unless they are subsolid nodules (including those with pure ground-glass or part-solid types) close to 6 mm in size with suspicious morphology or other risk factors[17]. Haller et al.[18] recommended classifying the incidental findings into major and minor groups. In this way, prevention of over-tracking the clinically insignificant pathologies such as millimetric nodules or congenital variations and elucidating exceptional conditions such as tumors, pulmonary embolism, and foreign bodies can be possible[18]. Onuma et al. reported 319/552 (58%) of patients with at least one extracardiac findings of which 22.7% of them were considered "important"[19]. Clinicians need to be aware of the incidental findings as well as the false-positive results and discuss them with patients, alongside the expected benefits of surveillance imaging[20]. From the perspective of CCTA, it would be favorable both for the patients and the clinicians to classify the incidental lung findings in FOV of CCTA according to their clinical significance.

CONCLUSIONS

Incidental pulmonary findings are common in CCTA, and they are often benign. Hence, the clinician and the patient must take a joint decision to agree to distinguish benign pathologies of no clinical significance from serious lesions, which are quite rare but vital.

AUTHORS' CONTRIBUTIONS

TE: Conceptualization, Data Curation, Formal Analysis, Writing – original draft, Writing – review & editing. **BYK:** Data Curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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Reflection of vaccine and COVID-19 fear in young groups in the COVID-19 pandemic

Remziye Can[1], Şerif Kurtuluş[2]*

SUMMARY

OBJECTIVE: This study aims to determine the fear of COVID-19 through the opinions of individuals under the age of 18 on the COVID-19 vaccine and vaccination.

METHODS: This cross-sectional study was conducted on 290 high school students studying in a central district between February 15, 2021, and March 1, 2021. The questionnaire consisted of questions about the sociodemographic characteristics of the students and COVID-19 infection and the Fear of COVID-19 Scale.

RESULTS: The age of the participants ranged from 14–18; 76.9% of the study group consisted of female students; and 76.9% of the participants declared that they live in middleincome households. Participants reported that they lived in the same house with at least 2 and a maximum of 12 people; 9.7% of the participants reported that they had a COVID-19 infection; 62.4% of the participants reported that they want to get the COVID-19 vaccine; and 55.2% of the participants reported that the COVID-19 vaccine will reduce the transmission. The mean obtained from the Fear of COVID-19 Scale is 3.38±4.75 in the whole group. It was determined that there was a significant difference between genders, the effect of the vaccine on the incidence, the status of having a COVID-19 infection, and the score of the Fear of COVID-19 Scale.

CONCLUSION: The attitudes of young individuals, who are one of the vulnerable groups during pandemic periods, toward vaccination are important in terms of infecting those they come into contact with and increasing the rate of infection.

KEYWORDS: Adolescent. COVID-19. Fear. Infection. Vaccine.

INTRODUCTION

Coronavirus (SARS CoV-2), which emerged in China in 2019, causing the illness of about 197 million people and the death of 4.2 million people worldwide, can be considered as a global unifying problem that the whole world is fighting simultaneously[1], because countries are in search of solutions to prevent the spread of the disease and other epidemics that may occur in the following years. Therefore, prevention studies, medical treatment, and vaccine studies continue simultaneously in many parts of the world[2]. Vaccination is the most effective way to control infectious diseases. However, there are many factors that affect the vaccination or non-vaccination status of individuals. Religious beliefs, family lifestyles, receiving alternative treatments, perceived risk of disease, effectiveness and side effects of the vaccine, social environment, and cultural values are among the factors that affect the frequency of vaccination[3,4]. Similar to adults, COVID-19 is common in children[5]. Children are leading among important groups in vaccination against infectious

[1]Mustafa Kemal Atatürk Vocational and Technical Anatolian High School, Nursing Public Health – Eskişehir, Turkey.
[2]Harran University, Faculty of Medicine, Department of Chest Diseases – Şanliurfa, Turkey.
*Corresponding author: drkurtulus1@gmail.com
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diseases[6]. Vaccination of the child group, which is one of the most vulnerable groups in the COVID-19 pandemic, remained in the background compared with other age groups due to the milder course of the disease and not being included in the vaccine efficacy studies. Since January 2020, regional and local measures, keeping the children under the age of 18 at home (restriction of educational institutions and outdoor activities), are known to cause feelings of hopelessness, anxiety, and stress. Studies have shown that stress, fear, and anxiety increase more in children and adolescent groups[6,7]. This study aims to determine the fear of COVID-19 by the opinions of individuals under the age of 18 on the COVID-19 vaccine and vaccination.

METHODS

This cross-sectional study was conducted on high school students studying at Eskişehir Mustafa Kemal Atatürk Vocational and Technical Anatolian high school in a central district between February 15, 2021, and March 1, 2021. This study was approved by the Harran University Ethical Committee (04.01.2021; session: 01; decision no: 26). In addition, permission was obtained from the Ministry of Health. Students were informed online before participating in the study, and they were asked to approve the voluntary participation form.

Inclusion criteria were as follows: studying at Eskişehir Mustafa Kemal Atatürk Vocational and Technical Anatolian high school, having a smartphone, and volunteering to participate in the study. The questionnaire link was first sent to classroom teachers via a messaging network. The classroom teachers shared the questionnaire link on the classroom messaging network and asked the students to fill it out.

The data were collected by applying an online questionnaire to the students. The first part of the questionnaire consisted of questions about the sociodemographic characteristics of the students and COVID-19 infection. The questionnaire defining the sociodemographic characteristics consisted of the student's age, gender, family income status, and the number of people living at home. This section consists of a total of nine questions: whether students have COVID-19 infection, whether they want to get the COVID vaccine, whether they think the COVID vaccine will reduce the transmission, and reasons for getting the COVID vaccine or not. In the second part, the fear experienced during the COVID period was evaluated with the Fear of COVID-19 Scale (FCV-19S). FCV-19S is a Likert-type scale consisting of seven questions in total. Each item is scored with five points ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). The score that can be obtained from the scale varies between 7 and 35, and the high score indicates that the fear of coronavirus has increased. The Fear of COVID-19 Scale was developed by Ahorsu et al. (2020) (Cronbach's alpha value is 0.86), and its Turkish validity and reliability were determined by Haktanır et al. (2020) (Cronbach's alpha value=0.83)[8]. The Cronbach's alpha value calculated for this study was 0.81.

The number of students studying at Eskişehir Mustafa Kemal Atatürk Vocational and Technical Anatolian high school was 619. The sample size was determined by the calculation made in societies whose universe[9] is known, which is 238. The study was completed with 290 students in accordance with the inclusion criteria.

The data obtained were evaluated with the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY) in the computer environment. The frequency and percentage distribution of descriptive data on sociodemographic and COVID-19 infection were calculated. The COVID-19 fear score was compared with independent variables by *t*-test in independent groups. A value of $p<0.05$ was considered statistically significant.

RESULTS

The age of the study group ranged between 14 and 18 years, and the mean was 15.57±1.22. While 53.5% of the study group was in 15 age group, 46.5% was in 16 age group; 76.9% of the students in the study group were females and 23.1% were males; and 76.9% of the participants declared that they live in middle-income households. The number of individuals that the study group lives with at home was 2–12, and the mean was 4 (Table 1).

Table 2 shows the distribution of the data of the study group on COVID-19 infection; 9.7% of the study group reported that they had a COVID-19 infection; and 62.4% of the study

Table 1. Sociodemographic characteristics.

	n	%
Gender		
Female	223	76.9
Male	67	23.1
Age		
15 and low	155	53.5
16 and above	135	46.5
Family income		
High	61	21.0
Medium	223	76.9
Low	6	2.1
Number of individuals living in the house	2–12 mean 4.37	

group stated that they wanted to have the COVID-19 vaccine. While 55.2% of those in the study group thought that the COVID-19 vaccine would reduce the transmission, 37.6% stated that they did not think that the COVID-19 vaccine would reduce the transmission. Among the reasons for the people in the study group who want to get the COVID-19 vaccine, the highest frequency is the concern of transmitting the virus to my family and loved ones with 46.2%. The reason of the 8.6% of the study group for getting the COVID-19 vaccine is the threat during the pandemic, and 7.9% of those is the illness and death anxiety; 30% of the study group did not want to be vaccinated with the concern that it may cause side effects, 5.9% because of not believing the effectiveness of the vaccine, and 3.4% for feeling like a guinea pig (Table 2).

The scores of the study group from FCV-19S range from 5–22, with a mean of 3.38±4.75 (data not shown in the table). According to the independent samples *t*-test, it was determined that scores of FCV-19S of the study group are significantly different according to gender (t=3.233, p=0.000). In the study group, the mean score of FCV-19S of those who do not think that the vaccine will have an effect on the incidence was higher than those who think that the vaccine will have an effect on the incidence, and it was found that there is a significant difference between them (t=1.348, p=0.027). It was found that the mean score of FCV-19S of those in the study group who did not want to be vaccinated was higher than those who wanted to be vaccinated, and there was a significant difference between them (t=0.471, p=0.036) (Table 3).

Table 2. Variables related to COVID-19 infection.

	n	%
Have you had a COVID-19 infection?		
Yes	28	9.7
No	262	90.3
Would you get the COVID-19 vaccine?		
Yes	181	62.4
No	109	37.6
Do you think COVID-19 vaccine have an effect on reducing the incidence?		
Yes	160	55.2
No	130	44.8
Reason for willing to get COVID-19 vaccine		
The fear of transmitting the virus to their family and loved	134	46.2
Threat of pandemic	25	8.6
Fear of disease and death	22	7.9
Reason for unwilling to get COVID-19 vaccine		
Side effect	84	30.0
Not believing the effectiveness of the vaccine	15	5.9
Feeling like a guinea pig	10	3.4

DISCUSSION

Pandemics in world history have always been trying times. COVID-19 has affected the lives of people around the world, including children and adolescents, in an unprecedented manner[7]. In the COVID-19 pandemic caused by the SARS CoV-2 virus origin, the number of cases, deaths, and the impact caused by the disease are in a wide range. It is known that the disease is mostly seen in vulnerable people, people with advanced age, and people with chronic diseases. However, in addition to these data, the adolescent group is one of the groups that are not considered at risk due to the low incidence of the disease. Although children appear to be less affected than adults, there have been cases in children since the infection emerged[10,11]. According to the systematic review of Ludvigsson (2020), pediatric cases constitute 1–5% of the cases[11]. In our study, it was determined that 9.7% of the participants were diagnosed with COVID-19. This frequency is almost 1 in 10 people. In South Korea, the frequency of cases reported in individuals under 19 during the epidemic period is 18%. Azhar et al. reported that 2% of the cases involved children in the SARS-CoV epidemic that spread in 2002[12]. In the light of these data, it is possible to say that the effect of SARSCov-2 on the population under the age of 18 is more severe than the pandemics experienced in the past. Therefore, the inclusion of children in the vaccination program may affect the course of the pandemic. Zimer et al. and Boehmer et al. emphasized that children and adolescents should also be included in vaccine groups so that the pandemic does not worsen[13,14].

Table 3. Comparison of COVID-19 Fear Scale Score with independent variables.

	Mean±SD	t-value	p-value	95%CI
Gender				
Female	3.87±0.33	3.233	0.000	0.825–3.393
Male	1.76±0.41			
Effect on the vaccine to the incidence				
Yes	3.04±4.16	1.348	0.027	0.348–1.860
No	3.80±5.38			
Would you get the COVID-19 vaccine?				
Yes	3.13±4.41	0.471	0.036	2.310–1.418
No	3.81±5.27			

Vaccination studies, which are the main preventive treatments, are of great importance, especially in periods when diseases such as pandemics spread rapidly, because vaccination increases population or herd immunity. The willingness of people for vaccination is possible only if they are adequately informed about this issue[15]. In our study, we found that six out of 10 participants (62.4%) wanted to be vaccinated, and almost four (37.6%) out of 10 participants did not want to be vaccinated. Brant et al. reported that 75.9% of the participants wanted to be vaccinated in their study examining the willingness of young people between the ages of 14 and 24 for vaccination[15]. In a study comparing the vaccine willingness with a mixed sample of doctors, nurses, and the society, 70% of the general population, compared with the doctor and nurse groups, reported that they wanted to have the COVID-19 vaccine for their children in the future[1]. Lucia et al. (2020) reported that, despite the potential risks of COVID-19 infection, 8 out of every 10 students were in favor of vaccination in their studies investigating the anti-vaccination among medical faculty students[16].

Vaccines, which are a medical measure in relation to preventing epidemics, are, unlike drugs, expected to have an effect on both the individual and the community level[17]. In our study, 55.2% of the participants think that the COVID-19 vaccine will reduce the transmission of COVID-19 disease. The results obtained show that one of every two students did not believe that the disease could be controlled by vaccination. In fact, in addition to individual effort, vaccination, which is a socially integrated mobility, is one of the most effective ways to control pandemics. Kurtulus et al.[4] reported that 74.9% of the participants in their studies involving 183 healthcare workers believed that the vaccine would reduce the incidence of COVID-19[4]. The reason why our study results are low compared with Kurtuluş et al.[4] study results may be due to the low level of knowledge of young people about the effect of vaccination studies on disease incidence.

Vaccination is an extremely safe, effective, and inexpensive method in preventing life threatening infectious diseases at all ages[18]. In addition, individuals' approach to vaccination varies depending on many environmental and cultural factors. Use of alternative medicine, religious beliefs, side effects of the vaccine, perceived risk, family lifestyle, and race are some of these[3,15]. In our study, 4 (46.2%) out of every 10 participants stated that they are willing to get the COVID-19 vaccine because of the concern of infecting their family and loved ones, and 3 (30%) out of 10 participants stated that they are unwilling to be vaccinated for the concern that it might cause side effects. Dror et al. found that 76% of them accept the vaccine because it is safe, 13% of them accept the vaccine because it is effective, and 11% of them accept the vaccine because it will alleviate the disease[1]. It is seen that the reasons for vaccination/anti-vaccination can vary from society to society. In order to structure the perceptions, it is essential to carry out awareness-raising activities for the societies by those who are competent in health education.

In the COVID-19 pandemic, measures such as quarantine and social distancing were taken to protect the health of the public. However, these measures also have negative effects[19]. In fact, it is known that fear of COVID-19 causes delays[20] in accessing health services and suicide[21]. In our study, the scores obtained from the FCV-19S ranged from 5–22, and the mean score was 3.38±4.75 (data not shown in the table). Our study results showed that the mean score of FCV-19S is significantly higher in females than that in males (Table 3). This is expected as it is known that women suffer more from psychological disorders than men[22,23]. As a result of womens' motivation to help and protect, the high level of anxiety brings with it the fear of COVID-19. In our study, it was determined that the scores obtained from FCV-19S were significantly higher in those who thought that the vaccine would affect the incidence of the disease compared with those who did not and in those who did not want to be vaccinated compared with those who did. Nyguyen et al. (2020) found that being a woman is a reason for the fear of COVID-19 in their study that investigated the fear of COVID-19 in medical faculty students[19]. Akarsu et al.[24], in their study examining the COVID-19 vaccine attitudes in individuals over the age of 18 through a web survey, reported that the gender of the people who wanted to have the COVID-19 vaccine and their willingness to be vaccinated were in a significant relationship[24].

As far as we know, our study contributed to the literature as the first study examining high school students' fear of COVID-19 and their views on vaccination. The COVID-19 infection continues to threaten the health of the public with different effects in different age groups. In addition to the complex infection effects it creates, it can cause psychological problems with restriction, quarantine, and closure measures. The attitudes of young individuals, who are one of the vulnerable groups during pandemic periods, toward vaccination are important in terms of infecting those they come into contact with and increasing the rate of infection. In addition, according to our findings of the study, being a woman, not wanting to be vaccinated, and thinking that the vaccine will not affect the disease incidence are variables that increase the fear of COVID-19. Our suggestion is to organize encouraging and informative programs that will improve young people's attitudes toward vaccination.

There were some limitations in our study. First of all, it was difficult to reach students who did not have a smartphone because the study was a web survey. Second, the crosssectional design of our study was a barrier to causal inference.

AUTHORS' CONTRIBUTIONS

RC: Conceptualization, Data curation, Formal analysis, Supervision, Validation, Visualization, Writing-original draft, Writing-review & editing. **ŞK:** Conceptualization, Data curation, Formal analysis, Supervision, Validation, Visualization, Writing-original draft, Writing-review & editing.

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Maternal autonomy and the rights of the unborn child: a necessary discussion

Fábio Roberto Cabar[1]*, Gabriela Aparecida Marson Binotti[2]

SUMMARY

OBJECTIVE: This study aimed to compare the opinion of freshmen and fifth-year students of the University of Sao Paulo School of Law in relation to the respect for maternal autonomy and knowledge of the existence and the need to protect the unborn child.

METHODS: Information was obtained from a questionnaire; responses were compared with appropriate statistical methods.

RESULTS: In total, 403 students answered the questionnaire, 75.2% being first-year students; 58.6% of the students were against State intervention in maternal autonomy, with no difference between groups. However, 55.1% of students were in favor of the defense of the welfare of the unborn, with the statistical difference between groups.

CONCLUSIONS: Among the first-year students, there is a contradiction about respect for maternal autonomy. Among the fifth-year students, most of them were unreservedly in favor of respect for maternal autonomy.

KEYWORDS: Personal autonomy. Fetus. Bioethics. Jurisprudence.

INTRODUCTION

Autonomy is associated with individual freedom, i.e., based on will. The patient has the right to consent or refuse procedures, diagnoses, or therapies to be performed, in a free, voluntary, and informed manner. Although it is not the treatment preferred by the physician, the patient's will prevails over the purely technical and professional decision. But, what about when the exercise of autonomy directly influences the fundamental rights of third parties?

Unborn is "one who is to be born," who was begotten and not yet born. The law protects his/her future rights so that it is not just the newly born who has legal protection. With regard to public law, the State protects the fetus by criminalizing induced abortion, so that the romanistic principles that a woman can freely dispose of her body and that the fetus is only "*portio viscerum matris*" are not accepted in Brazilian legislation, except in few situations.

But who is legitimate to decide on abortion and under what circumstances: the woman, the couple, society, the judicial, legislative, or medical institutions?

From a bioethical point of view, the legal prohibition of performing abortions confronts the ethical principle of beneficence and autonomy. The fetus is only protected by criminal law in cases of abortion, as it is not possible to criminalize the pregnant woman or the doctor in case of other damage, intentional or not, caused to the fetus. Thus, can the pregnant woman, in order to exercise her autonomy, put the fetus at risk? Whose task is it to protect the future of the fetus? These questions are still unanswered due to a Brazilian legislative insufficiency related to the protection of the unborn child.

METHODS

This prospective, cross-sectional study aimed to compare the opinion of freshmen and fifth-year students at the University

[1]Universidade de São Paulo, Faculdade de Medicina, Departamento de Obstetrícia e Ginecologia – São Paulo (SP), Brazil.
[2]Centro Universitário das Américas, Faculdade de Medicina – São Paulo (SP), Brazil.
*Corresponding author: fabio.cabar@hc.fm.usp.br
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of São Paulo School of Law (FDUSP) regarding respect for maternal autonomy and the existence and need to protect the unborn child.

A questionnaire was applied to those students who were selected according to the following inclusion criteria: being first-year or fifth-year student at FDUSP and having signed the free and informed consent form. Students who answered the questionnaire inappropriately and who dropped out after signing the consent form were excluded. Questionnaires were administered in person or by email.

Responses were statistically assessed, and quantitative measures were assessed using mean, median, minimum, and maximum; qualitative variables were evaluated using absolute and relative frequencies (%). To assess the association between two qualitative variables, the χ^2 test or Fisher's exact test was considered, when appropriate. When the aim was to compare the means of two independent samples, the *t*-test was considered. The significance level adopted was 5%.

RESULTS

Of the 900 students enrolled in the first or fifth year at FDUSP, 403 (44.8%) answered the questionnaire, of whom 300 being first-year students and 103 being fifth-year students, and 53.8% were women, 97% were single, and only 2.5% had children. The mean age was 21.2 years, with a standard deviation of 5.2 years. When the groups were compared, it was observed that the sample of first-year students was more homogeneous in terms of gender than the sample of the fifth-year students: while in the first-year students 47.8% of respondents were females, in the fifth-year students, 72% of respondents were females. This difference was statistically significant, with p<0.001 (χ^2 test). There was no statistically significant difference between the groups regarding the marital status of the participants (p=0.59 – Fisher's exact test) and the presence of children (p=0.273 – Fisher's exact test).

Toward maternal autonomy

When asked about the court decision that subjected a pregnant woman to perform a cesarean against her will, 58.6% of the students said that they were against this decision. When the responses of the two groups were compared, there was no statistically significant difference between them, both groups disagreeing with the position taken by the judge of Law: 58.7% of the first-year students disagreed with the judge, while 58% of the fifth-year students had such opinion (p=0.907 – χ^2 test). Such response pattern shows that, in this type of situation, most of both groups would respect the pregnant woman's decision.

Students were also asked about the decision of an HIV-positive pregnant woman who refuses to take antiretroviral drugs during pregnancy, exposing the fetus to the risk of intrauterine infection. In this case, most students (55.1%) disagreed with the pregnant woman's opinion; in the analysis of the groups, 60.7% of the first-year students disagreed with the pregnant woman's decision, while 38% of the fifth-year students had the same opinion. This difference was statistically significant (p<0.001 – χ^2 test).

When asked about possible punishment for this pregnant woman, 60.5% answered that the pregnant woman who neglected the use of antiretroviral medication should be punished. Thus, 62.7% of the first-year students answered that the pregnant woman should be punished, while 54% of the fifth-year students had the same opinion. There was no statistically significant difference between groups (p=0.127 – χ^2 test).

Necessity and legal existence of protection for the unborn child

Students were asked if they believed that the legal protection of the unborn child was necessary: 85.6% answered YES and that this protection is necessary, with a statistically significant difference between the groups (p=0.034 – χ^2 test): 83.5% of first-year students approve the legal protection of the unborn child, and 92% of fifth-year students have the same opinion.

In total, 90.1% of students responded that the unborn child is protected by civil law. Among the first-year students, 87.5% believe that the unborn child is civilly protected, while 98% of fifth-year students have the same opinion. This difference was statistically significant (p=0.002 – Fisher's exact test).

With regard to criminal protection, 81.1% of all respondents answered that the unborn child is protected by criminal law. In the group of first-year students, 80.2% believe that the unborn child is protected by criminal law; among the fifth-year students, this number rose to 84% without, however, reaching a statistical difference (p=0.462 – Fisher's exact test).

Relationship between maternal autonomy and the rights of the unborn child

Among those who responded that abortion should always be legalized, 78.2% responded that the unborn child should be protected by law. Still, all students who are in favor of banning abortion are in favor of legal protection for the unborn child. This difference was statistically significant (p<0.001).

When the groups are analyzed, it is observed that 72% of the first-year students who defend the liberation of abortion also defend the legal protection of the unborn child. When analyzing the data referring to the answers of the fifth-year students, it is noticed that 90.5% of the students who are in favor

of the unrestricted legalization of abortion are also in favor of legal protection for the unborn child. Only 8% of fifth-year students believe that legal protection for the unborn child is not necessary.

Comparing the groups, 71.4% of the first-year students who are in favor of allowing abortion are in favor of the autonomy of the pregnant woman, that is, they do not agree with the performance of a cesarean by court decision. Among the fifth-year students, 69.1% of those who are in favor of allowing abortion are also in favor of maternal autonomy when deciding on the mode of delivery and do not accept that a court decision determines that a cesarean is performed.

The answers were compared, within the groups, in respect of the opinion regarding the legalization of abortion and the legal position to be adopted regarding the pregnant woman who decides not to undergo medical treatment during pregnancy. Among the first-year students, 60.7% would not respect the pregnant woman's decision; of those who defend maternal autonomy when performing an abortion, 51.8% would not respect maternal autonomy when she decided not to take the medication. Among the fifth-year students, 38% would not respect the pregnant woman's decision. Among those who defend the legalization of abortion, 30.9% would not respect the pregnant woman's decision not to take medication during pregnancy.

Of all students who responded to the survey, 60.5% said that pregnant women who did not take medication during pregnancy should receive a punishment. Among those who defend the legalization of abortion, 55.6% defend a punishment for pregnant woman who puts the life of the unborn child at risk.

When comparing the groups, 62.7% of the first-year students defended punishment for the pregnant woman; 59.5% of those who defend the legalization of abortion also defend a punishment for the pregnant woman who did not take the medicine and put the unborn child's life at risk. Among the fifth-year students, 54% defend a punishment for negligent pregnant women; among those who advocate abortion, 47.6% advocate punishment.

Among those who were against performing a cesarean by the court decision, 43.6% of them would not respect maternal autonomy with regard to their decision not to take medication during pregnancy. When the analysis is carried out by groups, among the first-year students, 48.9% of those who do not agree with the performance of a cesarean by the court decision do not respect the pregnant woman's decision. In contrast, 27.6% of fifth-year students who responded that they did not agree with a cesarean section by the court decision do not respect the pregnant woman's decision not to take medication during pregnancy.

DISCUSSION

No study in the literature can demonstrate the opinion of law students regarding the conflict between the autonomy of the pregnant woman and the right of the unborn child. Such a survey is of paramount importance, as they are future jurists who will decide cases where there is no clear legislation on this matter.

A Brazilian judge ruled that a pregnant woman, at her 42 weeks of pregnancy, had to undergo a cesarean, against her will. In the field of Medicine, the limits of medical intervention and the responsibility of the pregnant woman to assume the consequences of her choice were questioned. It is not only the autonomy and right that the woman has over her body and her life that this case is about but also the right to life that the fetus has. And the right of the unborn child? Can the mother put him/her at risk? Whose mission is it to protect it, when the actions of the pregnant woman put the life and future of the fetus at risk?

In another situation of similar confrontation between maternal autonomy and the right of the unborn child, Cabar et al.[1] described the case of a child who was born and infected by HIV because his/her mother, infected by this virus, refused to take the medication that could reduce the risk of fetal infection. How should the doctor act toward this pregnant woman who rejects the beneficial treatment for her child? Should it respect the pregnant woman's autonomy and put the unborn child's life at risk? Should the jurist interfere in favor of the unborn child or should he respect the autonomy of the pregnant woman? These questions are still unanswered.

When asked about this court decision, 58.6% of the students said they were against it, respecting the pregnant woman's decision. When asked about the decision of the HIV-positive pregnant woman who refused to take antiretroviral drugs during pregnancy, exposing the fetus to the risk of intrauterine infection, 55.1% of them disagreed with the pregnant woman's opinion, with greater discordance among the first-year students.

This pattern of responses deserves considerations: while in the first situation (judicial decision), there was a favorable position of the majority regarding respect for maternal autonomy, and in the second situation (pregnant woman with HIV), most students responded that the pregnant woman's opinion should not be respected, that is, most were in favor of fetal well-being. On the one hand, this fact may be related to the appeal of the infectious disease still without curative treatment, with serious stigma; on the other hand, it may be that the technical lack of knowledge among law students regarding the consequences of not having adequate obstetric intervention can justify such a pattern of responses.

Regarding the legal protection of the unborn child in the Brazilian legal system, the majority responded that the unborn

child is protected by civil law, with 85.6% responding that the legal protection of the unborn child is necessary.

However, Brazil protects the health of the unborn child exclusively through the criminalization of abortion (Articles 124–128 of the Brazilian Penal Code). In other crimes that protect health (e.g., injury, infanticide, and homicide), there is no protection for the fetus, as it is not considered a living human person[2], so there is a legislative insufficiency related to the legal protection of the unborn child. In most Western countries, the legislation is similar to the Brazilian one (in the sense that there is no protection for the unborn child), except for the fact that some countries allow abortion. Exceptions to this are Spain, a country in which the attitude of the doctor or the pregnant woman that may harm the physical or mental development of the fetus is considered a crime[3]; in the United States, there is a law that criminally punishes people who may have caused harm (including death) to unborn children, in addition to the crime of harm to the pregnant woman.

The questions to be asked at this point are as follows: how to protect the unborn child and, at the same time, respect the autonomy of the pregnant woman? How should the doctor and the lawyer behave in these situations?

In most developed countries, the legislation allows abortion to save the pregnant woman's life and to preserve her physical or mental health, when the pregnancy resulted from rape or incest, in cases of fetal anomalies, for economic or social reasons and at the request of the woman. In contrast, in Latin America and the Caribbean, abortion is allowed in few situations, especially in those associated with the preservation of the woman's life.

There is no doubt that the prohibition of abortion is a legal protection mechanism for the unborn child, but it removes the maternal autonomy to decide about her own body, preventing her from ending a pregnancy. Of the 197 students (78.2%) who responded that abortion should always be legalized, they also responded that the unborn child should be protected by law. Such a response is inconsistent, as decriminalizing abortion means giving pregnant women the autonomy to decide whether or not to continue pregnancy. By giving women this power, the protection offered by antiabortion laws is removed from the unborn child. How to defend the legal protection of the unborn child and wish that the pregnant woman can end the pregnancy according to her own will?

Criminal Law expresses a contradiction, as it protects the right to life, by prohibiting abortion, and positions itself against the autonomy of pregnant women. However, it does not offer any other protection to the unborn child's life.

CONCLUSIONS

This cross-sectional and prospective study allowed us to conclude that among the first-year students, there is a contradiction regarding respect for maternal autonomy; in contrast, among the fifth-year students, most students were in favor of maternal autonomy.

Most students believe that there is civil and criminal legal protection for the unborn child.

There is a contradiction among most students: while they defend the legalization of abortion, they are in favor of punishing the mother who puts the life of the unborn child at risk.

AUTHORS' CONTRIBUTIONS

FRC: Conceptualization, Data curation, Formal analysis, Writing – original draft. **GAMB:** Formal analysis, Writing – original draft.

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Recovery of motor function in rats with complete spinal cord injury following implantation of collagen/silk fibroin scaffold combined with human umbilical cord-mesenchymal stem cells

Wu-Sheng Deng[1], Xiao-Yin Liu[2,3], Ke Ma[2], Bing Liang[2], Ying-Fu Liu[5], Ren-Jie Wang[2], Xu-Yi Chen[2], Sai Zhang[2]*

SUMMARY

OBJECTIVE: This study aimed to assess the effect of the collagen/silk fibroin scaffolds seeded with human umbilical cord-mesenchymal stem cells on functional recovery after acute complete spinal cord injury.

METHODS: The fibroin and collagen were mixed (mass ratio, 3:7), and the composite scaffolds were produced. Forty rats were randomly divided into the Sham group (without spinal cord injury), spinal cord injury group (spinal cord transection without any implantation), collagen/silk fibroin scaffolds group (spinal cord transection with implantation of the collagen/silk fibroin scaffolds), and collagen/silk fibroin scaffolds + human umbilical cord-mesenchymal stem cells group (spinal cord transection with the implantation of the collagen/silk fibroin scaffolds co-cultured with human umbilical cord-mesenchymal stem cells). Motor evoked potential, Basso-Beattie-Bresnahan scale, modified Bielschowsky's silver staining, and immunofluorescence staining were performed.

RESULTS: The BBB scores in the collagen/silk fibroin scaffolds + human umbilical cord-mesenchymal stem cells group were significantly higher than those in the spinal cord injury and collagen/silk fibroin scaffolds groups ($p<0.05$ or $p<0.01$). The amplitude and latency were markedly improved in the collagen/silk fibroin scaffolds + human umbilical cord-mesenchymal stem cells group compared with the spinal cord injury and collagen/silk fibroin scaffolds groups ($p<0.05$ or $p<0.01$). Meanwhile, compared to the spinal cord injury and collagen/silk fibroin scaffolds groups, more neurofilament positive nerve fiber ensheathed by myelin basic protein positive structure at the injury site were observed in the collagen/silk fibroin scaffolds + human umbilical cord-mesenchymal stem cells group ($p<0.01$, $p<0.05$). The results of Bielschowsky's silver staining indicated more nerve fibers was observed at the lesion site in the collagen/silk fibroin scaffolds + human umbilical cord-mesenchymal stem cells group compared with the spinal cord injury and collagen/silk fibroin scaffolds groups ($p<0.01$, $p< 0.05$).

CONCLUSION: The results demonstrated that the transplantation of human umbilical cord-mesenchymal stem cells on a collagen/silk fibroin scaffolds could promote nerve regeneration, and recovery of neurological function after acute spinal cord injury.

KEYWORDS: Rats. Collagen. Silk fibroin. human mesenchymal stem cells. Nerve regeneration. Spinal cord injuries.

[1]Gansu University of Chinese Medicine, College of Integrated Traditional Chinese and Western Medicine – Gansu Province, China.
[2]Pingjin Hospital Brain Center, Tianjin Key Laboratory of Neurotrauma Repair, Characteristic Medical Center of Chinese People's Armed Police Force – Tianjin, China.
[3]Sichuan University, West China Hospital, Department of Neurosurgery – Chengdu, China.
[4]Logistics University of People's Armed Police Force, Clinical School of Medicine – Tianjin, China.
[5]Cangzhou nanobody technology innovation center – Cangzhou, China.
*Corresponding author: zhangsai718@vip.126.com
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INTRODUCTION

Spinal cord injury (SCI) that results in high mortality and disability rates is a major global health problem[1]. SCI brings about huge impact on property and mental to patients, and also seriously restricts social stability[2]. Thus, development of functional scaffold will become a new strategy for SCI treatment.

Experimental strategies utilizing different types of cells are being studied extensively[3]. Adult mesenchymal stem cell can modulate immune response, secrete cytokines, and inhibit inflammation and apoptosis[4]. However, stem cell implantation alone does not achieve satisfactory results in acute SCI repair[5], which might be related to the lack of structural basis. Therefore, combined with a bionic organization scaffold, will augment hUC-MSCs growth, and promote the recovery of SCI.

The ideal biomaterials for spinal cord repair should possess excellent biocompatibility, nontoxic degradation, and suitable mechanical properties. Collagen is the most important extracellular matrix component in the body. Due to its abundance, excellent biocompatibility and low antigenicity, collagen has been widely used in various tissue engineering applications[6]. However, the weaknesses of collagen scaffolds are poor mechanical strength and rapid biodegradability[7].Silk fibroin is a unique natural protein with high mechanical strength, remarkable elasticity and environmental stability[8]. Incorporation of silk fibroin could compensate for the drawbacks of utilizing a collagen scaffold alone[9]. Our goal was to evaluate the effect of the collagen/silk fibroin scaffolds (CSFSs) seeded with human umbilical cord-mesenchymal stem cells (hUC-MSCs) on functional recovery after acute complete SCI. The implantation of CSFSs combined with hUC-MSCs may be candidates for SCI treatment[10].

METHODS

Ethics statement

All experimental procedures were performed in accordance with laboratory animals form US National Institute of Health (NIH), and approved by the Ethics Committee of Characteristic Medical Center of Chinese People's Armed Police Force (CPAPF).

Fabrication of CSFS

The CSFS were obtained as previously reported[11]. Briefly, the fibroin and collagen were mixed (mass ratio, 3:7), and the composite scaffolds were produced.

Isolation, culture, and identification of hUC-MSCs

The harvest of the human umbilical cord was approved by the Characteristic Medical Center of CPAPF (approval N°. PJLEC2019), and consent was obtained from the donator. hUC-MSCs were isolated, cultured, and identified as described previously[12]. hUC-MSCs were identified by flow cytometry and immunofluorescence.

Scaffold biocompatibility

For cell seeding, 100 µl of MSCs suspension (1×10^5 cells/mL) was seeded onto CSFSs followed by incubated at a 37°C, 5% CO_2 incubator for 7 days. Then, the growth of the MSCs were observed under an inverted phase-contrast microscope and a scanning electron microscope (SEM) (Hitachi, Tokyo, Japan). Finally, the CSFSs co-cultured with MSCs were coated with gold, the MSCs growth were observed under a SEM. At 1, 3, 5 and 7 days after seeding MSCs, Cell Counting Kit-8 (CCK-8, Solarbio Science & Technology Co., Ltd.) was performed to assess the proliferation of hUC-MSCs co-cultured with CSFSs.

Spinal cord injury and transplantation

The adult female specific-pathogen-free Sprague-Dawley rats (n=40, 260±20 g) (animal batch N°. 2019-0025) were randomly divided into the Sham group (without SCI, n=10), SCI group (spinal cord transection without any implantation, n=10), CSFS group (spinal cord transection with implantation of the CSFS, n=10), and CSFS + hUC-MSCs group (spinal cord transection with the implantation of the CSFS co-cultured with hUC-MSCs, n=10).

The surgery procedure was slightly modified according to previous report[13]. Immediately after the SCI, a 2-mm-diameter CSFS was transplanted into the completely transected gap of the CSFS group, and the CSFS co-cultured with 1×10^6 hUC-MSCs was implanted into the gap of the CSFS + hUC-MSCs group.

Assessment of neurological function

Before surgery and 1, 2, 3, 4, 6, and 8 weeks after surgery, the rats were individually rated on the 21-point Basso-Beattie-Bresnahan (BBB) locomotor rating scale (n=10 for each group). The motor evoked potential (MEP) was measured in each rat as described previously[14] 8 weeks after the SCI (n=10 for each group).

Histological analysis

At eight weeks after modelling, the samples were incubated with the primary antibodies overnight at 4°C: a mouse anti-neurofilament (NF, 1:200, Abcam), a rabbit anti-myelin basic protein monoclonal (MBP, 1:200, polyclonal, Millipore). The sections were incubated in Alexa Fluor 568-conjugated (1:1000, Invitrogen, Carlsbad, CA, USA) or Oregon Green 488-conjugated secondary antibodies (1:1000, Invitrogen, Carlsbad, CA, USA) for 1 h at RT.

Modified Bielschowsky's silver staining was used to observe nerve fibers. Then, ammonium silver alcohol solution was added to spinal cords sections (200 µl/section) for 5 min. Finally, the samples were directly reduced in 10% formaldehyde until they became dark brown and then rinsed 3 times.

Statistical analysis

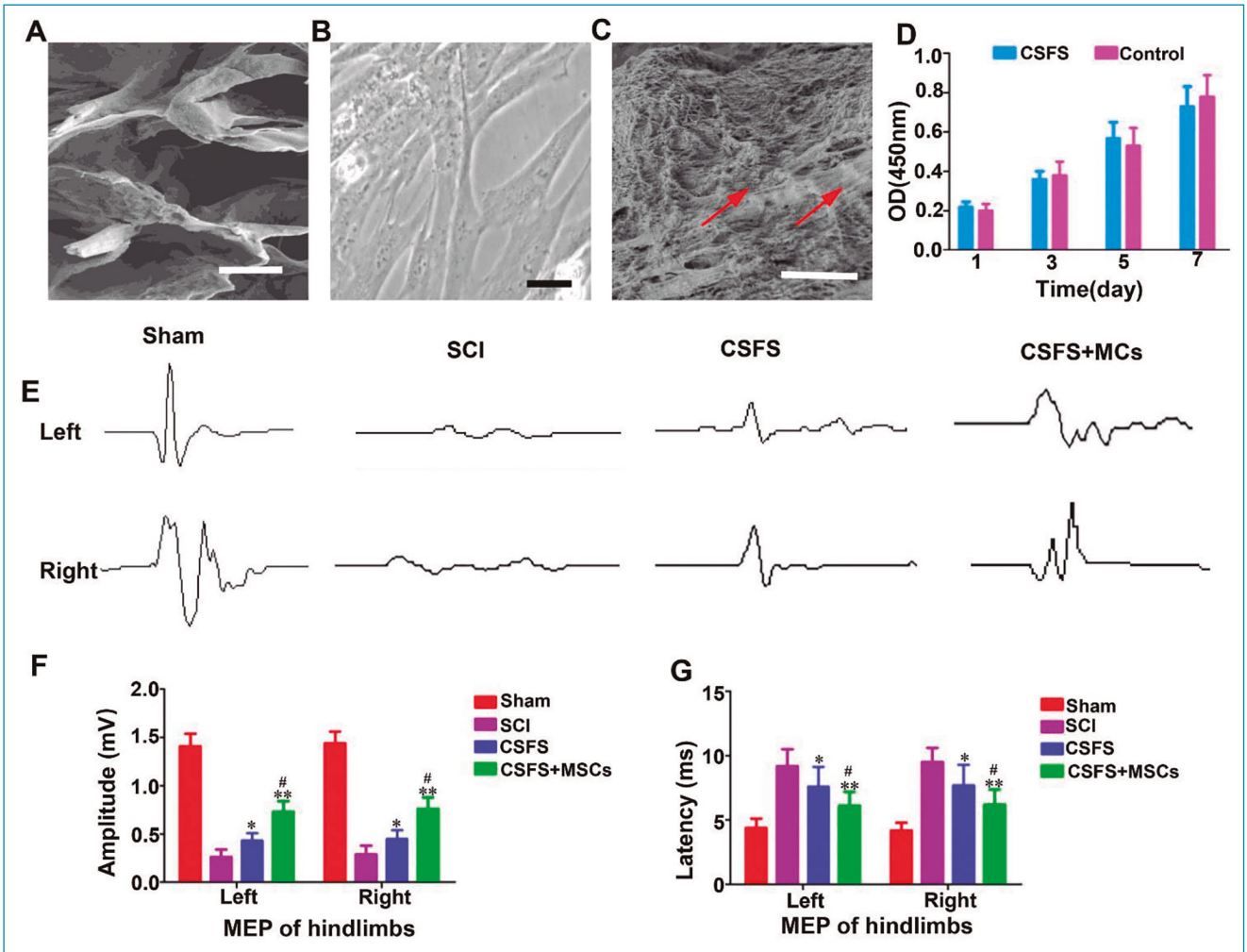
Data are presented as the mean ± standard deviation (SD). Data were analyzed by using the SPSS 15.0 package (SPSS, Chicago, IL, USA). One-way analysis of variance was used for multiple-group comparisons. Statistically significant difference in 2 parameters was performed by 2-tailed Student's t-tests. P values less than 0.05 were statistically significant.

RESULTS

Structure and biocompatibility of the CSFS

SEM images showed that the CSFS had a three-dimensional porous structure and that the pores were interconnected (Figure 1A). Phase-contrast microscopy images after 3 days of incubation with hUC-MSCs revealed that the cells were mostly fusiform (Figure 1B). After the CSFSs were incubated with the hUC-MSCs for 7 days, SEM images showed that the hUC-MSCs adhered firmly to the surface of the CSFS and were growing well inside the pores (Figure 1C).

There was no statistically significant difference between the OD values of the two groups at any time point (p>0.05; Figure 1D).



*p<0.05, **p<0.01 *versus* SCI group; #p<0.05, ##p<0.01, *versus* CSFS group. CSFS: collagen/silk fibroin scaffold; MSCs: mesenchymal stem cells; MEP: motor evoked potential; SCI: spinal cord injury. Scale bars: 5 µm in C; 10 µm in A; 100 µm in B. OD: optical density.

Figure 1. Morphology and characterization of human umbilical cord-mesenchymal stem cells (hUC-MSCs), the collagen/silk fibroin scaffold (CSFS), and electrophysiological results for all groups. (A) Scanning electron microscope (SEM) images of the CSFS. (B) hUC-MSCs morphology. (C) Morphology of the CSFS co-cultured with hUC-MSCs: the red arrows indicated hUC-MSCs. (D) Cell Counting Kit-8 assay of the hUC-MSCs cultured with the CSFS. (E) MEP traces of rats. (F, G) Amplitude (F) and latency (G) of the MEP.

Neurological function in rats

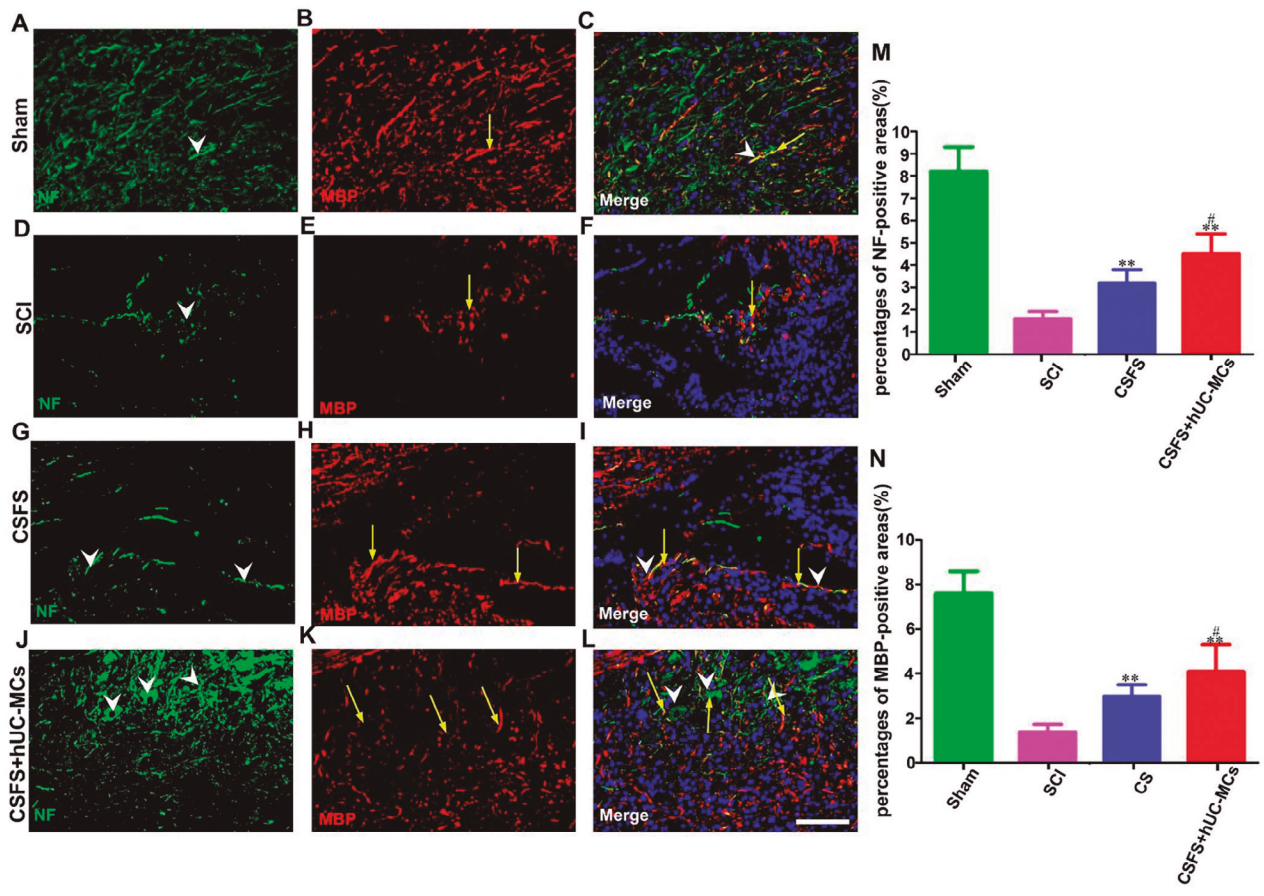
At 3, 4, 6, and 8 weeks after injury, the BBB scores in the CSFS + hUC-MSCs group were significantly higher than those in the SCI and CSFS groups ($p<0.05$ or $p<0.01$; . The amplitude and latency were markedly improved in the CSFS + hUC-MSCs group compared with the SCI and CSFS groups (Figures 1E–G).

Regeneration of nerve fiber and myelin sheaths in rats

The results indicated plentiful NF-positive fiber in lesion areas in the CSFS and CSFS+hUC-MSCs groups (Figures 2G and 2J). The relative density of NF-positive staining (equivalent to nerve fiber number) in the lesions were higher in the CSFS+hUC-MSCs group than in the CSFS and SCI groups ($p<0.05$ or $p<0.01$, Figure 2M).

For percentages of MBP-positive myelin sheaths in lesion areas, the CSFS+hUC-MSCs group exhibited higher area than the SCI and CSFS groups ($p<0.01$, $p<0.05$, Figures 2E, 2H, 2K, 2N). NF and MBP double immunofluorescence staining results demonstrated that, compared to the SCI group and the CSFS group, more NF positive nerve fiber ensheathed by MBP positive structure at the injury site were observed in the CSFS+hUC-MSCs group (Figures 2F, 2I, 2L).

The spinal cord in the Sham group was intact and nerve fibers were neatly arranged (Figure 3A). Compared with the SCI group and CSFS group, more nerve fibers was observed at the lesion site in the CSFS+hUC-MSCs group (Figure 3B-D). The axonal number in the CSFS+hUC-MSCs group dramatically increased compared to CSFS group ($p<0.05$ or $p<0.01$, Figure 3E).



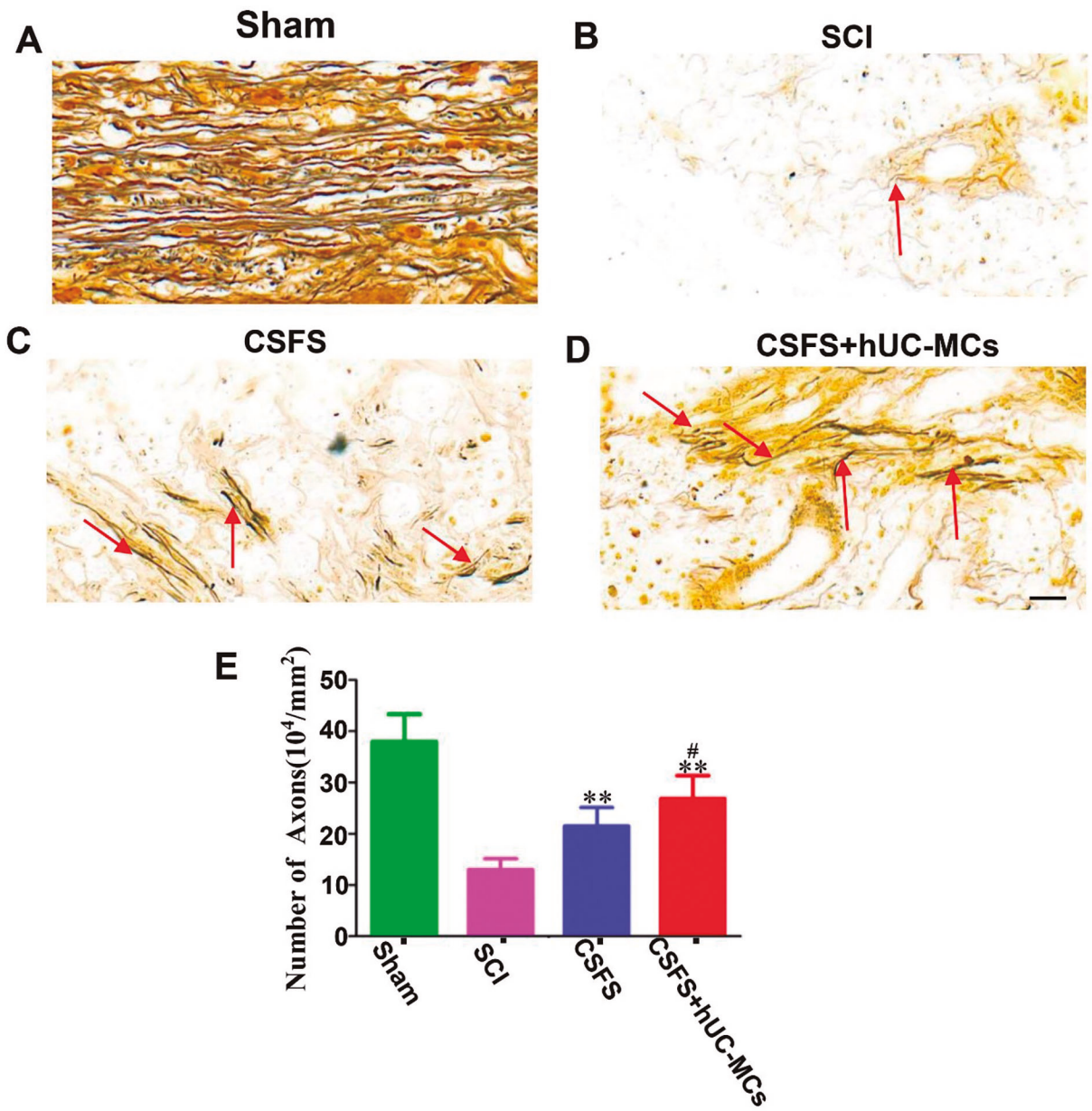
p<0.01 vs the SCI group. #p<0.05 ***versus* CSFS group. Scale bars=50 μm in (A–L). n= number of animals under each condition (n is expressed as dots in the bars). In A–N, n=10. NF: neurofilament; MBP: myelin basic protein.

Figure 2. Regeneration of NF and myelin sheaths in the lesions. (A, D, G, J) Staining for NF in the lesions of each group. (B, E, H, K) MBP-positive myelin sheaths in the lesions of each group. (C, F, I, L) Immunofluorescence staining exhibiting MBP-positive myelin sheaths (B, E, H, K, yellow arrow) surrounding positive nerve fiber (A, D, G, J, white arrow) in the graft site. (M, N) Statistical analyses of percentages of NF-(M) and MBP-positive myelin sheaths positive areas (N) in the lesions.

DISCUSSION

Restoration of neurological function after SCI is still a huge challenge for clinicians. The microenvironment at the injury site prevents axon regeneration[15]. Excellent biocompatible materials can bridge axons through glial scar tissue and play an important role in regulating the microenvironment and improving axonal regeneration[16].In this study, we reported that a CSFS combined with hUC-MSCs could promote axonal regeneration, myelination, and locomotion recovery in rats with acute complete spinal cord transection.

Motor functional recovery is one of the indicators for assessing therapeutic effect of SCI. The locomotor recovery was the best in the CSFS + hUC-MSCs group, indicating that the CSFS contributed to the reconstruction of motor functions



*p<0.05, **p<0.01 ***versus*** the SCI group. #p<0.05 ***versus*** CSFS group. Scale bars=50 μm in (A–D). n= number of animals under each condition (n is expressed as dots in the bars). In A–D, n=10.

Figure 3. Bielschowsky's silver staining of the spinal cord tissues in rats. The spinal cord tissues on the Sham group (A), the SCI group (B), the CSFS group (C) and the CSFS+hUC-MSCs group (D). All red arrows indicated the nerve fibers.

after SCI. Furthermore, the improvement of MEP in the CSFSs adsorbed with hUC-MSCs group was significantly better than other groups. The results in MEP further demonstrated that this strategy facilitated reestablishment of new reticular circuitry after SCI.

Mesenchymal stem cells are considered to be a promising therapy for SCI[17]. However, several controversies exist about the method of mesenchymal stem cell transplantation in SCI model. MSCs injection can result in cell migration to non-targeted organs[18]. Moreover, the complex injury milieu may affect the survival and differentiation of directly implanted MSCs[19]. After the MSCs and CSFSs were co-cultured, SEM results showed that MSCs attached firmly on the surface of the CSFSs, and the cells grew inside the pores. The results have demonstrated that CSFSs can provide a favorable environment to support MSCs survival. Furthermore, previous studies reported cells could grew along collagen nanofibers in many tiny channels, and had no adverse impacts on the expression of proteins and cell neurotropic factor[20]. In current studies, the CSFSs presented a porous structure, which is beneficial to cell adhesion and sufficient exchange of nutrients and oxygen[11].

The pathophysiological changes provide strong evidence for functional recovery. Many literatures have shown that collagen could reduce MSCs migration, fill the injured gap, and act as a carrier for transplanted cells or endogenous cells[21]. In this study, the myelination of axons and NF in the CSFS + hUC-MSCs group were significantly superior to other groups. MSCs could also facilitate myelination by differentiating into oligodendrocytes[22]. The cytokines secreted by the stem cell could promote the expression of MBP and NF[23]. These results demonstrated that the axon regeneration and myelination could have a rapid and effective conduction of nerve impulses and improve the recovery of neurological function. The improvement of neurological function in the CSFS+ hUC-MSCs group might partly be due to the ability of CSFS that guided the orderly regeneration of neural fibers, reduced the formation of glial scar and contributed to the reconstruction and regeneration of synapses[24,25].

CONCLUSIONS

Following completely transected SCI, the implantation of the hUC-MSCs-laden CSFS has shown obvious therapeutic effects for SCI repair, and the combinatorial therapy used in this study may have very great prospects for clinical application.

AUTHOR'S CONTRIBUTIONS

WD: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **XYL:** Conceptualization, Data Curation. **KM:** Conceptualization, Formal Analysis. **BL:** Conceptualization. **YFL:** Data Curation. **RJW:** Data Curation. **XYC:** Resources. SZ: Resources.

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SARS-CoV-2 association with hemoglobin and iron metabolism

Elaine Maria Borges Mancilha[1]*, José Salvador Rodrigues de Oliveira[2]

INTRODUCTION

In March 2020, the World Health Organization (WHO) declared COVID-19 pandemic, a disease related to the new coronavirus that causes a severe acute respiratory syndrome, which was named as SARS-CoV-2. The severe form of this disease presents pulmonary involvement in the form of aggressive and extensive interstitial pneumonia, which is triggered by a sustained systemic acute inflammatory response known as "cytokine storm." This has been previously described in the literature as a complication of a group of diseases that can be categorized under the term "hyperferritinemic syndrome." Its exponents include hemophagocytic syndrome, adult Still's disease, catastrophic antiphospholipid syndrome, and septic shock[1,2].

It has previously been demonstrated that SARS-CoV-2 binds to hemoglobin through ACE2, CD147, Cd26, and other receptors that are present on the surface of erythrocytes. After this association, virus attacks the beta1 chain of hemoglobin which leads to dysfunctional hemoglobin in addition to hemolysis, thereby reducing the oxygen supply to the body, causing tissue hypoxia, a remarkable characteristic of COVID-19[3,4].

Esaki demonstrated that the amino acid sequence of the coronavirus spike protein is identical to hepcidin, a protein that acts as the main systemic regulator of iron metabolism. Therefore, this similarity between hepcidin and coronavirus spike protein can lead to a mimetic effect, suggesting that SARS-CoV-2 can increase serum hepcidin and then ferritin, and cause hyperferritinemic syndrome[5].

Therefore, the association between dysfunctional hemoglobinopathy and SARS-CoV-2-related hyperferritinemia may affect the oxygen transport capacity of erythrocytes, thereby leading to hypoxia, while causing tissue damage due to non-transferrin bound iron (NTBI), and subsequently releasing free radicals at the inflammation sites[6].

REVIEW ON IRON METABOLISM AND HEPCIDIN

Iron (Fe) metabolism is mainly regulated by the coordination between erythropoiesis and Fe stores. Two mechanisms are mainly involved in the regulation of this homeostasis: the intracellular mechanism that is dependent on the cytoplasmic Fe store, and the systemic mechanism in which hepcidin plays a crucial role.

Intracellular Fe homeostasis

Dietary Fe^{2+} is absorbed after binding to heme carrier protein 1 (HCP1) in the brush border membrane of the duodenal enterocytes and HCP1 imports it into the intracellular medium. Fe^{2+} is then released from the protoporphyrin by heme oxygenase and can be stored as ferritin or exported to the blood[7,8].

Intracellular Fe^{2+} is exported to the plasma through ferroportin (FPT), a Fe exporting protein, and after the action of hephaestin, Fe^{2+} is transformed into Fe^{3+} that binds to transferrin (Tf) and circulates in the plasma[7,8].

There is no specific mechanism to eliminate the excessive iron resulting from the cellular uptake and recycling of red blood cells. Therefore, the homeostasis of serum Fe requires a coordination between the sites of absorption, utilization, and storage; this signaling is conducted by hepcidin[7,8].

Systemic iron homeostasis

Hepcidin is a peptide that acts as a negative regulator of Fe metabolism[9,10]. It has the ability to bind to FPT, located in the enterocytes and bone marrow, in addition to being present in macrophages of the liver and spleen, the organs that are also responsible for filtering senescent red blood cells and storing intracytoplasmic Fe[11].

When serum hepcidin is at high levels, the hepcidin-FPT complex is formed and hepcidin blocks the release of Fe from

[1]Universidade Federal de São Paulo – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Department of Clinical and Experimental Oncology – São Paulo (SP), Brazil.
*Corresponding author: elaine_mancilha@hotmail.com
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the macrophage reticuloendothelial system. As a result, Fe accumulates in the hepatocytes and macrophages. The decrease in plasma Fe levels results in a low transferrin saturation (TS) ratio and less stimulus for erythropoiesis[9,10].

Regarding the intestinal absorption of Fe, hepcidin inhibits iron uptake by the enterocytes through binding with FPT of the basolateral membrane and thus its consequent internalization[12].

Serum Fe levels regulate hepcidin expression. In case of iron overload (IO), its expression is increased, while in conditions such as anemia and hypoxemia its expression is generally reduced. In an acute inflammatory state, as well as in COVID-19, IL-6 acts directly on the hepatocytes, stimulating the production of hepcidin and consequently leading to a decrease in TS and an increase in intracytoplasmic ferritin[7,8].

Plasma iron circulation

Transferrin (Tf) is the protein responsible for the transport of Fe through plasma, and it promotes auto-oxidation reactions involving Fe and prevents the formation of oxygen free radicals (reactive oxygen species [ROS]) in the bloodstream, which will occur if Fe is transported in its free and toxic form.

Fe-saturated Tf binds to the transferrin receptor (TfR) present on the cell surface, which is available in two isoforms, namely, TfR1 and TfR2[13]. The most recent studies suggest that while TfR1 plays a crucial role in Fe endocytosis, TfR2 functions as a sensor of the available Fe pool in the body and modulates the production of hepcidin in the liver through the activation of the BMP pathway[14].

Tf competes with human hemochromatosis protein (HFE) for TfR1 binding[8,9]. HFE protein while interacting with TfR1 detects the degree of TS and signals the hepatocytes whether there is a need for Fe absorption in the intestinal lumen, and based on this information, the production of hepcidin is stimulated. Under conditions of high TS, there is increased binding of Tf to its receptor, and subsequently, free HFE signals the nucleus to induce hepcidin synthesis.

Iron storage

Ferritin is a molecule that comprises 24 heavy chain (21 kDa) and light chain (19 kDa) subunits. It is synthesized by the liver and exhibits the function of being an easily accessible intracellular Fe store[13,14].

The synthesis of ferritin subunits is regulated by RNA transcription in the hepatocytes, which is induced after the binding of iron regulatory proteins (IRP) to an iron responsive element (IRE). When intracellular Fe concentration is low, the binding of IRP to IRE suppresses the response for the production of ferritin. Conversely, when the intracellular Fe concentration is high, IRP is degraded, making its binding to the IRE impossible and then leading to ferritin synthesis[13,15].

Serum ferritin (SF) concentration is a reliable marker of the body Fe reserves[11]. In situations where ferritin level is increased, as it is an acute phase protein, it is always necessary to assess the underlying existence of inflammatory diseases, infectious diseases, and neoplasms. It is necessary to assess whether there is an IO that can be determined by high TS[9].

In humans, the ideal TS level is 30%, and thus, when it is less than 16%, there is Fe deficiency, a characteristic of iron deficiency anemia. However, when it is greater than 45%, there are signs of IO. When TS is >70%, a free form of iron begins to accumulate in the plasma, known as non-transferrin bound iron (NTBI)[4,6], thereby causing IO in the parenchymal cells. Free Fe catalyzes the conversion of free radicals from oxygen. Free ROS in the cytoplasm leads to the damage of organelles, especially the DNA in the nucleus and mitochondria[9,10].

DYSFUNCTIONAL HEMOGLOBINOPATHY IN COVID-19

The literature reinforces the hypothesis of the involvement of erythrocytes in COVID-19; the free heme resulting from hemolysis present in the bloodstream of a patient who is undergoing "cytokine storm," associated with hyperferritinemia, contributes to endothelial damage and to the remodeling of pulmonary vessels[6]. The destruction of erythrocytes leads to anemia and consequently hypoxia, thereby leading to systemic vasodilation, but with pulmonary vasoconstriction, it leads to an increase in fibrinogenesis in the pulmonary microvasculature. The increase in IL-6 in the inflammatory phase of COVID-19 increases hepcidin, which further leads to pulmonary hypertension through stimulating myocytes in the pulmonary alveoli, in addition to alveolar wall exudation secondary to local inflammation[15,16].

The formation of oxygen free radicals on hemolysis of erythrocytes and release of free Fe leads to mitochondrial damage in the activated macrophages and pulmonary endothelium, further perpetuating the inflammatory process and hyperstimulating the release of cytokines, especially IL-6. Other inducers for the production of hepcidin are obesity and high level of glycated hemoglobin, which increase the expression of cd147 in hemoglobin, and this association increases the risk of further complications[9].

INCREASED HEPCIDIN IN COVID-19

The role of iron toxicity in the pathophysiology of COVID-19 is related to the hepcidin mimetic effect of SARS-CoV-2, with consequent internalization of ferroportin,

both in the gastrointestinal tract and reticuloendothelial system, thereby causing a blockage in the availability of SF, which leads to anemia and hyperferritinemia, and ultimately ferroptosis[5,17].

Through mimicking the action of hepcidin, SARS-CoV-2 exaggeratedly increases the concentration of intratissue (e.g., liver, spleen, bone marrow, and muscles)ferritin, while there is a reduction in the availability of SF, and consequently, a reduction in erythrocyte production. This decrease in circulating erythrocytes perpetuates systemic hypoxemia and hinders tissue oxygenation, which is already impaired in patients with acute respiratory syndrome.

OXIDATIVE STRESS AND FERROPTOSIS

SARS-CoV-2 infection also causes mitochondrial dysfunction in bronchial epithelial cells and macrophages, and therefore, the mitochondria becomes dysfunctional for regulating intracytoplasmic Fe metabolism with an increase in ROS, and the process culminates in what may be referred to as ferroptosis[18].

Excess Fe can be tolerated to a limited extent, as is the case of silent hypoxia. Ferroptosis associated with multiorgan oxidative stress can precipitate the "cytokine storm" in later stages of the disease, for instance, in critically ill patients. The laboratory examination of critically ill patients indicates low hemoglobin and high ferritin levels in non-surviving patients[19].

Tissue Fe sequestration results in an increase in ferritin in the pulmonary epithelium, which is still associated with an increase in cytokines and immune cells, such as lymphocytes and monocytes, in the pulmonary capillaries. This is probably related to the physiological need to protect the lung cells from oxygen deprivation[20].

SYSTEMIC HYPOXEMIA AND HYPERFERRITINEMIA

Patients with COVID-19 exhibit silent hypoxia described as hypoxemia, which is associated with normal capnia reflecting normal gaseous exchange. Since CO_2 is the body dyspnea sensor, the patients present only dyspnea in the final stages of the disease when CO_2 is extremely high and there is progression of hyperferritinemia affecting the integrity of the alveolar capillary membrane, along with inflammation, edema, and pulmonary cell necrosis[16].

According to Sonnweber et al.[21], patients with severe SARS-CoV-2 exhibited persistent hyperferritinemia even after 2 months of disease, however, without persistent levels of inflammatory markers, such as C-reactive protein (CRP) and IL-6. Patients with persistent hyperferritinemia still exhibited greater pulmonary involvement on computed tomography (CT) scans and worsened performance status after a long period of illness, which indicates that hyperferritinemia in these cases is not only an inflammatory marker, but also it exerts a direct influence on the pathophysiology of the disease[21].

Interaction of SARS-CoV-2 with iron metabolism and low oxygen supply may be related to ancestral phylogenetic mechanisms, which date back to environments with low oxygen and highly available Fe levels. Alternatively, the evolution of viral replication is well adapted to this type of microenvironment, where the Fenton oxidative reaction is favored[22,23].

Viruses generally stimulate increased iron deposition in the host cells. Conversely, the immune system tends to control excess iron through increasing TSAT, with the stimulation to TFR1 and TFR2 iron saturation sensors, receptors that can be used by viruses to enter the host cells[24].

Generally, laboratory findings commonly found in patients with COVID-19, such as low hemoglobin, hyperferritinemia, low serum iron, thrombocytopenia, increased RDW and DHL, suggest that the hypothesis of the dysregulation of iron metabolism associated with inefficient erythropoiesis is a possible mechanism underlying the pathophysiological changes in patients with COVID-19.

COVID-19 combines hypoxic anemia (low hemoglobin concentration) with hypoxemic hypoxia (low hemoglobin saturation). Oxygen deprivation and iron accumulation in the lungs cause pulmonary vasoconstriction and shunting despite pneumonia[25]. These changes can be observed in the pathognomonic clinical manifestation of SARS-CoV-2, in which the patients present severe oxygen desaturation without presenting hypercapnia and no compensatory tachypnea.

CONCLUSIONS

SARS-CoV-2 is a disease that causes silent hypoxia associated with a severe hyperinflammatory state that triggers a "cytokine storm" along with persistent hyperferritinemia and systemic hypoxemia, and severe endothelial damage to the lung parenchyma caused by the free radicals. Since hyperferritinemia is not only an inflammatory marker but also actively causes tissue damage, its mechanism of action needs to be elucidated to broaden our understanding in the future studies.

AUTHORS' CONTRIBUTIONS

EMBM: Writing – original draft, Writing – review & editing.
JSRO: Supervision, Writing – review & editing.

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Prophylactic blood transfusion prior to elective invasive procedures

Marcelo Antônio Oliveira Santos-Veloso[1,2,3]*, Gustavo Lago Oliveira de Souza[1,4], Alessandra Ferraz de Sá[1,5]

INTRODUCTION

In Brazil, approximately 3.3 million blood transfusions are performed annually, of which 62.4% correspond to packed red blood cells (PRBCs), 17% to platelet concentrates (PC), and 13% to fresh frozen plasma[1]. The use of blood products (BPs) is one of the most common interventions in clinical practice and can save lives when indicated.

In both developed and developing countries, inappropriate prescription of blood components occurs in up to 36% of cases[2]. The rational prescription of transfusion therapies is essential due to limited resources and growing demand[3]. Moreover, several studies have shown that aggressive correction of anemia, thrombocytopenia, and coagulopathies does not necessarily result in better clinical outcomes[4].

These factors show the importance of individually tailoring the indications and establishing evidence-based transfusion programs[5]. However, several international medical guidelines still recommend the prescription of BP based on low-quality studies or expert opinion[6,7].

In this study, a narrative review of the literature was conducted regarding the evidence for the prescription of BP prophylaxis for elective invasive procedures in clinically stable patients with anemia, thrombocytopenia, or coagulopathies.

The included studies were classified according to the quality of the scientific evidence following the 2011 Oxford Center for Evidence-Based Medicine recommendations (Table 1)[8].

CENTRAL VENOUS CATHETER PUNCTURE-RELATED TRANSFUSION

Evidence regarding the use of blood components prior to central venous catheter (CVC) puncture in patients with blood dyscrasias is scarce. Most international guidelines recommend performing thrombocytopenia and international normalized ratio (INR) correction before the puncture but at variable cut-off points[7,9]. Nevertheless, classic coagulogram parameters (i.e., prothrombin time, INR, and platelet count) have been poor predictors of bleeding-related complications after CVC puncture[10].

A meta-analysis including 4,387 CVC insertions revealed a 5.1% risk of bleeding complications. The efficacy of blood transfusions in preventing these complications could not be determined due to the high heterogeneity and low methodological quality of the studies[11].

ESOPHAGOGASTRODUODENOSCOPY

In clinical practice, esophagogastroduodenoscopy (EGD) plays an essential role in the diagnosis and treatment of severe digestive bleeding. This is a heterogeneous clinical context, which may involve patients with or without hemodynamic instability, coagulation disorders, and/or thrombocytopenia.

Based on low-quality evidence, the American Society for Gastrointestinal Endoscopy recommends a minimum value of

[1]Hospital dos Servidores do Estado de Pernambuco, Serviço de Clínica Médica – Recife (PE), Brazil.
[2]Universidade Federal de Pernambuco, Centro de Biociências, Programa de Pós-Graduação em Inovação Terapêutica – Recife (PE), Brazil.
[3]Centro Universitário Maurício de Nassau, Curso de Medicina, Departamento de Saúde – Recife (PE), Brazil.
[4]Hospital Barão de Lucena, Serviço de Urgência e Emergência – Recife (PE), Brazil.
[5]Fundação de Hematologia e Hemoterapia de Pernambuco, Serviço de Hematologia – Recife (PE), Brazil.
*Corresponding author: marcelosantos.med@gmail.com
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Table 1. Oxford Centre for Evidence-Based Medicine levels of evidence according to the study design.

Grades of recommendation	Level of evidence	Therapy, prevention, and etiology	Prognosis	Diagnosis	Differential diagnosis or prevalence
A	1A	Systematic review of RCTs	Systematic review of cohort studies. CDR validated in different populations	Systematic review of Level 1 diagnostic studies. CDR with 1b studies from different clinical centers	Systematic reviews of cohort studies (current or prospective)
	1B	RCT with narrow confidence interval	Cohort study with <20% loss. CDR validated in a single population	Validating cohort study with good reference standards. CDR tested within one clinical center	Prospective cohort study with good follow-up
	1C	Results of all or none studies	All or none case-series	Sensitivity and specificity close to 100%	All or none case-series
B	2A	Systematic review of cohort studies	Systematic review of retrospective cohort studies	Systematic review of Level >2 diagnostic studies	Systematic review of 2b and better differential diagnosis studies
	2B	Cohort study or low-quality RCT	Retrospective cohort study, CDR validated on split-sample	Exploratory cohort study with good reference standards. CDR validated only on split samples or databases	Retrospective cohort study or poor follow-up
	2C	"Outcomes" research. Ecological studies.	"Outcomes" research	–	Ecological studies
	3A	Systematic review of case–control studies	–	Systematic review of 3b and better studies	Systematic review of 3b and better studies
	3B	Case–control study	–	Nonconsecutive study or without consistently applied reference standards	Nonconsecutive cohort study, or very limited population
C	4	Case-series, poor quality cohort, and case–control studies	Case-series, poor quality prospective cohort studies	Case–control study, poor or nonindependent reference standard	Case-series or superseded reference standards
D	Expert opinion without explicit critical appraisal or based on basic science (physiology, bench research)				

RCT: randomized clinical trial; CDR: clinical decision rule.

$20'10^3$ platelets/mm^3 to perform EGD in patients at low risk of bleeding and $50'10^3$ platelets/mm^3 in those at high risk[12]. Meanwhile, the British guidelines recommend performing EGD with platelet reserve in patients with less than 50–$80'10^3$ platelets/mm^3 [13]. However, two systematic reviews demonstrated that the existing evidence is insufficient to establish a cutoff point for performing EGD in thrombocytopenic patients and that the current recommendations are based on expert opinion[14,15].

Some randomized controlled trials (RCTs) evaluated the transfusion of PRBCs in patients with upper gastrointestinal

bleeding and showed lower mortality associated with the use of restrictive strategies (transfusion to maintain Hb 7–8 g/dL)[16]. The European Society of Gastrointestinal Endoscopy guideline corroborates this strategy recommending Hb values between 7 and 9 g/dL[17].

As for coagulopathy, no study demonstrated the risk of a new bleeding event in patients with elevated INR (2.5 or higher) or the use of anticoagulants[18]. Despite this, a cohort indicates that performing early EGD (<24 h) is safe in patients after partial INR correction, with a similar risk to patients with no coagulopathies[19]. The International Consensus Group recommends the correction of coagulopathies in advance due to the benefits of early EGD and low evidence of complications, provided this does not delay endoscopy[20].

BRONCHOSCOPY

Bronchoscopy is a well-established complementary method for investigating respiratory system pathologies, including bronchoalveolar lavage, lung parenchyma biopsy, and therapeutic procedures. The incidence of hemorrhagic complications after bronchoscopy is approximately 0.44%[21].

According to the latest guideline of the American Association of Blood Banks, bronchoscopy can be safely performed in patients with a platelet count ≥20´10³/mm³. This recommendation is mainly based on observational studies with limited sample sizes[22]. Despite this, a recent cohort study observed a low rate of bleeding complications in 1,711 cancer patients with thrombocytopenia, including those with a platelet count <20´10³/mm³. Approximately, 45% of the patients with 10–20´10³ platelets/mm³ did not receive prophylactic PC transfusion, and even so, there was no significant difference in bleeding complications[23]. In the case of levels <10´10³ platelets/mm³, PC transfusion before the procedure is plausible due to the high risk of spontaneous bleeding[10].

RENAL BIOPSY

A major complication associated with renal biopsy is hemorrhagic bleeding, occurring in approximately 0.6–4.9% of cases[24]. Some of the risk factors for post-biopsy bleeding are as follows: female sex, advanced age, elevated INR, hypertension, and increased baseline creatinine levels[25,26]. The use of ultrasound in clinical practice allowed the use of open biopsies in some specific cases, as well as CT-, laparoscopic-, or transjugular-guided biopsies.

The use of BPs, especially PRBCs, tends to be more strongly influenced by pre-procedure baseline hemoglobin values rather than by the decrease in hemoglobin levels during the biopsy, the presence of perinephric hematoma, or the need for post-procedure surgical approach[27]. In a large meta-analysis of randomized clinical trials, Salpeter et al. do not recommend routine blood transfusion after renal biopsy because of increased mortality, higher incidence of acute myocardial infarction, pulmonary edema, and bacterial infections[28]. However, the cutoff point for blood transfusion in these patients is controversial, and there are no major RCTs on the use of blood concentrates before or after this procedure[27].

Regarding platelet transfusion, the thrombocyte level decrease is associated with the development of symptomatic hematoma[29]. In a retrospective study, Simard-Meilleur et al. demonstrated that the risk of this complication is inversely proportional to the serum platelet level, being 11% in patients with >200´10³ platelets/mm³ and 40% in those with levels <100´10³ platelets/mm³ [29].

LIVER BIOPSY

The most severe complications of liver biopsies are intraperitoneal hemorrhage, hemobilia, and hematoma formation. The risk of clinically relevant bleeding complications that result in hemodynamic compromise or require some form of intervention ranges from 0.01 to 0.5%[30,31].

Both organ dysfunction and hepatosplenomegaly as a result of chronic liver diseases may result in blood dyscrasias, either by INR change or by platelet destruction and dysfunction. Thus, the American Association for the Study of Liver Diseases recommends the correction of thrombocytopenia to serum levels below 50–60´10³ platelets/mm³ [32]. Regarding INR, the Society of Interventional Radiology defines its cutoff point for performing biopsy as an INR ≤1.5–1.8 and <2.5 for the general population and for patients with chronic liver disease (CLD), respectively[33].

In the largest RCT evaluating the performance of percutaneous liver biopsy in patients with advanced CLD, the HALT-C indicated an increased risk of post-procedure bleeding in patients with platelet counts ≤60´10³/mm³ (5.3% versus 0.4%; p<0.001) and INR≥1.3[34]. However, this study excluded thrombocytopenia <50´10³/mm³, and no patients with INR>1.5 experienced bleeding events.

FINAL ANALYSIS

This study found few and sometimes contradictory data on the indication of blood component transfusion before invasive procedures. Most published studies correspond to observational studies with heterogeneous results and several methodological limitations.

This study found a significant inconsistency in recommendations between the guidelines evaluated and also regarding the evidence available in the literature, indicating that such recommendations are based on expert opinion.

Table 2 shows a synthesis of the main studies, their recommendations, recommended cutoff values for platelet count and INR, and data on the quality of evidence. Figure 1 presents the final recommendations based on these results.

Table 2. Synthesis of evidence levels and recommendations for studies evaluating prophylactic blood transfusion and/or bleeding risk related to elective invasive procedures.

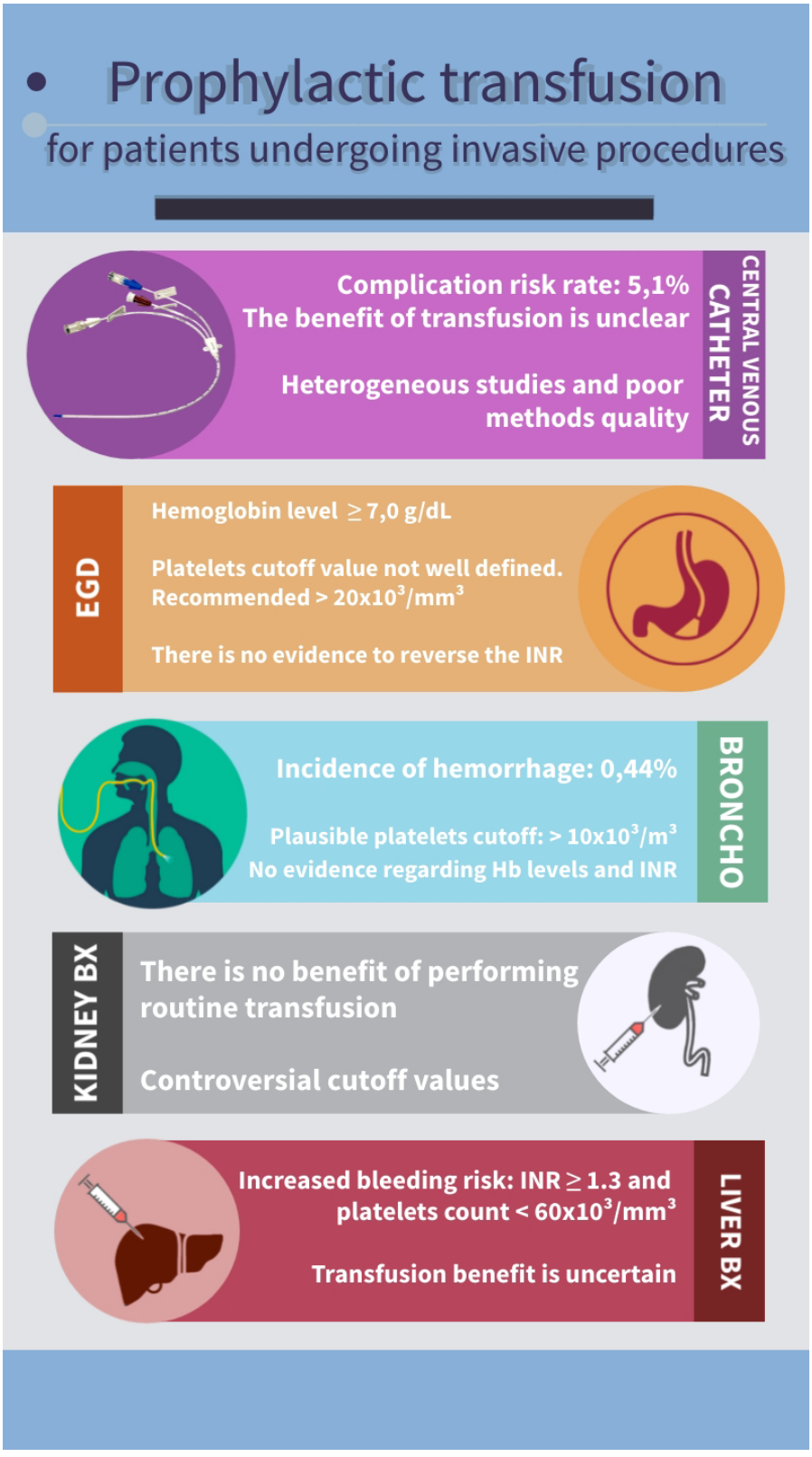
Procedure	Platelet count[π]	INR	Recommendation*	LOE[¥]	Comments	References
CVC puncture	–	–	Benefit is unclear. Prophylactic transfusion or if bleeding after the procedure seems equally acceptable alternatives	2a	Systematic review of 13 observational studies. High heterogeneity	Cabrini L. et al. 2017[11]
	20´10³	3.0	The benefit of prophylactic reversion of coagulopathies or thrombocytopenia correction is unclear	2a	Systematic review: 01 RCT e 21 observational study. High heterogeneity. Studies of poor to moderate quality	van de Weerdt E.K. et al. 2017[35]
	30´10³	1.5–3.0	Prophylactic reversion of coagulopathies with FFP could not be evaluated	2b	Open-label RCT, concealed, 4 centers, with 81 patients. Compared FFP versus placebo. Truncated due to slow recruitment	Müller M.C. et al. 2015[36]
	50´10³	1.5	Thrombocytopenia or increased INR were not related to the risk of bleeding. Prophylactic correction is not recommended	2c	Open-label not randomized trial with 196 subjects in 02 intensive care units	Weigand K. et al. 2009[37]
EGD	50´10³	–	The platelet count cutoff of 50´10³ is safe to perform EGD. In patients in which this value is difficult to reach, a cutoff of 20´10³ is reasonable	4	Retrospective study in one site with 588 oncology patients, which of 20% had a performance status of 3 or 4	Abu-Sbeih H. et al. 2019[38]
	20–50´10³	–	Safe procedure in thrombocytopenic patients. Low risk of bleeding, no severe or fatal bleeding. Prophylactic platelet transfusion should be individualized	2b	Systematic review of 11 observational studies. High heterogeneity. High proportion of oncology patients	Tong M.C. et al. 2015[15]
	50´10³	–	The study results demonstrate a trend to no difference in risks for a platelet count 10–20´10³. Conversely, the authors suggest transfusion for a platelet count <50´10³ based on guideline recommendations	2a	Systematic review of 20 studies: 4 RCT and 16 observational studies. High proportion of oncology patients	Razzaghi A. and Barkun A.N. 2012[14]
Bronchoscopy	10´10³	–	Prophylactic transfusion is not routinely recommended. In patients whose platelet count is <10´10³, transfusion seems reasonable due to spontaneous bleeding risk	4	Retrospective cohort in one center with 1,711 patients. Only pre-procedure platelet count was analyzed. The authors could not assure the absence of transfusion during or after the procedures in patients without evidence of bleeding. Lung biopsy and BAL were not assessed	Faiz S.A. et al. 2019[23]

Continue…

Table 2. Continuation.

Procedure	Platelet count[n]	INR	Recommendation*	LOE[¥]	Comments	References
Bronchoscopy	30´10³	–	Prophylactic transfusion recommended for a platelet count <30´10³, including diagnosis purposes and BAL	4	Retrospective cohort with 150 patients. Prophylactic transfusion was routinely performed. Confusion bias. Biopsies not assessed	Nandagopal L. et al. 2016[39]
	20´10³	–	Bronchoscopy, including with biopsy, is safely performed for a platelet count ≥20´10³	2b	Prospective observational study with 234 patients, with a follow-up of 18 months. Bronchoscopist blinded. Thrombocytopenia <20´10³ and INR<1.3 were excluded. No occurrence of bleeding or hemorrhage with hemodynamic instabilities	Carr I.M. et al. 2012[40]
Renal biopsy	–	–	Lower pre-procedure Hb is associated with the higher risk of transfusion after biopsy despite the absence of bleeding. Transfusion prescription should be individualized and consider other risk factors instead of only Hb	2c	Prospective study with 910 adults which evaluated bleeding, need for transfusion or death 24 h after percutaneous biopsy	Whittier W.L. et al. 2016[27]
	–	–	No recommendations. Symptomatic hematoma was associated with platelet count and hemodialytic therapy	4	Retrospective cohort study with 287 inpatients and outpatients. No cutoff defined to guide blood product transfusion. Desmopressin was used in 33% of patients	Simard-Meilleur M.-C. et al. 2014[29]
	≥50´10³	1.3	No recommendations. A platelet count <150´10³ was associated with increased risk of hemorrhagic complications	2b	Retrospective cohort study with 219 patients with SLE in a tertiary center. Desmopressin use was excluded. Possibility of information bias	Chen T. et al. 2012[41]
Liver biopsy	60´10³	–	Indication and benefit of prophylactic blood product transfusion prior to liver biopsy in cirrhotic patients is unclear	5	Narrative review including 15 studies with cirrhotic patients. Heterogeneous studies. No systematic approach or critical information appraisal	Alvaro D. et al. 2021[30]
	50´10³	–	Image-guided liver biopsies are safe in patients with a platelet count >50´10³/mm³	2b	Retrospective cohort study in one center with 5,987 patients. Information bias, events identified from medical records. Small number of events	Boyum J.H. et al. 2016[31]
	60´10³	1.3	Percutaneous liver biopsy should be avoided in patients with a platelet count <60´10³ due to increased risk of bleeding	2b	Multicentric open-label RCT including 2,749 percutaneous biopsies. No stratification to the usage of an ultrasound device, needle type, or the number of attempts. Thrombocytopenia <50´10³/mm³ was excluded and no patients with INR>1.5 has bleed	Seeff L.B. et al. 2010[34]

INR: international normalized ratio; LOE: level of evidence; CVC: central venous catheter; RCT: randomized clinical trial; FFP: fresh frozen plasma; EGD: esophagogastroduodenoscopy; BAL: bronchoalveolar lavage; Hb: hemoglobin; SLE: systemic lupus erythematosus.
*Recommendations of international guidelines were not listed in this table, since they are already mentioned in the text and mostly based on the opinion of experts (LOE 5).
[n]Platelets/mm³.
[¥]According to the Oxford Centre for Evidence-Based Medicine Classification.



EGD: esophagogastroduodenoscopy; Broncho: bronchoscopy; Bx: biopsy; INR: international normalized ratio.

Figure 1. Recommendations for prophylactic blood transfusion prior to main elective invasive procedures.

CONCLUSIONS

Few studies evaluated the indications of prophylactic blood transfusion for bleeding complications in patients with anemia, thrombocytopenia, or coagulopathies. The recommendations of international guidelines do not always reflect critical analyses of the available scientific evidence and should be reviewed and applied in clinical practice with caution.

AUTHORS' CONTRIBUTIONS

MAOSV: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Writing – Original Draft, and Writing – Review and Editing. **GLOS:** Conceptualization, Formal Analysis, Investigation, Methodology, and Writing – **ORIGINAL DRAFT. AFS:** Supervision and Writing – Review & Editing.

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REVIEW ARTICLE
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Thoracoscopy in the treatment of persistent arterial ductus arteriosus in neonates

Giovanna Costa Moura Velho[1]*, Ana Luísa Barbosa Gouveia[1], Arthur Bispo de Almeida Pinto[1], João Guilherme Marques Castello Branco Levy[1], Mayara Maranhão Jorge[1], Alberto Vilar Trindade[1], Antônio Claudio Dias Amaral[2]

INTRODUCTION

Patent ductus arteriosus (PDA) is a congenital deformity. The ductus arteriosus is essential for neonatal circulation, and normally after 2–3 days of life in terms of newborns, it closes. When occlusion does not occur, there is an increase in pulmonary flow associated with systemic hypoperfusion. The major risk factor for PDA is preterm birth and delayed canal closure, which is inversely proportional to gestational age (GA). An estimated 80% of infants with a GA between 25 and 28 weeks will present with PDA[1].

In 1977, indomethacin, a prostaglandin synthesis inhibitor agent, became the clinical therapy for ductus arteriosus closure in premature infants. However, in situations in which PDA is refractory to clinical management or when the side effects of clinical treatment outweigh the benefits, its surgical ligation is indicated[1].

Although open thoracic surgery is common for PDA ligation or clipping, thoracoscopic PDA closure is an alternative surgical procedure that requires a smaller incision, facilitates postoperative recovery, reduces pain, results in shorter hospital stay, and improves respiratory function. There is also a decrease in the incidence of chest wall deformity in the long term, including scoliosis and breast deformity, leading to better aesthetic results[2,3].

Minimally invasive surgery is increasingly performed in pediatrics, but the physiological characteristics of neonates are associated with a higher risk of intraoperative complications[4].

Collectively, the studies that make up the current literature on the subject are from centers with extensive experience in minimally invasive surgery, as such, there is still a need for more series of reports comparing thoracoscopy with standard thoracotomy in terms of efficacy, morbidity, and conversion rates, especially in neonates and premature babies[3,5]. Therefore, the objective of this study is to compare thoracoscopy with thoracotomy in the treatment of PDA in neonates.

METHODS

This study aimed to conduct a narrative review of the literature *via* an electronic search of the following databases: MEDLINE, SciELO, LILACS, and ScienceDirect. The articles were selected according to the search for the following DeCS descriptors: "Cardiac Surgical Procedures," "Congenital, Hereditary, and Neonatal Diseases and Abnormalities," "Ductus Arteriosus Patent," "Thoracoscopy," and "Minimally Invasive Surgical Procedures."

For the inclusion of articles, we selected mainly those published from 2015 to November 2020, without criteria for the language of origin. Personal communications, conference proceedings, case reports, and duplicates were excluded.

For better organization and applicability of this study, the Population, Intervention, Comparison, and Outcome (PICO) method was used. *(P) Study population:* full-term or premature neonate patients who submitted to thoracoscopy for the treatment of PDA; *(I) intervention:* thoracoscopy; *(C) comparison:* results of thoracoscopy with those of thoracotomy to treat PDA; *(O) outcome:* thoracoscopy is the procedure of choice for the treatment of PDA due to a decreased incidence of chest wall deformity, shorter hospital stay, and faster postoperative recovery.

[1]Centro Universitário de Brasília – Brasília (DF), Brazil.
[2]Hospital de Base do Distrito Federal, Thoracic Surgery Unit – Brasília (DF), Brazil.
*Corresponding author: giovanna.mouravelho@gmail.com
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RESULTS

In the first stage, we actively searched for articles using descriptors and specific keywords. Thus, 109 articles were recognized, of which 32 were chosen according to their relevance based on the titles and abstracts. Subsequently, two duplicates were excluded. Table 1 summarizes the information from the most relevant articles: authors, year of publication, title, duration of the study, type of study, study description, patient group, study results, and limitations.

DISCUSSION

The arterial duct (AD) is an essential vascular conduit for fetal circulation because it enables communication between the systemic and the pulmonary circulation. The AD anatomically connects the left pulmonary artery to the descending aorta, allowing the passage of more oxygenated blood into the fetal systemic circulation[6].

After 24–48 h from birth, the AD undergoes physiological obliteration to ensure the functioning of the pulmonary circulation. However, the persistence of this communication may occur in the neonatal circulation[5,7]. If PDA is not treated, it can result in heart failure, endocarditis, ventricular hypertrophy, and systemic hypoperfusion[1,8].

Pathophysiology of PDA

When the AD fails to close, blood flow is maintained through it. However, the flow is reversed due to pulmonary and systemic pressure changes that occur after birth, as demonstrated in Figure 1[1].

The expansion of the lung abruptly decreases the pulmonary pressure and the loss of the placental circulation, which is of low pressure, and results in increased systemic pressure. Thus, the flow within the AD is reversed, with blood exiting the aorta and proceeding to the pulmonary artery[1]. This reversal causes an increase in the pulmonary circulation and associated systemic hypoperfusion, as the already oxygenated blood returns to the lung[1].

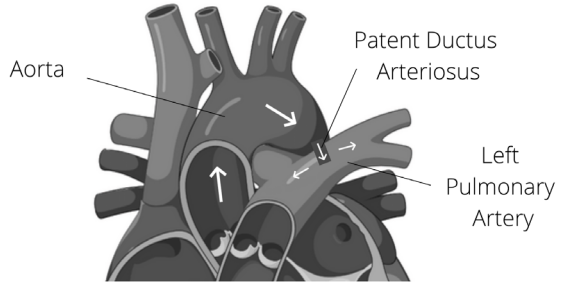

Figure 1. Blood flow with patent ductus arteriosus.

The PDA is related to three factors, namely, prostaglandins (PGs), O_2, and nitric oxide (NO). PGs are essential to maintain the patent ductus. In patients with PDA, the AD endothelium has a higher level of PG receptors[1]. In addition, the AD endothelium is less sensitive to O_2, which would cause its constriction[9,10].

Treatment

The goal is to close the PDA or minimize complications until its spontaneous closure[1]. For diagnostic confirmation, echocardiography is the gold standard, as it can assess the diameter of the AD and the flow through the shunt[11,12]. The clinical findings of the disease, the patient's weight, and the morphology of the duct are important factors for the choice of treatment[8].

The initial treatment is usually clinical. Surgery is utilized when the pharmacological approach is contraindicated, as in the case of complications, including necrotizing enterocolitis, intraventricular hemorrhage, and renal failure[8,13].

Percutaneous access is another option for AD closure[1,5,8,14,15]. However, comparative meta-analyses have shown that reoperations are more common in patients treated with percutaneous closure than with surgical ligation[5,16-18].

Thoracotomy

The goal is to directly ligate the AD. The incision is made laterally to the left and the duct is clipped. It is used in patients refractory to pharmacological treatment or contraindicated for clinical treatment[7].

This safe and reliable approach has similar mortality and complication rates to thoracoscopy[3]. However, there are observational data indicating that open surgery is associated with worsening neurodevelopment of the neonate[18]. In addition, the procedure presents some immediate complications, such as rib fractures, which could be avoided with thoracoscopy[3,14,15].

Thoracoscopy

Thoracoscopy is a minimally invasive method widely used as a treatment for aortic abnormalities, diaphragmatic hernia, and esophageal atresia. This is possible due to the optimization of surgical technologies and newly available equipment[1,8].

Multiple studies in the literature support the efficacy and safety of thoracoscopy as a form of treatment for PDA[19]. Complication rates range from 0.75–5% and the surgical success rate from 98.2–99.1%. Comparative studies between thoracotomy and thoracoscopy showed that there are no differences in safety or efficacy between the procedures[5]. However, there was a decrease in postoperative pain, in the incidence of chest wall deformities, such as scoliosis, and in surgical time and hospital stay after thoracoscopy[3,8].

Table 1. Information from most relevant articles included in the review.

Authors	Title	Duration of the study	Type of study	Description of the study	Patients	Results	Limitations
Muller, et al.[3]	Thoracoscopy Versus Open Surgery for Persistent Ductus Arteriosus and Vascular Ring (VA) Anomaly in Neonates and Infants.	1997–2016	RetrospectiveWW	Age, weight, echocardiography, preoperative symptoms, conversion rate, and short-term postoperative data were analyzed.	n=24 PDA: 13 VA: 11 Patients operated on due to PDA or vascular ring. Thoracoscopy was indicated for patients with clinical failure and/or PDA with hemodynamic symptoms. Thoracoscopy was indicated for patients with clinical failure and/or PDA with hemodynamic symptoms. The mean age was 34 days and the mean weight was 1800 g for patients with PDA.	The group that underwent thoracoscopy and the group that underwent thoracotomy did not have different short-term results (length of hospital stay, surgical time, and postoperative complications). Thoracoscopy causes less pain, especially in neonates and preterm infants. Minimally invasive surgery also causes a decrease in the risk of postoperative chest wall deformities.	Analyses of short-term results. All patients submitted to thoracoscopy due to persistent ductus arteriosus (PDA) were premature, except for one [gestational age (GA) = 37 weeks]. The mean GA was 29.5 weeks, and the mean weight was 1.255 g. The smallest neonate weighed 795 g, and his surgery was converted to thoracotomy due to lack of space. Three cases needed to be converted to thoracotomy due to anesthetic reasons. Conducted in only one institution.
Wei, et al.[5]	Comparison of Outcomes Following Thoracoscopic versus Thoracotomy Closure for Persistent Patent Ductus Arteriosus.	2000–2017	Retrospective	The following were analyzed: surgical time, length of hospital stay, postoperative complications, and reoperations. Exclusion criteria: weight <3.3 kg and/or presence of cardiac comorbidities requiring interventions and/or comorbidities that would require prolonged hospitalization or admission to the neonatal intensive care unit (ICU).	N = 173 Thoracoscopy: 127 Thoracotomy: 46 Patients who submitted to elective surgeries for treatment of PDA.	The length of hospital stay was shorter for patients who submitted to thoracoscopy (1.05 days) than for thoracotomy patients (2.27 days). During the study, conversion to thoracotomy was performed in seven patients; six due to lack of visualization and one due to ductal hemorrhage. Seven patients in the thoracoscopy group had a residual flow on PDA. One was diagnosed during thoracoscopy by transesophageal echocardiography and was converted to thoracotomy. Two others were diagnosed postoperatively and required reoperation. There was no difference in the rates of reoperation or complications, except for drain placement, in which there were rates of 50% in thoracotomy and 11% in thoracoscopy. One patient who submitted to thoracotomy suffered permanent vocal cord injury.	The prolonged thoracoscopy time may be due to the learning curve of the professionals at the institution. The study followed up on 58% of the patients for an average of 1 year. Conducted in only one institution.

Continue...

Table 1. Continuation

Authors	Title	Duration of the study	Type of study	Description of the study	Patients	Results	Limitations
Stankowski, et al[7]	Minimally Invasive Thoracoscopic Closure versus Thoracotomy in Children with Patent Ductus Arteriosus.	2003–2015	Retrospective	The patients were divided into two groups according to the surgical technique (thoracoscopy and thoracotomy). The following technical indices were analyzed: length of hospital stay, rate of patients with chest drains, and postoperative complications. Exclusion criteria: pre-existing cardiac abnormalities requiring simultaneous surgical intervention. During the follow-up period of the study, 22 patients were excluded; 4 due to perioperative death, 3 due to lack of data, and 15 due to conversion to thoracotomy.	N = 173 Patients were classified as low birth weight (LBW) and not low birth weight (NBPN). A greater number of patients with LBW who submitted to video-assisted thoracoscopic surgery (VATS) had heart failure and bronchopulmonary dysplasia at birth. Mean birth weight, weight at surgery, and age were lower in patients with BPN. In patients with NBPN, there was a greater mean diameter of the arterial duct.	Patients undergoing VATS spent less time with the chest drain and less time in the pediatric cardiothoracic ICU. Perioperative mortality was similar in both groups. Fewer complications in VATS, with a lower rate of blood transfusion. There were no statistically significant differences in mortalities.	Conducted in only one institution.
Stankowski, et al.[8]	Descriptive Review of Patent Ductus Arteriosus Ligation by Video-Assisted Thoracoscopy in Pediatric Population: 7-year Experience.	2012–2018	Retrospective	Cohort study was divided into two groups, namely, early phase (2012–2014) and late phase (2015–2018). Due to the learning curve of the institution, early and late outcomes were analyzed.	N = 127 2012–2014: N = 73 2015–2018: N = 54 Patients submitted to thoracoscopy after failure or contraindication of conservative clinical treatment. Mean age 1.7 years. 38.6% of patients were premature. Six patients (4.7%) had chromosomal abnormalities.	The average surgery time was 56.1 min, and that of the last 15 thoracoscopies was 38 min. The average conversion rate to thoracotomy was 16.5%. During the early phase, there was a 20% conversion to thoracotomy. During the late phase, there was a 5% conversion to thoracotomy. The mean number of days of hospitalization was 2.2 days. Only two patients who were discharged from the hospital experienced adverse effects during the follow-up period of the study. The patients who underwent thoracoscopy without conversion did not obtain chest deformities. The 5-year survival rate of the study was 93.6%.	The learning curve of the hospital staff, who started performing thoracoscopies in 2012, influenced the results of the initial phase (2012–2014). Conducted in only one institution.

Continue...

Table 1. Continuation

Authors	Title	Duration of the study	Type of study	Description of the study	Patients	Results	Limitations
Stankowski, et al.[24]	Conversion to Thoracotomy of Video-Assisted Thoracoscopic Closure of Patent Ductus Arteriosus.	2012–2017	Retrospective	The following were analyzed: preoperative period, in-hospital period, postoperative period, and rates, and reasons for surgery conversion.	N = 112 Thoracoscopy: 93 Thoracoscopy with conversion: 19 Patients who submitted to PDA closure by VATS technique. The patients were divided into two groups, namely, those who did not need conversion and those who required it.	The causes reported for conversion were as follows: incomplete closure of the duct (31.6%), ductal bleeding after clipping (26.3%), inadequate visualization (26.3%), cardiopulmonary instability after insufflation (10.5%), and injury of the pulmonary vein during preparation (5.3%). There was one death in each group in the immediate postoperative period. In the group requiring conversion, most of the patients required transfer to the neonatal ICU. Late postoperative period: All ducts presented successful closure. Two patients presented low-grade scoliosis.	Due to the learning curve, there was a reduction in the number of conversions in the last 2 years of the survey. The number of patients in the group of surgeries converted to thoracotomy was low for data comparisons.
Stankowski, et al.[25]	Surgical Closure of Patent Ductus Arteriosus in Extremely Low Birth Weight Infants Weighing Less than 750 grams.	2006–2016	Retrospective	The study was divided into two groups as follows: Early phase (2006–2012): all the patients underwent surgery by posterolateral thoracotomy (PT); Late phase (2012–2016): all the patients underwent VATS, requiring two conversions to PT. Inclusion criteria: birth weight <750 g, PDA with diameter ≥2 mm, left atrium to aorta ratio ≥ 1.5, presence of left to right shunt, and impaired cardiac performance. Exclusion criteria: PDA associated with any other cardiac abnormalities that needed to be surgically corrected in a classical manner.	N = 31 Thoracotomy: 16 Thoracoscopy: 15 (two conversions) Patients with primary pharmacological treatment failure.	All the patients survived the operation and were transferred to the ICU. Two children who underwent VATS required conversion; one due to hemodynamic instability and another due to difficulty in visualizing the channel. Nine children needed the insertion of a drain; seven after thoracotomy, and two after VATS. The mean mechanical ventilator time in the survivors was 19 days. Routine postoperative echocardiography confirmed complete duct closure in all the patients. During the follow-up period, two patients died at home 139 days and 310 days, respectively, after surgery. Late residual shunt occurred in two children during the study follow-up period. However, none of the shunts were hemodynamically significant, and so they did not require further treatment.	Conducted in only one institution.

Yet, the greatest limitation of thoracoscopy is the lack of training of professionals. Some studies showed that surgeons must perform at least 50 procedures to feel comfortable, and even more procedures are needed to reduce the surgical time of the thoracoscopic option. Therefore, the learning curve of surgeons should be taken into consideration. The more clinical cases a surgeon has performed, the more it is expected that the surgical time and the length of hospital stay will decrease[5,20,21].

Some studies have reported that demonstrated shorter hospital stay, while others found no such difference. However, the studies that did not find such a difference were carried out with fewer patients and mainly investigated premature infants. Therefore, there is currently a consensus that thoracoscopy reduces the length of stay in the neonatal intensive care unit (ICU). This may be due to the reduced need for placing drains in patients[5,7,22,23].

The technological development of minimally invasive surgical instruments for better adaptation to the bodies of neonates should improve compliance rates with the thoracoscopic method and decrease therapeutic costs[5,24,25].

Finally, thoracoscopy is more cost-effective than thoracotomy because there is less need for drains and re-intervention and lower complication rates, such as vocal cord injury and pneumothorax[5,24].

CONCLUSIONS

Based on the analyzed studies, it is possible to confirm that thoracoscopy and conventional surgery are equally safe and effective, regardless of the child's age. Thoracoscopy is associated with a shorter hospital and ICU stay, is less traumatic and painful, and has a shorter operative time, excellent cost–benefit ratio, good aesthetic results, and low rate of acute complications. Before the end of thoracoscopy, monitoring *via* transesophageal echocardiography is essential to verify residual flow regardless of the surgeon's experience. Conversion to conventional surgery is rare and does not result in increased complications. It is essential to have a specialized and trained team for the success of this procedure. Finally, more clinical studies comparing these techniques are needed to encourage the medical community to choose thoracoscopy as a surgical treatment for PDA.

AUTHORS' CONTRIBUTIONS

GCMV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing-original draft, Writing – review and editing. **MMJ:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Writing – review and editing. **JGMCB:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Writing – review and editing. **LABAP:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Writing – review and editing. **ALBG:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft, Writing – review and editing. **ACDA:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. **AVT:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE
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Update of the epidemiological distribution of COVID-19 variants: a review article

Thomás Cavalcanti Pires de Azevedo[1], Vanessa Santos Cavalcante Melo[1], Renata Maciel da Silva[1], Beatriz Guerra de Holanda Barbosa[1], Lucas Zloccowick de Melo Christofoletti[1], Giovanna Maria Correia Silva do Nascimento[1], Guilherme Santos Lins de Oliveira[1], Fabiano Timbó Barbosa[1,2,3], Célio Fernando de Sousa-Rodrigues[1,2,4], Fernando Wagner da Silva Ramos[1,4,5]

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in the current pandemic that has spread since 2019, being the virus responsible for the "Coronavirus Disease 2019" (COVID-19)[1]. This disease was responsible for more than 171,708,011 infections worldwide, until June 7, 2021, and more than 3,697,151 deaths. Concomitantly, with the development of vaccines, about 447,911,020 human beings have been vaccinated and more than 2,049,141,878 doses have been applied, in accordance with World Health Organization (WHO)[2].

Viruses are known to have the ability to constantly mutate in such a way that they give rise to variants that persist for a long time or disappear in a short period of time. During the pandemic, several countries recorded these events[3]. In this context, the WHO is working on a global surveillance system so that all countries can collaborate with new information on variants of SARS-CoV-2[4].

Scientific teams are studying the range of circulation of these new variants, the effect that these mutations can have on potential reinfection, diagnosis, vaccination, severity, and disease transmission. Countries are working with the WHO on how surveillance systems can be strengthened or adapted to assess the potential variations of the virus through continuous systematic clinical and epidemiological surveillance, establishing genetic sequencing when possible and accessing international findings to send sequencing samples and phylogenetic analysis[5].

The pandemic spread of a virus in virgin populations can select mutations that alter pathogenesis, virulence, and/or transmissibility. The ancestral form of SARS-CoV-2 that emerged from China has now been largely replaced by strains containing the D614G mutation, replacement of aspartic acid with glycine (Asp 614-para-Gly) in the viral spike protein. However, this change in the virus seems to have evolved into greater transmissibility in humans, rather than greater pathogenicity, due to the association with higher viral loads in the upper respiratory tract than those observed with the ancestral strain[6-9].

As of May 25, 2021, there are four variants of concern to WHO around the world: South Africa (B.1.351, May 2020), United Kingdom (B.1.1.7, Sep 2020), India (B.1.617, Oct 2020), and Brazil (P.1, Nov 2020)[10].

Thus, the purpose of this study is to describe the geographic distribution of the most worrying variants of COVID-19.

METHODS

The present review was performed in MEDLINE (PubMed) and LILACS, following the recommendations of the Preferred

[1]Centro de Estudos Superiores de Maceió – Maceio (AL), Brazil.
[2]Universidade Federal de Alagoas – Maceio (AL), Brazil.
[3]Hospital Geral do Estado de Alagoas – Maceio (AL), Brazil.
[4]Universidade Estadual de Ciências da Saúde de Alagoas – Maceio (AL), Brazil.
[5]Secretaria Municipal de Saúde – Maceio (AL), Brazil.
*Corresponding author: nandobiomedico@hotmail.com
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Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11]. The search terms used were SARS-CoV-2, COVID-19, and variants to find articles published until June 7, 2021. The exclusion criteria were inappropriate topics or not relevant to the purpose of the study (Figure 1).

Genomic sequencing

Since the start of the pandemic in 2020, global science has relentlessly sought to encode the genetic sequence of SARS-CoV-2 to advance vaccine development. Concomitantly, it was noticed, in some countries around the world, that the genomes of the viruses that infect some human beings had some differences from the genome of the new coronavirus responsible for the COVID-19 pandemic. In a study published in April 2020, the genomic sequences of Italian, Chinese, Mexican, German, and Australian patients were compared, reaching the conclusion that not all sequences belonged to the same viral strain[12].

In another phylogenetic study with 160 SARS-CoV-2 genomes collected from different regions of the world, it was verified that the existence of three central variants differ mainly by protein alterations[13]. Therefore, the genome of the new coronavirus is very subject to mutations, favoring the difficulty in the production of antibodies and the recognition of the immune system against the viral antigen[14].

Much of this mutant capacity of SARS-CoV-2 is associated with the Spike receptor-binding domain (RBD), especially in the region of the Spike glycoprotein that regulates virus binding at the angiotensin-converting enzyme 2 (ACE2) receptor that remains located on the surface of human cells[15].

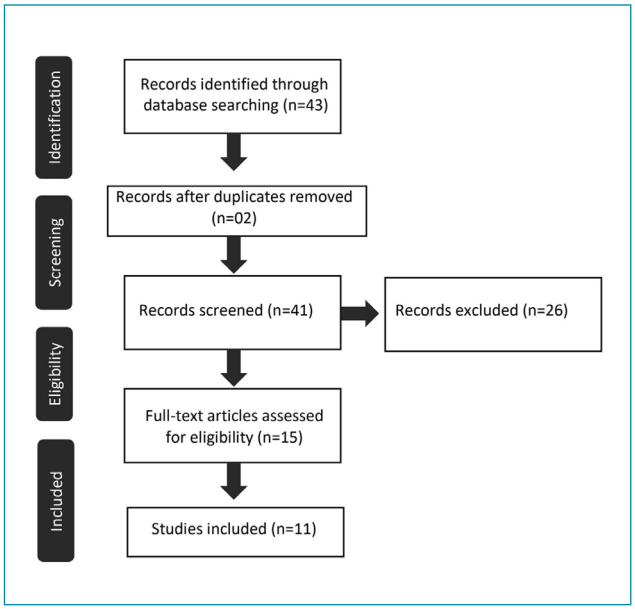

Figure 1. Flow chart to demonstrate the search strategy.

The D614G substitution increases the replication ability of SARS-CoV-2 in primary epithelial cells, with an advantage in the upper respiratory tract epithelial cells in nasal and large (proximal) epitheliums of the airways that express greater amounts of human ACE2 (hACE2) receiver[6-8]. In addition, Korber et al.[9] concluded that the D614G substitution does not significantly change the morphology of SARS-CoV-2, the peak cleavage pattern, and the *in vitro* neutralization properties in the context of the live virus.

Viral variants

According to the WHO, SARS-CoV-2 variants can be divided into variants of interest (VOIs) and variants of concern (VOCs). As of June 1, 2021, there are four variants of concern, and they are found in the UK, South Africa, Brazil, and India. Regarding the VOIs, six were documented[16] (Table 1).

The variant B.1.1.7 contains eight mutations in Spike, and the strain is associated with many additional mutations throughout the SARS-CoV-2 genome. Among the Spike mutations, N501Y is suggested to increase the ACE2-RBD interaction. Double deletion of H69-V70 amino acids in Spike's N-terminal domain (NTD) often co-occurs with one of the three mutations in RBD: N501Y, N439K, or Y453F. Y453F is associated with an outbreak in Denmark, with and without the presence of a ΔH69/V70 deletion, but is also found in people in the UK. The N439K mutation usually occurs with ΔH69/V70, but it also frequently occurs without the ΔH69/V70 mutation. In an in vitro selection study with Regeneron antibodies, Y453F and N439K were found to escape neutralization by REGN10933 and REGN10987 that comprise the REGN-COV2 cocktail regime. It has also been reported that N439K resists neutralization while maintaining the virus' fitness /infectivity. Another mutation of obvious concern in B.1.1.7 is P681H, proximal to the furin cleavage site that has often appeared independently and has come to dominate the local epidemic in Hawaii[17-19].

A new strain of SARS-CoV-2 has been discovered in South Africa, 501Y.V2, which is composed of nine alterations in the Spike protein. However, although this new strain is associated with greater transmissibility and not immunogenicity, it is known that the accumulation of mutations can result in a space for viral neutralization. The nine alterations in the Spike protein can be divided into groups that include four protein substitutions and a deletion (L18F, D80A, D215G, Δ242-244, and R246I)[20]. In Brazil, viral mutations were also found in this same region of the Spike protein[21].

Table 1. SARS-CoV-2 VOCs and VOIs, as of June 1, 2021.

Pango lineage	First detected in	Earliest samples	Characteristic spike mutations
Variants of concern (VOCs)			
B.1.1.7	United Kingdom	Sep 2020	69/70del, 144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
B.1.351	South Africa	May 2020	D80A, D215G, 241/243del, K417N, E484K, N501Y, D614G, A701V
P.1	Brazil	Nov 2020	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G H655Y, T1027I, V1176F
B.1.617.2	India	Oct 2020	L452R, D614G, P681R, ± (E484Q, Q107H, T19R, del 157/158, T478K, D950N)
Variants of interest (VOIs)			
B.1.427/B.1.429	United States of America	Mar 2020	S13I, W152C, L452R, D614G
P.2	Brazil	Apr 2020	E484K, D614G, V1176F
B.1.525	Multiple countries	Dec 2020	Q52R, A67V, 69/70del, 144del, E484K, D614G, Q677H, F888L
P.3	Philippines	Jan 2021	141/143del, E484K, N501Y, D614G, P681H, E1092K, H1101Y, V1176F
B.1.526	United States of America	Nov 2020	L5F, T95I, D253G, D614G, A701V, + (E484K or S477N)
B.1.616	France	Feb 2021	H66D, G142V, 144del, D215G, V483A, D614G, H655Y, G669S, Q949R, N1187D

Source: World Health Organization. COVID-19 Weekly Epidemiological Update. Edition 41, published 25 May 2021.

CONCLUSION

This review showed that much of this mutated capacity of SARS-CoV-2 is associated with the Spike RBD that regulates virus binding to the angiotensin-2 converting enzyme receptor (ACE2). The VOCs to WHO detected so far (June 7, 2021) have been mapped in the UK, South Africa, Brazil, and India. It is known that they are more associated with greater transmissibility than pathogenicity. However, there is still a need for further studies to identify whether current vaccines will be effective in inducing antibody production against the variants and whether such variants will be responsible for new waves of infection in the current pandemic.

AUTHORS' CONTRIBUTIONS

TCPA: Data curation, Writing – original draft, Writing – review & editing. **VSCM:** Data Curation, Writing – original draft, Writing – review & editing. **RMS:** Data Curation, Writing – original draft, Writing – review & editing. **BGHB:** Data Curation, Writing – original draft, Writing – review & editing. **LZMC:** Data Curation, Writing – original draft, Writing – review & editing. **GMCSN:** Data Curation, Writing – original draft, Writing – review & editing. **GSLO:** Data Curation, Writing – original draft, Writing – review & editing. **FWSR:** Methodology, Writing – original draft, Writing – review & editing. **CFSR:** Methodology, Writing – original draft, Writing – review & editing. **FTB:** Methodology, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE
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Systematic review of insulin-like growth factor 1 gene expression in women with breast cancer

Danylo Rafhael Costa-Silva[1], Maria da Conceição Barros-Oliveira[1], Benedito Borges da Silva[1]*

INTRODUCTION

Cancer incidence and mortality are rapidly growing worldwide, representing a serious global health problem[1]. Breast cancer is the most frequently diagnosed malignant neoplasm in the majority of countries and is the leading cause of cancer death among women[2]. In the year 2018, approximately 2.1 million new cases of breast cancer were estimated to occur worldwide[3]. Breast cancer is a complex disease of unknown and multifactorial etiology, in which one of the main risk factors is genetic alteration[4,5]. Thus, genetic mutations of breast cancer (BRCA) 1 and *2* genes are related to the increased risk of hereditary breast and ovarian cancer over time[6]; however, the participation of genes in breast cancer has not yet been fully elucidated[4,5]. Thus, changes in expression levels of the insulin-like growth factor 1 (IGF-1) gene have been evaluated in breast cancer; however, there is a need for further elucidation of the association between changes in IGF-1 levels and increase in the risk, survival, and disease progression of breast cancer[7].

The IGF system consists of two peptidic hormones (IGF-1 and IGF-2), two cell surface receptors (IGF-1R and IGF-2R), and at least six IGF-binding proteins (IGFBP 1-6) that control normal growth and differentiation in most of the tissues[8]. In combination with the growth hormone, insulin, and sex hormones, IGF-1 acts as a crucial regulator of cell growth, differentiation, and apoptosis, as it has striking mitogenic and antiapoptotic activities in cancer cells, acting synergistically with estrogen to promote tumor growth[9]. Epidemiological and experimental evidence attempted to clarify the role of the IGF-1 axis in human breast cancer and showed controversial results. While some studies indicated that increased levels of IGF-1 gene expression are associated with a better prognosis in breast cancer[10], other authors have suggested that increased levels of IGF-1 gene expression could be associated with increased cell proliferation in breast cancer[11,12]. Thus, altered levels of IGF-1 gene expression may be related to better prognosis or unfavorable outcomes and greater aggressiveness in breast cancer[13,14]. However, there is a scarcity of studies on this subject in women with breast cancer. This motivated us to detail, in a systematic review, the available studies in the databases to investigate the influence of IGF-1 gene expression levels in women with breast cancer.

METHODS

Search strategy

This study was carried out using the PubMed, Scopus, and Web of Science databases. Searches were conducted between February 2, 2019, and May 15, 2019. The search strategy included the crossing of the following descriptors: "breast cancer" OR "breast neoplasm" AND "IGF-1" AND "gene"; "breast cancer" OR "breast neoplasm" AND "IGF-1" AND "expression"; "breast cancer" OR "breast neoplasm" AND "IGF-1" AND "mRNA"; "breast cancer" OR "breast neoplasm" AND "IGF-1" AND "gene" AND "expression."

Study selection and eligibility criteria

A collection of eligibility criteria was used to select articles from the literature. Inclusion criteria were studies published between 2009 and 2019, English language publications, and human studies addressing the gene expression of IGF-1 in breast cancer. Exclusion criteria were duplicate articles, articles with only abstracts available, literature reviews, editorials, letters to the editor, conference proceedings, and articles related to breast cancer and IGF-1 that did not quantitatively analyze the levels of gene expression.

[1]Universidade Federal do Piauí, Rede Nordeste de Biotecnologia – Teresina (PI), Brazil.
*Corresponding author: beneditoborges@globo.com
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Data extraction and quality assessment

All identified studies were independently reviewed by two authors for the relevance of the inclusion/exclusion criteria. After a primary examination, all the complete studies retrieved were subjected to a more detailed evaluation and were compared and verified to ensure equivalence in the selection and analysis of articles. The selection process of the studies was mapped according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[10].

RESULTS

A total of 2,370 studies were identified through PubMed databases (n=749), Scopus (n=330), and Web of Science (n=1,291). After selecting and applying the inclusion and exclusion criteria, five articles were included in the present systematic review, according to the flow chart detailing the process of identification, selection, eligibility, and final inclusion of the studies (Figure 1). The description of the selected studies is shown in Table 1.

The association between IGF-1 mRNA expression levels in tumor tissues of women with breast cancer and the characteristics of the disease was examined by Mu et al.[15]. A significant association was found between increased levels of IGF-1 mRNA expression and small tumors (<2 cm), low-grade tumors, and estrogen receptor (ER)- or progesterone receptor (PR)-positive tumors. The survival analysis showed that women with high IGF-1 mRNA expression had a lower risk of disease recurrence and death compared to those with low expression.

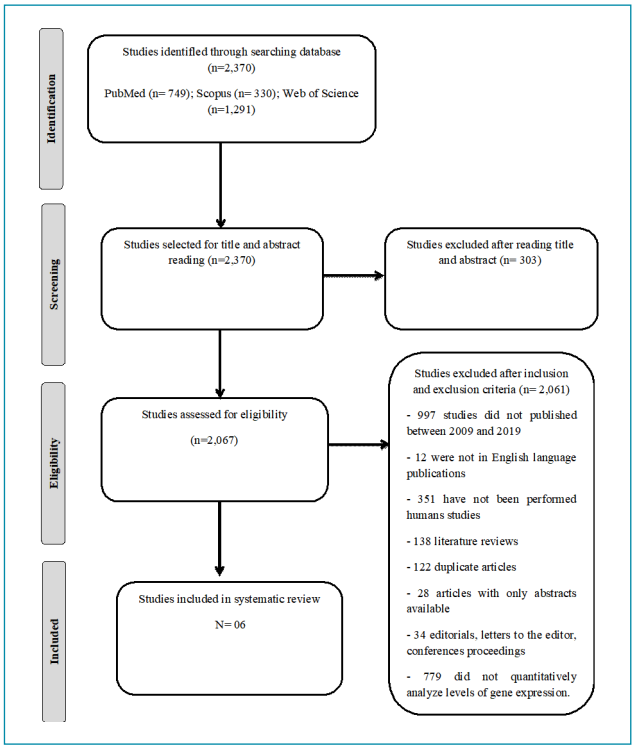

Figure 1. Flowchart detailing the process of identification, selection, eligibility, and final inclusion of the studies.

In another study, Mu et al.[13] showed that increased levels of IGF-1 mRNA expression were associated with the luminal subtype A, normal-like, and less aggressive tumors (ER-positive, low-grade, and node-negative tumors). However, decreased levels of IGF-1 mRNA expression were associated with the basal, human epidermal growth factor receptor 2 (HER2), and luminal B subtypes. Thus, the results of their studies showed an inverse association between IGF-1 mRNA levels and the prognosis of the disease.

Chong et al.[11] analyzed the relationship between IGF-1 mRNA expression levels in breast tumors and adjunctive normal tissues (TNAs) and the clinicopathological and prognostic factors of women with breast cancer. No correlation was observed in tumor tissue and TNAs between IGF-1 mRNA expression levels and clinicopathological factors such as histological grade, lymph node status, and tumor size; however, increased levels in tumor tissue and TNAs were associated with increased disease-free survival (DFS).

Raval and Trivedi[7] studied the levels of IGF-1 mRNA expression in TNAs of women undergoing mastectomy for breast cancer treatment. Significantly, the lower levels of IGF-1 mRNA expression were observed in the breast tumors, regardless of age, menopausal status, tumor size, lymph node status, and histological stage when compared with those in the TNAs. On the other hand, in this study, the low expression was associated with more advanced stages. Thus, a significant inverse correlation was observed between stage, histological type, and levels of IGF-1 mRNA expression.

Christodoulou et al.[12] analyzed the in-tumor expression of IGF-1 mRNA in patients with trastuzumab-treated HER2-positive metastatic breast cancer and showed that IGF-1 mRNA expression levels were higher in patients over the age of 50 years at the time of the initial diagnosis and absence of bone metastases. In contrast, decreased levels were associated with histological grade III, distal, and mainly visceral metastases. Chong et al.[16] showed that tumors with high levels of IGF-1 mRNA expression were associated with a significantly longer time to develop resistance to tamoxifen.

DISCUSSION

The studies evaluated in this systematic review have shown controversial results related to the levels of IGF-1 gene expression in women with breast cancer. Mu et al.[15] showed that elevated IGF-1 mRNA expression was associated with indicators of good prognosis. These results agree with previous studies that showed that elevated levels of IGF-1 mRNA were associated

Table 1. Description of the selected studies.

Author	Type of study	Characteristic population	Sample size	Conclusion
Mu et al.[15], 2009	Cohort	Italian women	204 cases of breast cancer	High levels of IGF-1 mRNA expression were associated with small tumors, earlier stages of the disease, low-grade tumors, ER- or PR-positive tumors, and a better prognosis.
Mu et al.[13], 2012	Cohort	Italian women	204 cases of breast cancer	High levels of IGF-1 mRNA expression were associated with the luminal A and normal-like subtype, with less aggressive tumors and a better prognosis.
Chong et al.[11], 2011	Cohort	English women	132 cases of breast cancer	IGF-1 mRNA levels did not correlate with clinic pathological factors. However, increased levels of IGF-1 mRNA expression were associated with higher DFS.
Raval and Trivedi[7], 2016	Cohort	Indian women	106 cases of breast cancer	Significantly lower levels of IGF-1 mRNA expression were observed in breast tumors regardless of age, menopausal status, tumor size, lymph node status, and histologic grade. There were no associations with OS and DFS.
Christodoulou et al.[12], 2018	Cohort	Greek women	227 cases of breast cancer	High levels of IGF-1 mRNA expression were associated with older age and absence of bone metastases. Already decreased levels of expression were associated with histological grade III and metastases.
Chong et al.[16], 2011	Cohort	English women	92 cases of breast cancer	High levels of IGF-1 mRNA expression were associated with delay in developing resistance to tamoxifen. Decreased levels of IGF-1 mRNA expression were associated with tamoxifen-resistant tumors.

ER: estrogen receptor; PR: progesterone receptor; DFS: disease-free survival; OS: overall survival.

with better prognosis of the disease[17]. Mu et al.[15] suggested that high-grade tumors that invade adjacent tissues or spread to distant organs may become less dependent on IGF-1 regulation and that small and low-grade tumors respond well to IGF-1 signals, while in another study, they showed that increased levels of IGF-1 mRNA expression were associated with luminal A and normal-like subtypes.

In a study by Chong et al.[11], even though correlation was not observed between IGF-1 mRNA expression levels and clinicopathological factors such as histological grade, lymph node status, and tumor size, increased levels of IGF-1 mRNA expression in tumor tissue and TNAs were found to be associated with higher DFS, and this was statistically independent of other clinicopathological features[11]. These findings agree with previous studies where high IGF-1 mRNA expression was established as an independent predictor of higher DFS and OS[17] and suggesting that the IGF-1 gene may increase cell differentiation in certain types of cancer, and this would be associated with less aggressive cancers and consequently with better prognosis.

Raval and Trivedi[7] showed significantly lower levels of IGF-1 mRNA expression in breast tumors in women compared with those in TNAs. These findings suggesting the existence of a paracrine relation within the local environment of the cancerous mammary tissue, where the expression may differ according to the type of cell present within the tissues, and the greater expression of IGF-1 in TNAs would stimulate cell proliferation and inhibit apoptosis, causing the levels to be high in TNAs and low in breast tumors[7].

The findings of Christodoulou et al.[12] in women with HER2-positive breast cancer treated with trastuzumab showed elevated levels of IGF-1 mRNA expression in women older than 50 years at the time of diagnosis and absence of bone metastases. On the contrary, decreased levels of IGF-1 mRNA expression were found in patients with histological grade III and visceral distal metastases, which may be justified by the fact that IGF-1 could be involved in the mechanism of resistance to treatment with trastuzumab[18], suggesting that cross-communication of IGF-1/HER2 may occur via autocrine and/or paracrine signaling in breast cancer[18]. Chong et al.[16] has shown that higher levels of IGF-1 mRNA expression are associated with lower tamoxifen resistance in breast cancer. Some studies have shown that resistance to tamoxifen may be due to altered downstream cellular pathways involving IGF-1[19]. However, patients with tamoxifen-sensitive breast cancer had not yet used the drug at the time of the biopsy and were under estrogenic stimulation, which could explain the higher levels of IGF-1 mRNA in these patients, unlike breast cancers resistant to tamoxifen that become independent of estrogen stimulation, and as IGF-1

tends to correlate with estrogen, this may justify low levels of IGF-1 mRNA in these tumors[16]. A probable explanation for conflicting results found among the authors is due to the limitations of the studies evaluated, especially lack of standardization in the methodology, where different protocols of gene expression analysis were used, and heterogeneous samples with relatively small sample numbers and with different ethnicities.

CONCLUSIONS

This systematic review provides evidence that increased or decreased levels of IGF-1 gene expression may be associated with clinicopathological aspects of breast cancer, DFS, OS, and resistance to tamoxifen in women with breast cancer. However, there is a shortage of studies on the subject, mainly with larger samples, in Latin American women with recurrence of breast cancer. Therefore, the elucidation of IGF-1 gene expression patterns through further studies may allow the characterization of women at high risk for breast cancer, as well as the development of strategies for prognosis and effective treatment, allowing better survival and reduction of progression of the disease.

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AUTHORS' CONTRIBUTIONS

DRCS: Conceptualization and design of the study, search and analysis of articles, writing of the original manuscript, and elaboration and revision of the graphic components (tables and figures). **MCBO:** study design, search, and analysis of articles, writing of the original manuscript, and elaboration and revision of graphic components (tables and figures). **BBS:** conceptualization and design of the study, revision and orientation of methodology, revision of graphic components (tables and figures), and revision of the original and final manuscripts.

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COMMENTARY
https://doi.org/10.1590/1806-9282.20210167

Commentary: "Factors related to adherence to antiretroviral treatment in a specialized care facility"

Yuexiao Yu[1], Xiaofei Li[1]*

Dear Editor,

We are glad to read this very valuable article entitled "Factors related to adherence to antiretroviral treatment in a specialized care facility." They[1] found that symptomatic patients have better adherence to therapy. The authors indicate that having aids decreases the probability of non-adherence to antiretroviral treatment by 92%. But in my opinion, there are still some issues that should be raised.

First of all, this is a small sample study. So how does the author sample? Is the sample representative? The author should give a detailed introduction to the environment of the subject. What is the size of the population of the city, is the sample a whole group sample or a multi-stage sample? The representativeness of the sample is the basis for reaching reliable conclusions.

As the author says, in Brazil, a study conducted in 55 health services specialized in the care for patients with HIV/aids showed large variations in the non-adherence rates throughout the country, ranging from 10.7–86.0%. Therefore, future research needs to pay attention to the representativeness of samples and large sample studies.

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[1]Yiwu Central Hospital, Department of infectious diseases – Zhejiang, China
*Corresponding author: xiaofeili2000@163.com
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COMMENTARY
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Comment on "Thrombopoietin is associated with the prognosis of gastric adenocarcinoma"

Bin Tan[1], Xixi Li[1], Lihua Tang[1]*, Lixin Chen[2]

Dear Editor,

We were pleased to read the study by Zhou et al.[1], and colleagues in which they found that thrombopoietin(THPO) may be a potent marker of gastric adenocarcinoma, providing a novel potential screening method for gastric adenocarcinoma. I would like to make some of my points.

To begin with, they concluded that THPO may be a potent regulator in gastric adenocarcinoma progression. However, the interpretation of the TCGA database and the pathophysiological relevance of the postulated pieces of evidence would need extensive reworking. m not convinced that the interpretation of the TAGA database is correct. In the TCGA database, the fold change of THPO expression between gastric cancer and normal gastric mucosa was not significant (1.28). In addition, THPO expression was decreased in gastric cancer tissues than in normal gastric mucosa in the GEO database. Thus, this manuscript would need extensive reanalysis of the TCGA and GEO databases.

Additionally, the study found that THPO would be deeply involved in gastric cancer progression. However, it was not reasonable to prove their hypothesis. They used the TCGA database for analysis of THPO expression in gastric cancer. However, just one database should be validated by other databases. There were several datasets have been proposed in public data using transcriptome data of gastric cancer tissues. I recommend that the authors analyze another database to convince their hypothesis. The authors presented the role of THPO on migration ability, but THPO also influences cell viability. Migration assay could be affected by cell viability, so the result of migration assay would be not clear to reflect the pure migratory ability of cancer cells.

AUTHORS' CONTRIBUTION

BT: Writing – original draft, Writing – review & editing.
XL: Writing – original draft, Writing – review & editing.
LT: Writing – original draft, Writing – review & editing.
LC: Writing – original draft, Writing – review & editing.

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[1]Taian Central Hospital, Department of Blood Transfusion – Taian, China
[2]Taian Central Hospital, Department of Gastroenterology – Taian, China
*Corresponding author: fengqichanglin886@126.com
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COMMENTARY
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Comment on "Multidisciplinary teams: perceptions of professionals and oncological patients"

Zhanshuo Gu[1], Peiyuan Cai[2]*

Dear Editor,

Recently we have read a research article entitled "Multidisciplinary teams: perceptions of professionals and oncological patients"[1]. In this study, the author obtained the satisfaction data from professionals and patients in the public and private medical institutions through survey questionnaires. Statistical methods were used to analyze the results of the data, and the conclusion was drawn that there were differences in the level of satisfaction of cancer multidisciplinary team treatment among different groups. This kind of research is of great significance to the scientific decision-making of public health and health care systems. However, due to the small number of samples and the lack of further detailed definition of sample composition, there are still some limitations in this study.

As clinicians, we have some questions and suggestions to discuss with the researchers:

First, according to the description of the article, in the process of data collection, different groups of professionals and patients related to different diseases applied different questionnaire contents. If the questionnaire used by each group is displayed in the form of an attachment, the relevant researchers will evaluate the objectivity and preciseness of the conclusion more objectively and accurately. As mentioned above, this kind of research needs multi-center and large sample data to produce scientific significance and social value, and the accumulation of such literature data is conducive to the ongoing and deepening of the research.

Secondly, in the sample of professionals, the gender ratio is over biased. Because of the differences in psychology and tolerance between men and women, we should pay attention to the deviation of the experimental results.

Finally, patient satisfaction is a subjective-descriptive result. As clinicians, we suggest that researchers further investigate patients' choice of follow-up treatment, which we think will be yielding more objective data and results.

AUTHORS' CONTRIBUTIONS

ZG: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **PC:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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[1]Taizhou Municipal Hospital, Department of Gastroenterology – Taizhou (Zhejiang), China.
[2]Taizhou Municipal Hospital, Department of Interventional Oncology – Taizhou (Zhejiang), China.
*Corresponding author: caipeiyuanTZH@163.com
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COMMENTARY
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Comment on "The impact of visceral fat and levels of vitamin D on coronary artery calcification"

Juan Zhang[1], Lianping He[1]*

Dear Editor,

It is our pleasure to read this interesting study by Isa Galvão Rodrigues et al.[1] This study shows that excess visceral fat was associated with subclinical atherosclerosis, regardless of other risk factors for cardiovascular disease. Furthermore, serum levels of 25-hydroxyvitamin D were not associated with calcification of coronary arteries (CCA) in its early stages. Although the study plays a vital role in the assessment of coronary atherosclerosis, I believe that there are some issues that should be discussed further.

First of all, in the results section, it is mentioned that hypertension and age >60 years were associated with CCA after adjusting for confounding variables such as gender, presence of diabetes, subcutaneous adipose tissue (SAT), and body mass index (BMI) (Table 3). However, the table fails to provide detailed parameters such as OR value and p-value of the items that eliminate confounding factors.

Furthermore, it is a vague statement that this study puts forward the point of relatively small sample size in the discussion section. The study does not calculate the sample size and degree of certainty, so this statement is inappropriate.

AUTHORS' CONTRIBUTION

THL, LPH: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review& editing.

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[1]Taizhou University, School of Medicine – Zhejiang, China.
*Corresponding author: lianpinghe@tzc.edu.cn
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COMMENTARY
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Comment on "Effect of competence health cultivation on the prevention and control of inadvertent perioperative hypothermia"

Man Wang[1], Shigao Wang[2]*, Chuanding Li[3]

Dear Editor,

We are very pleased to read the study by Wang R and his colleagues[1] in which they demonstrated that the medical staff can improve the quality of inadvertent perioperative hypothermia (IPH) prevention and management by health competence cultivation and feasible health management measures. However, there are still some issues that should be addressed according to my opinion.

To begin with, in the prospective nursing observation method section, this study recruited 120 patients who were divided into two groups: group A (guided by health competence) and group B (guided by routine nursing). Whether these 120 patients were randomized or not and the method of randomized grouping were not specified. It is not clear if the study has been approved by the Ethics Committee because the approval information was not provided throughout the study. In the statistical analysis section, the authors did not introduce the basic information of statistical methods and statistical software in detail.

Additionally, since this study was conducted on a small sample, how many patients in both groups had IPH-rated events? If IPH-rated events are infrequent, it may be appropriate to provide a specific number of cases who had IPH-rated events. In the results section discussing IPH-related events, the authors mentioned that the internal relationship analysis of the abnormal indicators reveals that hypothermia affects microcirculation metabolism and impairs body immunity. However, we fail to find these data on microcirculation metabolism and body immunity in the results section.

AUTHORS' CONTRIBUTIONS

MW: Data curation, Formal analysis, Writing – original draft. **SW:** Conceptualization, Data curation. **CL:** Conceptualization, Writing – review and editing.

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[1]Yingshan People' s Hospital, Department of Anesthesiology – Hubei, China.
[2]Jingmen traditional Chinese medicine hospital, Department of Anesthesiology – Hubei, China.
[3]Jingmen Recovery Hospital, Department of Anesthesiology – Hubei, China.
*Corresponding author: shigaowang886@163.com
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COMMENTARY
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Comment on "Seasonal variation of clinical characteristics and prognostic of adult patients admitted to an intensive care unit"

Guijun Xu[1], Xiaofei Li[2]*

Dear Editor,

We were lucky enough to read the study by Galvão et al.[1] in which they demonstrated that summer months presented a higher proportion of clinical and emergency surgery patients with higher mortality rates and sepsis at intensive care unit admission did not show seasonal behavior. This study shows us the year pattern of emergency surgery, which is of great reference value for disease prevention and treatment. However, some concerns should be raised in my opinion.

To begin with, there are many reasons for the higher mortality rates of adult patients admitted to an intensive care unit. The researchers did not analyze the annual data because it was not easy to see regularity when all the years were analyzed together. The author does not define the four seasons in the method section, because different countries have different understandings of the four seasons. To sum up, the author believes that the annual separate analysis, to find out the specific months of emergency cases will reach a peak.

In addition, Figure 4 found that the highest number of emergency cases occurred in 2014–2015, while the number of emergency cases decreased year by year, which is not related to local health service policies. Diagnostic levels, data integrity, and health policies all affect the relationship between the number of emergency cases and the month.

AUTHORS 'CONTRIBUTIONS

All authors have contributed equal to work.

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[1]Yiwu Central Hospital, Department of Nephrology – Zhejiang, China.
[2]Yiwu Central Hospital, Department of Infectious Diseases – Zhejing, China.
*Corresponding author: xiaofeili2000@163.com
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COMMENTARY
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Comment on "Physical performance is associated with visual acuity in university students: results of a school-based study"

Yandi Li[1], Xiaofei Li[1]*

Dear Editor,

I was very glad to read the study by Wu et al.[1] in which they demonstrated that physical exercise might help improve visual acuity and university students should practice strength exercises to improve physical performance. However, some concerns should be raised in my opinion.

To begin with, it is believed that there may be an accompanying relationship between physical performance and vision level, but not necessarily a causal relationship. The promotion of eye exercises may help prevent vision loss. Therefore, the authors may have exaggerated the relationship between physical exercise and vision. Whether physical exercise can promote vision improvement needs to be further tested by queue studies.

In addition, the author also did not account for the research object and research background. The specific location of the subjects from China, what is special here. All subjects were not described in detail, such as age, gender, family background, major, interests, and hobbies. Only by describing the general demographic characteristics in detail can we draw reliable conclusions.

AUTHORS 'CONTRIBUTIONS

All authors have contributed equal to work.

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[1]Yiwu Central Hospital, Department of infectious diseases – Zhejing, China.
*Corresponding author: xiaofeili2000@163.com
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COMMENTARY
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Commentary "The use of high-resolution MRI to detect thrombosis and lipid-rich carotid artery plaques in a patient with homozygous familial hypercholesterolemia"

Lijuan Chen[1], Xiaofei Li[2]*

Dear Editor,

We are glad to read this very valuable article entitled "The use of high-resolution MRI to detect thrombosis and lipid-rich carotid artery plaques in a patient with homozygous familial hypercholesterolemia." which published in Revista da Associação Médica Brasileira[1]. They found that high-resolution multi-contrast MRI played an excellent role in identifying carotid plaque components in a patient with homozygous familial hypercholesterolemia (HoFH). The authors indicate that data on carotid plaque burden may provide some information to patients with HoFH. The conclusions of their study are important for early screening of future arterial lipid plaques. But in my opinion, there are still some issues that deserve further discussion. In my opinion, we should combine a large number of relevant clinical cases to verify it.

It is novel and innovative to use high-resolution MRI testing plaque histology of patients with HoFH. Although the diagnostic accuracy of MRI is superior to CT in detecting thymomas[2], in this study, the conclusion that only one patient was followed up was unreliable, and this study should be an empirical report. Large samples of clinical queue studies are necessary if accurate conclusions are to be reached.

The authors do not describe some of the shortcomings or shortcomings of screening with MRI. For example, MRI screening results in higher pharmaceutical costs, so MRI is not yet a conventional screening tool. A simpler technique should be explored in future research.

AUTHORS 'CONTRIBUTIONS

All authors have contributed equal to work.

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[1]Yiwu Central Hospital, Department of Radiology – Zhejiang, China.
[2]Yiwu Central Hospital, Department of Infectious Diseases – Zhejiang, China.
*Corresponding author: xiaofeili2000@163.com

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