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Health and institutions in the post-pandemic

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The post-COVID-19 period will bring political, social, economic, and geopolitical transformations; among these, those of occupational and behavioral nature will be prominent.

The healthcare industry suffers from the direct impacts of the pandemic and will continue to face problems: in the private sector, recession and unemployment will cause health insurance plans to lose beneficiaries and face financial balance problems.

In the public sector, SUS will suffer from a greater overload, with interruptions in routine care, the absorption of patients who lost their health insurance plans, a reduction in the public budgets and government funding capacity: survival will require reflections around the sustainability of the system and organizational changes in its institutions to increase their efficiency[1].

In the 21st century, with new scenarios, technological and management innovations, healthcare cannot maintain its archaic and slow structures and legal formats, with no updates to allow fast reactions and of suitable dimensions for problems, bringing peace to citizens and optimizing public spending[2].

Among the issues that require modernization are the legal and administrative structures, such as the models of direct and indirect public administration.

Direct administration (DA) contemplates the management bodies (ministry and state and municipal health departments) and the state and municipal units providing healthcare services. Created in the 1930s based on models from European countries, this was particularly useful for the central administration government bodies, with professionalization and depoliticization of public actions. However, it is not a suitable model for health units that require agility in decision-making and administrative swiftness. Autonomy is extremely limited; the process of hiring a professional takes at least 134 days. Replacing a professional working on emergency units is disastrous. Third-party procurement and hiring do not take less than two months, which makes it difficult to meet demands in emergencies and even in routine. Purchases based exclusively on the lowest price to avoid problems can be a waste of resources when quality is ignored, particularly in healthcare, where there is a wide variety of innovative and high technology materials.

Slow administrative, operational, and technical actions are sources of waste of resources, the typical Brazilian hell: when there is a bed available, there is no professional, or there is a bed and a professional but no medicine or equipment, which in any case prevents services from being provided to the public. The

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frustration of professionals and administrators is huge and the fear of making emergency procurements and hirings, which will later be assessed by control bodies, also affects decision making. Low wages, too, make it more difficult to hire administrators.

Indirect administration unfolds into autarchy (some university hospitals), public legal foundations, mixed economy companies, and public companies. Created at the end of the 1960s to overcome the difficulties of DA, it was increasingly restrained and, currently, it is almost as bad as the more traditional model for modern healthcare administration.

Two solutions were found for this problem in the State of São Paulo: the 'support foundations' (Philanthropic private legal foundation) and social healthcare organizations (*Organizações Sociais de Saúde*- OSS).

The foundations, created to support universities and specialized hospitals in the 1970s (40 years ago), promote operational agility, higher productivity, and quality in actions; however, they bring consequences such as the coexistence of two institutions for the same purpose as well as hiring personnel using different legal regimes (statutory and through the Brazilian Consolidation of Labor Laws - CLT), difficulties in establishing equal pay, and the possibility of different conflicts in the work environment[3]. However, they streamline operations, such as the hiring of personnel and procurement of materials and equipment, following regiments rigorously drawn based on the law and approved by control bodies. Without them, it would be impossible to provide assistance, research, and education.

The OSS, created in the 1990s (22 years ago), fully service the SUS, including hospitals, outpatient clinics, imaging, and logistics services, currently totaling 120 units managed by 31 organizations[4]. These are public services, contracted and regulated by DA, but with autonomy. Governed by their own legislation, they relate to the health departments through management contracts that specify the products to be delivered during a certain period. They have a personnel regulation that governs the recruitment, selection, admission, promotion, and dismissal of employees, and a procurement and hiring regulation that governs the acquisition of goods, execution of contracts, and other commitments, allowing for management governance and sustainability. They are periodically evaluated and remunerated according to the goals established and negotiated between the parties, based on the geographic, demographic, and epidemiological needs of each location and region. A secretary team is responsible for the management, and quarterly assessments are carried out by a commission formed by 10 internal and external members, including representatives of the Legislative Assembly, State Health Council, and recognized health professionals. The control bodies regularly evaluate the service operation and results.

One of the solutions to improve the administration of DA units is to transfer their management to the OSS, analyzing the convenience of such action on a case by case basis. An important point to make this kind of transformation viable is the existence and expansion of partners, preventing an excessive concentration of units in a few institutions, something that is not always true in all regions of the country, but which is more feasible in São Paulo. This is not simple, but it is possible.

Universities hospitals as autarchys deserve their own studies since their mission is beyond assistance but the basis for research and teaching, with institutional relations that require more complex organizational settings.

Health regulatory agencies are considered autarchy.

For managing bodies (DA), health ministry and departments, legal and operational solutions must be found so that they too can become agile in making the decisions that are of interest to the population, in the planning, coordination, and regulation of healthcare actions, including by strengthening units responsible for contract assessment. This implies the participation of the Legislative, Executive, and Judiciary powers and Civil Society.

Autonomy, with transparency, is the solution to deploy, with quality, policies that will result in healthcare programs and services, thus reducing the fragility of the system.

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Should ethanol be considered a treatment for COVID-19?

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Dear Editor,

The Coronavirus has impacted the global community and currently has hot spots in their first phase[1]. There are no treatments or vaccines that are universally recognized by the medical communities. The use of alcohol, specifically, ethanol, is ubiquitous with disinfection practices in venues including healthcare facilities, such as hospitals and medical practices, K-12 schools and higher education institutions, workplaces ranging from office buildings to manufacturing facilities, transportation hubs, and military bases worldwide. In addition, there is a significant volume of peer-reviewed literature that focuses not only on ethanol's general disinfection properties but also its anti-viral properties[2-5].

Ethanol has been shown to have a direct impact on human coronaviruses such as Severe Acute Respiratory Syndrome (SARS) coronavirus, Middle East Respiratory Syndrome (MERS), coronavirus (endemic) human coronaviruses (HCoV). These viruses can exist for several days on surfaces like plastic and glass. It has been demonstrated that disinfectant agents can effectively reduce coronavirus infectivity in a very short time (< 60 seconds). For example, ethanol is 62%–71%, effective, hydrogen peroxide is 0.5% effective, sodium hypochlorite is 0.1% effective, while other compounds are not as effective (0.05%–0.2% for benzalkonium chloride, 0.02% for chlorhexidine digluconate)[3]. Ethanol holds the most promise not only because of its efficacy but also because there is a vast literature on the effects of ethanol, in beverages and as a disinfectant. This raises the question: if ethanol can be effectively delivered and make direct contact with a viral infection, can it be used as a treatment for COVID-19?

Any type of inhalation therapy for a pulmonary condition has the potential to be significantly more effective than a tablet-based on the direct administrative route. Economical and reliable technology that is well understood has been developed and tested by tens of millions of users for "vaping." While there are negative connotations with this term, the health effects are typically attributed to the long term use of additives such as nicotine and the vaping juice. There is a clinical trial[6] about to start in the U.S., entitled "The Impact of Vaping Ethanol in the Evaluation of Impairment", at Virginia Commonwealth University (ClinicalTrials.gov Identifier: NCT03826303). From the clinical trials website; "The purpose of this research study is to find out about ethanol-containing e-cigarettes impact on ethanol breath tests, field sobriety tests, or other tests of sobriety. Ethanol is a common part of e-cigarette liquids." The technology and its bulk solvents proposed

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here are already being incorporated (planned) in a clinical setting[6].

While there is no definitive work, the current published studies suggest that moderate doses and short-term use of the common bulk solvents (glycerin, propylene glycol) would have minimal or no health effects. There are published studies that indicate trace levels of toxic materials in the vapor generated by the glycerin-propylene glycol combination[7] and that propylene glycol can be an irritant over an extended period of time[8, 9]. Glycerin is widely used in the food and health care industries and published work indicate it has anti-viral and anti-bacterial properties[10]. It is also used in formulations to increase the uptake rate and efficacy of certain drugs, presumably through its ability to dehydrate biomaterials[11].

Our suggestion is to consider a human trial in which a glycerin-propylene glycol-ethanol formulation is administrated as an inhaled vapor for COVID-19 patients. It is not being suggested as a cure, but rather a method that might work to reduce the viral load in the patient's lungs. Because this solvent combination is already being used by many of the world's citizens, including some that are stricken with COVID-19, this might eliminate or reduce some of the regulations a new treatment may be required to meet. We are proposing a formulation that *potentially* can:

1. reduce the viral load in the lungs (see table 1) to the benefit of a patient's immune system;
2. reduce the number of active viruses that are dissipated by an infected individual through sneeze or cough.

To provide an example from our work, in one trial each 4-second inhalation consists of 7.4 uL of ethanol, which can potentially inactivate five percent of the total viral load. This does not take into account the effect of the other two bulk solvents. Two treatments of 0.8 mL would *hypothetically* be enough to completely inactivate the entire viral load in the lungs. We do not anticipate it will approach this level of efficacy, but the inhalation administration may control or reduce the activity of the viral infection. While dosing studies would be needed, an educated guess is a patient might utilize between 2 and 10 treatments per day, each consisting of 0.5 to 0.8 mL volume. A total treatment might last between one and three weeks with the goal of lowering the viral load to a level where the body's immune system can become effective again.

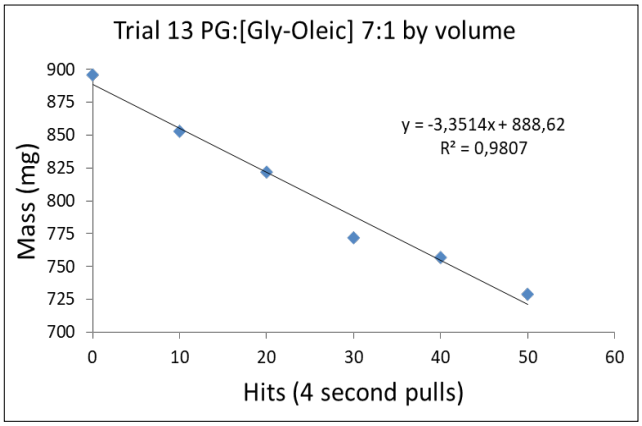
The vaporizer used for our different compositions has a consistent delivery quantity (see graph 1) for a range of compositions tested. The vaporization technology is economical, rugged, easily cleaned, and well understood. The use of ethanol in these devices is currently being evaluated in a U.S. Clinical trial not for medical efficacy, but for the ability of ethanol to impair a user. An aerosol generator in which the ethanol might be delivered and dissolved in water is not considered because of the dilution factor and subsequent loss of efficacy. Glycerin has antiviral properties and has the approval of the FDA to treat wounds. Propyleneglycol (PG) is used in pharmaceutical formulations. Some studies indicate it aids in the uptake and penetration rate of different pharmaceuticals, including antivirals and fatty acids.

TABLE 1. CALCULATION OF THE AMOUNT OF ETHANOL DELIVERED TO THE LUNGS DURING INHALATION; ALL VALUES ARE ROUGH ESTIMATES BUT ARE DERIVED FROM PUBLISHED VALUES FOR OTHER VIRUSES OR OUR EXPERIMENTS.

a. The COVID-19 viral load is estimated at 20 million virus per mL of lung tissue.
b. With 6000 mL of lung tissue (adult) there are 120 billion viruses, rounded up to 200 billion viruses (note many of these are in infected cells).
c. Assume it takes ten million molecules of ethanol to disinfect/inactivate one virus.
d. The density of ethanol is about 0.8 grams/mL.
e. 200 billion viruses will need (10 million ethanol's x 200 billion) = $2x10^{18}$ molecules of ethanol (molar mass = 46 g/mol)
f. ($2x10^{18}$ EtOH) / (6×10^{23} EtOH/mol) = 3.3×10^{-6} moles ethanol
g. (3.3×10^{-6} mol) x (46 g/mol) = 0.000153 grams = 153 ug ethanol or 122.4 uL.
In our vaporizer, an estimate is 18 pulls by the vacuum, each lasting 4 seconds, to completely vaporize a 0.8 mL solution composed of: (i). 4 parts Propylene Glycol, (ii). 1 part Glycerin, (iii). 1 part EtOH, (0.133 mL of EtOH in the 0.8 mL solution)
Each four-second inhalation consists of 7.4 uL of ethanol, which is enough to inactivate approximately six percent of the viral load*. This does not take into account the efficacy of the other two bulk solvents. Two treatments of 0.8 ml would *hypothetically* be enough to completely inactivate the entire viral load in the lungs. We do not anticipate it will approach this level of efficacy but the administration may control or reduce the activity of the viral infection.

* These values will change with the type of vaporizer used, the inhalation capabilities of the user, etc.

GRAPH 1. A TOTAL OF FIFTY PULLS (SEPARATE INHALATIONS) WAS USED WITH A FATTY ACID-GLYCERIN COMPOSITION AND ITS DELIVERY (MEASURED BY THE LOSS OF MASS IN THE VAPORIZER) WAS FAIRLY CONSTANT OVER 50 (< 4 SECOND) PULLS. THE VOLUME VAPORIZED VARIES WITH THE COMPOSITION OF THE SOLVENT.



The COVID-19 pandemic is still a significant problem in many Latin American countries, with Brasil having the highest number of infections and death, followed by Peru[12]. Given the lack of treatments for this disease and the relative safety of this approach, we suggest ethanol might be considered for a clinical trial.

Our ongoing work with drug development for tuberculosis and cancer has focused on a novel approach to the treatment of these diseases. In addition to the pharmaceutical agent, additional components are included in the formulation at low levels, including antagonists, molecular level building blocks, nutrients, and an additional toxic complex. These additional species are aimed at both accelerating certain processes in the target and interfering with others, weakening it and allowing the primary species to work more effectively. A future endeavor in this area might include the testing of additives such as ammonium chloride, specific fatty acids, glucose, DMSO, a copper-lysine complex, etc. at low levels to increase the efficacy of the alcohol. We have been considering inhalation as a method for the treatment of pulmonary *MTb* infections and pivoted to viral infections when the current pandemic surfaced. The process of vaporization is widely used in our society and the use of ethanol as a disinfectant and more specifically as an anti-viral agent that has efficacy against COVID-19 has some acceptance by the medical community. Links to representative publications from our group related to COVID, tuberculosis, and cancer are provided[13-17]

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Autoimmune encephalitis (AIE)

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

INTRODUCTION

Autoimmune encephalitis is an inflammatory disease characterized by a subacute involvement of short-term memory and very diverse symptomatology (psychotic symptoms, atypical clinical manifestations, and epileptic seizures), which makes the differential diagnosis a real challenge. Paraneoplastic neurological syndromes (PNS) are rare and associated with the antibodies of the collapsin response mediator protein (CV2/CRMP5), with a bad prognosis. However, with the recent discovery of antibodies directed at the membrane surface, today it is recognized that a large proportion of cases have no underlying neoplasia (*non-paraneoplastic)*, thus presenting better prognosis. Paraneoplastic limbic encephalitis (PLE) is a type of autoimmune encephalitis that involves the hippocampus, amygdala, frontal basal, and insular regions and is linked to tumors and antibodies against intracellular neuronal antigens, manifesting typically through seizures and mental and behavioral changes. Although in some cases it appears to involve exclusively the limbic regions, there are several clinical characteristics that imply the involvement of other areas outside the limbic system. For this reason, authors prefer the term Autoimmune Encephalitis (AIE).

In the pathophysiology of AIE, the disease can be classified based on its location, the causal antigens, and the probable mechanisms of the disease. Generally, antibodies for intracellular antigens are associated with underlying malignancies, in contrast to membrane antigens, which generally do not reflect the presence of a tumor but can be associated with tumors in some cases. Thus, an extensive search for any underlying malignancies must always be considered in patients with suspected AIE.

The antibodies for intracellular antigens (neuron) are glutamic acid decarboxylase (Gaed), Hu, or Anna1 (Hu-Abs), Ma2, CV2, and amphiphysin. Autoimmune neuronal lesions triggered by the antibodies, which follow the deleterious action of cytotoxic T lymphocytes, are the most probable pathogenic mechanism. These damages appear to be irreversible and the prognosis is generally poor. An exception appears to exist in patients with Gaed antibodies: these patients may have AIE, epilepsy, or other neurological syndromes; its association with tumors is uncommon and recovery is possible, although patients are generally less responsive to immunotherapies.

Antibodies against cellular membrane surface antigens are the VGKC complex (LGI1, CASPR2), NMDA, Ampa, Gaba-B, and glycine receptors. This category has been increasingly recognized as much less associated with malignant diseases, and the disease is believed to be mediated by the very antibodies. These diseases tend to have a better response to immunotherapy. The first syndrome to be recognized in this category was the VGKC-complex antibody syndrome.

Due to the great variety of diseases that must be excluded during the differential diagnosis, the diagnosis of encephalitis is often difficult and delayed.

Clinical setting

Patients with a diagnosis of autoimmune encephalitis associated with neoplasia.

Clinical question

In autoimmune encephalitis, is the treatment with immunoglobulins better than the conventionally used corticosteroids or plasmapheresis?

Eligibility criteria

PATIENT

P - Patients with paraneoplastic autoimmune encephalitis

INTERVENTION

I - Treatment with immunoglobulin

COMPARISON

C - Treatment with corticosteroids or plasmapheresis

OUTCOME

O - Effectiveness or harm

Search strategy. Databases searched: Medline, PubMed. Randomized clinical trial (RCT). No time or language restrictions. Full text or summary of data. Clinical and non-intermediary outcomes.

Search

Encephalitis AND (((((Immunoglobulin OR Immunoglobulins OR Globulins)) AND ((Autoimmune OR Autoimmune Diseases OR N-methyl-D-aspartate receptor OR NMDAR OR leucine-rich OR glioma-inactivated protein-1 OR LGI1 OR contactin-associated protein-2 OR Caspr2 OR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor OR AMPAR OR γ-aminobutyric acid-A receptor OR GABAAR OR γ-aminobutyric acid-B receptor OR GABABR OR Glycine R) OR (N-methyl-D-aspartate receptor OR NMDAR OR leucine-rich OR glioma-inactivated protein-1 OR LGI1 OR contactin-associated protein-2 OR Caspr2 OR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor OR AMPAR OR γ-aminobutyric acid-A receptor OR GABAAR OR γ-aminobutyric acid-B receptor OR GABABR OR Glycine R))) = 3036

Eligibility criteria for the studies

1. Patients with paraneoplastic autoimmune encephalitis.

2. Treat with immunoglobulin.

3. Study design: case series or observational cohorts or clinical trials.

4. No time restrictions.

5. Language: portuguese, english, spanish, and italian.

After assessing the studies based on title, design, and language, 450 were selected. After assessment of the abstracts and the final selection, 33 studies were left for full-text analysis, namely: 32228575 32123047 31782181 31874360 31796119 31473641 30449706 31286710 30979857 30182259 30177907 29166136 29759996 28585453 28935354 28959704 29399043 28154970 28150403 26940288 27632180 27242065 27776544 27056053 27428233 26694143 26889260 26770517 26277996 25465439 23290630 20159432 17397768.

Anexos: Table 1 - Inclusion and exclusion. Table 2 - Analysis of the full texts included. Table 3 - Results in patients with lung cancer.

Studies selected based on the search strategy – 3,036

Excluded for not answering to the PICO during the assessment of the title – 2,586.

Selection of 450 studies.

Selection by abstract: 417 excluded for being unrelated to the clinical question.

Selection of 33 studies.

Analysis of the full texts: 28 excluded – review – Non-paraneoplastic – case report – guidelines – No comparison. Table 1 in the annex.

A total of 5 studies were selected - included in the review.

RESULTS

Eleven patients with a mean age of 63 years were assessed at the Hospital of the Hebei Medical University, from February 2016 to October 2016, with encephalitis of unknown etiology and a positive test for receptor antibody (anti-GABA-B) in the blood and/or cerebrospinal fluid[13]. Five patients were diagnosed with small-cell lung tumors. The therapy established at first was neurological symptomatic medication and first-line immunotherapy (steroid and/or immunoglobulin). Patients with a diagnosis of lung cancer also received specific treatment (surgery and/or chemotherapy and/or radiotherapy). In the evaluation of outcomes, we used the modified Rankin Scale (mRS) for therapeutic effects (mRS <2: complete neurological setting, mRS 2: partial neurological improvement) and functional outcome (mRS 2: favorable prognosis, mRS> 2: poor prognosis). In cancer patients, the evolution of the mRS scale was 2 → 1 (complete response) in two patients, 3 → 2 (partial response) in one patient, 4 → 3 (partial response) in one patient, and 5 → 5 (no response) in another.[13] (Table 3 in annex).

In the Peking Union Medical College Hospital, between June 2011 and October 2014, 10 women with a mean age of 23 years diagnosed with ovarian teratoma associated with paraneoplastic encephalitis with positive antibodies against N-methyl-D-aspartate receptor (anti-Nmdar) were assessed.[24] After resection of the tumors, all patients received first-line immunotherapy with intravenous immunoglobulin (IVIG) associated or not to corticosteroids and plasmapheresis; in the event of failure, a second line of medication was instituted. Nine patients had significant relief of neurological symptoms during the mean follow-up time of 14.2 months, with 13.7±5.5 days for relief of symptoms after the surgery[24].

A multi-institutional observational study (2007-2012) evaluated 135 patients with positive NMDAR antibodies in serum or cerebrospinal fluid (CSF) who met the criteria previously described[31]. In the hospitals of the universities of Pennsylvania and Barcelona, all other patients were collected from 200 centers worldwide (32 countries), with a total of 577 patients. The treatment, which did not have a defined protocol, included first-line immunotherapy (steroids, immunoglobulin, plasmapheresis), second-line immunotherapy (rituximab, cyclophosphamide), and tumor resection. In the evaluation of outcomes, the antibodies were assessed at the onset of symptoms, and after 4, 8, 12, 18, and 24 months. Of out 501 patients (mean follow-up of 24 months): 472 (94%) were treated with first-line immunotherapy or tumor resection, with the improvement of 251 patients (53%) in 30 days. The first-line therapy failed in 221 patients; of these, 125 (57%) received second-line treatment with improvement in comparison to those who did not (OR 2.69, CI 1.24 to 5.80, p=0.012).

In the first 24 months, 394 of 501 patients achieved a good result (mRS from 0 to 2 in an average of 6 months) and continued to improve for 18 months after the onset of symptoms, with the death of 30 patients. The predictors of good outcomes were early treatment (OR 0.62, CI 0.50 to 0.76, p<0.0001) and no admission to the ICU (OR 0.12, CI 0.06 to 0.22, p<0.0001)[31].

A retrospective analysis of 24 patients diagnosed with newly acquired encephalitis and neurxo-psychiatric deficit underwent an investigation for positive anti-NMDA receptor in a medical center in Taiwan[9]. All patients were medicated with corticosteroids and/or immunoglobulin and/or plasmapheresis with first-line therapy. With treatment failure in 14 patients, these received second-line medication, with immunoglobulin and rituximab and/or cyclophosphamide. There was no comparative arm for the therapy. Seventeen patients were admitted to an intensive care unit due to an altered level of consciousness, epileptic status, and impending respiratory failure. The average length of hospital stay was 60.38+/- 62.2 days. This may be due to a greater awareness of doctors regarding combined therapy. In the first six months, 20 patients (20/24), i.e., 83% achieved a good outcome, with mRS ≤2, and 15 patients (15/24), i.e., 62.5% recovered completely[9].

Thirty-three patients (21 women and 12 men) and with a mean age of 29.7 years and a diagnosis of encephalitis, neuropsychiatric abnormalities, and positive anti-NMDAR in the CSF, associated or not with other diagnoses, were treated in the Department of Neurology of the Beijing Xuan Wu Hospital between January 2011 to December 2013[28]. The treatment using corticosteroids, intravenous immunoglobulin, and plasma exchange alone or in combined therapy is the first line. Cyclophosphamide or azathioprine were used in isolation or in combination when the first line failed. In the evaluation of outcomes, the *modified Rankin Scale (mRS)* was used to estimate the neurological status: *mRS = 0 corresponds to complete restoration; mRS = 1-2 corresponds to significant improvement; mRS> 2 corresponds to a partial improvement*. The outcomes of treatment in 3 of 33 patients with teratoma were: a 29-year-old patient treated with immunoglobulin for nine days plus symptomatic medications presented a gradual recovery in two months of assessment and mRS=3. In another, a 34-year-old, the medication used were corticosteroids in association with immunoglobulin and symptomatic treatment; recovery was complete in the assessment after three months with mRS=0. The third patient, a 23-year-old, was medicated with corticosteroids, immunoglobulin, and plasmapheresis and presented a gradual improvement in the 12-month assessment and mRS=3 (Table 4, in annex)[28].

Synthesis of evidence

After a detailed search in the literature, we could not find any randomized clinical trials dealing specifically with the clinical question at hand. We obtained a list of observational cohorts, case reports, and reviews. They also did not respond to the comparison of drugs proposed in the PICO. In the analysis of selected cohort studies, there is no clear guideline of the therapeutic approach for paraneoplastic encephalitis. The therapies are not presented or tested in an isolated manner, but always associated in several ways, such as in the first line, i.e., with steroids, immunoglobulin, plasmapheresis, and, as the second line, i.e., as rituximab, cyclophosphamide, azathioprine. This is due to the severity of cases and, oftentimes, the ineffectiveness of the therapy initially chosen, something that leads physicians to opt for other therapies and their associations. This shows an apparent contradiction, as in the greater the treatment, the worse the outcome; but in truth, the relationship is the worse the patient, the more treatments are combined. Thus, therapies and associations seem to be similar in regard to efficacy, with low quality of evidence.

Recommendation

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

This work was developed with the participation of members of the Comitê Estadual de Medicina Baseada em Evidência Científica das Unimeds do Estado de São Paulo, through of (virtual) meetings.

ANNEXES

TABLE 1. INCLUSION AND EXCLUSION (WITH REASONS)

STUDY	DESIGN	REASON FOR EXCLUSION
Li TR (2020)	REVIEW	EXCLUDED - review
Munõz LA (2020)	RETROSPECTIVE COHORT	EXCLUDED - non-paraneoplastic
Zhang L (2020)	RETROSPECTIVE COHORT	EXCLUDED - no comparison
Dubey D (2019)	RCT	EXCLUDED - non-paraneoplastic
Mason G (2019)	COHORT	EXCLUDED - immunotherapy alone
Liu H (2019)	CASE REPORT	EXCLUDED - case report
Zhang X (2019)	RETROSPECTIVE COHORT	EXCLUDED - no comparison
de Bruijn MAAM (2019)	OBSERVATIONAL COHORT	EXCLUDED - non-paraneoplastic
Kong SS (2019)[9]	RETRO OBS COHORT	INCLUDED
Melamud LI (2018)	MEDICAL CHART REVIEW	EXCLUDED - non-paraneoplastic
Chen Z (2018)	COHORT	EXCLUDED - non-paraneoplastic
Chiang S (2018)	CASE REPORT	EXCLUDED - non-paraneoplastic
Cui J (2018)[13]	CASE REPORT	INCLUDED
Iizuka T (2017)	SÉRIE DE CASOS	EXCLUDED - no immunoglobulin
Wang Y (2017)	RETRO COHORT	EXCLUDED - children
Shin YW (2017)	COHORT observational	EXCLUDED - review
Mackeon G (2017)	SYSTEMATIC REVIEW	EXCLUDED - review
Bartolini L (2017)	Electronic search	EXCLUDED - decision of treatment
Hattori Y (2017)	CASE REPORT	EXCLUDED - case report
Abdul-Rahman (2016)	COHORT	EXCLUDED - case report
Huang Q (2016)	OBSERVATIONAL COHORT	EXCLUDED - non-paraneoplastic
Li Z (2016)	COHORT	EXCLUDED - non-paraneoplastic
Nosadini M (2016)	RETROSPECTIVE COHORT	EXCLUDED - study in children
Bai Y (2016)[24]	COHORT	INCLUDED
Von Rhein B (2017)	RETROSPECTIVE COHORT	EXCLUDED - non-paraneoplastic
Yu J (2016)	RETRO COHORT	EXCLUDED - no comparison
LIU.J (2016)	CASE REPORT	EXCLUDED - no immunoglobulin
Huang X (2015)[28]	COHORT observational	INCLUDED
Liu J (2015)	REVIEW	EXCLUDED - case report
Dubey D (2014)	Case report review	EXCLUDED - non-paraneoplastic
Titulaer MJ (2013)[31]	COHORT observational	INCLUDED
Breese EH (2010)	CASE REPORT	EXCLUDED– case report
Feasby T (2007)	REVIEW	EXCLUDED - guidelines

TABLE 2. CHARACTERISTICS OF THERAPEUTIC STUDIES

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOME	FOL-LOW-UP TIME
Cui J 2018[13]	N=11 patients with suspected encephalitis with anti-GAB-AB receptor antibodies of unknown etiology. 5 patients with small cell tumor	First-line immunotherapy + standard treatment for lung cancer (surgery and/or CT and/or RT)	Corticosteroids vs IVI vs corticosteroids + IVI	Complete neurological and functional response; partial response and no response	11 months
Bai Y 2016 [24]	N=10, 10 women and mean age of 23 years with ovarian teratoma associated with anti-NMDAR encephalitis. Treated with TU resection AND immunotherapy, combined or not.	N=3 patients received only first-line immunotherapy with intravenous immunoglobulin therapy (IVIG).	N=7 patients received intravenous immuno-globulin and glucocor-ticoids. N=4 patients received intravenous immunoglobulin, glucocorticoids, and plasmapheresis	Improvement of mental and neurological symptoms	14.2 months
Titulaer MJ 2013 31	N=577 patients included for demographic analysis and treatment. 501 followed-up for at least 4 months. There was no predefined treatment protocol.	N=251 The first-line immu-notherapy was defined as the use of steroids, IVIG, or plasma exchange alone or combined.	N=125 The second line of immunotherapy included rituximab or cyclophosphamide alone or combined.	Good outcomes included - mRS improvement without ICU admission, ear-ly treatment, low severity	Average of 24 months
Kong SS 2019 [5]	N=24 Patients with positive anti-NMDA receptor AB, 16 women, and 71% younger than 18 years. 3 had neo-plasias.	N=24 All patients were treated with corticosteroids and/ or immunoglobulin and/ or plasmapheresis with 1st line (14 received 2nd line with immune. and rituximab and/ or cyclophosphamide) No patients were treated with IVIG alone.	Non-Comparative study	4 patients (16.7%) had a recurrence of the disease or relapse; 10 patients with 1st line therapy, 4 with respira-tory failure; and 6 admitted to the ICU; 14 patients with 2nd line treatment, 9 with re-spiratory failure, 4 relapsed	6 months
Huang X 2015 [28]	N=33 Patients with autoim-mune encephalitis, average age of 29.7 years. With anti-NMDAR encephalitis + N=3 cases with ovarian tera-toma and 01 cervical TU.	Of the 33 patients, 20 received antiretroviral drugs; N=331 1st line with immune steroid and plasmapheresis; None of the patients received IVIG alone	Non-comparative study	Average hospitalization = 36 days; Full recovery (asymptomatic) = 24, with 9 patients partially recovered (mild not detailed residual symptoms), among these, two with associated teratoma.	7.8 months

TABLE 3. RESULTS IN PATIENTS WITH LUNG CANCER[13].

Patients	Tumor	Immunotherapy	Tumor treat-ment	Anti-epileptic treatment	Response to treat-ment	Initial à follow-up mRS	Follow-up months
1	SCLC	cort	Surgery	yes	Complete	2à1	11
5	SCLC	IVIg + cort	CT + rad	yes	Complete	2à1	14
8	SCLC	IVIg	Surgery/CT	yes	Partial	4à3	12.5
9	SCLC	IVIg	Surgery/CT	yes	No response	5à5	7
11	SCLC	IVIg + cort	CT	yes	Partial	3à2	7

Reference: Table 3. Tumor association, treatment, and outcome.[13] SCLC = small cell lung cancer. IVIg = immunoglobulin IV. Cort = corticosteroids. CT = chemotherapy. Rad = radiotherapy. mRS = modified Rankin Scale score.

TABLE 4. RESULTS FROM PATIENTS WITH TERATOME[28].

Age years	Therapy dura-tion (days)	Corticosteroids	Immunoglobulin	Plasmapheresis	Other drugs	Follow-up (months)	Clinical course	mRS
29	9	yes	no	no	yes	2	G	3
34	20	yes	yes	no	yes	3	F	0
23	10	Yes	yes	yes	yes	12	G	3

Reference: Table 3. Treatments and follow-up[28]. Other drugs: acyclovir, anticonvulsant, antiepileptics. Clinical course - G = gradual improvement, F = total improvement.

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AMB Guidelines: COVID-19

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QUESTION: Is there a specific pre-hospital treatment for COVID-19?

Answer: There is no evidence to support the use of any pre-hospital treatment, both as a prophylactic (to reduce the incidence of new cases) or in suspected or confirmed cases (to reduce mortality) – recommendation number 7 of 10 recommendations.[1]

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POINT OF VIEW

Standardization of penile hemodynamic evaluation through color duplex-doppler ultrasound

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SUMMARY

INTRODUCTION: *The vascular evaluation of the erectile function through Color Duplex-Doppler Ultrasound (CDDU) of the penis can benefit the therapeutic decision-making process. Unfortunately, there is no standard procedure for CDDU conduction, a fact that results in high result-interpretation variability.*

OBJECTIVE: *The aims of this review are to promote greater standardization during CDDU of the penis and discuss the fundamental principles for its accurate conduction.*

METHODS: *CDDU is initially conducted with the penis in the flaccid state; the whole penis must be assessed (images at B mode) with a high-frequency linear transducer (7.5 -18 MHz). Intracavernous injection of vasodilating agents (prostaglandin E1, papaverine, phentolamine) is performed to induce a rigid erection. Serial measurements at different times should be taken during the CDDU session and penile rigidity must be assessed in each evaluation.*

RESULTS: *It is important to monitor the erection response after the vasoactive agent (hardness scale), and scanning during the best-quality erection should be contemplated. Manual self-stimulation, audiovisual sexual stimulation (AVSS), and vasoactive agent re-dosing protocols must be taken into account to reduce the influence of psychogenic factors and to help the patient to get the hardest erection possible. Such measurements contribute to the maximal relaxation of the erectile tissue, so the hemodynamic parameters are not underestimated.*

CONCLUSIONS: *CDDU is a relevant specialized tool to assess patients with erectile dysfunction; therefore, this guideline will help to standardize and establish uniformity in its conduction and interpretation, taking into consideration the complexity and heterogeneity of CDDU evaluations of the penis.*

KEYWORDS: *Erectile dysfunction. Erectile dysfunction/diagnosis. Ultrasonography. Ultrasonography, Doppler.*

INTRODUCTION

Color Duplex-Doppler Ultrasound (CDDU) of the penis was first described by Lue et al.[1] and remains one of the most important tools available to assess patients with ED[2,3]. CDDU of the penis is an objective diagnostic method, but it requires specific training. An objective hemodynamic evaluation through CDDU has prognostic importance and helps to choose the best treatment strategy[4,5]. Possible indications for

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CDDU include: young patients with primary ED, pelvic trauma history, drug abuse, pre-operative evaluation for Peyronie's disease, psychogenic ED documentation, and medicolegal situations[6].

The lack of standardized hemodynamic evaluation through CDDU is one of the main limitations of this method[7]. It explains the great variability in performing and interpreting penile hemodynamic studies in both clinical practice and scientific studies. These factors have contributed to the fact that CDDU is often considered unreliable, as it may lead to mistaken treatment protocols[8].

The aim of the present article is to establish standard operational procedures to minimize confounders in order to help predict with reasonable accuracy the etiology of ED. It is also our goal to discuss the basic principles of drug-induced erection.

Basic Principles in Sexual Medicine

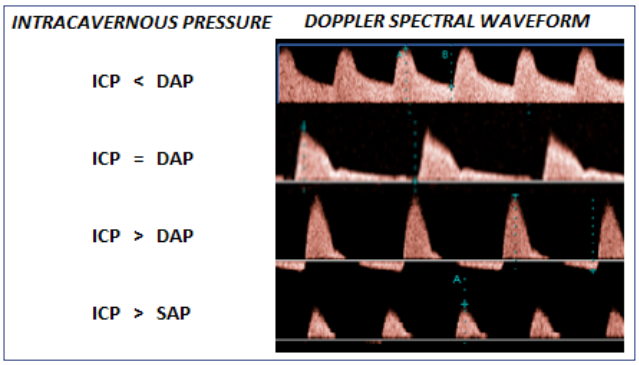
Erection anatomy and physiology

A. Blood flow and veno-occlusive mechanism

The erectile tissue is mainly composed of smooth muscle, elastic fibers, and endothelium, which together form the sinusoids of the corpora cavernosa. Arterial supply is achieved through the internal pudendal artery, which branches out and gives origin to the cavernous artery. The venous drainage of the cavernous tissue is performed by a surface and deep vein system; however, the subtunical venules promote blood exit from the intracavernous space during erection.

Blood flow increases during sexual stimulus without changes in systemic blood pressure. The smooth muscle relaxes and expands, as the sinusoids get full of blood. This expansion generates relative venous drainage reduction, mainly because of the passive venoconstriction of the subtunical veins, which triggers the veno-occlusive mechanism. Axial rigidity increases exponentially when the compression of the subtunical venules is complete[9]. There is blood flow in systole, but not in diastole (diastole zero), when ICP becomes equal to the diastolic blood pressure (DBP). In a progressive way, the reverse diastole phenomenon, which is featured by blood inflow in the systole and blood efflux in diastole, happens when ICP is higher than DBP. ICP can eventually be higher than the systolic peak pressure, and this process makes blood inflow in systole minimal or even absent[10]. The correlation between CDDU findings and Doppler velocity is shown in Figure 1.

FIGURE 1. DOPPLER TRACING BEHAVIOR PRESENTING PROGRESSIVE INTRACAVERNOUS PRESSURE (ICP) DURING ERECTION. ICP = INTRACAVERNOUS PRESSURE; DBP = DIASTOLIC BLOOD PRESSURE; SBP = SYSTOLIC BLOOD PRESSURE.



B. Pharmacology

Oral drugs act through nitric oxide pathways and increase Cyclic GMP concentration inside the muscle cell because they inhibit the enzyme responsible for Cyclic GMP degradation, known as type 5 phosphodiesterase (PDE5)[11]. Intracavernous vasoactive agents act through direct muscle relaxation. The most common agents are papaverine, phentolamine, and prostaglandin.

On the other hand, sympathomimetic agents contract the intracavernous smooth muscle and antagonize the veno-occlusive mechanism of erection. Etilefrine is the medication available in Brasil presenting the greatest selectivity to alpha-receptors, which should be preferred to minimize beta-adrenergic activity.

C. Clinical evaluation

Having a basic evaluation is fundamental to exam conduction. Medical history, including comorbidities, medication use, and previous pelvic or retroperitoneal surgery must be questioned. The patient must be asked about his hardest erection, which would be the minimal erection hardness to be obtained during the exam. Information about ED chronology and the permanence of nocturnal erections can be quickly obtained.

D. Erection Hardness Scales

The examiner must get used to constantly reassessing erection quality during CDDU sessions through visual evaluation and penis palpation. In order to facilitate this evaluation, there are validated erection quality scales, among them is the EHS (*Erection Hardness Score*), which is the most common and broadly used.

It is possible to use a 0-10 erection scale, whose score 6 (or 60%) corresponds to the minimal hardness for penetration. This decimal scale is easily comprehensible and can be converted into the EHS scale.

Exam Preparation

CDDU can be performed in clinics and/or hospitals, as long as these facilities are well equipped. The vascular ultrasonography assessment of the penis is dynamic and requires an intracavernous injection (ICI) of vasodilating agents in order to help the patient achieve the hardest erection possible[7,12,13]. Thus, the examiners must be familiar with the physiology of erection and recognize common confounding factors and artifacts in order to perform an adequate interpretation. Moreover, the examiner must be able to identify and/or treat prolonged erections and priapism caused by ICI.

Technical preparation

A. About the location

i. CDDU must be performed in a quiet location, due to the influence of psychological and environmental effects on the erectile response;
ii. Equipment to provide audio-visual sexual stimuli is an interesting tool, because it helps patients to get a harder erection with smaller doses of vasoactive agents;
iii. Medication vials properly stored are required, these include vasoactive agents and sympathomimetics for the eventual need of reversion.

B. About the equipment

i. Ultrasound device with Doppler;
ii. High-Frequency Linear Transducer (7.5 – 18 MHz);
iii. Device to store the images and a printer.

Exam conduction

The CDDU exam starts with the penis in a flaccid state. The whole penis must be scanned through longitudinal and cross-sectional images at mode B by using a high-frequency linear transducer (7.5 – 18 MHz). This assessment aims at seeking changes in the eco-texture of both the erectile tissue and the tunica albuginea.

Measurements of the internal diameter of the cavernous arteries (right and left) and, optionally, of the peak systolic velocity (PSV) in the cavernous arteries at spectral Doppler mode can be performed at the beginning of the exam. Although there are some studies presenting good predictive PSV values at flaccid state, the universal consensus lies in conducting CDDU with drug-induced erection[14-16]. In order to do so, it is important to administer vasoactive agents[1,5,17]. There is no consensus about the dose to be administered for erection induction; however, the dose is expected to be the least necessary to generate a hard erection (EHS 4). If such an erection is not possible, at least a bedroom quality erection (BQE) should be obtained, which may require re-dosing of ICI. Therefore, there is no standard dosage to be universally used, because each patient has a different response to intracavernous pharmacotherapy. A re-dosing protocol based on frequent reassessments is able to minimize the adrenergic effect and allows satisfactory relaxation of the smooth muscle. Yet, there is no consensus about the proper medication, dose, and the number of injections at re-dosing[18].

The transducer position during cavernous artery evaluation can change from the crura to the base of the penis - on its ventral or dorsal aspect. Conceptually, there would be no problem in assessing the cavernous arteries at any point of their extension, since cavernous bodies are tridimensional structures that work as a single cavity. However, some studies have already assessed the influence of transducer position and they have shown that more proximal evaluations overestimate the PSV values, whereas the most distal evaluations underestimate EDVs[19]. Overall, we suggest the readings should be made on the ventral face, close to the penoscrotal junction, in order to avoid artifacts resulting from too proximal or too distal positions.

Step-by-step guide for CDDU examination

A. Turn the ultrasound device on to start the exam; select the transducer and the appropriate configurations.
B. Explain all the steps of the evaluation to the patient and ask his consent to proceed.
C. Instruct the patient to lie on a horizontal dorsal decubitus position and to relax as much as possible.
D. Place the transducer with transmitter gel on the base of the penis to start scanning.
E. Assess the anatomy of the corpus cavernousum and spongiosum, and record any abnormalities in the eco-texture.
F. Take cross-sectional and longitudinal images of both cavernous arteries (at proximal aspect/

third of the penile shaft) and report possible anatomic variations. Measure the intraluminal diameter of the left and right cavernous arteries and record the appropriate nomenclature.

G. Use a syringe (0.5-3mL) with insulin needle (27-30 gauge, 0.5-in) and hold the penis tight; inject the vasodilating agent in the dorsolateral aspect of the proximal or middle third of the penile shaft, and take it away from the dorsal neural bundle. Press the injection site for 10 seconds in order to avoid agent reflux to surface planes. Register the drug-administration time.

H. AVSS use is recommended, mainly in anxious patients. In order to do so, the patient must stay alone in the examination room during the time to stimulate smooth muscle relaxation[7,20].

I. Take images of left and right cavernous arteries at mode B. Turn the Doppler mode on, regulate the sample and the angle (<60 degrees) in order to measure the PSV[21].

J. Repeat the same procedure to both cavernous arteries and distinguish the laterality in the records.

K. It is essential to assess PSV and EDV at the erection peak because these measurements are the most important clinical evaluations. The evaluation is based on the time after the injection, it can also be taken at 5, 10, 15, and 20 minutes, as long as the hardness is assessed - at each new assessment time - for proper interpretation.

L. Take cross-sectional and longitudinal images of the cavernous arteries (similar to step G) at hardness peak or maximum hardness (EHS 4) and measure the intraluminal diameter at both sides. Register the acquired data and the respective laterality.

M. After the exam, ask the patient to wait from 30 minutes to 1 hour to evaluate possible collateral effects caused by the pharmacological induction agent (prolonged painful erection, priapism, discomfort in the area where the drug was injected).

N. If the patient presents a prolonged painful erection, it is worth reversing it in order to avoid priapism. We do not recommend waiting for more than 4 hours to perform the reversion, since prolonged erections for longer than 1 hour can cause edema in the cavernous bodies, a fact that considerably reduces patient's response to sympathomimetic agents and increases the need of aspiration. The administration of an alpha-adrenergic selective agonist (e.g., 1-2 mg etilefrine) in the cavernous body every 5-10 minutes - until completing one full hour - can be adopted for detumescence. Symptoms such as acute hypertension, headache, reflex bradycardia, tachycardia, palpitations, or cardiac arrhythmias must be monitored through a cardiac monitor and serial blood pressure must be taken. In some cases, the patient must be subjected to cavernous body aspiration in order to help detumescence and, consequently, to reduce the amount of administered alpha-adrenergic, as well as to reduce adverse reaction time.

O. The examination report must be detailed and express all calculated and collected data throughout the assessment (mode of report in appendix). Clinical impressions also have to be informed in the report (for example, patient anxiety during the study, among others).

P. Send the patient home and give him overall orientations and warnings (for example, priapism signs) and, whenever necessary, schedule a follow-up visit.

Q. File all images and the report in the patient's medical records.

Interpretation of hemodynamic parameters

The following parameters are often used in the hemodynamic evaluation of systemic vessels and they are also useful for ED evaluation[7,14-16,20]: Peak Systolic Velocity (PSV); End Diastolic Velocity (EDV); Resistivity Index (RI); Pre and post diameter of cavernous arteries. The cavernous artery diameter has limited value and has also been questioned due to its incapacity to predict the proper hardness, mainly in patients presenting suspicion of atherosclerosis and increased cardiovascular risk[22]. Changes in intracavernous diameter (sagittal and transverse), as well as in PSV, EDV, and RI can be evaluated in each cavernous artery at different moments. There can be differences in the basal features to find PSV between fast and slow responders.

An objective rigidity evaluation must be routinely performed before each reading of hemodynamic parameters. This approach minimizes false diagnosis of cavernous veno-occlusive dysfunction since similar

findings are obtained in cases of adrenalin-mediated failure to obtain optimal rigidity[10,23].

The PSV measurement to assess arterial competence enables researchers to accept values between 25-30 cm/s as the lower normality limit[3,10]. A PSV higher than 30 cm/s highlights normal arterial flow after proper pharmacological stimulus; on the other hand, a PSV < 25cm/s is a diagnostic of arterial insufficiency. Confirmatory studies based on angiography have shown that a velocity limit higher than 25 cm/s leads to 92% accuracy in arterial integrity diagnostic[2,10].

EDV and RI measurements bring information about the mechanism of penile veno-occlusion. A EDV > 5 cm/s and RI < 0.75 show veno-occlusion associated with normal arterial function[10,15]. Lack of specificity for venous leak caused by arterial insufficiency is the main limitation of this exam. Proper arterial inflow with short-duration semi-rigid erection and persistent diastolic flow > 5 cm/s (attention to the angle) - at all moments of the study - suggests venous leak[10,15]. However, it is important to be while reporting this condition since it is irreversible and has a great influence on the patient's treatment, mainly because rigidity loss during the exam or suboptimal ICI dosage generates similar traces and can cause pseudo-diagnostics. The literature has demonstrated that up to 50% of veno-occlusive dysfunction reports are equivocal[24]. Table 1 demonstrates possible CDDU diagnoses according to hemodynamic parameters. Figure 2 shows Doppler ultrasound waveform in different hemodynamic diagnoses.

Recording relevant findings

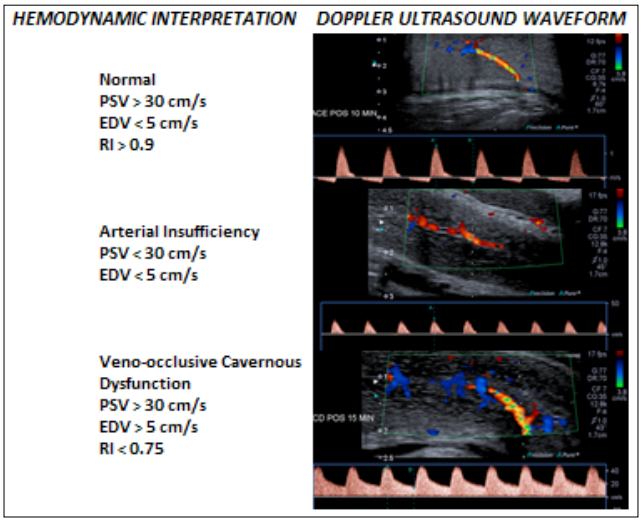
Proper data recording evidences high-quality care of patients; this has to be a priority. Images must contain the exam date and patient identification; moreover, anatomical structures must be properly named. It is fundamental to keep permanent files of all exams and medical reports for clinical and legal purposes,

TABLE 1. HEMODYNAMIC CLASSIFICATION BASED ON CAVERNOUS ARTERY VELOCITIES.

Doppler parameters Hemodynamics	PSV (cm/s)	EDV (cm/s)	RI
Normal hemodynamics	≥ 30	< 5 With preferential 0 (zero) or negative	>0.9
Arterial insufficiency	< 25	< 5	-
Veno-occlusive cavernous dysfunction	≥ 30	≥ 6	< 0.75
Mixed dysfunctions		Different combinations	

PSV = Peak systolic velocity; EDV = Ending diastolic velocity; RI = Resistant index

FIGURE 2. DOPPLER ULTRASOUND WAVEFORM IN DIFFERENT HEMODYNAMIC DIAGNOSES.



as well as to make a precise description of the following parameters:

1. It is important to record the patient's relevant information such as age, dose, and type of drug used. The following assessed parameters must be recorded, ideally:
   i. Longitudinal and cross-sectional diameters of the left and right cavernous arteries before and after pharmacological induction;
   ii. PSV, EDV, and RI during different examination times of the two cavernous arteries;
   iii. final drug-dose administered during the exam.

2. Data evaluation and interpretation:
   i. Hardness data must also be documented during the hemodynamic evaluation of the penis through CDDU.
   ii. Structural abnormalities in the penis related to tunica albuginea, corpus cavernous, and spongy (heterogeneity, hyperechoic areas, and plaques), as well as in the arteries, must be reported.
   iii. It is necessary to recognize Doppler artifacts such as aliasing, acoustic shadow, mirror image, among others[23].
   iv. Sometimes, it is difficult to properly interpret blood flow direction in some regions of the vascular tree, mainly in bifurcations, ramifications, stenoses, and in areas distal to plaques. Variations in blood flow direction depend on transducer positioning and on the appropriate use of the angle, among others. Thus, the

examiner must be an expert in the method to avoid wrong evaluations and interpretations[25].

CONCLUSIONS

The hemodynamic evaluation of the penis by color Doppler is a very useful tool for a specialized evaluation of ED. Evaluation of hemodynamic velocities without a deep understanding of the erectile mechanism may lead to wrong interpretations and negative consequences to the patient. Examiners must improve their skills in drug-induced erection and hardness scores in order to provide more sophisticated evaluations.

Author's Contribution

FC, OCS, and EPM were responsible for the initial concept and design. FC and EPM drafted the manuscript. OCS revised it critically for important intellectual content. FC, OCS, and EPM performed the literature review. FC, OCS, and EPM helped revise and edit the final version of the manuscript. All authors read and approved the final manuscript.

RESUMO

INTRODUÇÃO: *A avaliação vascular da função erétil por meio da ultrassonografia com Doppler colorido do pênis (UDCP) pode trazer benefícios na tomada de decisão. Infelizmente, a falta de padronização na condução de UDCP resulta em alta variabilidade do exame, além de poder comprometer a interpretação dos resultados.*

OBJETIVO: *Os objetivos desta revisão são promover uma maior padronização durante o UDCP e discutir os princípios fundamentais para sua correta condução e interpretação.*

MÉTODOS: *O UDCP é conduzido inicialmente com o pênis no estado flácido; todo o pênis deve ser avaliado (imagens no modo B) com um transdutor linear de alta frequência (7,5 -18 MHz). A injeção intracavernosa de agentes vasodilatadores (prostaglandina E1, papaverina, fentolamina) é realizada para induzir uma ereção rígida. Medições seriais em momentos diferentes podem ser realizadas durante a sessão da UDCP e a rigidez peniana deve ser estimada em cada avaliação.*

RESULTADOS: *É importante monitorar a resposta da ereção após o agente vasoativo (escala de rigidez), bem como realizar avaliação hemodinâmica durante a ereção de melhor qualidade. Os protocolos de estimulação sexual manual e audiovisual (AVSS) e redosagem de agente vasoativo devem ser levados em consideração para reduzir a influência de fatores psicogênicos e ajudar o paciente a obter a ereção mais rígida possível. Tais medidas contribuem para o relaxamento máximo do tecido erétil, de modo que os parâmetros hemodinâmicos não são subestimados.*

CONCLUSÕES: *O UDCP é uma ferramenta especializada relevante para avaliar pacientes com disfunção erétil; portanto, esta diretriz ajudará a padronizar e estabelecer uniformidade em sua condução e interpretação, se considerarmos a complexidade e a heterogeneidade das avaliações do pênis por UDCP.*

PALAVRAS-CHAVE: *Disfunção erétil. Disfunção erétil/diagnóstico. Ultrassonografia. Ultrassonografia Doppler.*

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Gastrointestinal emergency care during the COVID-19 pandemic: rapid communication

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SUMMARY

OBJECTIVE: *Social distancing during the COVID-19 pandemic has been associated with a decrease in the search for medical care. High-risk patients have avoided hospital environments fearing infection. We hypothesize that there was also a decrease in the search for medical care related to gastrointestinal emergencies. The aim of this study is to evaluate the frequency of consultations for severe gastrointestinal emergencies during and before the months of the pandemic.*

METHODS: *This was a transversal study. The inclusion criteria were cases of consultation in the emergency department for gastrointestinal diseases that required hospitalization, from January to April, from 2015 to 2020. The pediatric population (under age 12) was excluded.*

RESULTS: *A total of 2,457 cases of cases was included. The number of emergency hospitalizations for gastrointestinal cases decreased during the first four months of 2020: 108, 112, 82, and 77, respectively. Comparing April of 2020 with previous years, there was a lower than expected number of cases during the social distancing period (P=0.002).*

CONCLUSION: *This study reports a pronounced decrease in consultations for severe gastrointestinal emergencies during the pandemic. Governments and society should be aware that health crises do not halt the natural occurrence of noninfectious diseases; otherwise, an increase in mortality from these morbidities may arise.*

KEYWORDS: *Coronavirus Infections. Emergencies. Emergency Medical Services. Gastrointestinal tract.*

INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (COVID-19)[1] has generated large-scale social and behavioral changes, mostly because of lockdown and social distancing[2]. The advice to stay home except for essential activities has been associated with a decrease in the demand for medical care for symptoms not related to COVID-19.

High-risk patients have avoided hospital environments fearing infection. In a study conducted in Spain, it was observed a decrease of fifty percent in emergency coronary interventions during this period[3]. In China, there was a four-fold increase of the time to seek medical care for myocardial infarction in comparison with the previous years[4]. A 65.4%

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decrease in emergency surgery was observed in another study in Spain[5].

We hypothesize that there was also a decrease in the search for medical care related to gastrointestinal emergencies. To that purpose, we conducted a study in a tertiary hospital to evaluate the frequency of consultations for severe gastrointestinal emergencies during and before the months of the pandemic.

METHODS

This was a transversal study. A data survey of consultations in the emergency department that required hospitalization, from January to April, from 2015 to 2020, was conducted. The period of social distancing in the city was from March 18th to April 30th. A query in the system of hospitalizations due to emergency, based on the International Classification of Diseases 11[6], was conducted. All cases of gastrointestinal emergencies were included. The pediatric population (under age 12) was excluded. The patients' data were obtained from the computer system records. The Chi-square test was used to compare months and adjust residual analysis to detect categories with higher and lower than expected frequencies (+/- 1.96). The statistics software used was IBM SPSS version 20.0.

This study was approved by the Ethical Committee of the Hospital (number 4.044.906) and is in accordance with Resolution 466/2012 of the National Health Council of the Ministry of Health.

RESULTS

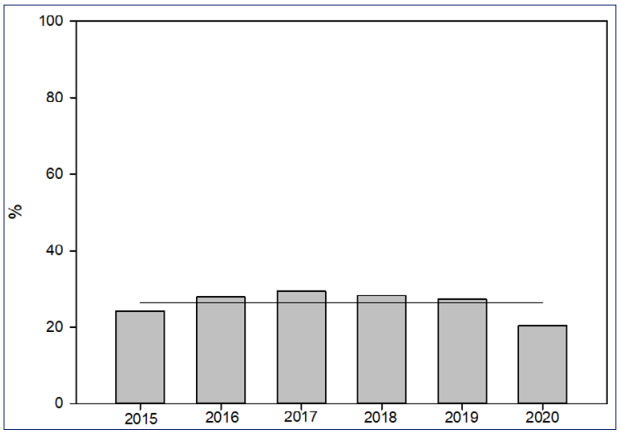
A total of 2,457 cases was included. The majority were women (53%), and the mean age was 53.5 years (DP=22.6). The most common morbidity was acute appendicitis (21.7%), followed by acute cholecystitis (7.3%), and diverticulitis (5.7%). The number of consultations each month are detailed in Table 1.

TABLE 1. NUMBER OF CONSULTATIONS FOR SEVERE GASTROINTESTINAL EMERGENCIES FROM JANUARY TO APRIL, FROM 2015 TO 2020.

Year							
Month	2015	2016	2017	2018	2019	2020	Total
1	74	80	98	109	123	108	592
2	97	113	95	107	92	112	616
3	114	103	99	104	100	82	602
4	91	114	121	126	118	77	647
Total	376	410	413	446	433	379	2457

The emergency hospitalizations for gastrointestinal cases decreased during the first four months of 2020: 108, 112, 82, and 77, respectively. Comparing April of 2020 with previous years, there was a lower than expected number of cases during the social distancing period (see Figure 1). For example, appendicitis cases in April 2015 to 2020 were: 33, 25, 22, 24, 36, and 13.

FIGURE 1. FREQUENCY OF CONSULTATIONS FOR SEVERE GASTROINTESTINAL EMERGENCIES IN APRIL FROM 2015 TO 2020. THE LINE INDICATES THE EXPECTED FREQUENCY OF CASES IN THE MONTH AND YEAR BELLOW (CHI-SQUARE TEST, P=0.002; ADJUSTED RESIDUALS: -1, 0.7, 1.5, 1.0, 0.5, -2.9).



DISCUSSION

This study reports a pronounced decrease in consultations for severe gastrointestinal emergencies during the pandemic and social distancing. To our knowledge, this is the first publication regarding the consequences of COVID-19 both in clinical and surgical gastroenterology. There is a similar study by Cano-Valderrama et al.[5] in Spain, but they analyzed only 173 surgical cases. They reported a 65.4% decrease in emergency interventions (P<0.001)[5].

There is a limitation in this analysis because it is based in a single hospital. However, it brings worrying issues. We do not know the outcomes of patients who were not treated for potentially life-threatening conditions, such as acute appendicitis.

CONCLUSION

New pandemics may emerge. Governments and society should be aware that these health crises do

not halt the natural occurrence of noninfectious diseases; otherwise, an increase in mortality from these morbidities may arise.

Author's Contribution

CL conceptualized the article, obtained Ethical approval, collected and analyzed the data, drafted the manuscript, reviewed and revised the manuscript, approved the final draft as submitted, and reviewed the final manuscript for resubmission. ENT, LWG, and MRMT analyzed the data, drafted the manuscript, reviewed and revised the manuscript, approved the final draft as submitted.

Conflict of Interest

The authors disclose no conflicts.

RESUMO

OBJETIVO: *O distanciamento social durante a pandemia por COVID-19 tem sido associado a uma redução na busca por atendimento médico. Pacientes de alto risco têm evitado ambiente hospitalar com receio de infectar-se. Nossa hipótese é de que houve também uma redução no atendimento médico a emergências gastrointestinais. O objetivo deste estudo é avaliar a frequência de consultas por emergências gastrointestinais graves durante e antes da pandemia.*

MÉTODOS: *Estudo transversal. O critério de inclusão foram casos de consulta em emergência por patologia gastrointestinal que tenham requerido hospitalização, de janeiro a abril dos anos 2015 a 2020. A população pediátrica foi excluída.*

RESULTADOS: *Um total de 2.457 casos foi incluído. O número de hospitalizações via emergência durante os primeiros quatro meses de 2020 foi: 108, 112, 82 e 77, respectivamente. Comparando abril de 2020 com anos anteriores, houve um número de atendimentos abaixo do esperado (p=0,002).*

CONCLUSÃO: *Este estudo relata uma redução pronunciada em atendimentos por emergências gastrointestinais graves na pandemia. Governos e sociedade devem estar cientes de que tais crises de saúde não interrompem a ocorrência natural de doenças não infecciosas, do contrário poderá ocorrer um aumento na mortalidade por outras morbidades.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Emergências. Serviços médicos de emergência. Trato gastrointestinal.*

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Tubulovillous adenoma of the duodenal papilla: radiological-endoscopic and anatomopathological correlation in the surgical proposal

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SUMMARY

Tubulovillous adenomas of the duodenal ampulla are rare neoplasms. The present report describes a case with radiological-endoscopic and pathological correlation in which the patient underwent duodenal pancreatectomy with good postoperative progression. With advanced imaging methods, especially magnetic resonance and endoscopic ultrasound, locoregional aspects and extraluminal, lymphovascular, and metastatic invasion have been increasingly discussed as contributors to therapeutic decision making. This progression improves lesion staging and is especially useful in selecting eligible candidates for endoscopic treatment.

KEYWORDS: *Intestinal neoplasms; Adenoma; Villous Adenoma; Diagnostic Imaging; Magnetic Resonance Imaging*

INTRODUCTION

Tubulovillous adenomas account for approximately 1% of all duodenal tumors[1-3]. Most of them are initially asymptomatic. Fluctuating jaundice and biliary colic may progressively appear with the growth of these tumors. Less frequently, pancreatitis and upper gastrointestinal bleeding have been reported[1-3]. In addition to diagnosis, complementary imaging tests with increasingly improved resolution can improve individualized surgical planning and discussion.

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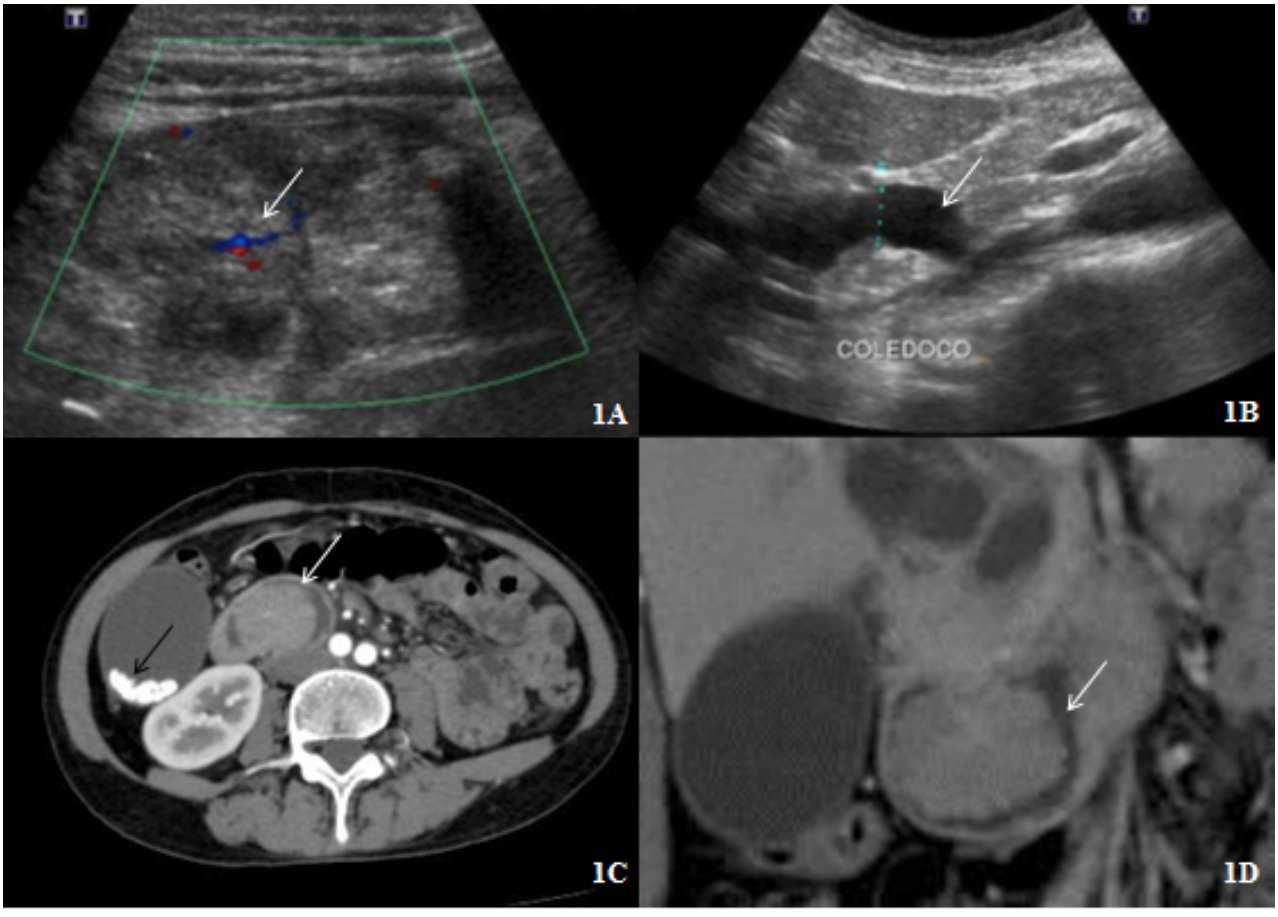
CLINICAL CASE

A 61-year-old white female patient who was born in São Paulo, Brasil had a body mass index of 21 kg/m² and grade I hypertension that was well controlled with medications. She had no other comorbidities or pathological history. The patient reported pain in the right hypochondrium accompanied by 10-kg weight loss, vomiting, fluctuating jaundice, and intermittent fever (38.5 °C) for approximately 6 months. On physical examination, she exhibited regular general condition, jaundice (2+/4+), and pain on deep palpation in the right hypochondrium. Other organs did not exhibit significant changes. Laboratory tests showed hyperbilirubinemia at the expense of direct bilirubin (4.4 mg/dL).

Abdominal ultrasound (US) showed cholecystolithiasis with a solid mass close to the distal bile duct. The size of the mass was 5.5 cm in the longest axis. It exhibited inside flow on Doppler study and intrahepatic and extrahepatic bile duct dilation (Figures 1A and 1B). Diagnostic investigations included multislice computed tomography (CT) (Figures 1C and 1D), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP) (Figures 2A, 2B, and 2C). Imaging examinations revealed a swirl-patterned solid mass in the duodenal papillary topography (called the "intraduodenal cerebellum" sign by the authors due to the swirl pattern of the tumor surface). The mass was 5.5 cm × 4.0 cm × 2.5 cm in size and associated with intrahepatic and extrahepatic bile duct dilation up to the mass plane with no evidence of lymphovascular or metastatic involvement.

Upper digestive endoscopy with biopsy and endoscopic retrograde cholangiopancreatography (ERCP) showed a multilobulated polypoid lesion sized 5–6 cm

FIGURE 1. ABDOMINAL ULTRASOUND SHOWED A SOLID MASS CLOSE TO THE DISTAL BILE DUCT. IT EXHIBITED INSIDE FLOW ON DOPPLER STUDY (A, UPPER LEFT) AND INTRAHEPATIC AND EXTRAHEPATIC BILE DUCT DILATION (B, UPPER RIGHT). AXIAL (C, LOWER LEFT) AND CORONAL (D, LOWER RIGHT) COMPUTED TOMOGRAPHY SECTIONS SHOW CHOLECYSTOLITHIASIS (BLACK ARROW) AND A SOLID MASS IN THE DUODENAL PAPILLARY TOPOGRAPHY (WHITE ARROWS). THE MASS WAS 5.5 CM × 4.0 CM × 2.5 CM IN SIZE, WITH MODERATE AND HOMOGENEOUS IMPREGNATION AFTER CONTRAST AND A SWIRL SURFACE PATTERN (CALLED "INTRADUODENAL CEREBELLUM" SIGN BY THE AUTHORS DUE TO THE SWIRL PATTERN OF THE TUMOR SURFACE).



in the region of the papilla of Vater. Histopathological analysis (Figure 2D) showed a tubular adenoma with high-grade intraepithelial neoplasia of the duodenal papilla. Considering a suspected malignant transformation and the extent of the lesion, duodenal pancreatectomy was selected in the present case. Histopathological diagnosis of the surgical specimen was tubulovillous adenoma of the papilla of Vater with superficial foci of well-differentiated adenocarcinoma and duodenal surgical margins (proximal and distal). Distal pancreas and the bile duct were free of neoplasia, with no lymph node involvement or vascular invasion (stage I) (Figures 3A, 3B, 3C, 3D). Chronic calculous cholecystitis was also present with extensive pseudo-pyloric metaplasia. The patient exhibited good postoperative progression. She was discharged in good general condition and is still under outpatient follow-up.

FIGURE 2. CORONAL SECTION OF T1-WEIGHTED MAGNETIC RESONANCE IMAGE AFTER CONTRAST SHOWS HOMOGENEOUS MASS IMPREGNATION IN THE DUODENAL PAPILLARY TOPOGRAPHY IN ADDITION TO CHOLECYSTOLITHIASIS (A, UPPER LEFT). DIFFUSION-WEIGHTED IMAGES WITH A B-VALUE OF 1,000 SHOW RESTRICTION OF WATER MOLECULE DIFFUSION BY THE MASS (B, UPPER RIGHT). MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY (C, LOWER LEFT) SHOWS INTRAHEPATIC AND EXTRAHEPATIC BILE DUCT DILATION UP TO THE MASS PLANE IN THE DUODENAL PAPILLARY TOPOGRAPHY. UPPER DIGESTIVE ENDOSCOPY (D, LOWER RIGHT) SHOWS A LESION IN THE POST-BULBAR REGION IN THE DUODENAL PAPILLARY TOPOGRAPHY, WITH A LOBULATED AND WHITISH SURFACE, DEFINED LIMITS, AND A VESSEL IN ITS CENTER ASSOCIATED WITH ADJACENT WHITISH MUCOUS LINING.

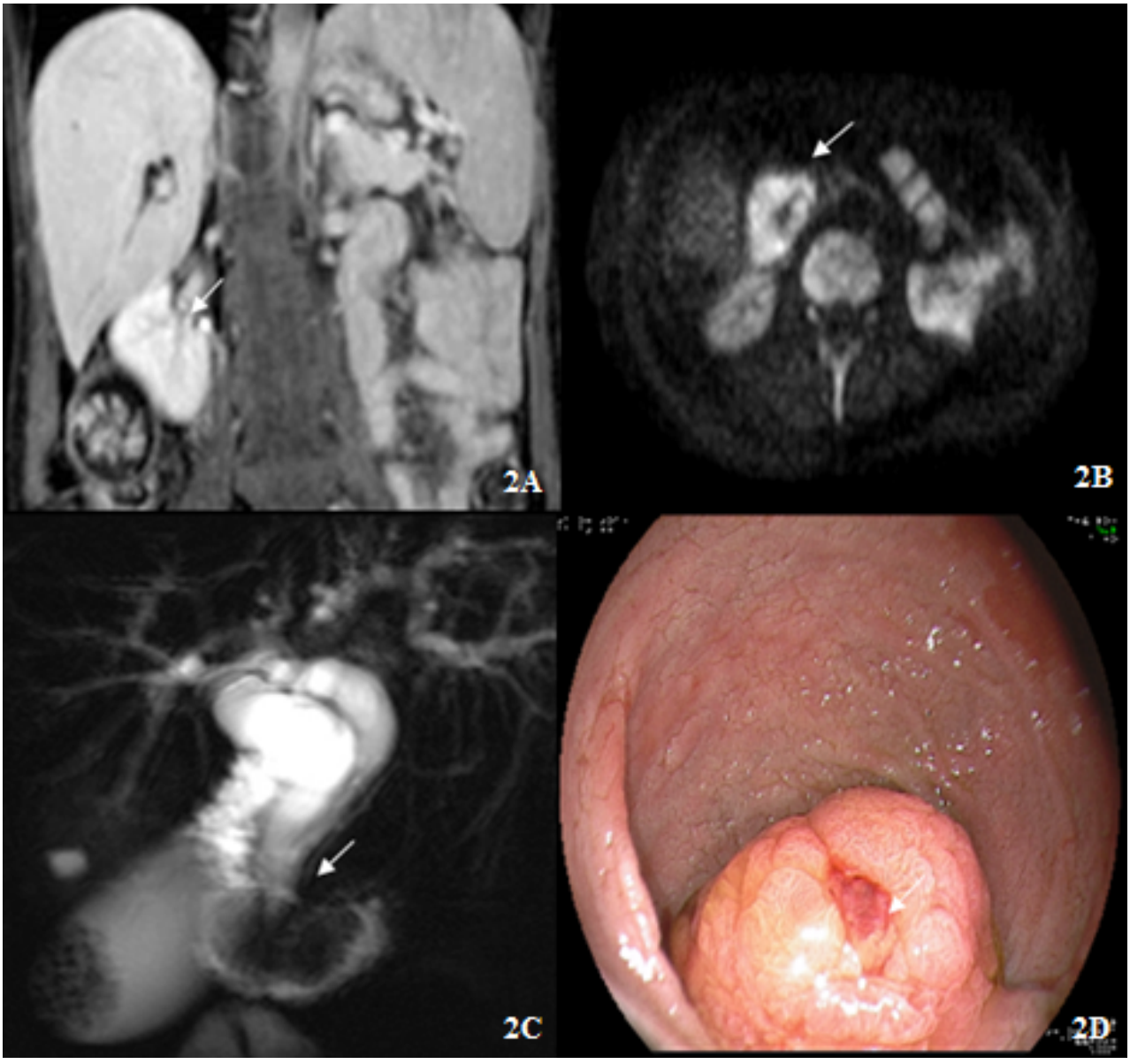
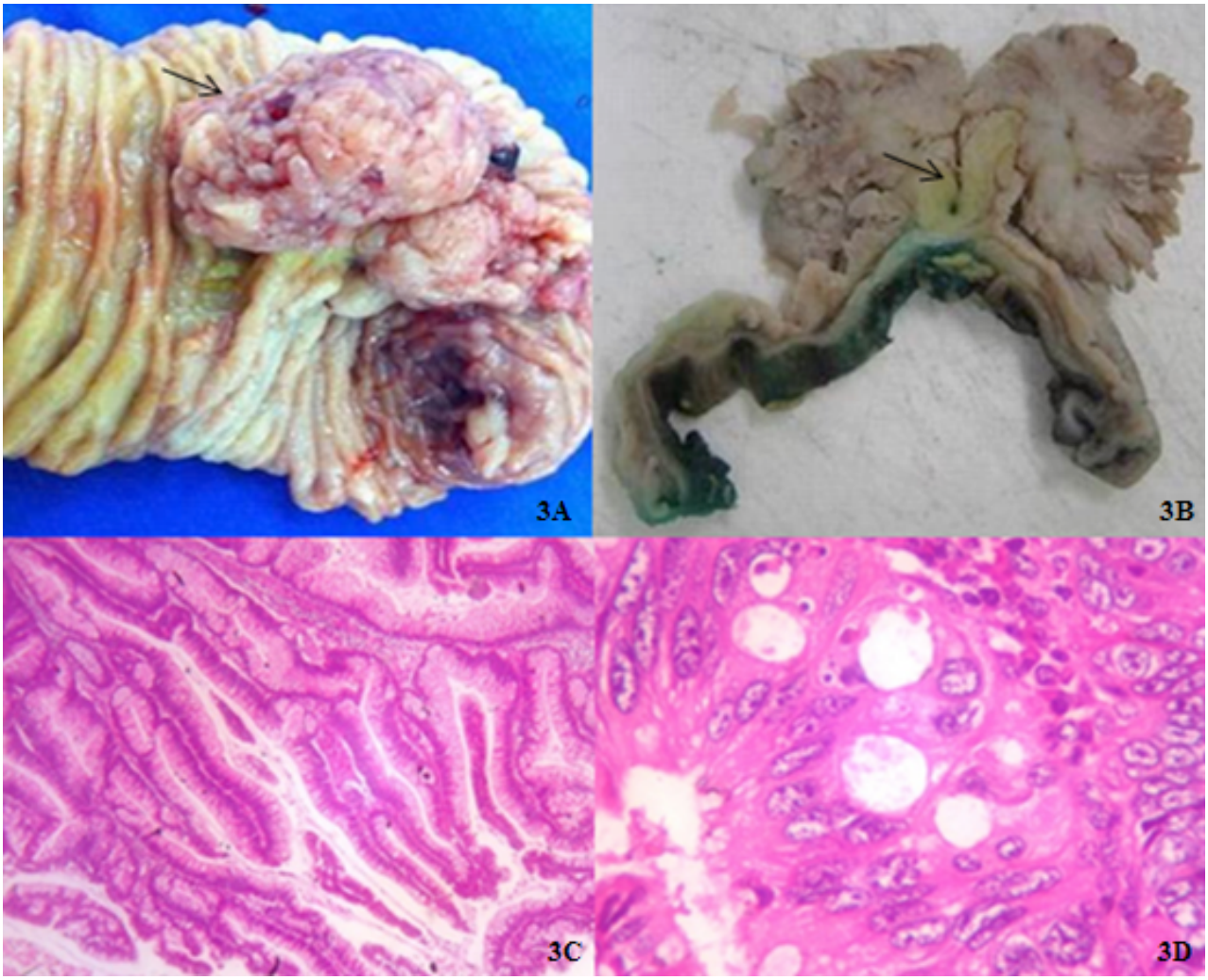


FIGURE 3. MACROSCOPICALLY, SURGICAL SPECIMEN (A) SHOWS A POLYPOID LESION MEASURING 5.5 CM × 4.0 CM × 2.5 CM, WITH IRREGULAR SURFACE, VILLOUS APPEARANCE, AND FRIABLE CONSISTENCY. MACROSCOPIC ANATOMOPATHOLOGICAL EVALUATION (B) SHOWS THE TRANSVERSE SECTION OF THE LESION AT THE LEVEL OF THE BILE DUCT (ARROW), SHOWING A CEREBELLAR PRESENTATION WITH A SWIRL PATTERN SIMILAR TO THAT OBSERVED IN THE RADIOLOGICAL IMAGES. MICROSCOPIC EXAMINATION (C) SHOWS VILLOUS STRUCTURES LINED BY COLUMNAR EPITHELIUM WITH PALISADED ARRANGEMENT OF NUCLEI (HEMATOXYLIN AND EOSIN, 100×). SUPERFICIAL ADENOCARCINOMATOUS FOCI WITH ATYPICAL NUCLEI FORMING GLANDULAR STRUCTURES (D) ARE OBSERVED (HEMATOXYLIN AND EOSIN, 400×).



DISCUSSION

The major duodenal papilla or the ampulla of Vater is a small nipple-like elevation located on the posteromedial wall of the descending part of the duodenum. It is formed by the union of intramural portions of the bile duct and the main pancreatic duct. Periampullary tumors are present at approximately up to 2.0 cm from the duodenal papilla. The four most common types are tumors of the cephalic portion and the uncinate process of the pancreas (50–70%), tumors of the duodenal ampulla, tumors of the duodenum, and tumors of the distal bile duct[1-3]. The complex anatomy of the periampullary region, which is closely related to the pancreas and the biliary tract, is associated with difficulties in diagnostic accuracy and in staging via imaging examinations. Recent emphasis on MRI and endoscopic ultrasound (EUS) has improved the controversial management of these tumors and underlined the need for multidisciplinary treatment[1-3].

Benign neoplasms of the ampulla of Vater are premalignant and rare lesions, with very few cases reported in the literature[1-3]. Currently, these lesions are being diagnosed with greater frequency due to greater availability of imaging methods such as US, CT, EUS and due to improved patient screening and follow-up in the presence of risk factors. Ampullary adenomas are sporadic or associated with familial polypoid syndromes such as familial adenomatous

polyposis[4-6]. Adenomas are more common in the colon and are rarely observed in the small intestine. Duodenal tubulovillous adenoma was first described by Perry in 1893 and was called duodenal papilloma. Duodenal tubulovillous adenomas are very uncommon, accounting for approximately 1% of all duodenal tumors[4-6]. Most of the duodenal tumors are present in the descending part of the duodenum and in the periampullary region. The onset of this lesion is mainly between the fifth and the seventh decade of life and the prevalence is similar between sexes[5-7]. These tumors are named according to staging and morphology as villous adenomas, papillary adenomas, villous papillomas, tubulovillous adenomas, or villous glandular polyps[8].

Considering the presence of malignancy in approximately 30% to 40% of the tubulovillous adenomas (similar to the adenoma-adenocarcinoma sequence in colorectal tumors) and the size (larger tumors generally have a greater chance of malignancy), histological type (villous: carcinomas are more frequent), location (ampullary lesions are more likely to contain carcinomatous foci than duodenal or small intestine lesions), number (multicentric tumors have a higher rate of malignancy), and recurrence rate; the surgical approach involves local resection (endoscopic resection, ampullary resection, or duodenotomy) and follow-up or duodenal pancreatectomy. However, the selection of treatment approach is still controversial[9-11]. Duodenal pancreatectomy was selected in the present case due to the suspected malignant transformation and the extent of the lesion.

Propaedeutic imaging methods such as US, CT, MRCP, ERCP, EUS, and intraductal US improve the diagnosis and surgical management. Imaging examinations are important in surgical planning to evaluate the extraluminal extent of invasive tumors, lymphovascular involvement, and the presence of metastases. In the absence of lymphovascular involvement and metastases, locoregional aspects have been discussed as contributors to therapeutic decision making. Advanced staging methods are especially useful tools to select eligible patients for endoscopic treatment[12-14].

The tomographic appearance of duodenal tubulovillous adenoma is not specific, with attenuation and varying degrees of contrast impregnation. However, larger tumors may present a swirl surface pattern similar to the one observed in the present case, which resembles the image and the macroscopic aspect of the cerebellum (called "intraduodenal cerebellum" sign by the authors due to the swirl pattern of the tumor surface). This presentation may be caused by villous projections and friable tumor pattern on imaging and macroscopic examination. Knowledge about the tumor appearance may help define a suspected imaging diagnosis[4,15,16]. Imaging differentials allow the inclusion of pseudo-tumors (tumors that can simulate a polypoid mass on CT, but have the same imaging characteristics as the rest of the duodenal mucosa), non-neoplastic hyperplasia of duodenal submucosal glands (Brunner's glands), other duodenal polyps such as epithelial (mucosal lesions) and intramural polyps (submucosal lesions such as stromal tumor of gastrointestinal origin and other mesenchymal tumors), duodenal carcinoma, ampullary carcinoma, metastases, and lymphoma[15,16]. Another advantage of CT is the possibility of local staging of any vascular invasion in cases of more aggressive lesions.

Recently, an algorithm was suggested to manage ampullary adenoma diagnosed at biopsy[12,14]. EUS/CT were suggested for staging in the presence of one of the following characteristics: tumors larger than 1 cm, high degree of dysplasia, ulceration, irregular margins, and spontaneous bleeding or friable consistency on endoscopic examination. In the absence of any of the aforementioned characteristics, management options include endoscopic resection and surveillance. Patients undergoing local surgical or endoscopic resection require prolonged follow-up with imaging examinations. Treatment options in EUS/CT staging with invasive characteristics such as lymphovascular invasion, intraductal growth, and metastases include surgical approach/ablative therapy[12,14]. EUS can accurately predict the depth of mucosal invasion in the preoperative evaluation of periampullary and duodenal adenomas, making it possible to consider endoscopic therapy or local resection in selected patients, avoiding more extensive surgery[14].

MRI has shown a good correlation with histopathological findings in the evaluation of peritumoral invasion of adjacent periampullary tissues, with significant sensitivity (88%), specificity (100%), accuracy (96%), positive predictive value (100%), and negative predictive value (94%)[4]. Although it has lower spatial resolution compared to CT, the high anatomical resolution of MRI can identify signal changes in

structural disorders of the periampullary region, pancreatic cephalic portion, main pancreatic duct walls, and the common bile duct[4]. An associated MRCP allows a noninvasive panoramic evaluation of the biliary and pancreatic pathways through heavily T2-weighted images. Good locoregional evaluation of periampullary tumors can improve surgical planning and management.

CONCLUSION

Tubulovillous adenomas of the duodenal papilla are rare neoplasms that are being diagnosed with greater frequency. Multidisciplinary approach and recent imaging advances with emphasis on EUS and high tissue resolution of MRI have allowed discussions regarding new surgical approaches such as endoscopic therapy in selected cases.

RESUMO

Os adenomas túbulo-vilosos da ampola duodenal são neoplasias raras. Neste trabalho apresentamos um caso com correlação radiológico-endoscópica e patológica, tendo a paciente sido submetida à duodenopancreatectomia com boa evolução pós-operatória. Com os avanços dos métodos de imagem, em especial da ressonância magnética e ultrassonografia endoscópica, aspectos locorregionais, além da invasão extraluminal, linfovascular e metastática, têm sido discutidos de maneira crescente como contribuintes na decisão terapêutica. Essa evolução contribui para o melhor estadiamento destas lesões e é especialmente útil para selecionar candidatos elegíveis ao tratamento endoscópico.

PALAVRAS-CHAVE: *Neoplasias Intestinais; Adenoma; Adenoma Viloso; Diagnóstico por Imagem; Imagem por Ressonância Magnética.*

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ORIGINAL ARTICLE

Tuberculosis in Northeastern Brasil (2001-2016): trend, clinical profile, and prevalence of risk factors and associated comorbidities

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SUMMARY

OBJECTIVE: *To describe the temporal trend, clinical profile, and the prevalence of risk factors and associated comorbidities in new cases of tuberculosis in the Northeast (2001-2016).*

METHODS: *A prevalence study involving all tuberculosis cases registered in Northeast Brasil, 2001-2016. Data were obtained from the National System of Notification of Disorders. For statistical analysis, the inflection point regression model and descriptive statistics were used.*

RESULTS: *331,245 cases of tuberculosis were reported. The overall incidence rate decreased from 44.84/100,000 inhabitants (2001) to 30.92/100,000 inhabitants (2016), with a decreasing trend (AAPC: -2.3; p<0.001). The profile was characterized by men (73.53%), age 20-59 years (73.56%), pulmonary tuberculosis (86.37%), positive smear microscopy (54.78%). The main risk factors and comorbidities were: AIDS (4.64%), HIV (12.10%), Diabetes mellitus (5.46%), alcohol (11.63%), institutionalized, (4.31%) and deprived of liberty (2.30%). The cure rate was 70.66% and the abandonment rate was 9.11%.*

CONCLUSIONS: *Even with a reduced incidence, tuberculosis represents a real public health problem in the Northeast region. The profile was characterized by a male population, in economically-active age, lung smear-positive pulmonary presentation, and the risk factors and comorbidities of Aids, TB/HIV co-infection, diabetes mellitus, alcohol consumption, institutionalized and deprived of freedom reflect the complexity of the challenges in facing the disease.*

KEYWORDS: *Tuberculosis. Epidemiology. Risk factors.*

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by any of the seven species that make up the *Mycobacterium tuberculosis* complex; however, the most important sanitary wise is *M. tuberculosis*. Transmission occurs from the inhalation of particles from the airways of bacillary individuals[1,2].

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TB is one of the top ten causes of death from a single infectious agent throughout the world. In 2018, 77,788 new cases of the disease were reported in Brasil, with an incidence of 34.8/100,000 inhabitants. In that same year, the Northeast ranked second regarding the number of cases (26.20%; n=19,075) and third in incidence coefficient (33.1/100,000 inhabitants)[3].

Whereas the epidemiological context, the Ministry of Health drew up the *National Plan for the End of Tuberculosis as a Public Health Problem*, with goals to, by 2035, reduce the incidence coefficient to less than 10/100,000 inhabitants and the TB mortality coefficient to less than 1/100,000 inhabitants[3,4], and have no families affected by TB expenses that surpass citizens' socioeconomic condition. The national plan defines strategies divided into three main groups: i) prevention and integrated care focused on individuals with TB; ii) bold policies and support system; and (iii) intensification of research and innovation[4].

Based on the above, the objective of this study was to describe the temporal trend, clinical profile, and prevalence of associated risk factors and comorbidities in new cases of tuberculosis in the Northeast (2001-2016).

METHODS

Study design, population, and period

This is a prevalence study involving all TB cases recorded in the period of 2001-2016 in Northeastern Brasil.

Study locale

The study was conducted in the Northeast region of Brasil, which is composed by nine states (Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe, and Bahia) and has a population of 56.9 million inhabitants, corresponding to 27.62% of the Brazilian population[5].

Study variables and collection procedures

We included in the study an epidemiological indicator (coefficient of incidence per 100,000 inhabitants) and 18 variables (age, clinical presentation, 1st of sputum bacilloscopy, 2nd sputum bacilloscopy, sputum culture, rapid TB test, outcome status, AIDS, alcoholism, diabetes *mellitus*, mental illness, illicit drugs, smoking, HIV testing, institutionalization, population deprived of liberty - PDL, homeless population, and health professional).

The data related to TB cases were extracted from the Brazilian Case Registry Database (*Sistema de Informações de Agravos de Notificação*) and the population data were extracted from IBGE.

Statistical treatment

The statistical treatment was completed in two stages. In the first stage, we carried out the analysis of the temporal trend using a joinpoint regression model[6]. The trends were sorted as ascending, descending, or stationary. We calculated the annual percent change (APC) and the average annual percent change (AAPC) with a confidence interval of 95% (95% CI) and a significance level of 5%. The analysis was made using the Joinpoint regression program (version 4.6.0.0, National Cancer Institute, Bethesda, MD, USA). In the second stage, a descriptive analysis was completed (absolute and relative frequencies) of the clinical variables and comorbidities.

Ethical aspects

The present study used secondary data in the public domain, for which reason the appreciation by the Human Research Ethics Committee was dismissed.

RESULTS

Trend analysis

The incidence of TB in the Brazilian Northeast dropped from 44,84/100,000 in 2001 to 30.92/100,000 in 2016. The regression model showed two distinct temporal behaviors: the first was stationary between 2001-2004 (APC: 0.54%; p=0.7), and the second was of decline between 2004 and 2016 (APC: -2.99%; $p < 0.001$). This reduction was also observed in the analysis according to sex. In men, the incidence was reduced from 55.81/100,000 in 2001 to 41,98/100,000 in 2016, with two distinct temporal behaviors: stationary between 2001-2005 (APC: 0.01%; p=1.0), and in decline from 2005 (APC: -2.37%; $p < 0.001$). In women, the incidence was reduced from 33,97/100,000 to 20,30/100.000, with a stationary trend in 2001-2004 (APC: 0.45%; p=0.8), and in decline from 2004 (APC: -4.18%; $p < 0.001$). (Figure 1).

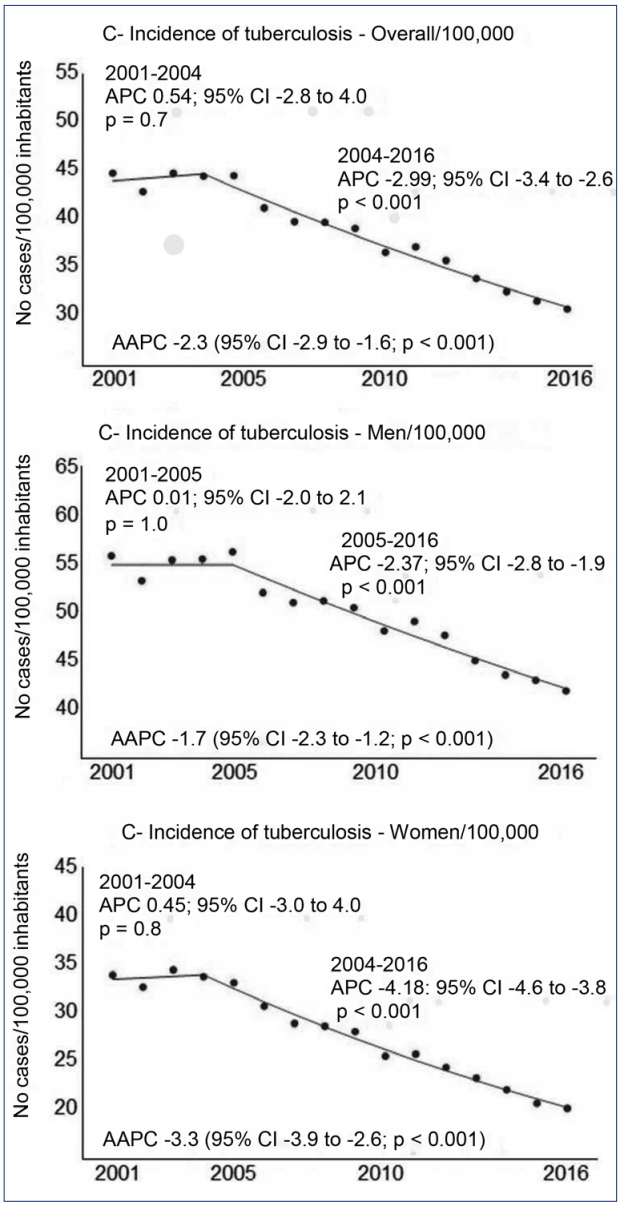
Clinical profile, risk factors, and prevalence of associated comorbidities

Out of the 331,245 TB cases registered in the Brazilian Northeast, the profile was characterized by males

(63.53%; n=210,454), age between 20 and 59 years (73.56%; n=243,670) and pulmonary clinical presentation (86.37%; n=286,080). A total of 54.78% (n=181,469) of cases was positive in the 1st sputum bacilloscopy, 17.90% (n=59,307) in the 2nd sputum bacilloscopy, and 5.92% (n=19,601) in culture. In addition, 5.22% (n=346) of individuals who underwent the molecular rapid test presented resistance to rifampicin. The cure rate was 70.66% (Table 1).

Regarding the risk factors and comorbidities, the following stood out: Aids (4.64%; n=15,372), alcoholism (11.63%; n=38,516), diabetes *mellitus* (5.46%; n=18,077), mental illness (1.87%; n=6,197), illicit drugs (0.86%; n=2,858), and smoking (1.80%; n=5,962); 43.93% (n=145,506) of individuals were tested for HIV, with a rate of 12.10% of seroreacting (n=17,602), considering only those who were tested, and 5.31% considering all the cases. Of the total, 4.31% were institutionalized, and prisons stood out (2.30%; n=7,628) (Table 2).

FIGURE 1



DISCUSSION

The study showed important nuances of TB in the Brazilian Northeast. Even in the face of the difficulties in combating TB, the temporal analysis showed a significant decrease in the incidence of the disease in the Northeast region during the period studied, following the same pattern of reduction observed in Brasil[7]. It is possible to associate this reduction to the Brazilian government's efforts in combating the disease, most prominently the strengthening of tuberculosis control programs in municipalities and states[3], and the greater coverage of the actions of the Family Health Strategy in recent years[8].

In the state of Piaui, the actions carried out by the Family Health Strategy, whose coverage reached 98.7% in 2016[7], and the decentralization of TB control actions in Primary Care may result in greater access to diagnosis and treatment, and, consequently, in reducing the transmission of the disease[8]. Similar advances were also observed in Paraíba: in 2007, the priority municipalities already had 95% of the healthcare units with the TB control program implemented, and of these, 55% already used the strategy of supervised treatment[9].

Even with significant advances, many problems still prevent the consolidation of TB control programs. In 2018, for example, the cure rate in Paraíba was 55.5% and the abandonment rate was 10.4%, which shows that the state is still far from achieving the goals recommended by the WHO[3]. A similar context is also observed in the neighboring state of Pernambuco, in which the cure rate was 73.3% and the abandonment rate was 9.3%[3]. This scenario shows that it is still necessary to strengthen the actions for combating TB in the Northeast[10,11].

In addition to the magnitude of the disease, it is necessary to reflect on the clinical profile and the prevalence of risk factors and associated comorbidities. In this study, 63.53% of the cases were in men, which is similar to the findings of other investigations, in which this population was approximately twice as affected[12-14]. The resistance in looking for assistance in health services as well as less access to these services by this population are conditions that hinder the early

TABLE 1. SOCIODEMOGRAPHIC AND CLINICAL CHARACTERIZATION OF NEW CASES OF TUBERCULOSIS IN RESIDENTS OF THE NORTHEAST REGION, BRASIL, 2001-2016.

Variables	Ignored n=90 (0.03%)		Male n=210454 (63.53%)		Female n=120701 (36.44%)		Total n = 331245 (100%)	
	n	%	n	%	n	%	n	%
Age range								
0-10	5	5.55	4317	2.05	3520	2.92	7842	2.37
10-19	6	6.66	14692	6.98	12845	10.64	27543	8.31
20-59	69	76.68	158336	75.24	85265	70.64	243670	73.56
60 or more	10	11.11	33028	15.69	19031	15.77	52069	15.72
Blank	-	-	81	0.04	40	0.03	121	0.04
Presentation								
Pulmonary	72	80.00	183654	87.27	102354	84.80	286080	86.37
Extrapulmonary	13	14.44	22211	10.55	16138	13.37	38362	11.58
Pulmonary + extrapulmonary	5	5.56	4515	2.15	2183	1.81	6703	2.02
Blank	-	-	74	0.03	26	0.02	100	0.03
1st Bacilloscopy- sputum								
Positive	52	57.78	118375	56.25	63042	52.23	181469	54.78
Negative	16	17.78	43984	20.90	26058	21.59	70058	21.15
Not performed	22	24.44	47129	22.39	31032	25.71	78183	23.60
Does not apply	-	-	895	0.43	542	0.45	1437	0.44
Blank	-	-	71	0.03	27	0.02	98	0.03
2nd Bacilloscopy- sputum								
Positive	5	5.55	39100	18.58	20202	16.74	59307	17.90
Negative	1	1.11	19364	9.20	11585	9.60	30950	9.34
Not performed	6	6.67	36767	17.47	21347	17.68	58120	17.55
Blank	78	86.67	115223	54.75	67567	55.98	182868	55.21
Sputum culture								
Positive	4	4.44	12728	6.05	6869	5.70	19601	5.92
Negative	4	4.44	7610	3.62	4288	3.55	11902	3.59
Ongoing	7	7.78	11382	5.41	6819	5.65	18208	5.50
Not performed	75	83.34	178663	84.89	102697	85.08	281435	84.96
Blank	-	-	71	0.03	28	0.02	99	0.03
Rapid TB test								
Detectable sensitive to rifampicin	1	1.11	3211	1.53	1262	1.05	4474	1.35
Detectable resistant to rifampicin	-	-	226	0.11	120	0.10	346	0.10
Not detectable	-	-	515	0.24	286	0.24	801	0.24
Inconclusive	-	-	656	0.31	352	0.29	1008	0.30
Not performed	1	1.11	20251	9.62	10579	8.76	30831	9.31
Blank	88	97.78	185595	88.19	108102	89.56	293785	88.70
Outcome								
Cure	53	58.89	144541	68.70	89470	74.12	234064	70.66
Abandonment	7	7.78	21140	10.04	9039	7.49	30186	9.11
Death from tuberculosis	-	-	5304	2.52	2038	1.69	7342	2.22
Death from other causes	4	4.44	9699	4.61	4255	3.52	13958	4.21
Transfer	15	16.67	22103	10.50	11485	9.52	33603	10.15
DR-TB	2	2.22	555	0.26	314	0.26	871	0.26
Change of scheme	-	-	230	0.11	153	0.13	383	0.12
Failure	-	-	31	0.01	15	0.01	46	0.01
Primary abandonment	-	-	112	0.05	55	0.05	167	0.05
Blank	9	10.00	6739	3.20	3877	3.21	10625	3.21
Total	90	100	210454	100	120701	100	331245	100

Legend: TB: Tuberculosis; DR-TB: Drug-Resistant tuberculosis.

TABLE 2. RISK FACTORS AND COMORBIDITIES ASSOCIATED WITH NEW CASES OF TUBERCULOSIS IN RESIDENTS OF THE NORTHEAST REGION, BRASIL, 2001-2016.

Variables	Ignored n=90 (0.03%)		Male n=210454 (63.53%)		Female n=120701 (36.44%)		Total n=331245 (100%)	
	n	%	n	%	n	%	n	%
AIDS								
Yes	5	5.56	10816	5.14	4551	3.77	15372	4.64
No	10	11.11	86630	41.16	49165	40.73	135805	41.00
Blank	75	83.33	113008	53.70	66985	55.50	180068	54.36
Alcoholism								
Yes	-	-	34029	16.17	4487	3.72	38516	11.63
No	15	16.67	84639	40.22	56892	47.13	141546	42.73
Blank	75	83.33	91786	43.61	59322	49.15	151183	45.64
Diabetes *mellitus*								
Yes	2	2.22	10654	5.06	7421	6.15	18077	5.46
No	14	15.56	101018	48.00	54469	45.13	155501	46.94
Blank	74	82.22	98782	46.94	58811	48.72	157667	47.60
Mental Illness								
Yes	1	1.11	4130	2.00	2066	1.71	6197	1.87
No	12	13.33	106287	50.50	58633	48.58	164932	49.79
Blank	77	85.56	100037	47.50	60002	49.71	160116	48.34
Illicit drugs								
Yes	-	-	2447	1.16	411	0.34	2858	0.86
No	2	2.22	21909	10.41	12167	10.08	34078	10.29
Blank	88	97.78	186098	88.43	108123	89.58	294309	88.85
Smoking								
Yes	-	-	4779	2.27	1183	0.98	5962	1.80
No	2	2.22	19854	9.43	11478	9.51	31334	9.46
Blank	88	97.78	185821	88.30	108040	89.51	293949	88.74
HIV test								
Positive	5	5.55	12455	5.92	5142	4.26	17602	5.31
Negative	7	7.78	63259	30.06	34169	28.31	97435	29.41
Ongoing	5	5.56	19940	9.47	10524	8.72	30469	9.20
Not performed	73	81.11	114729	54.52	70839	58.69	185641	56.05
Blank	-	-	71	0.03	27	0.02	98	0.03
Institutionalized								
No	10	11.11	83662	39.75	48987	40.59	132659	40.05
Prison	-	-	6607	3.14	1021	0.85	7628	2.30
Care home	-	-	155	0.07	63	0.05	218	0.07
Orphanage	-	-	285	0.14	149	0.12	434	0.13
Psychiatric Hospital	-	-	318	0.15	99	0.08	417	0.12
Others	-	-	3565	1.70	1990	1.65	5555	1.68
Blank	80	88.89	115862	55.05	68392	56.66	184334	55.65
PDL								
Yes	-	-	2657	1.26	166	0.14	2823	0.85
No	3	3.33	21214	10.08	11754	9.74	32971	9.95
Blank	87	96.67	186583	88.66	108781	90.12	295451	89.20
Homeless Pop.								
Yes	-	-	432	0.20	160	0.13	592	0.18
No	2	2.22	23023	10.94	11658	9.66	34683	10.47
Blank	88	97.78	186999	88.86	108883	90.21	295970	89.35
Health prof.								
Yes	-	-	178	0.08	257	0.21	435	0.13
No	2	2.22	23256	11.05	11558	9.58	34816	10.51
Blank	88	97.78	187020	88.87	108886	90.21	295994	89.36
Total	90	100	210454	100	120701	100	331245	100

Legend: AIDS: Acquired immunodeficiency syndrome; HIV: Human immunodeficiency virus; PDL: Population deprived of liberty; Homeless pop.: Homeless ppulation; Health prof.: Health professionals.

diagnosis of the disease[13,15]. In addition, men are more exposed to factors that may compromise immunity, such as illicit drugs, smoking, and chronic diseases, such as diabetes *mellitus* and HIV[12,13].

The involvement of the economically active population is another issue that deserves attention. Similar results were observed in Rio de Janeiro (44% of the cases)[16], Mato Grosso do Sul (49.9%)[17], and Rio Grande do Sul (near 50%)[18]. The start of treatment requires temporary removal from work, which may, to a greater or lesser degree, compromise the economic situation of households[19].

In addition, the treatment of TB impacts the economy of the country itself[20] since it requires specific human resources for the program, in addition to operational costs[21]. In 2018 alone, the total cost of TB in Brasil was US$ 57 million[2].

The predominance of the pulmonary presentation (86.37%) and bacillary cases (54.78%) is also in line with the literature[12,16-18].]It is estimated that a person with positive bacilloscopy infects from 10 to 15 people over the period of one year[21]. It is important to emphasize that the percentage of bacillary individuals may be even higher since 23.60% of the cases did not undergo this exam.

Associated with this, the rates of cure (70.66%) and abandonment (9.11%) represent additional challenges for TB control. Low percentages of cure and high rates of treatment abandonment have been observed throughout the country[16,18]. The complexity of this process is justified by the existence of multiple factors, among which those of personal nature stand out, such as the use of alcohol[13,19,22], illicit drugs[22], and smoking[23], as do those related to the availability and quality of services offered to the patients, as already discussed[24]. We must highlight that the minimum cure rate recommended must be greater than or equal to 85% and the maximum abandonment rate is 5%[4].

In addition to these factors, the TB/HIV coinfection also deserves mention. In this study, 12.10% of individuals tested were reactive for HIV, similar to what was observed in other states of the country[16,17]. Research carried out with the Brazilian population has shown that the cure is lower for patients with HIV (50.74% in HIV-positive patients and 71.10% in HIV-negative patients); in contrast, the abandonment rate is higher in this population (13.60% in coinfected patients and 9.52% in patients with TB only)[14]. It is noteworthy that 56.04% of the patients did not undergo HIV testing, which shows the magnitude of the challenge in combating the disease since the strategy recommends HIV testing in 100% of the TB cases diagnosed.

Even considering all the methodological care, the present study has limitations: (i) a large number of variables without information, particularly those representing risk factors and associated comorbidities; ii) use of secondary data from health information systems that may not express the reality; and (iii) the quality of the information, which has often been questioned, mainly due to the weaknesses faced by health monitoring services in smaller municipalities.

Finally, the study showed consistent evidence on the maintenance of the tuberculosis chain of transmission in the Northeast and the magnitude of the challenges to be faced. The epidemiological characterization and identification of risk factors and comorbidities represent an important step to the development of strategies that can help in the process of combating the disease.

Author's Contribution

All authors participated in the development of the concept, planning of the study, data collection and analysis, discussion of the results, scientific writing, as well as in the review and approval of the final version of the work.

RESUMO

OBJETIVO: *Descrever a tendência temporal, o perfil clínico e a prevalência de fatores de risco e comorbidades associadas em casos novos de tuberculose no Nordeste (2001-2016).*

MÉTODOS: *Estudo de prevalência envolvendo todos os casos de tuberculose registrados no Nordeste do Brasil, no período 2001-2016. Os dados foram obtidos do Sistema de Nacional de Agravos de Notificação. Para a análise estatística, empregaram-se o modelo de regressão por pontos de inflexão e a estatística descritiva.*

RESULTADOS: *Foram notificados 331.245 casos de tuberculose. A taxa de incidência geral reduziu de 44,84/100.000 habitantes (2001) para 30,92/100.000 habitantes (2016), com tendência decrescente (AAPC: –2,3; p<0,001). O perfil foi caracterizado por homens (73,53%), idade 20-59 anos (73,56%), tuberculose pulmonar (86,37%), baciloscopia positiva (54,78%). Os principais fatores de risco e comorbidade foram: Aids (4,64%), HIV (12,10%), Diabetes mellitus (5,46%), álcool (11,63%), institucionalizados (4,31%) e população privada de liberdade (2,30%). A taxa de cura foi 70,66% e a de abandono, 9,11%.*

CONCLUSÕES: *Mesmo com redução da incidência, a tuberculose representa um real problema de saúde pública na região Nordeste. O perfil caracterizado pela população masculina, idade economicamente ativa, forma pulmonar com baciloscopia positiva e os fatores e comorbidade Aids, coinfecção TB/HIV, diabetes mellitus, consumo de álcool, institucionalizados e privados de liberdade refletem a complexidade dos desafios para o enfrentamento à doença.*

PALAVRAS-CHAVE: *Tuberculose. Epidemiologia. Fatores de risco.*

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ORIGINAL ARTICLE

STOP-Bang and NoSAS questionnaires as a screening tool for OSA: which one is the best choice?

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SUMMARY

INTRODUCTION: *Currently there has been significant growth in the number of patients with suspected obstructive sleep apnea (OSA) referred to sleep clinics. In this sense, screening and stratification methods of the severity of this pathology have become increasingly relevant.*

OBJECTIVE: *To evaluate the performance of the NoSAS and STOP-Bang scores in the screening of OSA in a sleep clinic.*

METHODS: *Prospectively, for 12 months, all patients referred by primary care physicians to our sleep unit for clinical evaluation and who underwent in-lab polysomnography (PSG), also completed the NoSAS score (Neck circumference, Obesity, Snoring, Age, Sex) and STOP-Bang (Snoring, Tiredness, Observed apnea, Pressure (high blood), BMI, Age, Neck circumference, Gender). A ROC (receiver operating characteristic) analysis was used to find the scores that simultaneously maximize sensitivity and specificity for each diagnosis.*

RESULTS: *Of the 294 individuals included, 84% had OSA, of which 28.8% were mild, 34.8% moderate, and 36.4% were severe.*

USING THE NOSAS SCORE FOR PREDICTING OSA, MODERATE TO SEVERE OSA, AND SEVERE OSA, THE ROC AREA WAS: *0.770 (95% CI: 0.703-0.837), p<0.001, sensitivity of 57.5%, and specificity of 83.0% for a score of 12; 0.746 (95% CI: 0.691-0.802), p<0.001, sensitivity of 68.2% and specificity of 75.4% for a score of 13; 0.686 (95% CI: 0.622-0.749), p<0.001, sensitivity of 71.1% and specificity of 58.3% for a score of 13, respectively.*

USING THE STOP-BANG SCORE FOR PREDICTING OSA, MODERATE TO SEVERE OSA, AND SEVERE OSA, THE ROC AREA WAS: *0.862 (95% CI: 0.808-0.916), p<0.001, sensitivity of 68.4% and specificity of 85.1% for a score of 5; 0.813 (95% CI: 0.756-0.861), p<0.001, sensitivity of 77.3% and specificity of 66.1% for a score of 5; 0.787 (95% CI: 0.732-0.841), p<0.001, sensitivity of 70.0% and specificity of 79.9% for a score of 6, respectively.*

CONCLUSIONS: *The ROC area was consistently high for both scores confirming the diagnostic ability of the NoSAS and STOP-Bang questionnaires for all OSA severities. Thus, our results suggest that these questionnaires may be a powerful tool for the screening and stratification of patients in the diagnosis of OSA. Overall, the diagnostic ability of the STOP-Bang was higher than the NoSAS.*

KEYWORDS: *Sleep apnea, obstructive. Surveys and questionnaires. Health surveys.*

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INTRODUCTION

Obstructive sleep apnea syndrome (OSA) is characterized by obstruction of the upper respiratory tract leading to increased respiratory effort with inadequate ventilation. These episodes are essentially accompanied by desaturation, increased activity of the sympathetic nervous system with frequent arousals. It can lead to chronic intermittent hypoxia, hypercapnia, and sleep fragmentation. There is an independent association of OSA with increased morbidity and mortality due to metabolic disorders, neurovascular and cardiovascular disease, and impaired neurocognitive function[1-3]. Snoring and daytime sleepiness are the main complaints and observed apnea is the most specific symptom. The epidemiological statistics show that 23.4% of females and 49.7% of males are diagnosed with OSA[4].

Due to the growing number of patients suspected of having OSA being referred to sleep clinics, the screening methods have become increasingly important. The difficulty of diagnosis is related to the availability and accessibility of cardiorespiratory sleep studies. Consequently, a simple and reliable method for screening high-risk groups is needed.

The NoSAS Score test (Appendix A) is a simple and easily employed tool that assesses 5 parameters: Neck circumference, Obesity, Snoring, Age, and Sex and assigns 4 points for a neck circumference of more than 40 cm, 3 points for a body-mass index of 25 kg/m² to less than 30 kg/m², or 5 points for a body-mass index of 30 kg/m² or more, 2 points for snoring, 4 points for being older than 55 years, and 2 points for being male[5]. The score ranges from 0 to 17 and the patient has a high probability of OSA if they score 8 or higher in the NoSAS[5]. This allows the identification of individuals at risk for the disease and rules out others without risk, with a negative predictive value (NPV) of 90% and 98% in two different cohorts[5]. The NoSAS score has been validated in Portugal by standard validation instruments[6].

The STOP-Bang questionnaire (Appendix B), is a scoring protocol containing eight Yes or No questions (score: 1/0, ranging from a value of 0 to 8), making it a theoretically simple screening method[7]. A score of 3 or more revealed high sensitivity (83.6%) for detecting OSA in a surgical population, but also for identifying moderate and severe OSA (92.9% and 100%, respectively)[7]. The STOP-Bang questionnaire has been validated in Portugal by standard translation and validation instruments[8].

METHODS

Objective

The present study aimed to evaluate the performance of the NoSAS and STOP-Bang scores as screening tools for the diagnosis of OSA in a respiratory and sleep clinic.

Study design

A prospective study, 12 months in duration, beginning in January 2017. We consecutively enrolled all patients with a suspicious sleep disorder, referred by primary care physicians to our sleep unit for clinical evaluation, and who underwent in-lab polysomnography (PSG).

During the clinical consultation, every patient was asked if they accepted to participate in the study, regardless of the reasons for being referred, which included clinical suspicion of a specific sleep disorder or referral for isolated symptoms.

All patients included were required to complete the NoSAS and STOP-Bang questionnaires, with information concerning neck circumference, body mass index (BMI), snoring, age, gender, tiredness, observed apnea, and high blood pressure (blood pressure > 140/90 mmHg or treatment for hypertension).

There was no interference by the research staff in the interpretation or completion of the questionnaires.

Patients previously diagnosed with OSA, additional diagnoses obtained throughout the sleep study (like obesity/hypoventilation syndrome, and central sleep apnea), all cases of technical error during data collection, and patients unable to read and/or write were excluded from the study.

Sleep studies, scoring, and diagnosis

At the specialized sleep center, all patients were submitted to a standard PSG, using the patient's usual bedtime, overnight. A standardized setting made up of surface electrodes was used and included: electroencephalogram, electrooculogram, electrocardiogram, and submental and lower limb EMG. Besides this data, additional information was collected regarding thoracic and abdominal respiratory effort, snoring and body position sensors, pulse oximetry, and oronasal airflow (thermistor and pressure sensor). A certified PSG technician scored the PSG recordings under the supervision of a sleep physician who reviewed the final reports. The sleep physician and technician were both blinded to the study report (clinical information, NoSAS, and

STOP-Bang questionnaires). The scoring was made manually, following the recommendations of the American Academy of Sleep Medicine[9]. Apnea was defined as a decrease of at least 90% of airflow from baseline, lasting 10 seconds or longer. Hypopneas was defined as a decrease of at least 30% of airflow from baseline, lasting 10 seconds, associated with either arousal or a ≥3% O2 saturation decrease. The mean number of apneas and hypopneas per hours of sleep (apnea-hypopnea index [AHI]) was calculated. Both diagnosis and severity of OSA were classified based on the AHI: >5-15/h - mild, >15-30/h - moderate, and >30/h – severe[9,10].

Additional diagnoses obtained throughout the sleep study were defined according to the International Classification of Sleep Disorders - Third Edition[11]. However, our study was exclusively focused on OSA, so all other diagnoses were ignored or excluded.

Statistical Analysis

Statistical analysis was carried out using the IBM SPSS® statistical program, version 25 (the Statistical Package for the Social Sciences).

The categorical variables were described with frequencies and percentages and the quantitative variables with mean, median, standard deviation, maximum, and minimum. All associations between the presence of OSA and each of the possible risk factors were established using logistic regression, which estimated their odds ratios (ORs). The Wald test was considered significant when its p-value did not exceed 0.05.

To measure the diagnostic ability of the NoSAS and STOP-Bang scores for different AHI cut-offs, we determined the area under the receiver operating characteristic (ROC) curve and the value of the score where both sensitivity and specificity maximized.

RESULTS

Of the 294 patients, 70.7% were male, aged 53.5 ± 12.1 years, with a neck circumference of 41.0 ± 3.6 cm and a BMI of 30.8 ± 5.1 kg/m2. OSA was present in 84.0% of the patients, 28.8% with mild OSA, 34.8% moderate, and 36.4% severe. Descriptive summary statistics and comparison of OSA and non-OSA groups are displayed in Table 1.

Using the NoSAS score for predicting OSA, moderate to severe OSA, and severe OSA, the area under the ROC curve (AUC) was: 0.770 (95% CI: 0.703-0.837), p<0.001, sensitivity of 57.5% and specificity of 83.0% for a score of 12; 0.746 (95% CI: 0.691-0.802), p<0.001, sensitivity of 68.2% and specificity of 75.4% for a score of 13; 0.686 (95% CI: 0.622-0.749), p<0.001, sensitivity of 71.1% and specificity of 58.3% for a score of 13, respectively. Using the STOP-Bang score for predicting OSA, moderate to severe OSA, and severe OSA, the AUC was: 0.862 (95% CI: 0.808-0.916), p<0.001, sensitivity of 68.4% and specificity of 85.1% for a score of 5; 0.813 (95% CI: 0.756-0.861), p<0.001, sensitivity of 77.3% and specificity of 66.1% for a score of 5; 0.787 (95% CI: 0.732-0.841), p<0.001, sensitivity of 70.0% and specificity of 79.9% for a score of 6, respectively. Figure 1 illustrates these results.

The predicted probabilities of having OSA of a specific severity with the corresponding NoSAS score are illustrated in Figure 2. With each incremental increase in the score, from 0 to 7, the probability of having no sleep apnea diminished, while the probability of having mild, moderate, or severe sleep apnea increased continuously. With any score greater than 7, only the probability of having moderate or severe sleep apnea increased. With a score greater than 13, only the probability of having severe sleep apnea increased.

The predicted probabilities of having OSA of a specific severity with the corresponding STOP-Bang score are also illustrated in Figure 2. With each incremental increase in the score from 0 to 3, the probability of having no sleep apnea diminished, while the probability of having mild, moderate, or severe sleep apnea increased continuously. With any score greater than 4, only the probability of having moderate or severe sleep apnea increased. With a score greater than 5, only the probability of having severe sleep apnea increased.

DISCUSSION

Due to the high prevalence of undiagnosed OSA and its comorbidities, a quick and reliable screening tool is needed for a prompt prediction of OSA. Since they can be applied and scored easily, as part of routine daily practice, questionnaires can be appropriate tools for that purpose. Moreover, analysis of the questionnaire performance in specific populations can provide clinicians with a set of predictive parameters for different levels of OSA severity, which can

be used as a crucial guide for diagnostic and therapeutic decisions.

In our study, the present results show that both scores can add great value and be a very useful and powerful tool in primary care. Overall, the diagnostic ability of the STOP-Bang was higher than the NoSAS. This could be explained by the fact that the STOP-Bang (and not NoSAS) assesses important parameters, including excessive daytime sleepiness, observed apnea, and high blood pressure. Moreover, excessive daytime sleepiness evaluated by the Epworth's Score was more prevalent in the OSA group, reflecting that the Epworth Score must be used as a complement.

Numerous questionnaires and other clinical screening tools for OSA have been analyzed previously and some papers are worth being mentioned. A study by Tan et al.[12] evaluated STOP-Bang and compared its performance to the NoSAS score and Berlin questionnaires. They concluded that the performance of all three questionnaires were similar to the AUC values clustered around 0.682–0.748[12]. In regard to the validation of a Portuguese version of the STOP-Bang in primary care, by Rebelo-Marques et al.[8], when using this model for the prediction of OSA, the diagnostic ability of the STOP-Bang was superior to the NoSAS score (the AUC was 0.847). According to Lye et al.[13], the AUC of the NoSAS score (0.724) was higher than that of the Epworth Sleepiness Scale (ESS) (0.544). They concluded that overall the NoSAS score performed better than the ESS[13]. A systematic review of screening questionnaires for OSA by Abrishami et al.[14] concluded that the evidence regarding the accuracy of OSA questionnaires is associated with promising but inconsistent results. This inconsistency could be due to studies with heterogeneous designs (population, questionnaire type, and validity). Nevertheless, the STOP-Bang questionnaire is suggested due to its higher methodological quality, accurate results, and easy to use features[14].

Furthermore, our study has limitations that must be mentioned. The fact that our sample consisted mainly of obese men with an average age of over 50 years may have conditioned our results.

CONCLUSIONS

The ROC area was consistently high for both scores, confirming the diagnostic ability of the NoSAS and STOP-Bang questionnaires for all OSA severities. Thus, our results suggest that these questionnaires may be a powerful tool for the screening and stratification of patients in the diagnosis of OSA and can help primary care clinicians decide which patients to further investigate with a nocturnal recording. The Epworth Score must be used as a complement. Overall, the diagnostic ability of the STOP-Bang was higher than the NoSAS. Nevertheless, more studies are needed to evaluate the efficacy of these scores in younger populations, with a predominance of female and non-obese individuals, in cardiovascular disease or minimally symptomatic patients.

APPENDIX A

NoSAS score
1: Neck circumference >40 cm - 4 points
2: Obesity
- BMI 25 kg/m² to <30 kg/m² - 3 points
- BMI ≥30 kg/m² - 5 points
3: Snoring - 2 points
4: Age >55 years – 4 points
5: Sex: male – 2 points

APPENDIX B

STOP-Bang questionnaire
1: Do you SNORE loudly (louder than talking or loud enough to be heard through closed doors)?
2: Do you often feel TIRED, fatigued, or sleepy during daytime?
3: Has anyone OBSERVED you stop breathing during your sleep?
4: Do you have or are you being treated for high blood PRESSURE?
5: BMI more than 35kg/m2?
6: AGE over 50 years old?
7: NECK circumference > 16 inches (40cm)?
8: GENDER: Male?

ANNEXES

FIGURE 1. AREA UNDER THE ROC CURVE (AUC) FOR ALL OSA (AHI: >5/H), MODERATE TO SEVERE OSA (AHI: >15/H) AND SEVERE OSA (AHI: >30/H)

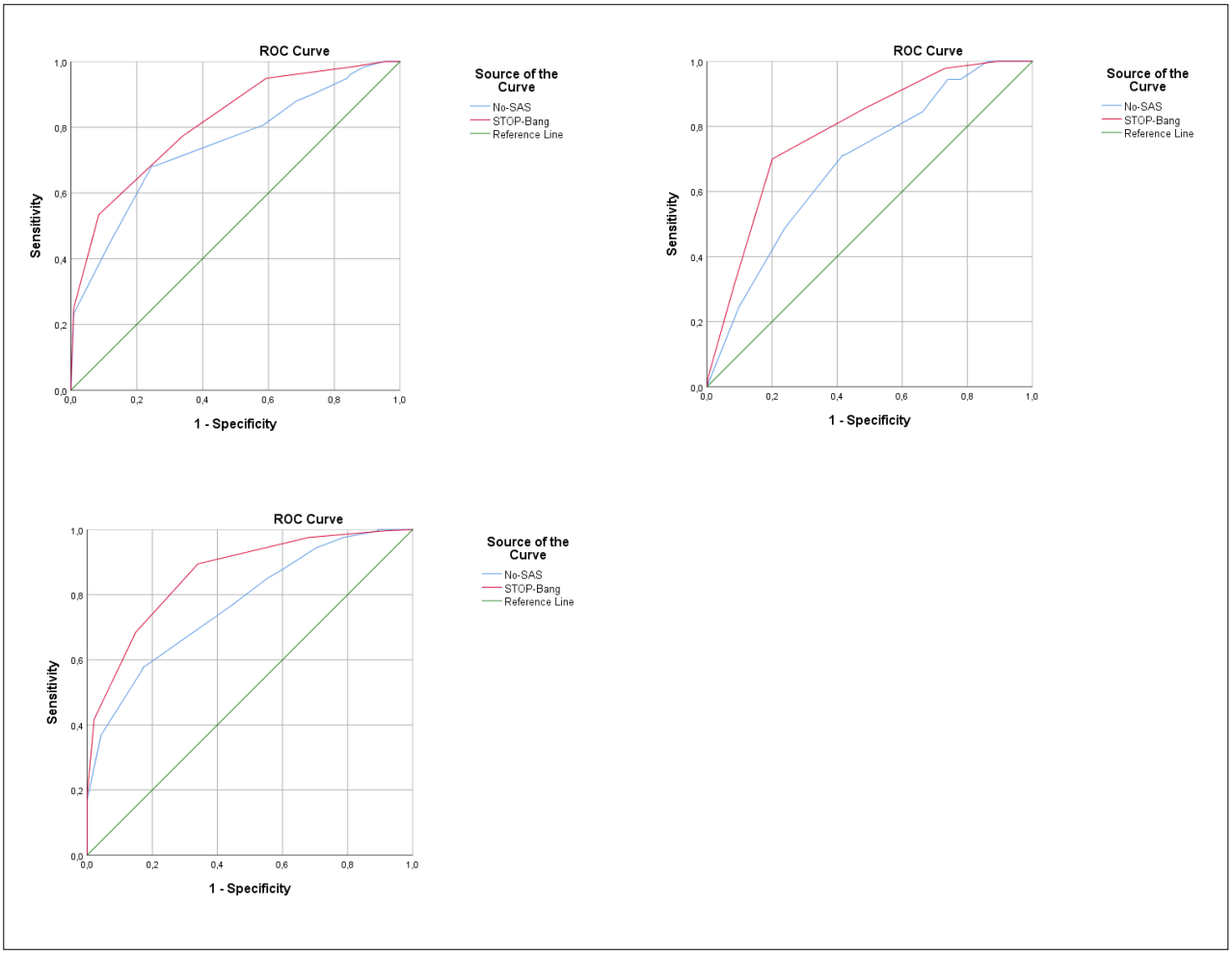

FIGURE 2. PLOT OF PREDICTED PROBABILITIES FOR DIFFERENT OSA SEVERITIES WITH THE CORRESPONDING NOSAS AND STOP-BANG SCORES.

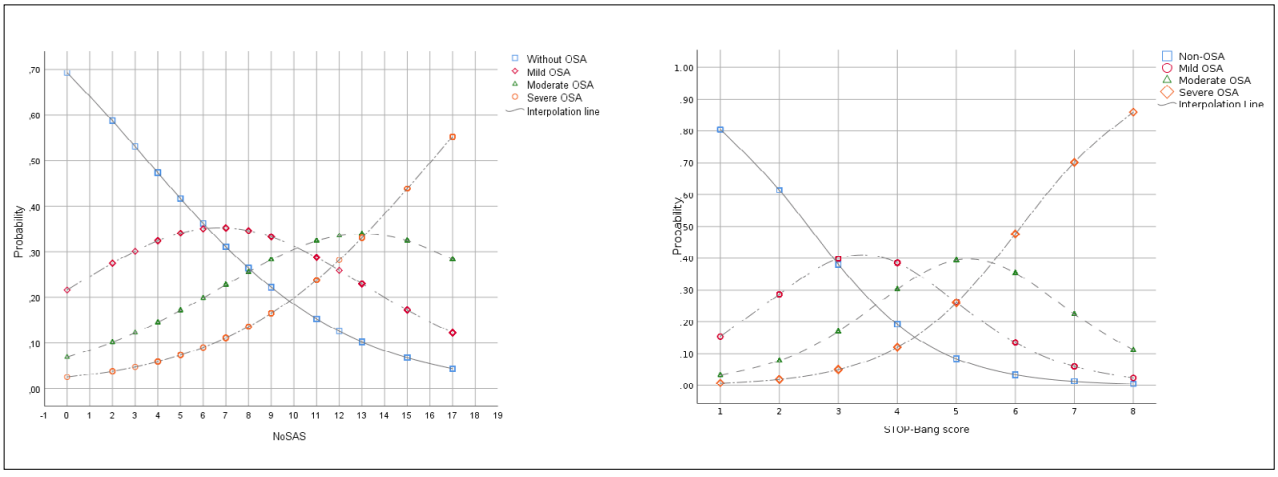

TABLE 1. SUMMARY STATISTICS OF THE PATIENT POPULATION AND COMPARISON OF THE OSA AND NON-OSA GROUPS.

Variable	OSA		OR - Yes/No (CI 95%); Logistic Regression	P [a]
	Yes N=247 (84.0%)	No N=47 (16.0%)		
Age (years) Average ± SD Median(mín; máx)	 55.81±11.43 56 (20; 82)	 47.49±13.06 47 (23; 77)	1.062 (1.032; 1.093)	<0.001
Tiredness (n) (%) Yes No	 150 (60.7) 97 (39.3)	 22 (46.8) 25 (53.2)	 1.757 (0.938; 3.291) 1	 0.078 (NS)
Observed apnea (n) (%) Yes No	 179 (72.5) 68 (27.5)	 16 (34.0) 31 (66.0)	 5.100 (2.623; 9.915) 1	 <0.001
Pessure (high blood) Yes No	 150 (60.7) 97 (39.3)	 14 (29.8) 33 (70.2)	 3.645 (1.855; 7.161) 1	 <0.001
Epworth's Score Average ± SD Median(min; max)	 10.97±5.35 11 (1; 24)	 9.15±5.19 8 (2; 20)	1.067 (1.004; 1.135)	0.036
Minimum saturation Average ± SD Median (min; max)	 78.41±10.63 81.0 (0.0; 92.0)	 88.30±4.34 90.0 (74.0; 95.7)	0.731 (0.657; 0.814)	<0.001
Neck circ. > 40 cm (n) (%) Yes No	 150 (60.7) 97 (39.3)	 9 (19.1) 38 (80.9)	 6.529 (3.023; 14.104) 1	 <0.001
Obesity (n) (%) BMI<25 BMI 25-30 BMI ≥ 30	 14 (5.7) 102 (41.3) 131 (53.0)	 13 (27.7) 21 (44.6) 13 (27.7)	 1 4.510 (1.854; 10.973) 9.357 (3.634; 24.096)	<0.001 0.001 <0.001
Snoring (n) (%) Yes No	 241 (97.6) 6 (2.4)	 42 (89.4) 5 (10.6)	 4.782 (1.396; 16.380) 1	 0.013
Gender (n) (%) Female Male	 63 (25.5) 184 (74.5)	 23 (48.9) 24 (51.1)	 1 2.799 (1.477; 5.305)	 0.002

[a] Teste de Wald; Abbreviations: OR = odds ratio; CI = Confidence Interval; BMI: body mass index; OSA: obstructive sleep apnea; NS: not significant.

RESUMO

INTRODUÇÃO: *Na atualidade tem se verificado um crescimento significativo no número de doentes com suspeita de apneia obstrutiva do sono (AOS) referenciados para consulta do sono. Nesse sentido, instrumentos de rastreio e estratificação da gravidade dessa patologia têm se tornado cada vez mais relevantes.*

OBJETIVO: *Avaliar e comparar o desempenho da escala NoSAS e Stop-Bang para o rastreio de AOS.*

MÉTODOS: *Estudo prospectivo durante 12 meses. Avaliados todos os doentes encaminhados aos cuidados de saúde primários do centro de medicina do sono que completaram o questionário NoSAS (Neck circumference, Obesity, Snoring, Age, Sex), Stop-Bang (Snoring, Tiredness, Observed apnea, Pressure [high blood], BMI, Age, Neck circumference, Gender) e foram submetidos a polissonografia. Utilizou-se uma análise ROC (receiver operating characteristic) para encontrar as pontuações que maximizam simultaneamente a sensibilidade e especificidade para cada diagnóstico.*

RESULTADOS: *Incluídos 294 indivíduos, 84% apresentavam AOS, sendo que em 28,8% a OAS era ligeira, 34,8% moderada e 36,4% grave.*

USANDO A ESCALA NOSAS PARA PREVISÃO DE AOS, AOS MODERADA A GRAVE E AOS GRAVE, A ÁREA ROC FOI: *0,770 (IC95%: 0,703-0,837), p<0,001, sensibilidade de 57,5% e especificidade de 83,0% para a pontuação 12); 0,746 (IC95%: 0,691- 0,802), p<0,001, sensibilidade de 68,2% e especificidade de 75,4% para a pontuação 13); 0,686 (IC95%: 0,622-0,749), p<0,001, sensibilidade de 71,1% e especificidade de 58,3% para a pontuação 13), respectivamente.*

USANDO A ESCALA STOP-BANG PARA A PREVISÃO DE AOS, AOS MODERADA A GRAVE E AOS GRAVE, A ÁREA ROC FOI: *0,862 (IC95%: 0,808-0,916), p<0,001, sensibilidade de 68,4% e especificidade de 85,1% para pontuação 5); 0,813 (IC95%: 0,756-0,861), p<0,001, sensibilidade de 77,3% e especificidade de 66,1% para a pontuação 5); 0,787 (IC95%: 0,732-0,841), p<0,001, sensibilidade de 70,0% e especificidade de 79,9% para a pontuação 6), respectivamente.*

CONCLUSÕES: *A área ROC foi consistentemente alta para as duas escalas, confirmando a capacidade diagnóstica dos questionários NoSAS e Stop-Bang para todos os graus de gravidade de AOS. Assim, os nossos resultados sugerem que esses questionários podem ser um importante instrumento para rastreio e estratificação de doentes no diagnóstico de AOS. Globalmente, a capacidade de diagnóstico do Stop-Bang foi superior à do NoSAS.*

PALAVRAS-CHAVE: *Apneia obstrutiva do sono. Inquéritos e questionários. Inquéritos epidemiológicos.*

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ORIGINAL ARTICLE

Value of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of lung and mediastinal lesions

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SUMMARY

OBJECTIVE: *To evaluate the value of EBUS-TBNA in the diagnosis of lung and mediastinal lesions.*

METHODS: *Prospective cohort study that included 52 patients during a 2-year period (2016 to 2018) who underwent EBUS-TBNA.*

RESULTS: *Among the 52 individuals submitted to the procedure, 22 (42.31%) patients were diagnosed with locally advanced lung cancer (N2 or N3 lymph node involvement). EBUS-TBNA confirmed the diagnosis of metastases from other extrathoracic tumors in the mediastinum or lung in 5 patients (9.61%), confirmed small cell lung cancer in 3 patients (5.76%), mediastinal sarcoidosis in 1 patient (1.92%), and reactive mediastinal lymph node in 8 patients (15.38%); insufficient results were found for 3 patients (5.76%). Based on these results, EBUS-TBNA avoided further subsequent surgical procedures in 39 of 52 patients (75%). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 86%, 100%, 100%, 77%, and 90%, respectively. No major complications were observed.*

CONCLUSIONS: *EBUS-TBNA is a safe, effective, and valuable method. This technique can significantly reduce the rate of subsequent surgical procedures required for the diagnosis of lung and mediastinal lesions.*

KEYWORDS: *Lung neoplasms. Lymph nodes. Biopsy, needle/methods. Mediastinal diseases/diagnosis. Endoscopic ultrasound-guided fine-needle aspiration. Image-guided biopsy.*

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INTRODUCTION

Various thoracic diseases, benign or malignant, include lung and mediastinal lesions, with varied etiologies and different evolutions. Given this wide variety of diseases, it is critical to make a definitive histopathological diagnosis so that patients can be offered the most appropriate and effective treatment. Different diagnostic modalities are available, including bronchoscopy with transbronchial biopsy, computed tomography-guided fine-needle aspiration, mediastinoscopy, thoracoscopy, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and, more recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Each of these procedures has specific indications, risks and benefits, and different statistical results, availability, and costs.

EBUS-TBNA is considered a minimally invasive procedure, performed under sedation on an outpatient basis. The method allows real-time evaluation of lung and mediastinal lesions, located adjacent to the main airways. In addition to lung cancers, EBUS-TBNA plays an important role in the diagnosis of benign and malignant mediastinal lymph nodes, with excellent results and low complication rates[1]. The method also allows diagnosing pulmonary and mediastinal inflammatory and infectious diseases, including sarcoidosis[2,3] and tuberculosis[4,5]. In addition, EBUS-TBNA can be useful for diagnosing malignant mediastinal lesions such as lymphomas[6] and mediastinal metastases of extrathoracic tumors[7].

The aim of this study is to evaluate the value of EBUS-TBNA in the diagnosis of lung and mediastinal lesions.

METHODS

This is a clinical and prospective observational study that included 52 patients who underwent EBUS-TBNA, over a period of 2 years (December 2016 – December 2018). All patients agreed to participate in the study and signed an informed consent form. The study was approved by the Ethics Committee on Human Research of Santa Casa de São Paulo under number 1,756,905.

Inclusion criteria

Patients who had pulmonary or mediastinal lesions, previously identified by chest CT, larger than 5 mm in size, and considered potentially accessible by EBUS-TBNA.

Inclusion criteria

Patients who had normal anatomical findings or vascular interposition that did not indicate nor allowed needle aspiration.

Procedures

EBUS-TBNA was performed on an outpatient basis under conscious or deep sedation and local anesthesia using a flexible convex ultrasound bronchoscope (Pentax® EB-1970K and Fujinon® EB-530US). Transbronchial aspirations were performed through a 22-gauge needle (Cook Medical® EchoTip® Ultra Endobronchial HD Ultrasound Needle and *Medi-Globe® SonoTip® EBUS Pro Needle*). All procedures were done by the same physician with previous expertise for this method. According to the IASLC - *International Association for the Study of Lung Cancer*[8] - a systematic evaluation of mediastinal stations was done, starting by placing the ultrasound probe on the left main bronchus and moving to the trachea, to study the following nodes: left pulmonary hilar (10 and 11L), left lower paratracheal (4L), subaortic (5), and upper left paratracheal (2L). The right main bronchus was studied in a similar manner, moving to the trachea to examine the following nodes: right pulmonary hilar (10 and 11 R), lower right paratracheal (4R), and upper right paratracheal (2R). The subcarinal node (7) was evaluated through the main carina, on both sides. Last, an ultrasound study of the lung lesion was performed, placing the device as close as possible to it, according to the anatomical location.

All lesions found were characterized according to their location, size, echogenicity, and shape. Based on the ultrasound characteristics, potentially malignant lesions[9] - round shape, a short axis greater than 8.3 mm, and sharp margins - were selected for ultrasound-guided fine-needle aspiration. The needle was passed into different parts of the lesion, and the negative-pressure suction technique was used with a 20 mL syringe in all cases. In this study, a rapid onsite cytologic evaluation was not performed, but a minimum of 3 punctures per lesion was set. All material was collected into a flask containing 10% formalin and sent for pathologic analysis using the cellblock technique. All pathological analyses were done by the same physician with previous expertise for this method.

Clinical follow-up

All patients were followed-up for at least 12 months after the procedure. Data on clinical progression,

complications, subsequent procedures and treatments performed were documented for analysis in this study. The following major complications were considered: excessive bleeding that was not self-limiting and that had evident clinical consequences and lung, pneumothorax, or pneumomediastinum infections. Adverse effects or allergic reactions to the medication used for sedation were considered anesthetic complications. Endoscopic findings such as immediate bleeding at the aspiration site, in small quantities, without hemodynamic repercussions and self-limiting, post-procedural coughing, and mild chest pain were considered inherent to the procedure and not classified as complications.

Patients with suspected lung cancer presenting negative results for malignancy by EBUS-TBNA were considered negative only after subsequent surgical confirmation (mediastinoscopy, thoracoscopy, or thoracotomy). Patients with suspected isolated mediastinal lymphadenopathy and suspected of having a benign reactional or inflammatory disease, with negative results by EBUS-TBNA, were considered negative in the absence of clinical or radiological worsening of the lesions in a clinical follow-up of at least 12 months after the procedure. The pathologist's interpretation of malignancy in the material obtained by EBUS-TBNA was considered sufficient and definitive for starting specific treatment.

Statistical analysis

The quantitative data were descriptively analyzed using summary measures, including the mean, median, minimum, maximum, and standard deviation (± SD). Categorical variables are expressed as frequencies and percentages. A contingency table was used to calculate the following values: sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, with their respective 95% confidence intervals. The sample size (n) was calculated and estimated as 47 patients for a 95% confidence interval, considering a total error margin of 20% and an estimated proportion of 0.8571. Statistical analyses were performed using Microsoft Excel® version 16.16.1.

RESULTS

A total of 55 patients were selected for the study. Of these, 3 patients were excluded from the sample for not undergoing aspiration: 1 patient for presenting vascular interposition in the needle's path, prohibiting safe access to the lesion; 1 patient due to normal extrinsic vascular compression findings (pulmonary artery ectasia); and 1 patient due to unsatisfactory clinical conditions (arrhythmia) for sedation, where the procedure was suspended by the anesthesia team.

The data for 52 remaining patients were thus included and analyzed in this study: mean age 61.5 ± 11.7 (26-84), 29 females and 23 males. For the procedure indication, we found: 16 (30.7%) patients with an isolated mediastinal lesion, and 36 patients (69.2%) with suspected lung cancer. Among the 52 patients, a total of 221 lesions were found and characterized as shown in Table 1. The results of the patients' histopathological diagnoses by EBUS-TBNA are shown in Table 2.

TABLE 1. CHARACTERIZATION OF THE LESIONS

Total lesions found	n= 221
Mean lesions per patient ± SD (variation)	4.25 ± 2 (1-8)
Number of lesions selected for aspiration, n (%)	64 (29%)
Number of aspirations performed per lesion, n (%)	4.58 ± 1.4 (3-7)
Lesion location	
subcarinal (level 7), n (%)	38 (17.2%)
lower right paratracheal (level 4R), n (%)	34 (15.4%)
lower left paratracheal (level 4L), n (%)	26 (11.8%)
right hilar (level 10R), n (%)	23 (10.4%)
pulmonary parenchyma, n (%)	18 (8.1%)
right interlobar (level 11R), n (%)	17 (7.7%)
left hilar (level 10L), n (%)	17 (7.7%)
upper right paratracheal (level 2R), n (%)	16 (7.2%)
upper left paratracheal (level 2L), n (%)	12 (5.4%)
left interlobar (level 11L), n (%)	12 (5.4%)
subaortic (level 5), n (%)	4 (1.8%)
mediastinum (extensive involvement)	4 (1.8%)
Lesion measurements	
mean horizontal axis ± SD (variation)	17.2 ± 13 (5-80) mm
mean vertical axis ± SD (variation)	11.5 ± 9.8 (5-70) mm

SD = standard deviation

TABLE 2. HISTOLOGICAL DIAGNOSES BY EBUS-TBNA

Negative for malignant neoplasia, n (%)	18 (34.6%)
Pulmonary adenocarcinoma, n (%)	17 (32.7%)
Pulmonary squamous cell carcinoma, n (%)	4 (7.7%)
Insufficient material, n (%)	3 (5.8%)
Pulmonary small cell carcinoma, n (%)	3 (5.8%)
Neuroendocrine carcinoma of the lung, n (%)	1 (1.9%)
Mediastinal metastasis of oropharyngeal carcinoma, n (%)	1 (1.9%)
Mediastinal metastasis of ovarian adenocarcinoma, n (%)	1 (1.9%)
Mediastinal metastasis of thyroid carcinoma, n (%)	1 (1.9%)
Mediastinal metastasis of breast carcinoma, n (%)	1 (1.9%)
Pulmonary metastasis of pleomorphic sarcoma, n (%)	1 (1.9%)
Mediastinal sarcoidosis, n (%)	1 (1.9%)

Of the 52 subjects who underwent the procedure, 22 (42.31%) were diagnosed with locally advanced lung cancer in the mediastinum, of which 18 had a diagnosis of N2 lymph node involvement (13 pulmonary adenocarcinomas, 4 squamous cell (epidermoid) carcinomas, 1 neuroendocrine carcinoma) and 4 had a diagnosis of N3 lymph node involvement (4 pulmonary adenocarcinomas).

EBUS-TBNA confirmed the diagnosis of metastasis of other extrathoracic tumors in the mediastinum or lung in 5 patients (9.61%), including 1 patient with metastatic oropharyngeal carcinoma in the upper right paratracheal mediastinal node (level 2R); 1 patient with metastatic breast carcinoma in the left hilar mediastinal node (level 10L); 1 patient with metastatic thyroid carcinoma in the right hilar mediastinal node (level 10R); 1 patient with metastatic ovarian carcinoma in the subcarinal mediastinal node (level 7); and 1 patient with metastatic pleomorphic sarcoma in the lung parenchyma.

Furthermore, EBUS-TBNA confirmed the diagnosis of 3 patients (5.76%) with small cell carcinoma of the lung parenchyma and 1 (1.92%) patient with mediastinal sarcoidosis.

The examination diagnosed 18 patients (34.61%) as negative for malignancy, as follows: 8 patients with initial suspicion of lung cancer – all confirmed negative by subsequent surgery; 2 patients with initial suspicion of lung cancer – diagnosed as squamous cell carcinoma by subsequent surgery; and 8 patients with initial suspicion of reactive/inflammatory isolated mediastinal lymph node enlargement without evidence of other pulmonary lesions – all followed-up for a minimum of 12 months without evidence of lesion progression by imaging methods and without clinical worsening.

The aspiration was insufficient in 3 patients (5.76%), and all were referred for subsequent surgery, in which a diagnosis of lymphoma was established in 2 patients and of pulmonary adenocarcinoma in 1 patient.

The following statistical values were calculated: sensitivity 86% (74-97% CI), specificity 100%, positive predictive value 100%, negative predictive value 77% (60-95% CI) and accuracy 90% (82-98% CI). There were no major complications caused by the method used in this study.

DISCUSSION

In this study, data sets of 52 patients were analyzed to determine the overall efficacy of the method when applied to patients with lung and mediastinal lesions, regardless of the initial suspicion of malignant or benign disease. These results are consistent with those reported in other studies[1,10], with high values for sensitivity - 86% (CI 74-97%), specificity - 100%, positive predictive value - 100%, negative predictive value - 77% (60-95% CI), and accuracy - 90% (82-98% CI). There was also an agreement with these studies concerning the procedure's safety, as no major complications were observed.

Likewise, the literature shows excellent results for EBUS-TBNA when used for patients with suspected lung cancer and mediastinal metastasis. In a meta-analysis[11] that included 1066 patients, the authors demonstrated that EBUS-TBNA can be considered a potential technique for the diagnosis and staging of patients with suspected lung cancer, with a sensitivity of 90%, specificity of 99%, positive predictive value of 99%, negative predictive value of 93%, and accuracy of 96%. In another two meta-analyses[12,13], the authors confirmed the excellent diagnostic performance of the method for mediastinal staging in patients with lung cancer, with a sensitivity of 88-93% and specificity of 100%. Only 2 complications were reported (0.15%).

In Brasil and in many developing countries, there is a high prevalence of infectious and inflammatory lung diseases, in particular tuberculosis and sarcoidosis. Furthermore, many individuals are exposed to environmental and occupational pollution and various physical and chemical agents without proper personal protective care, further increasing the possibility of lung or mediastinal lesions. In our study, 8 of 52 patients (16%) were diagnosed with benign diseases, and, in one individual, histological confirmation of sarcoidosis was possible. Studies show that EBUS-TBNA is efficient and safe for the investigation of patients with suspected mediastinal sarcoidosis and tuberculosis and that it has a diagnostic yield of over 80%[2-5]. Despite the high prevalence of tuberculosis in Brasil, in this study, we did not observe any patient diagnosed with this pathology by EBUS-TBNA. This may be explained by the fact that the patients were previously selected for the procedure and had no clinical, laboratory, or radiological signs of tuberculosis.

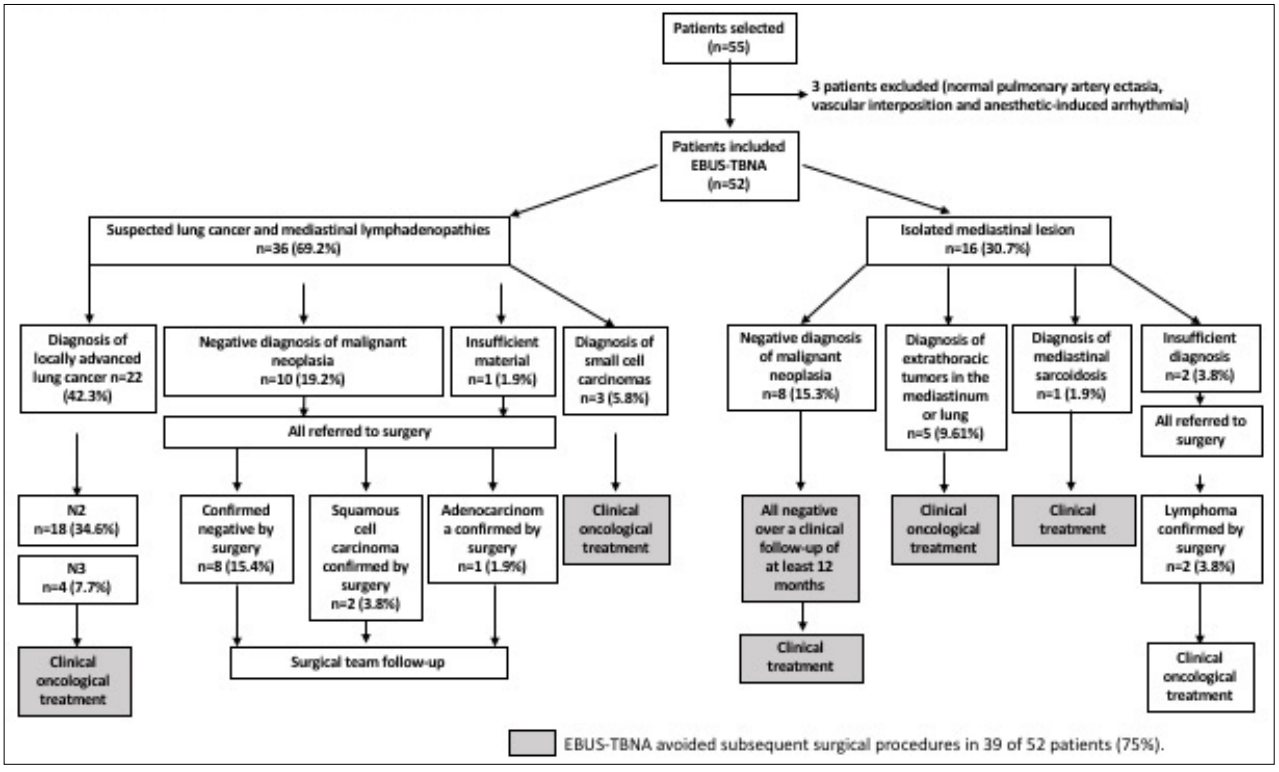
The diagnosis of lymphoproliferative disorders located in the mediastinum, including lymphoma, may be considered difficult to perform because it is necessary to collect biopsy macrofragments for adequate histopathological interpretation. In many

cases, this diagnosis is only possible through surgical procedures and fine-needle aspiration, such as in EBUS-TBNA, is only capable of acquiring filamentary material. In this study, obtaining fragments by EBUS-TBNA for adequate histopathological interpretation was challenging, and 3 patients with material deemed insufficient were referred for surgery and diagnosed with mediastinal lymphoma. In a systematic review[14] comprising patients with suspected mediastinal lymphoma, a large discrepancy was observed in the statistical results, with sensitivity ranging from 38-91%. Moreover, subsequent invasive surgical procedures were necessary for 13-47% of patients. Based on our findings and those in the literature, we can infer a limitation of the method for diagnosing lymphomas, and additional surgical procedures may be often required to obtain a conclusive diagnosis by collecting macrobiopsy fragments or even by removing the whole lesion.

For many years, mediastinoscopy has been considered the gold standard for the mediastinal staging of lung cancer. However, it is a more invasive procedure with higher mortality than EBUS-TBNA. Studies show a similar yield for EBUS-TBNA and mediastinoscopy for the mediastinal staging of lung cancer (sensitivity of 84% versus 86%, respectively) but with higher complication rates and lower false negative values for mediastinoscopy compared to EBUS-TBNA[15]. Current recommendations indicate that EBUS-TBNA should be performed as the first procedure in suspected malignant mediastinal lesions, followed by mediastinoscopy in the case of negative results[16]. In our study, 5 patients had false-negative biopsy results by EBUS-TBNA – all of whom were referred for subsequent surgery – and were confirmed as having a malignancy. Based on these results, we obtained a negative predictive value of 77% – below the other statistical results but within the range observed in other studies (67%-97%)[15]. Unlike these studies, which included only patients with suspected lung cancer, our study evaluated all individuals in a single group, including patients with suspected mediastinal lymphoma, in which EBUS-TBNA has limitations, which may explain this result.

Different studies have shown the important role of EBUS-TBNA in reducing the rate of subsequent surgical procedures necessary for diagnosing pulmonary and mediastinal lesions. In a prospective study[17] that included 105 patients who underwent EBUS-TBNA for lung cancer staging, it was found that the method avoided the need to perform 50 subsequent invasive procedures (29 mediastinoscopies, 8 thoracotomies, 4 thoracoscopies, and 9 CT-guided chest aspirations), concluding that EBUS-TBNA can have a large impact

FIGURE 1. CLINICAL COURSE OF PATIENTS SUBMITTED TO EBUS-TBNA.



on patient management. In another study with 215 patients[18], the authors demonstrated that when applied to benign and malignant thoracic injuries, EBUS-TBNA was able to avoid performing 104 subsequent invasive surgical procedures and 32 hospitalizations. In another prospective and randomized study[19], the authors evaluated the clinical efficiency and cost-effectiveness of endoscopic ultrasound compared to standard surgical staging alone in patients with lung cancer who were potential candidates for curative surgery. The authors observed a higher rate of unnecessary thoracotomies when the staging was performed by conventional surgical methods compared to endoscopic ultrasound (18% vs. 7%, respectively). Furthermore, the study concluded that the ultrasound staging method is more tolerable and more cost-effective than surgical staging alone.

In our study, EBUS-TBNA avoided other subsequent surgical procedures in 39 of 52 patients (75%). A total of 30 patients were sent directly for specific cancer treatment, with 22 diagnosed with locally advanced disease (N2 or N3 lymph node involvement), 5 diagnosed with metastases from other extrathoracic tumors, and 3 diagnosed with small cell carcinoma. In addition, 9 patients were referred for non-oncological clinical treatment, with 1 patient diagnosed with mediastinal sarcoidosis, and 8 diagnosed with reactionary/inflammatory mediastinal lymphadenopathies (Figure 1).

CONCLUSION

EBUS-TBNA is a safe, effective, and valuable method. This technique can significantly reduce the rate of subsequent surgical procedures required for the diagnosis of lung and mediastinal lesions.

Author's Contribution

Concept and study design: AC, RS. Data acquisition: AC, LC, FM, MC. Data analysis/interpretation: MS, FB. Statistical analysis: AC. Supervision or mentorship: LC, FM, MB, VD, RS. Manuscript writing: AC. All authors participated in the approval of the final version of the manuscript.

Competing interests

None for all authors.

RESUMO

OBJETIVO: *Avaliar a importância da ecoendoscopia endobrônquica com punção por agulha fina (Ebus-TBNA) no diagnóstico das lesões pulmonares e mediastinais.*

MÉTODOS: *Estudo prospectivo e do tipo coorte, no qual foram incluídos 52 pacientes, durante o período de dois anos (2016 a 2018), submetidos ao procedimento de Ebus-TBNA.*

RESULTADOS: *Do total de 52 indivíduos submetidos ao procedimento, 22 (42,31%) pacientes foram diagnosticados com neoplasia pulmonar localmente avançada (N2 ou N3). O método confirmou o diagnóstico de metástases de outros tumores extratorácicos no mediastino ou pulmão em cinco pacientes (9,61%), três pacientes (5,76%) com carcinoma de pequenas células, um paciente (1,92%) com sarcoidose, oito pacientes (15,38%) com linfonodomegalias reacionais/inflamatórias e resultado insuficiente em três pacientes (5,76%). O Ebus-TBNA evitou a realização de outros procedimentos cirúrgicos subsequentes em 39 de 52 (75%) pacientes. Foram calculados os valores de sensibilidade de 86%, especificidade de 100%, valor preditivo positivo de 100%, valor preditivo negativo de 77% e acurácia de 90%. Não foram observadas complicações maiores pelo método neste estudo.*

CONCLUSÃO: *O Ebus-TBNA é um método seguro, eficaz e de relevante importância. Este exame pode reduzir significativamente o número de procedimentos invasivos subsequentes necessários para o diagnóstico das lesões pulmonares e mediastinais.*

PALAVRAS-CHAVE: *Neoplasias pulmonares. Linfonodos. Biópsia por agulha/métodos. Doenças do mediastino/diagnóstico. Aspiração por agulha fina guiada por ultrassom endoscópica. Biópsia guiada por imagem.*

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ORIGINAL ARTICLE

Children First Study II: an educational programme on cardiovascular prevention in public schools can reduce parents' cardiovascular risk

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SUMMARY

OBJECTIVE: *The aim of this study was to analyze whether the implementation of a multidisciplinary educational programme for cardiovascular prevention in public schools can contribute to reducing the Fram*

INGHAM CARDIOVASCULAR RISK SCORE OF THE CHILDREN'S PARENTS AFTER ONE YEAR.

METHODS: *This was a prospective, community-based, case-control study carried out in public schools in Sao Paulo, Brasil. Students were randomized to receive healthy lifestyle recommendations by two different approaches. The control group received written cardiovascular health educational brochures for their parents. The intervention group received the same brochures for the parents, and the children were exposed to a weekly educational programme on cardiovascular prevention with a multidisciplinary health team for one year. Clinical and laboratorial data were collected at the onset and end of the study.*

RESULTS: *We studied 265 children and their 418 parents. At the baseline, the rate of parents with intermediate or high Framingham scores (risk of cardiovascular disease over the next 10 years greater than 10%) was 6.9% in the control group and 13.3% in the intervention group. After one year, the rate of parents with intermediate or high Framingham risk score was reduced by 22.2% in the intervention group and increased by 33.3% in the control group (p=0.031). The cardiovascular risk factors that improved in the intervention group were blood pressure, LDL-cholesterol (low-density lipoprotein cholesterol), and glucose levels.*

CONCLUSION: *An educational programme on cardiovascular prevention for school-age children in public schools can reduce the cardiovascular risk of their parents.*

KEYWORDS: *Cardiovascular diseases/prevention & control. Child. Parents. Education. Schools.*

BACKGROUND

Worldwide, the prevalence of cardiovascular disease has decreased in high-income countries, while there has been a significant increase in middle- and low-income countries[1]. Morbidity and mortality related to cardiovascular diseases have important socioeconomic impacts, suggesting the need to intensify preventive measures,

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which have a greater impact than curative measures, especially in low-income countries[1-4].

The prevention of cardiovascular diseases, whose key aspect is the control of atherosclerosis, depends on the adoption of healthy habits and the control of preventable cardiovascular risk factors such as sedentarism, obesity, dyslipidemia, hypertension, diabetes, and smoking. Governmental organizations promote health with an emphasis on education in schools[2], and this strategy has been supported by several recent studies that demonstrated a correlation between the cardiovascular risk factors of the children and their parents, such as the PEP Family Heart Study[5].

In a previous study, we demonstrated that health promotion policies in private schools can surpass what is assimilated by the children and reach their parents, changing the whole family culture and influencing parents' lifestyle habits and, ultimately, their cardiovascular risk[6]. Similar studies in England[7] and Germany[5] have also shown positive results. However, there is a shortage of studies that evaluate cardiovascular prevention with educational programmes in public schools with low-income families. In addition, low-income and developing countries such as Brasil are facing now a profound health challenge with the current scenario of cardiovascular morbidity and mortality that demands urgent preventive measures[3,8].

Therefore, the objective of this study was to evaluate whether the implementation of a multidisciplinary programme on cardiovascular health in public schools, aimed at presenting concepts of primary prevention of cardiovascular heart disease (CHD) to children, can contribute to a reduction in the cardiovascular risk of their parents.

METHODS

Study design

This was a one-year prospective, community-based, case-control study, conducted in two randomly chosen public schools in the city of Campo Limpo Paulista, Sao Paulo, in Brasil (the schools were selected from areas with the same average socioeconomic status as the city as a whole). These were urban schools with low-income students, and they were comparable in their characteristics. The students from these two schools and their parents received two different health interventions during the academic year, as in the methods of the Children First I Study conducted by Fornari et al.[6].

At one of the schools (the control group), we delivered written healthy-lifestyle educational brochures (nutrition, exercise, and smoking cessation) to the parents in April, June, and September 2012. At the other school (the intervention group), the same educational brochures were delivered to the parents and, in addition, the children were exposed to a weekly educational programme for cardiovascular disease prevention presented by a multidisciplinary health team throughout the 2012 school year.

The ethical committee of the Faculty of Medicine of the Sao Paulo University and the local school authorities approved this study. All parents and children signed informed consent.

Study population

We studied 418 parents of students aged 6 to 10 years old. The control group had 216 parents (mean age 37.9 years, 68.1% female), and the intervention group had 202 parents (mean age 39.5 years, 63.9% female).

The students evaluated were all the students from the first to the fifth grade of the elementary schools of the two schools studied, who attended school both in the morning and afternoon.

Sample size

The size of the sample was based on information from the Children First I Study[6], which was a pilot study with 30 parents from the same school that found that the proportion of parents with moderate/high Framingham cardiovascular risk was 10%. To aim for a 70% reduction in the number of parents in the moderate/high Framingham cardiovascular risk category ($p = 0.05$), we needed 150 parents in each group (control and intervention).

Exclusion criteria

To avoid the influence of potential confounders, we applied some exclusion criteria. We excluded children and/or parents who did not agree to participate in the study; those who were taking immunosuppressive drugs; parents with a known atherosclerotic disease such as angina or myocardial infarction, stroke and/or peripheral arterial disease; and parents with untreated hypothyroidism, hypopituitarism, nephrotic syndrome, chronic renal failure, storage diseases, lupus or acquired immunodeficiency syndrome.

Data collection

Data were collected at the beginning of the study (February 2012) and at the end of the academic year

(December 2012), on two consecutive weekends inside the school buildings, from the parents of the children at both schools. The survey included their personal and family history, weight, height, arterial blood pressure, and laboratory tests (glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides.

Multidisciplinary health team

A trained multidisciplinary health team that included nurses, physical education teachers, nutritionists, physiotherapists, and psychologists collected all the data from the children and their parents. This same multidisciplinary health team worked during the year with the children in the intervention group, presenting different activities directed at cardiovascular disease prevention that were supervised by the study researchers.

Measurements

A trained multidisciplinary health team manually performed all measurements in the parents according to the study guidelines. Weight and height were measured in triplicate, without shoes, and while wearing light clothing, using a digital scale accurate to 100g and a portable stadiometer accurate to 1 mm. The body mass index (BMI) was calculated as the weight in kilograms divided by the height squared in meters squared. Systolic and diastolic blood pressure were measured according to the technique recommended by national guideline[s9]. The subjects were seated and had rested for 5 minutes before the blood pressure measurement, which was taken twice on each arm using an appropriate cuff size; the two similar measurements were averaged for analysis. Blood was collected by traditional venepuncture, and fasting cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and glucose were determined by enzymatic methods. The stratification by socioeconomic status was obtained by national measurement parameters[10].

Risk factor definitions for parents

To measure and compare the cardiovascular risk of the parents, we used the Framingham score. The score estimates the risk of the individual having cardiovascular disease in the next 10 years and includes 3 levels: low risk (< 10% risk of CHD), intermediate risk (>10% risk of CHD), and high risk (>20% risk of CHD)[2]. We used the calculator available on the Framingham Project website, which uses the lipid profile as the basis for the calculation, to calculate the risk for the parents[11].

For the isolated risk factors, obesity was defined as a BMI ≥30 kg/m^2 according to the national guideline[9]; hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg[9]; and abnormal lipid levels were defined as total cholesterol >200 mg/dl, triglycerides >150 mg/dl, HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women, and LDL-cholesterol >130 mg/dl[12].

Multidisciplinary educational programme for cardiovascular prevention

In the intervention group, the children attended a cardiovascular health education programme that followed the same protocol used in the study by Fornari et al.[6], with hour-long weekly activities at the children's school. The intervention was carried out by the professionals of the multidisciplinary health team and was supervised by the study researchers. This intervention tried to teach children, in age-appropriate ways, the concepts of healthy nutrition, the importance of a more active lifestyle with more physical exercise, and the hazardous effects of smoking, all using videos, theatre with puppets or actors, sports, play, and educational games on cardiovascular health topics. Psychologists and teachers supervised this work, and children were not asked to feel responsible for their families' lifestyle modifications in either group.

Ethics approval and consent to participate

The study was approved by the ethical committee of the Clinical Hospital of the Faculty of Medicine of the Sao Paulo University (protocol no. 1147/09) and the local school authorities approved this study. All parents and children signed informed consent.

Statistical analysis

The categorical clinical variables were described as absolute and relative frequencies (percentages). The chi-squared test or Fisher's exact test (when at least one of the expected frequencies was less than 5) were used to verify the association between the categorical clinical variables in the study groups at the baseline. The continuous clinical variables were expressed as means and standard deviation, and the Student's t-test was used for comparisons between the two groups at the baseline. The analysis of the change in the number of parents in the high-risk categories of

the Framingham was performed with the McNemar test. All statistical analyses were performed by SPSS 17.0 for Windows, according to a predefined analysis plan. All tests were 2- tailed, and p-values of less than 0.05 were considered statistically significant.

RESULTS

We studied 418 parents and 265 children, with 216 parents in the control group (137 children) and 202 in the intervention group (128 children). In the control group, the mean age was 37.9 years, and 68.1% were female, while in the intervention group, the mean age was 39.5 years, and 63.9% were female.

At baseline, there were no differences between the two groups of parents (control and intervention) in terms of their clinical characteristics, with the exception of a higher prevalence of hypertension in the intervention group (29.7%) compared to the control group (19.4%, p=0.015) and abnormal cholesterol in the intervention group (41.1%) compared to the control group (28.7%, p=0.08). Table 1 shows that the continuous clinical characteristics were similar in the two groups, with the exception of higher levels of systolic blood pressure (122.4 in the intervention group vs. 118.8 in the control group, p=0.004), diastolic blood pressure (84.6 in the intervention group vs. 76.2 in the control group, p<0.001), total cholesterol (192.7 in the intervention group vs. 184.2 in the control group, p=0.009), and LDL-cholesterol (115.0 in the intervention group vs. 108.3 in the control group, 0.017) in the intervention group, pointing to a slightly higher risk profile in this group.

TABLE 1. CHARACTERISTICS OF PARENTS IN THE CONTROL AND INTERVENTION GROUPS AT THE BEGINNING OF THE STUDY (CONTINUOUS VARIABLES). VALUES ARE EXPRESSED AS THE MEANS (SD).

	Groups		
Variables	Control	Intervention	p [a]
Age (years)	37.9 (8.6)	39.5 (8.8)	0.070
BMI (kg/m2)	27.4 (5.5)	27.6 (5.1)	0.692
Systolic blood pressure (mmHg)	118.8 (15.4)	122.4 (13.8)	0.004
Diastolic blood pressure (mmHg)	76.2 (10.2)	84.6 (10.4)	< 0.001
Smoking	20 (9.3)	21 (10.4)	0.695
Total cholesterol (mg/dl)	184.2 (38.4)	192.7 (37.2)	0.009
Triglycerides (mg/dl)	120.0 (98.9)	128.2 (89.9)	0.109
HDL-cholesterol (mg/dl)	52.0 (18.6)	52.6 (15.2)	0.145
LDL-cholesterol (mg/dl)	108.3 (35.6)	115.0 (30.9)	0.017
Glucose (mg/dl)	85.6 (25.2)	85.8 (26.6)	0.847

a Statistical significance according to Wilcoxon test for comparisons of continuous variables between two independent groups at the baseline.

We found that, at the beginning of the study, 6.9% of the parents in the control group and 13.3% of the intervention group had intermediate/high Framingham risk scores, meaning that they had a >10% risk of developing CHD in the next 10 years. After the intervention with the children in the schools, we observed that the intervention group showed a reduction in the number of parents in this high-risk category of the Framingham (27 to 21 parents with >10% risk of developing CHD, p=0.031) compared to an increase in the control group (15 to 20 parents with >10% risk of developing CHD) (Figure 1).

In this sample, these findings correspond to a 22.2% reduction in the intervention group compared to a 33.3% increase in the control group. In other words, 22.2% of the parents in the intervention group were able to change to a low-risk category after the educational intervention with their children in schools.

Table 2 shows the continuous clinical characteristics of parents from the two groups before and after the educational intervention with children for a year. We observed that, in the intervention group, there was a reduction in systolic blood pressure (122.4 to 118.4 mmHg, p<0.001), diastolic blood pressure (84.6 to 80.1 mmHg, p<0.001), and glucose (85.8 to 80.3 mg/dl, p<0.001), and both groups demonstrated a reduction in HDL-cholesterol (52 to 46.9 mg/dl, p<0.001 in the control group and 52.6 to 46.4 mg/dl, p<0.001 in the intervention group). The control group also demonstrated an increase in the average Framingham risk score (3.7 to 4.1, p=0.001). (table 2)

DISCUSSION

Several studies have evaluated cardiovascular risk factor profiles among children and parents in the school environment[5,6,13,14]. However, few have evaluated the impact that a multidisciplinary intervention could have on the profile of parents' habits and cardiovascular risk factors, especially in populations with lower socioeconomic levels.

Golan et al.[13] conducted a small study (60 obese children) that evaluated the impact of two behavioral approaches (parents only *vs.* children only) for the treatment of childhood obesity on the parents' weight, eating habits, and activity habits, as well as their cardiovascular risk factors. He found that the

parents-only intervention was more effective at reducing the parents' weight than the children-only intervention. In our study, however, we conducted a more structured multidisciplinary educational approach with the schoolchildren, which included nutritionists, physical education teachers, nurses, physiotherapists, and school teachers who planned interventions tailored to the children's specific ages. We did not analyze only the parents' weight but rather included multiple cardiovascular risk factors that contribute to the Framingham cardiovascular risk score and prioritized the educational intervention with children as a way of evaluating children as the main tool for changing their parents' habits.

A study in Colombia with 1216 children and 928 parents showed that an educational intervention with children in schools led to an improvement in the knowledge, attitudes, and habits related to a healthy diet and a more active lifestyle in both parents and children[15]. Our study performed a more objective evaluation and detected the reduction of the parents 'cardiovascular risk after an educational intervention directed at the children.

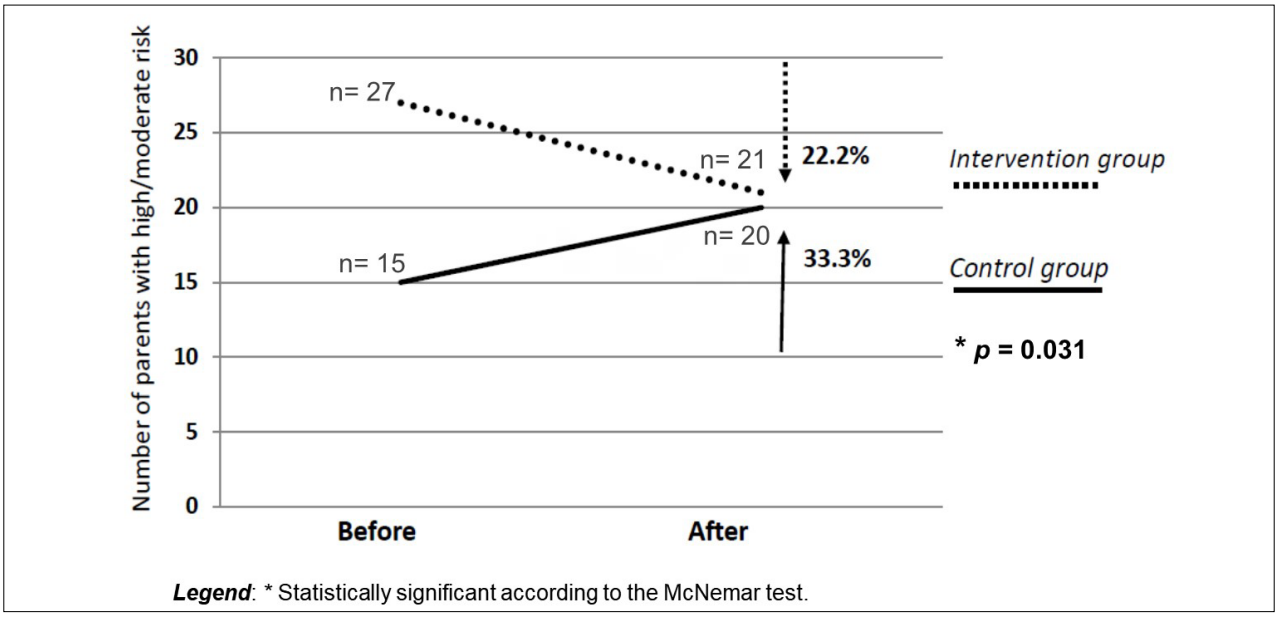
This study is a follow-up to the Children First I

TABLE 2. CHARACTERISTICS OF PARENTS IN THE CONTROL AND INTERVENTION GROUPS BEFORE AND AFTER THE CHILDREN'S EDUCATIONAL INTERVENTION (CONTINUOUS VARIABLES). VALUES ARE EXPRESSED AS THE MEANS (SD).

	Groups					
	Control			Intervention		
	Before	After	p a	Before	After	p a
BMI (kg/m2)	27.4 (5.5)	27.5 (5.4)	0.012	27.6 (5.1)	27.7 (5.2)	0.052
Systolic blood pressure (mmHg)	118.8 (15.4)	118.4 (16.7)	0.552	122.4 (13.8)	118.4 (12.9)	<0.001
Diastolic blood pressure (mmHg)	76.2 (10.2)	77.5 (10.1)	0.091	84.6 (10.4)	80.1 (8.9)	<0.001
Total cholesterol (mg/dl)	184.2 (38.4)	181.5 (40.8)	0.058	192.7 (37.2)	189.6 (37.8)	0.348
Triglycerides (md/dl)	120.0 (98.9)	137.4 (159.3)	0.003	128.2 (89.9)	137.6 (117.0)	0.071
HDL-cholesterol (mg/dl)	52.0 (18.6)	46.9 (11.4)	<0.001	52.6 (15.2)	46.4 (12.5)	<0.001
LDL-cholesterol (mg/dl)	108.3 (35.6)	114.7 (50.6)	0.766	115.0 (30.9)	122.1 (50.4)	0.008
Glucose (mg/dl)	85.6 (25.2)	83.8 (30.6)	0.003	85.8 (26.6)	80.3 (21.8)	<0.001
Average Framingham risk (%)	3.7 (4.9)	4.1 (5.7)	0.001	5.0 (6.3)	4.9 (6.2)	0.227

HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol. a Statistical significance according to Wilcoxon test for related samples.

FIGURE 1. PARENTS FROM THE INTERVENTION AND CONTROL GROUPS IN THE HIGH/INTERMEDIATE-RISK CATEGORIES OF THE FRAMINGHAM. PINTO CJM, 2020.



Study[6] that evaluated the reduction of parents' cardiovascular risk after an educational intervention with children in private schools with a higher average of socioeconomic level. After that study, we speculated whether the findings could be applied to public schools with lower-income families.

In the Children First I Study[6] there was a considerably greater reduction in the number of parents in the intermediate/high Framingham risk category at the end of the study (91%) when compared to the Children First II study (22.2%), although both reductions were statistically significant. However, some considerations need to be made regarding this different behavior in the two studies.

At the beginning of the Children First II Study, the intervention group demonstrated a slightly higher cardiovascular risk profile (Table 1), with higher systolic blood pressure levels (122.4 in the intervention group and 118.8 in the control group, p=0.004), higher levels of diastolic blood pressure (84.6 in the intervention group and 76.2 in the control group, p<0.001), higher total cholesterol levels (192.7 in the intervention group and 184.2 in the control group, p=0.009), and higher levels of LDL cholesterol (115 in the intervention group and 108 in the control group, p=0.017).

In addition to a slightly higher cardiovascular risk in the intervention group, another factor that increased the impact of reducing cardiovascular risk in this group was the fact that there was an increase in the cardiovascular risk of the control group by the end of the study. The average Framingham risk score increased in the control group (3.7 to 4.1 at the end of the study, p=0.001), (Table 2), and there was a 33.3% increase in the number of control group parents in the intermediate/high score category of the Framingham; at the same time, there was a 22.2% decrease in the number of parents in those categories in the intervention group (p=0.031) (Figure 1).

Some hypotheses may be put forward to explain the different results found in the Children First I and II studies. Perhaps high-income population groups have greater access to healthier foods such as fruits, vegetables, and low-fat alternatives. Indeed, a Brazilian study analyzed the treatment for dyslipidemia among patients with diabetes and observed that people with higher socioeconomic levels have better follow-up by private or insurance doctors, possibly explaining better health outcomes[16].

Another important factor that the researchers noticed was that public school teachers had less involvement in the didactic activities administered by the multidisciplinary team and, consequently, may have had a smaller contribution concerning the reinforcement of the concepts of cardiovascular health with the children. This hypothesis can be corroborated in a publication of similar studies from England[7] and Spain[17], that highlights that the involvement of children's teachers is essential to the success of the intervention.

In summary, the Children First II study showed that there was a reduction in the parents' cardiovascular risk influenced by the educational multidisciplinary intervention on cardiovascular health attended by their children in public schools.

Our study has some limitations. The sample size, despite being larger than that of the Children First I study[6] is still slightly small. The apparently smaller role of teachers in the multidisciplinary intervention in public schools cannot be adequately measured. Perhaps a study where the intervention was mediated primarily by the teacher in contact with the children and had the support of a multidisciplinary team at distance carried out in a multicentric format both in public and private schools, could clarify this question better.

In addition, our study, like the Children First I study[6], evaluated the results of one academic year, and we cannot confirm that these results would persist for a longer period. Other studies designed for longer periods of time and with greater sample sizes would be necessary to address these issues.

Another factor is that, at the baseline, the control and intervention groups had some differences in systolic and diastolic blood pressures and lipid profiles. This was a condition found by chance that could not be changed.

However, this study confirms the findings of the Children First I[6] study and provides more evidence that multidisciplinary health education interventions with children in schools can decrease their cardiovascular risk.

CONCLUSIONS

In conclusion, this study provided evidence that an educational program for cardiovascular prevention directed to school-aged children in public schools can reduce the FCR risk of their parents, especially in the intermediate/high-risk categories.

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Authors Contribuition

Cristiano J. M. Pinto - Contributed substantially to the conception and the design of the study, collected and analysed the data, drafted and critically revised the manuscript.

Luciana S. Fornari - Elaborated the conception and the design of the study, supervised the study and participated in the analysis, interpretation of data and writing the manuscript.

Silvia M. R. Oyama; Maria M. D. Rodrigues; Taciana Davanço - Participated in collected and analysed the data, in designing one or more parts of the education program and/or the workplace intervention.

Bruno Caramelli - Elaborated the conception and the design of the study, supervised the study and participated in the analysis, interpretation of data and writing the manuscript.

RESUMO

OBJETIVO: *Analisar se a implementação de um programa educacional multidisciplinar para prevenção cardiovascular em escolas públicas durante um ano pode contribuir para reduzir o escore de risco cardiovascular de Framingham dos pais das crianças.*

MÉTODOS: *Estudo prospectivo, de base comunitária, caso-controle em duas escolas públicas de São Paulo, Brasil. Os alunos foram randomizados para receber recomendações de estilo de vida saudável por duas abordagens diferentes. O grupo controle recebeu folhetos educacionais de saúde cardiovascular encaminhados para seus pais. O grupo intervenção recebeu os mesmos folhetos e as crianças foram expostas a um programa educacional semanal, durante um ano, com uma equipe multidisciplinar em prevenção cardiovascular. Dados clínicos e laboratoriais foram coletados no início e no final do estudo.*

RESULTADOS: *Foram sujeitos do estudo 418 pais das crianças das escolas. No início da pesquisa, o total de pais com escore de Framingham intermediário ou alto (risco superior a 10% de doença cardiovascular nos próximos dez anos) foi de 6,9% no grupo controle e de 13,3% no grupo intervenção. Após um ano, dentre os pais com escore de risco de Framingham intermediário ou alto, foi observada redução de 22,2% no grupo intervenção e aumento de 33,3% no grupo controle (p=0,031). Os fatores de risco cardiovascular que melhoraram no grupo de intervenção foram pressão arterial, LDL-colesterol (lipoproteína de baixa densidade) e glicemia.*

CONCLUSÃO: *Um programa educacional de prevenção cardiovascular para crianças em idade escolar, em escolas públicas, pode reduzir o risco cardiovascular de seus pais.*

PALAVRAS-CHAVE: *Doenças cardiovasculares/prevenção e controle. Criança. Pais. Educação. Instituições acadêmicas.*

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ORIGINAL ARTICLE

Metabolic compromise in women with PCOS: earlier than expected

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SUMMARY

Polycystic ovary syndrome (PCOS) is an endocrinopathy with unknown pathophysiology among women of reproductive age. Several studies have been conducted to determine the prevalence of metabolic syndrome (MetS) among PCOS patients. Recent studies have reported varied prevalence of metabolic syndrome (MetS) in women with PCOS. The aim of this study is to determine if women with PCOS are at a higher risk of MetS or some degree of metabolic compromise.

METHODS: *This is an observational study. A total of 96 women diagnosed with PCOS (according to the Rotterdam consensus criteria) were included. Variables of diagnostic criteria for MetS according to the ATP III were analyzed at the first consultation. Data analysis was performed using Epi Info™ 7.2.2.16.*

RESULTS: *We assessed the prevalence of obesity, blood pressure, glucose intolerance, and dyslipidemia in 96 women with PCOS and an average age of 28 (17-39) years. Forty percent of the women had BMI <25 kg/m2; 85.4% had blood pressure <130/85 mm Hg; 22.9% had HDL cholesterol >50 mg/dl, 57.3% had triglycerides <150 mg/dl, 63.5% had fasting glucose <100 mg/dl. According to the ATP III criteria for MetS, 8.33% met none of the criteria, 19.79% met one criterion, 15.63% two criteria, 41.67% 3 criteria, 13.54% 4 criteria, and 1.04% met the 5 criteria.*

CONCLUSION: *Considering the high prevalence of MetS or altered metabolic components in PCOS patients at the moment of the diagnosis, its regular screening is necessary to reduce the mortality and morbidity rates in these women.*

KEYWORDS: *Polycystic ovary síndrome. Metabolic syndrome. Obesity. Glucose intolerance. Dyslipidemias.*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrinopathy with unknown pathophysiology and a prevalence of 6-10% in reproductive-age women[1]. Although PCOS can manifest at any stage of reproductive life, it often develops during adolescence. Polycystic ovary syndrome is typified by both reproductive and

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hyperandrogenic features that include oligo-amenorrhoea, impaired fertility, hirsutism, acne, and androgenic hair loss. Polycystic ovary syndrome often also presents with hyperandrogenaemia.

Polycystic ovary syndrome is an important example of a metabolic disorder associated with insulin resistance, its manifestations include cardiometabolic risks and the effects of which are greatly amplified by obesity. Accordingly, PCOS is associated with heightened risk for the development of T2D, impaired glucose tolerance, dyslipidemia, non-alcoholic fatty liver disease, and obstructive sleep apnoea[2].

Several studies have been conducted to determine the prevalence of metabolic syndrome (MetS) among PCOS patients. Recent studies have reported a varied prevalence of metabolic syndrome (MetS) in women with PCOS[3,4]. The aim of this study is to determine if the women with PCOS are at a higher risk of MetS or some degree of metabolic compromise at the moment of diagnosis.

METHODS

Study design

This cross-sectional study was conducted at the Gynecological and Reproduction Section, Argerich Hospital, Argentina, from October 2010 to October 2018. Women diagnosed with PCOS during this period were consecutively enrolled.

Participants

Patients with PCOS were identified based on the revised 2003 Rotterdam consensus criteria, in which two out of three of the following conditions must be met: (1) the presence of oligo- and/or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries on ultrasonography. Other causes of hyperandrogenism, such as congenital adrenal hyperplasia, androgen-secreting neoplasms, and Cushing syndrome, were excluded. Women who had hypothyroidism or hyperprolactinemia, were on oral contraceptive medication within 3 months prior to the time of enrolment, were on insulin sensitizers, or who had established diabetes (type 1 or type 2) were also excluded from the study.

Measurements

Anthropometry and blood pressure

The height and weight of each subject were measured. The body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters. The BMI values were categorised as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25.0 to 29.9 kg/m²), and obese (≥30 kg/m²). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the sitting position after a 5-minute rest.

Biochemical assays

Venous blood samples were collected in the morning after an overnight fast on the second or third day of the patient's spontaneous or progesterone-induced menstrual cycle. Fasting glucose and lipid panel analyses including total cholesterol, triglycerides (TGs), HDL-C, and low-density lipoprotein cholesterol (LDL-C) were performed using Cobas 6000 C501 Roche.

Definition of variables and outcomes

We defined MS using the NHLBI/AHA ATP III guidelines. A diagnosis of MS was made when ≥3 of the following were present: (1) WC ≥80 cm, (2) TG ≥ 150 mg/ml, (3) HDL-C < 50 mg/ml, (4) blood pressure (BP) ≥130/85 mm Hg, and (5) fasting glucose ≥ 100 mg/ml[5].

Statistical analysis

Descriptive statistics were used to determine the characteristics of the study population.

Data analysis was performed using Epi Info™ 7.2.2.16.

RESULTS

We assessed the prevalence of obesity, blood pressure, glucose intolerance, and dyslipidemia in 96 women with PCOS, aged 28 (17-39) years. Forty percent of women had BMI <25 kg/m2; 85.4% had blood pressure <130/85 mm Hg; 22.9% had HDL cholesterol > 50 mg / dl, 57.3% had triglycerides <150 mg/dl, 63.5% had fasting glucose <100 mg/dl. Table 1

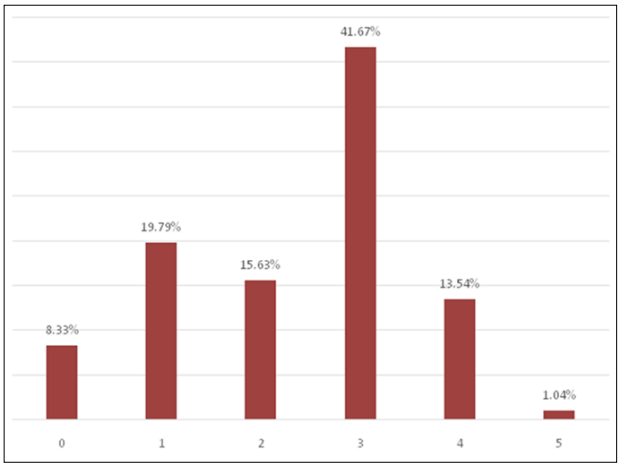
TABLE 1. METABOLIC LABORATORY RESULTS

Variable	Normal results (%)	Abnormal results (%)
BMI	40	60/ Obesity: 48
Blood pressure	85.4	14.6
HDL c	22.9	77.1
Triglycerides	57,3	42.7
Fasting glucose	63.5	27.1/DBT2: 9.4

At the time of the PCOS diagnosis, 44% of the patients met the diagnostic criteria for MetS.

According to the ATP III criteria for MetS, 8.33% met none of the criteria, 19.79% met one criterion, 15.63% met two criteria, 41.67% 3 criteria, 13.54% 4 criteria, and 1.04% met the 5 criteria. Figure 1

FIGURE 1. DIAGNOSTIC CRITERIA OF ATP III IN PCOS WOMEN



Analysis of results according to altered variable

Obesity: 83% presented low HDL; 46% had hypertriglyceridemia; 51% had altered fasting glucose.

Altered fasting glucose: 94.28% of the patients presented low HDL, 45.71% had altered triglycerides; 51.42 had BMI greater or equal than 30.

Altered blood pressure: 85.71% of the patients presented low HDL, 50% hypertriglycerides; 37.7% altered fasting glucose; 64.28% had BMI greater or equal than 30.

DISCUSSION

Women with PCOS present a number of systemic symptoms in addition to those related to the reproductive system. In fact, PCOS is associated with significant metabolic consequences[2].

MS is a complex of interrelated risk factors for CVD and diabetes. The clinical definition of the MS has been developed over the past two decades with the purpose of identifying individuals at increased risk of these diseases to put in place preventive measures that can reduce this risk[5].

In our current population, only 8.33 % of the patients did not show any metabolic alteration, and 43.75% some MetS. These alterations influence the development of metabolic disorders.

In women who are genetically predisposed to the development of PCOS, weight gain and obesity often result in clinical and biochemical manifestations. Accordingly, there are close links between obesity and PCOS[6]. The majority of women with PCOS in this study (60%) are either overweight (12%) or obese (48%). Weight-gain and obesity worsen insulin resistance and features of metabolic syndrome. Weight-gain and obesity in women with PCOS also promote worsening insulin resistance, and both metabolic dysfunction and the characteristic reproductive and hyperandrogenic features of this condition[6].

The most common lipid abnormalities among women with PCOS are elevated levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), and low high-density lipoprotein cholesterol (HDL-C) levels[4]. Moreover, obese and thin women with PCOS often present an atherogenic lipid profile, together with other biochemical cardiovascular risk factors.

In our patients, the parameter more affected was HDL-c (77% had values < 50 mg/ml), perhaps as a result of obesity and glycemic status. Only 22% of the patients in our population had HDL-C in the normal range. Considering that 40% of PCOS women had normal BMI, our results show that the decrease in HDL-c occurs independently of body weight.

In line with the present findings, previous cross-sectional studies including adolescent and young reproductive-aged women with PCOS have reported significantly higher blood pressure levels in them compared with controls. In our analysis, overweight/obesity was associated with hypertension, outlining the important role of excess weight as a determinant of hypertension in women with PCOS.

Hypertension develops in women with PCOS from hyperaldosteronism via the activation of the renin-angiotensin system. Previous studies have shown that women with PCOS appear to have higher aldosterone levels than age- and BMI-matched controls, though within normal limits[4]. Additionally, insulin resistance-related compensatory hyperinsulinemia has been implicated in the occurrence of hypertension in women with PCOS.

As mentioned, and given the high prevalence of some component of metabolic syndrome at the time of diagnosis of PCOS, we consider that they should be taken into account as an early complication of the syndrome.

The management of women with PCOS should focus on specific symptom manifestations and be tailored to the individual. According to the recently published international PCOS guidelines, global CVD risk should be routinely assessed in women with PCOS[2-4,7].

CONCLUSIONS:

PCOS is a chronic disease with health implications across the lifespan.

The increased metabolic risk can be found at the time of diagnosis of PCOS and not as a long-term complication.

Patients with PCOS should be fully evaluated to determine baseline metabolic parameters. Women with PCOS may require more regular screening at diagnosis for such risks as well as effective and targeted early lifestyle advice.

Considering the high prevalence of MetS or altered metabolic components in PCOS patients, its early diagnosis is necessary to reduce the mortality and morbidity rates in these women.

RESUMO

A síndrome dos ovários policísticos (SOP) é uma endocrinopatia com fisiopatologia desconhecida em mulheres em idade reprodutiva. Vários estudos foram realizados para determinar a prevalência da síndrome metabólica (SM) em pacientes com SOP. Estudos recentes relataram prevalência variada de síndrome metabólica (SM) em mulheres com SOP. O objetivo deste estudo é determinar se as mulheres com SOP apresentam maior risco de SM ou algum grau de comprometimento metabólico.

MÉTODOS: *Estudo de desenho observacional. Foram incluídas 96 mulheres diagnosticadas com SOP (de acordo com os critérios de consenso de Roterdã). Variáveis de critérios de diagnóstico para SM de acordo com o ATP III foram analisadas na primeira consulta. A análise dos dados foi realizada usando o Epi Info™ 7.2.2.16.*

RESULTADOS: *Avaliamos prevalência de obesidade, pressão arterial, intolerância à glicose e dislipidemia em 96 mulheres com SOP, com idade de 28 (17-39) anos. Quarenta por cento das mulheres tinham IMC <25 kg/m2; 85,4% tinham pressão arterial <130/85 mm Hg; 22,9% tinham colesterol HDL >50 mg/dl, 57,3% tinham triglicerídeos <150 mg/dl, 63,5% tinham glicemia de jejum <100 mg/dl. Segundo os critérios do ATP III para SM, 8,33% não possuíam critérios, 19,79% possuíam um critério, 15,63% possuíam dois critérios, 41,67% possuíam três critérios, 13,54% possuíam quatro critérios, 1,05% possuía os cinco critérios.*

CONCLUSÃO: *Considerando a alta prevalência de SM ou algum componente metabólico alterado em pacientes com SOP no momento do diagnóstico, sua triagem regular é necessária para reduzir as taxas de mortalidade e morbidade nessas mulheres.*

PALAVRAS-CHAVE: *Síndrome do ovário policístico. Síndrome metabólica. Obesidade. Intolerância à glucose. Dislipidemias.*

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ORIGINAL ARTICLE

Effects of hemodialysis, peritoneal dialysis, and renal transplantation on the quality of life of patients with end-stage renal disease

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SUMMARY

OBJECTIVE: *To evaluate the effects of hemodialysis, peritoneal dialysis, and renal transplantation on the quality of life of patients with end-stage renal disease (ESRD) and analyze the influencing factors.*

METHODS: *A total of 162 ESRD patients who received maintenance hemodialysis, continuous ambulatory peritoneal dialysis, and renal transplantation from February 2017 to March 2018 in our hospital were divided into a hemodialysis group, a peritoneal dialysis group, and a renal transplantation group. The baseline clinical data, serum indices, as well as environmental factors such as education level, marital status, work, residential pattern, household income, and expenditure were recorded. The quality of life was assessed using the short-form 36-item (SF-36) scale reflecting the Physical Component Summary (PCS) and the Mental Component Summary (MCS). One-way analysis of variance and logistic stepwise multiple regression analysis were performed to analyze the factors influencing the quality of life.*

RESULTS: *The renal transplantation group had the highest average scores for all dimensions of the SF-36 scale. The PCS and MCS scores of this group were higher than those of the hemodialysis and peritoneal dialysis groups. The peritoneal dialysis group had higher scores for physical functioning, physical role, bodily pain, general health, mental health, PCS, and MCS than those of the hemodialysis group. Age, HGB, GLU, and ALP were the main factors influencing PCS. Age, education level, residential pattern, medication expenditure, and monthly per capita income mainly affected MCS.*

CONCLUSION: *In terms of quality of life, renal transplantation is superior to peritoneal dialysis and hemodialysis.*

KEYWORDS: *Renal dialysis. Peritoneal dialysis. Kidney transplantation. Kidney failure, chronic.*

INTRODUCTION

End-stage renal disease (ESRD) is the end-stage of chronic kidney disease and is mainly manifested as an evident decrease in renal function. Metabolic waste cannot be independently eliminated, causing electrolyte imbalance and a series of poisoning symptoms[1]. As the population ages, the incidence rate of ESRD increases annually. Even with the continuous development of medical standards, the mortality rate remains high[2]. Renal replacement therapy is commonly used for ESRD in clinical practice, including

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hemodialysis, peritoneal dialysis, and renal transplantation[3]. Although life expectancy can be consequently increased, either treatment must be maintained for a long time, which has a serious impact on patients both physiologically and psychologically[4].

The quality of life is closely related to society and family, which has been defined by WHO as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns[5]. For ESRD patients, chronic dialysis evidently affects the quality of life, manifested as a decrease of social interaction and physical functioning, an increase of depression risk, and aggravation of symptoms including leg restlessness, muscle weakness, and fatigue[6]. The quality of life of patients with ESRD is poorer than that of the general population, which has been highly related to malnutrition[7-9]. Besides, the quality of life differs depending on the modality of renal replacement therapy. For instance, patients receiving renal transplantation have a better quality of life than those undergoing dialysis[10]. It is a concept including physical, psychological, social function, and economic dimensions as an important index for evaluating the prognosis of ESRD patients[11]. Additionally, the mortality and length of hospitalization of dialysis patients can be independently predicted by the quality of life, which has thus been suggested as a valuable supplement to clinical outcome measures[12].

Until now, how the quality of life of ESRD patients is affected by non-medical factors assessed by preference-based measures remains elusive. Therefore, it is necessary to determine the best treatment method and related factors, aiming to prolong life expectancy and improve the quality of life. We herein evaluated the effects of three alternative therapies on the quality of life of ESRD patients and the related influencing factors, providing a theoretical basis for the selection of treatment methods.

METHODS

Baseline clinical data

A total of 162 ESRD patients who received maintenance hemodialysis, continuous ambulatory peritoneal dialysis, and renal transplantation from February 2017 to March 2018 in our hospital were enrolled. Among them, 52 patients received hemodialysis, consisting of 32 males and 20 females aged 28-84 years old, (58.92 ± 10.32 on average). There were 16 cases of primary critical chronic glomerulonephritis, 10 cases of hypertensive renal injury, 8 cases of diabetic nephropathy, 6 cases of polycystic kidney disease, 5 cases of gouty nephropathy, and 7 cases with unknown causes. Hemodialysis was carried out 3 times weekly, 4h each time. Sixty patients received peritoneal dialysis, comprising 36 males and 24 females aged 26-81 years old, (59.63 ± 10.78 on average). There were 19 cases of primary critical chronic glomerulonephritis, 11 cases of hypertensive renal injury, 10 cases of diabetic nephropathy, 7 cases of polycystic kidney disease, 5 cases of gouty nephropathy, and 8 cases with unknown causes. The peritoneal dialysis solution was refreshed 4 times daily, 2L each time. Fifty patients were subjected to renal transplantation, including 30 males and 20 females aged 27-83 years old, (59.63 ± 9.96 on average). There were 13 cases of primary critical chronic glomerulonephritis, 8 cases of hypertensive renal injury, 10 cases of diabetic nephropathy, 6 cases of polycystic kidney disease, 4 cases of gouty nephropathy, and 9 cases with unknown causes. This study was approved by the ethics committee of our hospital, and written consent was obtained from all patients.

Inclusion criteria: 1) meeting the diagnostic criteria of ESRD; 2) age >18 years; 3) receiving hemodialysis and peritoneal dialysis for over 3 months, or renal transplantation over 6 months.

Exclusion criteria: 1) primary critical autoimmune diseases; 2) complication with malignant tumors; 3) complication with acute infection; 4) complication with severe liver and pulmonary diseases; 5) mental diseases or inability to cooperate with examinations; 6) patients who died within 3 months of enrollment.

Laboratory testing

Age, body mass index (BMI), gender, treatment time, blood pressure, levels of hemoglobin (HGB), low-density lipoprotein-cholesterol (LDL-C), calcium-phosphorus (Ca, P), total cholesterol (TCH), serum creatinine (SCR), urea nitrogen (UA), blood glucose (GLU), alkaline phosphatase (ALP), and C-reactive protein (CRP), as well as environmental factors such as educational level, marital status, work, residential pattern, household income, and expenditure were recorded.

Investigation tool

The quality of life was assessed using the short-form 36-item (SF-36) scale[13], which was completed

under the guidance of researchers. The SF-36 scale consists of 8 dimensions, i.e. physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The score of each dimension ranges from 0 to 100 points, and the higher the score, the better the quality of life. The Physical Component Summary (PCS) is reflected by PF, RP, BP and GH, and the Mental Component Summary (MCS) is reflected by VT, SF, RE, and MH.

Statistical analysis

All data were statistically analyzed by SPSS16.0 software. Categorical data such as the scale scores were expressed as mean ± standard deviation. The comparisons between the two groups were performed by the independent t-test, and those among multiple groups were conducted with one-way analysis of variance and logistic stepwise multiple regression analysis. $P<0.05$ was considered statistically significant.

RESULTS

Baseline clinical data

The three groups had similar age, gender ratio, BMI, blood pressure, and blood biochemical indices ($P>0.05$) (Table 1).

SF-36 scale scores

The renal transplantation group had the highest average scores at all dimensions of the SF-36 scale. The PCS and MCS scores of this group were higher than those of the hemodialysis and peritoneal dialysis groups. The peritoneal dialysis group had higher scores of PF, RP, BP, GH, MH, PCS, and MCS than those of the hemodialysis group ($P<0.05$) (Supplementary File, Table S1).

Univariate analysis of the effects of environmental factors on the quality of life

Univariate analysis showed that the PCS and MCS of ESRD patients were affected by whether they lived alone. MCS was associated with educational level, monthly drug expenditure, and monthly income per capita, whereas PCS was not related with other factors (Table 2).

Multivariate analysis of factors affecting the quality of life

Variable assignments are listed in Table S2 (Supplementary File). Multivariate analysis showed that age, HGB, GLU, and ALP were the main factors influencing PCS. Age, education level, residential pattern, medication expenditure, and monthly per capita income mainly affected MCS (Figure 1).

TABLE 1. BASELINE CLINICAL DATA

Index	Hemodialysis group (n=52)	Peritoneal dialysis group (n=60)	Renal transplantation group (n=50)	P
Age (year)	58.92±10.32	59.63±10.78	59.63±9.96	0.723
Male [case (%)]	32(61.54%)	36(60.00%)	30(60.00%)	0.983
Treatment time (month)	22.12±3.65	21.65±2.86	23.21±3.21	0.256
BMI ($kg·m^{-2}$)	24.53±3.82	26.11±2.78	25.33±3.26	0.384
Systolic pressure (mmHg)	123.37±12.89	128.18±13.33	127.87±13.46	0.543
Diastolic pressure (mmHg)	73.25±7.63	76.34±8.17	81.46±9.28	0.125
HGB ($g·L^{-1}$)	73.23±4.28	78.64±6.48	76.84±7.24	0.638
LDL-C ($mmol·L^{-1}$)	2.49±0.87	2.53±0.91	2.52±1.03	0.223
Ca ($mmol·L^{-1}$)	2.09±0.26	2.12±0.31	2.21±0.35	0.316
P ($mmol·L^{-1}$)	1.65±0.43	1.68±0.52	1.71±0.64	0.563
TCH ($mmol·L^{-1}$)	4.83±1.6	4.76±1.16	4.98±1.23	0.303
SCR ($mmol·L^{-1}$)	81.34±18.95	76.56±16.35	83.86±17.35	0.379
UA ($mol·L^{-1}$)	22.26±3.32	23.44±3.56	22.35±3.67	0.089
GLU ($mmol·L^{-1}$)	6.85±1.23	7.02±1.85	6.44±1.26	0.095
ALP ($g·L^{-1}$)	30.13±4.28	30.42±3.98	31.44±3.13	0.125
CRP ($mg·L^{-1}$)	4.89±1.06	4.96±1.32	4.85±0.93	0.113

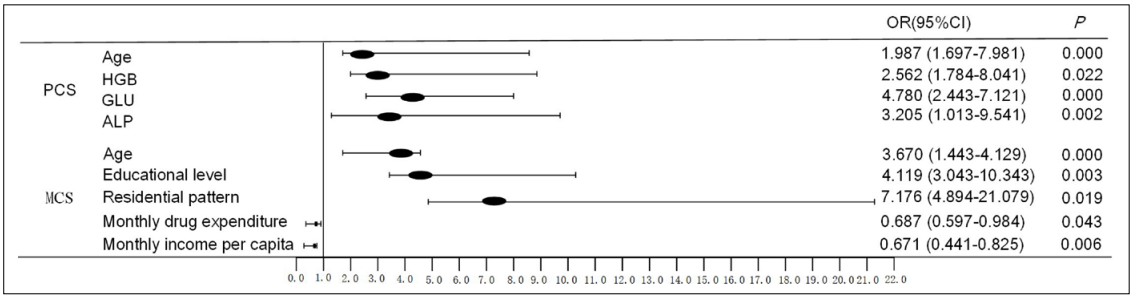
ALP: alkaline phosphatase; BMI: body mass index; Ca: calcium; CRP: C-reactive protein; GLU: glucose; HGB: hemoglobin; LDL-C: low-density lipoprotein-cholesterol; P: phosphorus; SCR: serum creatinine; TCH: total cholesterol; UA: urea nitrogen.

TABLE 2. UNIVARIATE ANALYSIS OF THE EFFECTS OF ENVIRONMENTAL FACTORS ON THE QUALITY OF LIFE

Factor	PCS	F/t	P	MCS	F/t	P
Educational level		0.728	0.288		3.249	0.036
Secondary technical school and above (n=30)	52.70±16.54			62.58±16.13		
Junior high school (n=54)	55.71±15.24			55.92±12.24		
Primary school (n=58)	53.35±13.69			48.02±8.18		
Illiteracy (n=20)	54.51±14.84			42.54±6.19		
Marital status		0.68	0.497		0.511	0.61
Married (n=124)	54.95±14.62			56.29±12.31		
Single or widowed (n=38)	56.76±13.42			55.15±11.03		
Living alone		3.332	0.001		4.871	0.000
Yes (n=36)	46.54±13.25			45.96±12.28		
No (n=126)	55.36±14.21			59.35±15.12		
Work		0.635	0.526		0.718	0.474
Yes (n=28)	55.02±14.93			57.54±12.02		
No (n=134)	53.26±12.98			59.37±12.31		
Monthly drug expenditure (X)		0.431	0.673		4.459	0.005
X≤1500 CNY (n=56)	56.84±14.32			48.68±10.22		
1500<X<2500 CNY (n=62)	55.81±13.13			58.90±12.21		
X≥2500 CNY (n=44)	56.32±15.54			65.07±17.17		
Monthly income per capita (X)		1.189	0.332		5.749	<0.001
X≤300 CNY (n=18)	58.02±16.02			42.32±9.18		
301<X<800 CNY (n=25)	53.14±13.89			54.12±13.76		
800<X<1500 CNY (n=32)	56.14±14.42			59.09±15.01		
X≥1500 CNY (n=60)	54.82±15.43			63.32±17.37		

CNY: Chinese Yuan; MCS: Mental Component Summary; PCS: Physical Component Summary.

FIGURE 1. MULTIVARIATE ANALYSIS OF FACTORS AFFECTING THE QUALITY OF LIFE. ALP: ALKALINE PHOSPHATASE; GLU: GLUCOSE; HGB: HEMOGLOBIN; MCS: MENTAL COMPONENT SUMMARY; OR: ODDS RATIO; PCS: PHYSICAL COMPONENT SUMMARY.



DISCUSSION

The purpose of ESRD treatment is no longer only to alleviate pain, prolong life, reduce complications and hospitalization rates. Improving patients' quality of life and returning them to family and society, or even getting them as close to normal life as possible has become an important direction of treatment[14]. There is still controversy about the choice of alternative treatments and the evaluation of therapeutic effects. The SF-36 scale is an important measurement of the quality of life and has been widely used in ESRD. At present, there is less analysis of the quality of life and its influencing factors in patients with ESRD in China compared with hemodialysis, peritoneal dialysis, and kidney transplantation.

In this study, the quality of life of renal transplant patients is better than that of patients who receive hemodialysis and peritoneal dialysis, probably because kidney transplant patients can autonomously excrete metabolic waste without the need for auxiliary equipment, regulate endocrine levels, and improve nutritional status. PF, BP, GH, and MH of hemodialysis

patients were worse than those of patients receiving peritoneal dialysis, and the differences between them were statistically significant. Makkar et al.[15] found that the quality of life of patients undergoing hemodialysis was significantly poorer than that of peritoneal dialysis patients. Possibly, compared with hemodialysis, peritoneal dialysis is simpler and easier to master, and patients do not need to rely on others to complete it themselves, which preserves their dignity. Hemodialysis may bring physical pain to the patients during arteriovenous fistula puncture, and is likely to cause hypotension, arrhythmia, or worsen heart function damage[16]. In contrast, peritoneal dialysis is relatively stable, with no sudden changes in body fluid volume, and a better protective effect on residual kidney function. In addition, the dependence of patients on hemodialysis machines severely limits their life and may also have a negative impact on their mentality[17].

This study analyzed the factors affecting the quality of life, and the results showed that age, education level, residential pattern, medication expenses, and monthly income were the main factors affecting MCS. For each therapy, ESRD patients need long-term maintenance treatment and medical review. Due to expensive medical expenses, and stress from the psychological, family, and social aspects, the patients often experience negative emotions such as anxiety and depression. The lack of roles in family and society, the decline in self-care ability, and even the need for family care have also seriously reduced the quality of life of patients[18]. Neumann et al.[19] found that the MCS scores of elderly patients were better than those of younger ones, indicating that the patients' understanding of the disease and the regulation of their own emotions were associated with age. Lu et al.[14] reported that elderly patients were more likely to accept their own limitations, so they were satisfied more easily. A higher level of education may lead to better mastery of dialysis operations and principles and better compliance with medical procedures, all contributing to the improvement of quality of life.

In this study, the main factors affecting patients' PCS included age, HGB, GLU, and ALP. Elderly patients have worse physical health due to degenerative organ function, more underlying diseases, and low immunity. Zazzeroni et al.[20] also reported that age was the main influencing factor for the PCS score of quality of life. HGB is an important indicator of whether there is anemia. Anemia is a common complication of ESRD, which can lead to arrhythmia and decreased heart function, which in turn leads to a series of cardiovascular events, and have a serious impact on patients' quality of life. Diabetes is one of the important factors that cause ESRD, and GLU concentration can reflect the severity of ESRD patients[21]. Marcacuzco et al.[22] found that the higher the GLU concentration, the more likely ESRD patients were to die. In a study of 1,753 patients with renal failure dialysis, high levels of ALP significantly affected all-cause mortality, cardiovascular mortality, and recent survival[23]. Herein, ALP was a major factor affecting the quality of life of ESRD patients.

CONCLUSION

In summary, in terms of the quality of life of patients, renal transplantation in 3 alternative treatment methods is superior to peritoneal dialysis and hemodialysis, and the quality of life of hemodialysis patients is even worse. In the future, it is necessary to expand the sample for multi-center prospective research, and improve patient data for different treatment times, so as to provide better interventions to further improve the quality of life.

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Author's Contribution

LZ: Study design, data collection and analysis, manuscript drafting; Yannan Guo: Study design, significant manuscript revision; Hua Ming: data collection and analysis, manuscript drafting.

RESUMO

OBJETIVO: *Avaliar os efeitos da hemodiálise, diálise peritoneal e transplante renal na qualidade de vida de pacientes na última fase da doença renal terminal (ESRD), bem como analisar os fatores influentes.*

MÉTODOS: *Um total de 162 pacientes de ESRD receberam hemodiálise de manutenção, diálise peritoneal ambulatorial contínua e transplante renal de fevereiro de 2017 a março de 2018 em nosso hospital. Eles foram divididos em grupo de hemodiálise, grupo de diálise peritoneal e grupo de transplante renal. Foram analisados os dados clínicos de base, índices-chave e os fatores ambientais, como nível educacional, estado civil, emprego, padrão residencial, renda e gasto familiar. A qualidade de vida foi avaliada pelo uso da escala de forma reduzida de 36 itens (SF-36), que reflete o Resumo da Escala Física (PCS) e o Resumo dos Componentes Mentais (PCS). Análise unidirecional de variações e análise de regressão logística múltipla foram realizadas para analisar os fatores que influenciam a qualidade de vida.*

RESULTADOS: *O grupo de transplante renal teve os maiores pontos médios em todas as dimensões da escala SF-36. Os pontos PCS e MCS desse grupo foram mais altos que os dos grupos de hemodiálise e diálise peritoneal. Além disso, o grupo de diálise peritoneal teve pontos mais altos em funcionamento físico, função física, dor corporal, saúde geral, saúde mental, PCS e MCS do que os do grupo de hemodiálise. Idade, HGB, GLU e ALP foram os principais fatores que influenciaram a PCS. Idade, nível educacional, padrão residencial, gastos em medicamentos e renda mensal per capita afetaram principalmente o MCS.*

CONCLUSÃO: *Quanto à qualidade de vida, o transplante renal é melhor que a diálise peritoneal e a hemodiálise.*

PALAVRAS-CHAVE: *Diálise renal. Diálise peritoneal. Transplante de rim. Falência renal crônica.*

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ORIGINAL ARTICLE

Prevalence of sarcopenia in kidney transplants and their association with determinant factors of muscle homeostasis

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SUMMARY

INTRODUCTION: *Sarcopenia is characterized by the involuntary loss of lean body mass associated with a progressive reduction of muscle strength.*

OBJECTIVE: *To determine the prevalence of sarcopenia in kidney transplant recipients and its association with the determining factors that control muscle homeostasis.*

METHODS: *We evaluated renal transplant recipients undergoing follow-up at the University Hospital of the Federal University of Maranhão from June 2017 to July 2018 and who met the inclusion criteria. Sarcopenia was defined according to the European criteria. The skeletal muscle mass index was measured by dual-energy radiological absorptiometry; the values <7,26 kg/m^2 for men and <5,5 kg/m^2 for women were adopted for muscle depletion. For handgrip strength, values of <30 kg for men and <20 kg for women were considered as reduced muscle strength. In both sexes, the cutoff point for walking speed was <0,8 m/s.*

RESULTS: *We evaluated 83 renal transplant recipients with a mean age of 48.8 ± 12,1 years and predominantly males (57,8%). The prevalence of sarcopenia was 19,3%. Among individuals without sarcopenia, 17,9% had a decrease in handgrip strength and 40,3% has altered gait speed.*

DISCUSSION: *Individuals submitted to renal transplant may develop sarcopenia while still young and already present altered muscle function and strength even before the depletion of lean body mass.*

CONCLUSION: *Early diagnosis may allow the prevention of sarcopenia and provide a better quality of life for patients.*

KEYWORDS: *Kidney transplantation. Sarcopenia. Muscle strength.*

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INTRODUCTION

Sarcopenia is a syndrome characterized by the involuntary loss of lean body mass (LBM) associated with a reduction of its strength and function and is a frequent change that accompanies the physiological process of aging. Although sarcopenia is usually associated with advanced age, it can accompany various chronic diseases in younger patients[1].

In chronic kidney disease (CKD), sarcopenia is associated with the results of a change in the balance between catabolism and anabolism that controls the homeostasis of muscles[1]. In individuals with CKD, sarcopenia promotes the loss of muscle strength already at the moment of conservative treatment and progresses with the loss of renal function[1]. In CKD, sarcopenia increases morbidity[1] and is strongly correlated with higher mortality, physical disability[2], and increased cardiovascular events[3].

When there is kidney failure, among the possible renal replacement therapies (RRT), transplant emerges as the best option[4]. Sarcopenia in renal-transplant patients (RxT) has been studied in recent years; however, the literature is still scarce.

Considering the association of sarcopenia with adverse events and that it can occur very early in individuals with CKD, impacting their prognosis and survival, the objective of this study was to determine the prevalence of sarcopenia in renal-transplant patients (RxT) and its association with the determining factors that control muscle homeostasis.

METHODS

This is a cross-sectional study conducted on RxT at the Center for Kidney Disease Prevention of the University Hospital of the Federal University of Maranhão (HUUFMA), from June 2017 to July 2018. This study was part of a larger study, entitled "Nutritional Status of Renal Transplant Patients in The State of Maranhão", which was approved by the Human Research Ethics Committee of HUUFMA (Opinion no 1.872.021).

Variables were used to calculate the sample size, with its upper and lower limits defined by tolerance and characterized by a measure defined by a number, based on unpaired data, considering there was no control group. The study was completed in 213 individuals. The following were adopted as inclusion criteria: individuals aged above 20 years, of both sexes, RxT, undergoing outpatient follow-up on HUUFMA. We did not include pregnant women and people with amputated limbs, suffering from neurological diseases or sequelae from cerebrovascular accidents who were predisposed to a reduction of handgrip strength (HGS) or cognitive impairment, in addition to those with contagious or chronic consumptive diseases. Thus, the final sample comprised 83 individuals who met the criteria. All those who agreed to participate in the study signed an informed consent form.

We adopted two classifications for Body Mass Index (BMI): the one proposed for adults by the World Health Organization[5] and Lipschitz[6] for the elderly. The distribution of abdominal fat was assessed by waist circumference (WC)[7].

Sarcopenia was defined per the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP)[8]. For the assessment of body composition, patients were submitted to densitometry tomography by dual-energy x-ray absorptiometry (DEXA). To determine the LBM, the relative skeletal muscle index (RSMI) was measured according to the criteria established by Baumgartner and defended by the European Working Group on Sarcopenia in Older People.[8] The State of LBM decrease was assigned to cases in which the RSMI values were lower than 7.26 kg/m² for men and 5.5 kg/m² for women.

The handgrip strength (HGS) was used to assess muscle strength. The cut-off point was <30 kg for men and <20 kg for women.[8]

Muscle performance was assessed by calculating the gait speed test. A speed of less than 0.8 m/s was considered a risk for sarcopenia.[8]

Data Analysis

The categorical variables were presented through frequencies and percentages, and quantitative variables, based on mean and standard deviation values (mean ± SD). The normality of the variables was tested by the Shapiro-Wilk test. The analysis of numerical variables by the presence of sarcopenia was carried out by student t-test for variables with normal distribution and Mann Whitney test for the others. The analysis of categorical variables by the presence of sarcopenia was carried out using the chi-square test. We adopted a 95% confidence interval (1.96 standard deviation and standard error of 5%). Analyses were made using the Stata software, version 14.0®.

RESULTS

We assessed 83 RxT (mean age 48.8 ± 12.1 years). The prevalence of sarcopenia was 19.3%. Adult patients with and without sarcopenia had a mean BMI in the range of eutrophy, but with a statistically significant difference (24.7±4.9 kg/m² *vs* 19.1±2.4 kg/m2, respectively; p-value = 0.018). Whereas elderly individuals without sarcopenia presented mean BMI values in the range of excess body weight (28.3 ± 4.3 kg/m²), while those with sarcopenia were in the range of eutrophy (24.3 ± 8.4 kg/m²); however no statistical difference was observed (p-value=0.070).

The mean values of the WC of the men and women showed a high risk for cardiovascular diseases for those without sarcopenia (94.6±11.9 cm and 87.5±13,6 cm, respectively) and low risk for those with sarcopenia (82.5±13.7 cm and 77.9±20.6 cm, respectively), but with a statistically significant difference only among men (p-value=0.007) (Table 2).

Men and women without sarcopenia also showed preserved (08.1 ± 0.8 kg/m² and 6.6±0.7 kg/m2, respectively) and significantly higher (p-value < 0.001) mean values of LBM when compared to the group with sarcopenia (6.7±0.4 kg/m² and 5.2±0.3 kg/m2, respectively), which were altered (Table 2).

The gait test showed an alteration for both groups assessed, but with a greater reduction of muscle performance in individuals with sarcopenia (0.74±0.17 m/s *vs* 0.68±0.40 m/s; p-value=0.009). HGS

TABLE 2. CLINICAL, ANTHROPOMETRIC, AND BIOCHEMICAL CHARACTERISTICS AND COMPARISON BETWEEN WITH SARCOPENIA AND WITHOUT SARCOPENIA IN THE POPULATION STUDIED, SÃO LUÍS - MA, 2019.

Variable	Without sarcopenia Mean ± SD	With sarcopenia Mean ± SD	p-value
Age (years)	49.4 ± 1.4	46.1 ± 3.6	0.463
BMI (kg/m^2)			
Adults	24.7 ± 4.9	19.1 ± 2.4	0.018
Elderly	28.3 ± 4.3	24.3 ± 8.4	0.070
WC (cm) Men Women	 94.6 ± 11.9 87.5 ± 13.6	 82.5 ± 13.7 77.9 ± 20.6	 0.007 0.161
Lean Body Mass (kg/m^2) Men Women	 8.1 ± 0.8 6.6 ± 0.7	 6.7 ± 0.4 5.2 ± 0.3	 <0.001 <0.001
Gait Test (m/s)	0.74 ± 0.17	0.68 ± 0.40	0.009
Hand Grip Strength (kg) Men Women	 30.6 ± 8.7 19.7 ± 3.2	 25.0 ± 4.9 18.7 ± 3.7	 0.021 0.476
Transplant Time (months)	65.4 ± 54.3	60.3 ± 61.7	0.503
Albumin (g/dL)	4.3 ± 0.4	4.3 ± 0.4	0.910
Hemoglobin (mg/dL)	12.78 ± 1.59	12.36 ± 1.64	0.356
Total cholesterol (mg/dL)	165.9 ± 38.1	175.3 ± 37.3	0.393
HDL-c (mg/dL)	50.3 ± 17.9	47.7 ± 16.8	0.662
LDL-c (mg/dL)	84.7 ± 33.2	88.7 ± 19.3	0.715
Triglycerides (mg/dL)	173.7 ± 110.1	157.3 ± 74.7	0.586
Blood Glucose (mg/dL)	106.3 ± 41.5	93.1 ± 27.2	0.231
Serum Creatinine (mg/dL)	1.50 ± 0.97	1.56 ± 0.60	0.832
Cclearance Creatinine (ml/min/1.73^2)	58.9 ± 19.7	55.9 ± 23.5	0.601

WC: Waist circumferenc

FIGURE 1. ALTERED CRITERIA FOR CHARACTERIZING SARCOPENIA IN THE POPULATION STUDIED, SÃO LUÍS - MA, 2019.

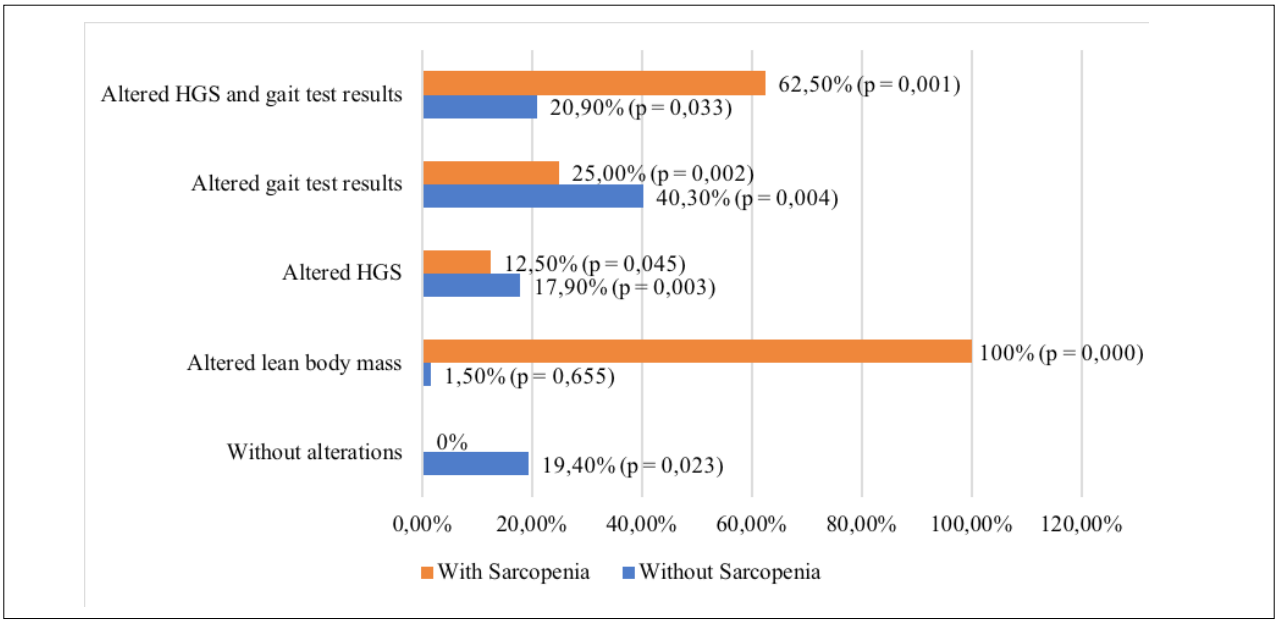

TABLE 1. SOCIODEMOGRAPHIC, CLINICAL AND NUTRITIONAL CHARACTERISTICS OF THE POPULATION STUDIED, SÃO LUÍS - MA, 2019.

Variables	N	%
Sex		
Female	35	42.2
Male	48	57.8
Age range		
≥ 20 <40 years	19	22.9
≥ 40 <60 years	49	59.0
≥ 60 years	15	18.1
Color		
White	8	9.6
Black	17	20.5
Brown	55	66.3
Others	3	3.6
Income		
>1 MW	3	3.6
1 to 2 MW	44	53.1
2 to 4 MW	23	27.7
≥4 MW	13	15.6
Formal education		
≤9 years	30	36.1
>9 years	53	63.9
Alcohol Consumption		
No former consumption	76	91.6
Yes	7	8.4
Smoking		
Not a former smoker	83	100.0
Type of donor		
Living	38	45.8
Deceased	45	54.2
RxT Time		
<6 months and < 1 year	14	16.9
≥ 1 year and <3 years	24	28.9
≥ 3 years and <5 years	11	13.2
≥ 5 years	34	41.0
Diabetes		
Present	13	16.2
Hypertension		
Present	70	87.5
Sarcopenia		
Present	16	19.3
BMI		
Low weight	6	7.2
Eutrophy	29	34.9
Overweight	32	38.5
Obesity	16	19.4

MW: minimum wage. BMI: body mass index.

was reduced only in men with sarcopenia (25.0 ± 4.9 kg), with a statistically significant difference (p-value=0.021) when compared to those without sarcopenia. On the other hand, for women, HGS was reduced in both groups (19.7 ± 3.2 kg and 18.7±3.7 kg; p-value=0.476) (Table 2).

Based on the analysis of the criteria for characterizing sarcopenia, it is possible to observe that among RxT patients with sarcopenia,12.5% presented decreased HGS (p-value = 0.045), 25.0% altered gait test results (p-value = 0.002), and 62.5% altered HGS and gait test results (p-value = 0.001). It is worth noting that, although only 1.5% of the cases without sarcopenia presented decreased lean body mass (p-value = 0.655), 17.9% had decreased HGS (p-value = 0.003), 40.3% altered gait test results (p-value=0.004), and 20.9% had both criteria altered (p-value=0.033) (Figure 1).

DISCUSSION

Studies on RxT indicate that sarcopenia occurs in younger age in comparison to the general population.[5,8-10] The only study conducted on RxT in Brasil found that the prevalence of this syndrome was more than double (49.6 %)[11], the highest percentage up until now reported in the literature. It is likely that sarcopenia in CKD starts during the period of conservative treatment, progressing with the loss of renal function and increasing morbidity.[1]

The prevalence of sarcopenia can also vary as a result of the methodology employed in its characterization since there is no universal operational definition and/or diagnostic criteria. In addition, the characteristics of the studied population can also interfere in the prevalence of sarcopenia since many factors lead to its development and progression, including advanced age, sedentary lifestyle, prolonged hospitalization, insulin resistance in the general population, among others.[8]

The BMI, in more than half of the sample (57.9%), remained in the range of overweight and obesity. It is worth noting that the index is not reliable regarding the differentiation of body fat (BF) and LBM, since throughout our lives can we maintain a stable weight and slowly lose LBM, gaining BF in equal volume, thus maintaining the same BMI for years; something that actually occurs in many people. In addition, sarcopenia can be difficult to identify, making it crucial to use other measurements that identify LBM.[12] We suppose that the weight gain in RxT is a result of several factors, such as recovery from anemia, a better quality of life, and increased appetite caused by the administration of steroids and immunosuppressants.[13]

Considering the above, it is necessary to raise questions about the quality of the diet of RxT, since this population is considered high risk for the development of obesity and changes in lipid and blood glucose metabolism due to the use of immunosuppressant drugs and the increased dietary freedom since dietary restrictions decrease dramatically post-transplant. The diet of a RxT individual is similar to that of a healthy one, without marked restrictions for sodium, phosphorus, and potassium, which causes this population to eat, in the postoperative stage, without pondering current and future complications, after all, they have gone through periods of dietary restriction.[14]

However, despite this share of RxT with excess weight and the preserved LBM, even in those without sarcopenia impaired HGS and gait were observed. According to findings of other studies, HGS was reduced in 40% of RxT.[4] There is already evidence of a dissociation between muscle mass and strength; the decline in HGS seems to be faster than the concomitant loss of LBM.[15]

This study presented as a limitation its cross-sectional design and the lack of assessment of adherence to the diet in the population studied. On the other hand, it presented as a strong point the assessment of sarcopenia in a population more susceptible to nutritional changes. In addition, we used the DEXA, considered the gold standard for assessing muscle mass with greater precision. Additionally, the research was carried out in a reference hospital for RxT in the state of Maranhão, the only center for renal transplant patient follow-up in the state.

CONCLUSIONS

Sarcopenia can develop in younger ages in RxT, and muscle strength and gait test results can be reduced even before a decrease in LBM. Another fact evidenced in this study was the prevalence of excess weight in this population, reinforcing the concern with the quality of the diet after RxT, since dietary restrictions decrease and these individuals have greater freedom in their food choices. This reinforces the importance of a thorough assessment of nutritional status in these patients, considering the differentiation of body composition and evaluating the individual holistically. Therefore, early diagnosis of the syndrome may allow for more rapid and effective intervention in RxT, preventing mobility disorders, falls, functional disability, and worsening of quality of life.

Author's Contribution

Cleodice Alves Martins and Ana Karina Teixeira da Cunha Françacontributed significantly in all stages of the project. The other authors contributed in data collection or analysis and interpretation and in the approval of the final version of the text.

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RESUMO

INTRODUÇÃO: *A sarcopenia é caracterizada pela perda involuntária da massa magra associada à redução da força e função muscular, de modo progressivo.*

OBJETIVO: *Determinar a prevalência de sarcopenia em transplantados renais e sua associação com os fatores determinantes que controlam a homeostase do músculo.*

MÉTODOS: *Foram avaliados indivíduos transplantados renais em acompanhamento no Hospital Universitário da Universidade Federal do Maranhão no período de junho de 2017 a julho de 2018 e que preencheram os critérios. A sarcopenia foi definida de acordo com o critério europeu. O índice de massa muscular esquelética foi medido por meio da densitometria computadorizada por absorciometria radiológica de dupla energia; valores <7,26 kg/m^2 para homens e <5,5 kg/m^2 para mulheres foram adotados para depleção muscular. Para força de preensão manual, valores de <30 kg para homens e <20 kg para mulheres foram considerados como redução da força muscular. Em ambos os sexos, o ponto de corte para velocidade de marcha reduzida foi <0,8 m/s.*

RESULTADOS: *Foram avaliados 83 transplantados renais, com média de idade de 48,8±12,1 anos e predominância de indivíduos do sexo masculino (57,8%). A prevalência de sarcopenia foi de 19,3%. Entre os indivíduos sem sarcopenia, 17,9% já tinham diminuição da força de preensão manual e 40,3%, alteração do teste de marcha.*

DISCUSSÃO: *Indivíduos submetidos ao transplante renal podem desenvolver sarcopenia jovens e apresentar alteração da função e da força muscular mesmo antes da depleção da massa magra.*

CONCLUSÃO: *O diagnóstico precoce pode permitir a prevenção da sarcopenia e propiciar melhor qualidade de vida aos pacientes.*

PALAVRAS-CHAVE: *Transplante de rim. Sarcopenia. Força muscular.*

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ORIGINAL ARTICLE

Hypophosphatemia and risk of refeeding syndrome in critically ill patients before and after nutritional therapy

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SUMMARY

OBJECTIVE: *To investigate the prevalence of hypophosphatemia as a marker of refeeding syndrome (RFS) before and after the start of nutritional therapy (NT) in critically ill patients.*

METHODS: *Retrospective cohort study including 917 adult patients admitted at the intensive care unit (ICU) of a tertiary hospital in Cuiabá-MT/Brasil. We assessed the frequency of hypophosphatemia (phosphorus <2.5mg/dl) as a risk marker for RFS. Serum phosphorus levels were measured and compared at admission (P1) and after the start of NT (P2).*

RESULTS: *We observed a significant increase (36.3%) of hypophosphatemia and, consequently, a greater risk of RFS from P1 to P2 (25.6 vs 34.9%; p<0.001). After the start of NT, malnourished patients had a greater fall of serum phosphorus. Patients receiving NT had an approximately 1.5 times greater risk of developing RFS (OR= 1.44 95%CI 1.10-1,89; p= 0.01) when compared to those who received an oral diet. Parenteral nutrition was more associated with hypophosphatemia than either enteral nutrition (p=0,001) or parenteral nutrition supplemented with enteral nutrition (p=0,002).*

CONCLUSION: *The frequency of critically ill patients with hypophosphatemia and at risk for RFS on admission is high and this risk increases after the start of NT, especially in malnourished patients and those receiving parenteral nutrition.*

KEYWORDS: *Critical care; Hypophosphatemia; Refeeding Syndrome; Malnourished; Nutritional Therapy.*

INTRODUCTION

Hypophosphatemia is recognized as a marker of refeeding syndrome (RFS)[1,2]. This change in the levels of phosphorus is more frequent among malnourished patients, in starvation, or among those with low calory intake[1,2].

A recent study showed that RFS occurred in 36.8%

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of the 337 patients in an intensive care unit (ICU), 72 hours after nutritional therapy (NT) was started[3]. In this study, hypophosphatemia was used to diagnose RFS[3]. For this reason, it is essential to correct the phosphorus level; the low serum value often goes undiagnosed or remains uncorrected on admission[4]. In this sense, studies show that 15% to 52% of the patients are hospitalized with hypophosphatemia[4-8].

This reduction of serum phosphorus, in the initial phase of NT, causes a rapid change in phosphorus from intravascular to intracellular, resulting in hypophosphatemia[1,2]. RFS usually begins on the third day after NT is started[3,9,10] and hypophosphatemia is a risk factor for its development[1-3,10-12]. For this reason, some authors started referring to RFS as hypophosphatemia syndrome or refeeding hypophosphatemia[6,12,13]. Phosphorus must be monitored to detect refeeding hypophosphatemia and, when it occurs, a caloric restriction must be instituted, with at least 1.3 g of protein/kg/day in the initial phase of refeeding[14].

In the Brazilian literature, we found review articles on the subject[15] and a single case report[16], but we did not find studies with data collected in Brasil. In this sense, it would be interesting to determine the frequency of hypophosphatemia in a national ICU, since this event is used as a marker of RFS in critical adult patients. Thus, the present study aimed to determine the presence of hypophosphatemia as a marker of RFS before and after the start of NT in intensive care patients.

METHODS

A retrospective cohort study performed with adult patients in the ICU of a tertiary hospital in Cuiabá-MT. The data collected from the medical charts refer to the period from 06/2014 to 12/2016. The study was approved by the Research Ethics Committee under CAAE: 47021715.0.0000.5541/2015 and is compliant with Resolution 196/96 of the National Health Council.

All patients admitted to the ICU, with age ≥18 years, of both sexes, and who had results of at least two examinations of serum phosphorus in the first week were considered eligible. The main variables were the phosphorus values on admission (P1) and after the start of NT (P2) and the association of hypophosphatemia with NT and nutritional status. The presence of hypophosphatemia (serum phosphorus <2.5 mg/dl) was defined as a risk marker for RFS on P1 and P2[3,5,7,8,13].

We collected data on patients' demographic, treatment (clinical or surgical), diet received (oral, enteral NT, parenteral or mixed NT [NT associated with oral or parenteral NT]), nutritional state, hospitalization time (days), and mortality. The inflammatory profile was established by PCR/serum albumin measured in the first 48 hours after hospitalization. The nutritional assessment was carried out by subjective global assessment (SGA)[17].

NT was initiated within the first 48 hours, in the presence of hemodynamic stability. Enteral NT, when prescribed, was initiated after confirming the tube location by X-ray. The nutritional needs were prescribed according to a routine published by our group, i.e., 25 to 30 kcal/kg and 1.25 to 2.0 g of protein/kg of body weight[18]. In the presence of hypophosphatemia, the replacement of serum phosphorus was established according to the value found[19]. For mild hypophosphatemia (2.3 to 3 mg/dl), there was a replacement of 0.16 mEq/kg at 4 and 6 hours; for moderate hypophosphatemia (1.6 to 2.2 mg/dl), of 0.32 mEq/kg at 4 and 6 hours; and for severe hypophosphatemia (<1.5 mg/dl), of 0.64 mEq/kg at 8 and 12 hours[19].

Statistical analysis

We used the chi-square test to analyze the categorical variables. The continuous variables were initially analyzed by the Levene test to verify their homogeneity, followed by the Kolmogorov-Smirnov test to determine their normality. The chi-square test for trend with Yates correction was used to evaluate the difference between hypophosphatemia at P1 and P2. The paired t-test was used to compare the mean values of P1 and P2. The data were expressed as numbers and percentages or mean and standard deviation. The *odds ratio* (OR) and a 95% confidence interval were used for comparisons of RFS and hypophosphatemia risk. We established a limit of statistical significance of 5% ($p \leq 0.05$). The statistical analysis was carried out using the SPSS statistical package for the Social Sciences 20.0 (SPSS Statistics; IBM, Armonk, NY, USA).

RESULTS

There were 1,302 eligible patients, of which 387 were excluded for not having the results of the first (n=2) and second (n=385) sample of serum phosphorus. We included in the study 917 patients with a mean age of 62.9±17.6 years, of which 464 (50.6%) were males. Of these, 576 (62.8%) were hospitalized

for clinical treatment, and 341 (37.2%) for surgical treatment.

Regarding their nutritional state, 13.3% (n=122) were eutrophic, 66.2% (n=607) were at risk of malnutrition or had moderate malnutrition, and 20.5% (n=188) had severe malnutrition. After 48 hours of hospitalization, 521 (56.8%) patients received some kind of NT (Figure 1). Thus, 329 (63.1%) received enteral nutrition, 43 (8.3%) received parenteral nutrition, and 149 (28.6%) received enteral nutrition supplemented with parenteral nutrition. The mean hospitalization time was 11.7±14.9 days and the mortality rate was 30.6% (n=202). The mean serum albumin was 2.93±0,57g/dL, the PCR was 104.2±92.0 mg/dL, and the PCR/albumin ratio was 42.7±40.3.

Hypophosphatemia and, consequently, the risk of RFS were identified in 25.6% (n=235) and 34.9% (n=320) of the cases, respectively at P1 and P2 (p<0.001). There was a 36.3% increase in the incidence of hypophosphatemia throughout the period studied (Figure 2). Table 1 shows that the mean phosphorus values on the second collection were lower than those on the first (p=0.004). However, this significant difference was not maintained when comparing only patients admitted with hypophosphatemia (p=0.194).

The patients who received NT had more chance of developing hypophosphatemia and a greater risk of RFS in P2 (OR=1.44, 95% CI, 1.1-1.89; p=0.01) when compared to those who received an oral diet. Patients who received parenteral nutrition (27/43; 62.8%) had more chances of hypophosphatemia when compared with the group that received enteral nutrition (124/329, 37.7%; OR=2.79 - 95% CI: 1.44-5.38; p=0.001) and with those who received enteral nutrition supplemented with parenteral nutrition (56/149, 37.6%; OR=2.80 - 95% CI: 1.39-5.65; p=0.002). The malnourished patients showed a tendency to develop more hypophosphatemia (p=0.051) in P2 than non-malnourished ones. However, the mean serum phosphorus in P2 (nourished: 3.42±1.68 *vs* malnourished: 3.14±1.55 mg/dl; p=0.04) was significantly lower among the malnourished patients. On admission, i.e., at P1 (nourished: 3.49±1.37 *vs* malnourished: 3.31± 1.29 mg/dl; p=0.22), there was no difference.

TABLE 1. SERUM PHOSPHORUS OF THE PATIENTS STUDIED.

Variables	Mean ± SD
Value at P1 (mg/dl)	3.33±1.3*
Value at P2 (mg/dl)	3.18±1.57
Value at P1 for hypophosphatemia (mg/dl)	1.87±0.42
Value at P2 for hypophosphatemia (mg/dl)	1.91±0.43

P1: results of serum phosphorus from the first collection (on admission); P2: results of serum phosphorus from the second collection (after the start of NT). Values expressed as mean±SD or numbers and percentages. *P=0.004 *vs* value at P2, (paired t-test)

DISCUSSION

Our results show that approximately 25% of critical patients were hospitalized with hypophosphatemia and, therefore, with a risk of RFS. In addition, there was an increase of approximately 36% in cases of patients with hypophosphatemia when the second collection of phosphorus was analyzed. In other words, after the start of NT, little more than 1/3 of the patients presented hypophosphatemia. This means that patients undergoing NT had nearly 1.5 more chances of developing hypophosphatemia and, consequently, the risk of RFS. Other studies have shown

FIGURE 1. TYPE OF DIET RECEIVED BY THE PATIENTS STUDIED.

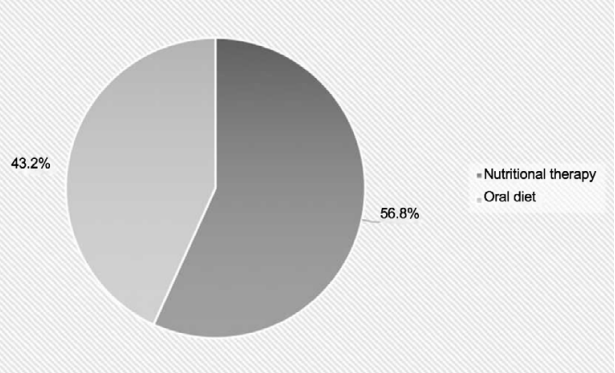
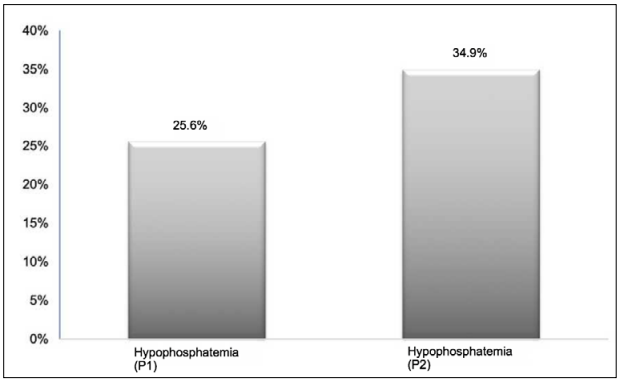


FIGURE 2. DISTRIBUTION OF THE HYPOPHOSPHATEMIA FREQUENCY AND RISK OF REFEEDING SYNDROME FOR PHOSPHORUS 1 (P1) AND PHOSPHORUS 2 (P2)*P<0.001 *vs* HYPOPHOSPHATEMIA (P1). CHI-SQUARED TEST FOR TREND WITH YATES' CORRECTION.



an occurrence of hypophosphatemia in intensive care patients similar to our findings and this abnormality is common and undiagnosed after the start of NT[3-6]. Another important point is that hypophosphatemia is used as a parameter for the diagnosis of RFS or "hypophosphatemia syndrome"[13,20].

Unfortunately, there is no universally accepted definition for diagnosing RFS with unambiguous criteria[21]. However, a systematic review has shown that hypophosphatemia is present in more than 95% of documented cases of RFS and that this phosphatemia is commonly used, in clinical practice, as a marker of RFS[1,3,10,13]. It is important to highlight that RFS, diagnosed pragmatically based on hypophosphatemia, is induced by refeeding, particularly when this is carried out in full during the first three days of NT[1,3,7,9,10]. Therefore, soon after admission and mainly in the second or third day of nutrition, it is fundamental to monitor phosphorus values to prevent RFS[1,10,11,13,14,17,19,21].

Our data show that not only ¼ of critical patients are already admitted with hypophosphatemia, but also that this abnormality increases after the start of NT when compared to patients who received an oral diet. Although we do not have numerical data on the calories and proteins offered, one may speculate that these patients undergoing NT received more calories and nutrients than the patients who received an oral diet. This may have contributed greatly to the greater decrease in serum phosphorus values in the NT group[1,2,3,17].

Although there was no significant difference, the number of patients with malnutrition showed a tendency of developing hypophosphatemia after the start of the diet when compared to nourished patients. However, serum phosphorus values showed that, on average, they were significantly lower in malnourished patients. Indeed, early diagnosis of the nutritional state helps the team to identify patients at risk of RFS who can benefit from a slower and more restricted supply of calories[11,12,14]. Our data are similar to those of the literature and show that malnourished patients are more prone to developing hypophosphatemia with the start of NT.

In the light of these results, although there was an intervention to correct the phosphorus levels, it seems to have been ineffective and, therefore, it is pertinent to monitor the serum phosphorus levels in critical patients before and after the start of NT. These patients should receive NT with a reduced supply of calories while the correction of electrolytes, especially of phosphorus, is carried out[1,8,11,14,17].

It should be remembered that unlike in an oral diet, in which the patient must voluntarily ingest foods, with parenteral or enteral NT the supply does not depend on their will. Thus, this invasive supply of calories may have contributed both to the drop of phosphorus values and to the increase in hypophosphatemia when the second collection of phosphorus was analyzed. In this regard, our data show that patients who received parenteral nutrition alone presented a higher risk of developing hypophosphatemia than those who received enteral nutrition alone or associated with parenteral nutrition. Indeed, the literature shows that hypophosphatemia has been more associated with parenteral nutrition[1], but it is interesting to note that this can also occur in patients receiving enteral nutrition[13].

Another important point is that in the initial phase of the inflammatory and neurohormonal response there is an accelerated muscle protein catabolism with the production of approximately 1,200 kcal/day[22]. Thus, it is vital to acknowledge this endogenous production of calories to avoid excess feeding and unfavorable outcomes, such as RFS[23].

In this context, Nice[11] recommends starting NT with less than 50% of the target caloric intake for patients with a risk of RFS. For some, it is recommended to start with 5 to 10 calories per kilogram of body weight associated with monitoring of blood glucose levels and the correction of phosphorus, magnesium, potassium, and thiamine levels[1,12,15].

Although the present study adds interesting data to the literature, it has limitations, such as the lack of the number of calories and proteins offered to patients. This would have enabled a better analysis of the results. Another limitation is the lack of a severity score; however, some studies have used the PCR/albumin ratio as an important marker of inflammation, prognosis, and mortality[24].

CONCLUSION

The prevalence of critical patients with hypophosphatemia and a consequent risk of RFS is high. This risk increases after the start of NT, especially in malnourished patients and those who receive parenteral nutrition alone. Thus, it is important to monitor the serum phosphorus during hospitalization and in the days following the start of NT.

Institution

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Author's Contribution

Amanda Coelho Ribeiro: Participated in the investigation, methodology, resource, and drafting.

Diana Borges Dock-Nascimento: Participated in the conceptualization, data analysis, methodology, resource, supervision, drafting, revision, and editing.

João Manoel Silva Jr: Methodology and drafting, revision, and editing.

Cervantes Caporossi: Formal analysis, methodology, and drafting.

José Eduardo de Aguilar-Nascimento: Formal analysis, methodology and drafting, revision, and editing.

RESUMO

OBJETIVO: *Determinar a frequência de hipofosfatemia como marcador da síndrome de realimentação (SR) antes e após o início da TN em pacientes críticos.*

MÉTODOS: *Coorte retrospectiva realizada com 917 pacientes adultos de um hospital terciário em Cuiabá-MT. Foi determinada a frequência de hipofosfatemia (fósforo <2,5 mg/dl) como marcador de risco de SR, para valores de fósforo sérico da admissão (P1) e após o início da TN (P2).*

RESULTADOS: *Foi observado um aumento significativo (36,3%) da hipofosfatemia entre P1 e P2 e, consequentemente, do risco de SR (25,6% **vs** 34,9%; p<0,001) com o início da TN. Após o início da TN, pacientes desnutridos apresentaram maior queda do fósforo sérico. Os pacientes com TN apresentaram aproximadamente 1,5 vez mais chance de desenvolver hipofosfatemia e risco de SR (OR=1,44 IC95% 1,10-1,89; p=0,01) quando comparado aos com dieta oral. Nutrição parenteral foi mais associada à hipofosfatemia **versus** nutrição enteral (p=0,001) e nutrição enteral suplementada com parenteral (p=0,002).*

CONCLUSÃO: *A frequência de pacientes críticos com hipofosfatemia e em risco de SR é alta e esse risco aumenta após o início da TN, especialmente nos desnutridos e naqueles recebendo nutrição parenteral.*

PALAVRAS-CHAVE: *Cuidados críticos. Hipofosfatemia. Síndrome de realimentação. Desnutrição. Terapia nutricional.*

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ORIGINAL ARTICLE

An estimate of the incidence and prevalence of laryngeal papillomatosis in São Paulo State (Brasil)

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SUMMARY

BACKGROUND: *Recurrent laryngeal papillomatosis, caused by the Human Papilloma Virus, has a significant economic impact worldwide and there are no epidemiological data of this disease in Brasil.*

OBJECTIVE: *The objective of the study was to estimate the incidence and prevalence of laryngeal papillomatosis of some otorhinolaryngology centers in São Paulo State (Brasil).*

METHODS: *A questionnaire containing data on the number of new and follow-up cases diagnosed with laryngeal papillomatosis was sent to the Otorhinolaryngology services (n=35) of São Paulo State (Brasil).*

RESULTS: *A total of 20 otorhinolaryngology centers answered the questionnaire. Of these, the five largest regional health centers were selected as follows: Campinas (42 cities – 4,536,657 inhabitants), Sao Jose do Rio Preto (102 cities – 1,602,845 inhabitants), Ribeirão Preto (26 cities – 1,483,715 inhabitants), Bauru (68 cities – 1,770,427 inhabitants), and Sorocaba (47 cities – 2,478,208 inhabitants). The incidence and prevalence of each regional health centers were, respectively: Campinas (5.51;7.27), Sorocaba (2.02;6.86), São José do Rio Preto (1.87;7.49), Ribeirão Preto (11.46;22.92), and Bauru (3.95;7.91).*

CONCLUSION: *The incidence and prevalence of the laryngeal papillomatosis of the five largest regional health centers of the interior of São Paulo State (Brasil) varied between 1.87 to 11.46 and 6.86 to 22.92 per 1,000,000 inhabitants, respectively for a total population of 11,871,852 inhabitants.*

KEYWORDS: *Papilloma. Larynx. Laryngeal neoplasms. Papillomaviridae. Epidemiology. Incidence. Prevalence.*

INTRODUCTION

Laryngeal papillomatosis is the most common benign neoplasm caused by the Human Papillomavirus (HPV)[1,2]. It is characterized by the presence of multiple proliferative and exophytic lesions of conjunctive tissues, covered by squamous epithelium, which happens especially in the anterior third of the vocal folds (figure 1). The disease course in children is more aggressive, undergoing several relapses and exposing

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the child to surgical interventions. The symptoms of permanent hoarseness can evolve to dyspnea and stridor, in more severe cases.

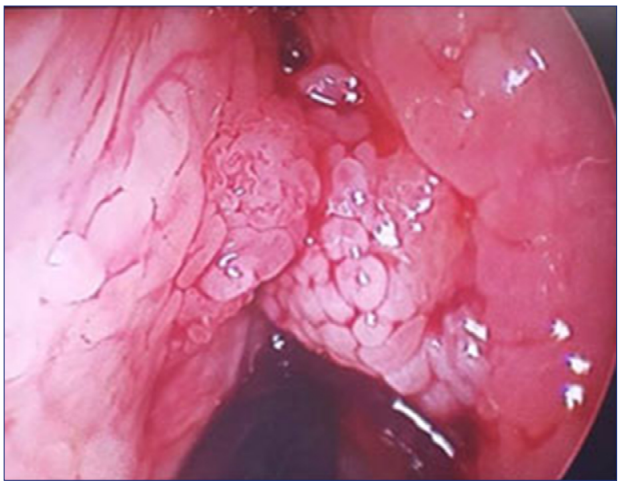
The pathways of contamination are not totally understood; however, sexual and vaginal transmission during pregnancy is discussed[3-6].

The diagnostic and treatment costs of diseases caused by HPV present an important economic impact worldwide[7]. International data indicate that, in 2003, the United States spent US$ 418 million in the treatment of diseases caused by HPV, while Italy spent 528,6 million Euros for the same treatment[7]. In Brasil, the lack of national epidemiological data regarding the incidence and prevalence of Recurrent Respiratory Papillomatosis (RRP) does not allow us to analyze the behavior of the disease in our population, as well as the benefit of preventive measures, like vaccination, available throughout the national territory in the past few years. Thus, this study aims to estimate the incidence and prevalence of Laryngeal Papillomatosis in some otolaryngology services in the interior of the São Paulo State.

METHODS

In Brasil, São Paulo health services are grouped into 16 health directories (https://www.ibge.gov.br/)[8]. After identifying each regional center and the number of cities in each of them for health care, the otolaryngology services were identified from the registered data in the Brazilian Association of Otolaryngology and Cervicofacial Surgery. From that point, a questionnaire was sent to the doctor responsible for the services of otolaryngology in these centers, containing questions regarding the number of new and follow-up cases with laryngeal papillomatosis diagnostic which were cared for during 2017. The contacts were made through postage, email, phone, and personal contact.

FIGURE 1. PAPILOMATOSE LARINGEA



Minimum Incidence and Prevalence

Minimum Incidence (I) of laryngeal papillomatosis by health region on the interior of the São Paulo State (table 1).

Data referring to the incidence of Laryngeal Papillomatosis in each health region were obtained through the following equation:

$$I = \frac{X}{N} X\ 1.000.000$$

X - number of newly diagnosed cases of recurring laryngeal papillomatosis in 2017 in a determined health region in the São Paulo State.

N - total population of this evaluated health region.

Minimum Prevalence (P) of recurrent laryngeal papillomatosis by health region of the interior of the state of São Paulo (table 1).

Data referring to the prevalence of Laryngeal Papillomatosis in each health region were obtained through the following equation:

$$P = \frac{Y}{N} X\ 1.000.000$$

Y - Number of follow-up cases of recurrent laryngeal papillomatosis in 2017 in a specific health region of the interior of the São Paulo State.

N - total population of this evaluated health region.

The study was approved by the Research Ethics Committee of the Botucatu School of Medicine (nº 2.700.908) on 06/04/2018.

RESULTS

Among the 35 otorhinolaryngology services that received the questionnaire, only 20 returned them. The health regions belonging to these centers were selected, totalizing 285 cities, as follows: Campinas (42 cities – 4,536,657 inhabitants), Sao Jose do Rio Preto (102 cities – 1,602,845 inhabitants), Ribeirão Preto (26 cities – 1,483,715 inhabitants), Bauru (68 cities – 1,770,427 inhabitants) and Sorocaba (47 cities – 2,478,208 inhabitants) (Table 1).

Table 1 shows that the incidence and prevalence of laryngeal papillomatosis varied between 1.87 to

11.46 and 6.86 to 22.92, per 1,000,000 inhabitants. In Ribeirão Preto the incidence and prevalence were higher than in the other cities. Adults were more compromised.

DISCUSSION

In our study, the incidence and prevalence of laryngeal papillomatosis in the five largest regional health centers of the interior of the São Paulo State (Brasil) varied from 1.87 to 11.46 and 6.86 to 22.92, per 1,000,000 inhabitants, respectively, for a total population of 11,871,852 habitants. Table 1 shows important variations between the health regions, with emphasis on the region of Ribeirão Preto, in which levels are three times higher than in the other regions. The literature does not have national data that allow us to analyze the regions comparatively. The lack of answers from the rest of the Otorhinolaryngological centers also impaired the scope of this study.

American estimates indicate that in the United States the incidence of laryngeal papillomatosis is near to 43 per 1,000,000 children aged 14 years or less[9]. Another study pointed to lower levels of incidence and prevalence, respectively, for the city of Atlanta (11.1 and 25.9 per 1,000,000 inhabitants) and Seatle (3.6 and 16.9 per 1,000,000 inhabitants)[10]. Campisi et al.[11] performed a national survey of children and youngsters in Canada and noticed an incidence of papillomatosis of 2.4 per 1,000,000 and a prevalence of 11.1 per 1,000,000 inhabitants. In 2014, Marsico et al.[12] published a longitudinal retrospective cohort study performed in the United States from data given by private and public insurers on the population aged from 0 to 17 years. The authors noticed an incidence of laryngeal papillomatosis, respectively for each insurer, of 5.1 and 10.3 per 1,000,000 habitants, with a peak of incidence between the ages of 0-4 years, and a prevalence rate of 14.5 and 29.3 per 1,000,000 habitants, respectively. They also highlighted the higher levels in children with lower socioeconomic status. In a retrospective study that included 48 cases of laryngeal papillomatosis diagnosed in a period of ten years in Senegal, Maïga et al.[13] registered 4.8 cases per year. As we have seen, the prevalence and incidence of papillomatosis vary greatly between regions and are influenced, probably, by different socioeconomic, cultural, and geographical conditions.

Laryngeal papillomatosis is a relatively rare disease in clinical practice, but with a high level of relapses and surgical interventions, which are exempt from sequelae to the laryngeal mucosa, with syneches and stenosis being the most terrible conditions, especially due to their predilection for the anterior portion of the glottis[1,14-17].

To be sure, in the long term, of the benefits of the treatments being adopted, especially regarding vaccination campaigns, it is necessary to know the data relative to the behavior of the disease regarding its incidence and prevalence in our population, data which are practically non-existent.

Vaccines against HPV were introduced in the United States in 2006, initially recommended only for girls and young women, being posteriorly amplified to include boys and young men. Currently, vaccination is recommended for all children of 11 or 12 years, women and men of, at most, respectively, 26 and 21 years, with the costs being borne by private insurers and public programs. Even after so many years of availability of the vaccine, the levels of incidence and prevalence of laryngeal papillomatosis are still high in the United States. The rate of adhesion to vaccination against this disease is around 43.8%[18].

TABLE 1. ESTIMATIVE OF INCIDENCE AND PREVALENCE OF LARYNGEAL PAPILLOMATOSIS IN HEALTH REGIONS OF LARGE CITIES OF THE SÃO PAULO STATE COUNTRYSIDE IN 2017, PER 1,000,000 INHABITANTS.

Regional Health Centers	Population (Inhabitants)*	Age range (in years)		New Cases (n)	Follow-up cases (n)	Incidence	Prevalence
		<20	≥20				
Campinas	4,536,657	31	27	25	33	5.51	7.27
Sorocaba	2,478,208	5	17	5	17	2.02	6.86
Bauru	1,770,427	12	9	7	14	3.95	7.91
Ribeirão Preto	1,483,715	20	31	17	34	11.46	22.92
São José do Rio Preto	1,602,845	5	10	3	12	1.87	7.49
Total	11,871,852	73	94	57	110	4.80	9.27

Source: IBGE (Brazilian Institute of Geography and Statistics) -2017[8]

In Brasil, vaccination was introduced in 2014, and it is indicated for girls between nine and 14 years and boys between 11 and 14 years. Unfortunately, we still do not have data in the literature that informs us of the number of children with laryngeal papillomatosis that have been forwarded to vaccination.

We believe that the initial epidemiological data presented in this study, which refers to a population of 11,871,852 habitants, totaling 285 cities of the São Paulo countryside, may guide future studies allowing the evaluation of the behavior of laryngeal papillomatosis in Brasil.

CONCLUSION

The incidence and prevalence of laryngeal papillomatosis in the five largest regional health centers of the interior of the São Paulo State (Brasil) varied from 1.87 to 11.46 and 6.86 to 22.92 per 1,000,000 inhabitants, respectively, for a total population of 11,871,852 habitants.

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We would like to thank the otolaryngology services that participated in this study by answering the questionnaires.

Author's Contribution

Regina Helena Garcia Martins: study design, data analysis, paper writing, final manuscript review and approval.

Gustavo Mercuri: study design, data preparation, data compilation and analysis.

Sergio Augusto Rodrigues: statistical analysis, data analysis, final approval.

RESUMO

CONTEXTO: *A papilomatose recorrente da laringe, causada pelo vírus do papiloma humano, tem um impacto econômico significativo em todo o mundo e não existem dados epidemiológicos dessa doença no Brasil.*

OBJETIVO: *O objetivo do estudo foi estimar a incidência e prevalência de papilomatose laríngea em alguns centros de otorrinolaringologia do estado de São Paulo (Brasil).*

MÉTODOS: *Um questionário contendo dados sobre o número de casos novos e de retornos diagnosticados com papilomatose laríngea foi enviado aos serviços de otorrinolaringologia (n-35) do estado de São Paulo (Brasil).*

RESULTADOS: *Vinte centros de otorrinolaringologia responderam ao questionário e, destes, os cinco maiores centros regionais de saúde foram selecionados da seguinte forma: Campinas (42 cidades - 4.536.657 habitantes), São José do Rio Preto (102 cidades - 1.602.845 habitantes), Ribeirão Preto (26 cidades - 1.483.715 habitantes), Bauru (68 cidades - 1.770.427 habitantes) e Sorocaba (47 cidades - 2.478.208 habitantes). A incidência e prevalência de cada centro de saúde regional foram, respectivamente: Campinas (5,51; 7,27), Sorocaba (2,02; 6,86), São José do Rio Preto (1,87; 7,49), Ribeirão Preto (11,46; 22,92), Bauru (3,95; 7,91).*

CONCLUSÃO: *A incidência e prevalência da papilomatose laríngea dos cinco mais importantes centros regionais de saúde do interior do estado de São Paulo (Brasil) variaram entre 1,87 e 11,46 e 6,86 e 22,92, por 1.000.000 de habitantes, respectivamente, para uma população total de 11.871.852 habitantes.*

PALAVRAS-CHAVE: *Papiloma. Laringe. Neoplasias laríngeas. Papillomaviridae. Epidemiologia. Incidência. Prevalência.*

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ORIGINAL ARTICLE

Morbidity and mortality due to surgical congenital malformations from the perspective of surgical neonatal ICU outside a maternity service: a retrospective cohort study

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SUMMARY

OBJECTIVE: *To describe the characteristics of patients treated at a level III surgical Neonatal Intensive Care Unit outside of a maternity service and analyze possible risk factors for mortality in this population.*

METHODS: *A retrospective cohort study evaluating patients admitted to a level III surgical Neonatal Intensive Care Unit from June/2015 to November/2017. Univariate analysis was performed by the Chi-square test and T-student test or Mann-Whitney test. Multivariate analysis by logistic regression was performed including in the model the variables with a P-value <0.2 in univariate analysis. Kaplan-Meier curve and Log-Rank test were performed using the variables that were statistically associated with death in the multivariate analysis. A significance level of a=5% and an error B=80% were adopted.*

RESULTS: *During this period, 246 patients were admitted to this service. 58 (23.8%) patients died, with a mean time until death of 18 days. Half of the patients had a clinical diagnosis of sepsis (50.6%), blood culture was positive in 25.2%, and gram-positive bacteria (48.4%) were the main pathogens isolated. The variables that remained in the final model after multivariate analysis were diagnosis of congenital heart disease (OR = 4.5; p = 0.016), clinical diagnosis of sepsis (OR = 8.1; p = 0.000), and isolation of gram-positive bacteria in blood culture (OR = 3.9; p = 0.006).*

CONCLUSION: *The level III surgical Neonatal Intensive Care Unit outside of a maternity service has a different profile of morbidity and mortality, and death was associated with the diagnosis of congenital heart disease, the clinical diagnosis of sepsis, and the isolation of gram-positive bacteria in the blood culture*

KEYWORDS: *Infant mortality. Congenital abnormalities/surgery. Intensive care units, neonatal.*

INTRODUCTION

Currently, neonatal deaths account for more than half of infant mortality in Brasil, and early neonatal death (in up to 7 days) is its main component, indicating a close relationship between prenatal care and delivery assistance.[1] Maternal and perinatal factors, such as prematurity and perinatal infections,

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are the main causes of death in the neonatal period, followed by congenital malformations, which together account for 80% of deaths during the 1st year of life.[1] However, when infant mortality is considered as a whole, the deaths due to congenital malformations have surpassed the perinatal causes in recent years, being consolidated as the main cause of death in the first year of life. This is due to the growth in mortality due to this cause, which rose from 11.4% in 2000 to 20.7% in 2013.[1] One explanation for that could be the improvement of health care service quality, resulting in the maintenance of life in the early neonatal phase due to better access and quality of service in Neonatal Intensive Care Units (NICU), which in turn enables higher rates of diagnostic and notification of these malformations.[2]

Congenital malformations are morphogenetic changes capable of causing functional changes, with a global prevalence of 2-3%.[3] The impact of congenital malformations on infant mortality depends on several factors, including the effectiveness of primary prevention that the prevalence of anomalies, and, above all, the access to, availability and quality of health care services for medical and surgical treatment to preserve life.[4]

The last census of the Brazilian Association of Intensive Medicine (AMIB) in 2016 showed that the number of NICUs represents 24.2% of all ICU services in the country[5]. The number of beds in Bahia represents 21.7% of the Northeast, and 13.5% of them are located in the capital. NICUs outside maternity services are infrequent in Brasil since they usually are located in general hospitals with maternity services. Souza et al.[6] demonstrated that 82.4% of the services of NICU/PICU were located in general hospitals, in a study conducted in 2002 in the city of São Paulo. This distribution of services is logical, considering that out of the total number of deaths in the 1st year of life, 7.1% occur in the first hour of life, and 24.7% in the first day of life, demonstrating the importance of services located where it is possible to have immediate access so as to act during the most critical period for mortality. [1]

The Surgical NICU of the Martagão Gesteira Hospital was inaugurated in 2015 as a level III NICU and was consolidated as a reference service for the entire state of Bahia. It services mainly newborns with congenital defects that require a surgical NICU to undergo a surgical procedure to preserve life at this stage. This service is located in a pediatric hospital outside a maternity service; thus, the assistance presents some limitations due to the need for transport for other services and suffers from a lack of important information for patient care, such as reliable documentation of prenatal care and data relating to the labor conditions. Thus, we couldn't find in the literature any studies performed at a service that presents a parallel with the characteristics mentioned above.

Therefore, this study is justified because it is an analysis of a level III surgical NICU service outside a maternity service, which is an unusual service model, which is a reference for the entire state of Bahia, servicing a extensive geographic area of great importance in the Northeast of the country, a region that still lacks studies when compared to large centers of the South, and Southeast regions and that represents the highest rate of neonatal deaths in the country (38.3%).[7] Thus, the goal of this study was to establish the epidemiological profile of patients treated in this service and analyze which factors were more closely related to neonatal mortality to improve the planning of preventive health care for this population.

METHODS

This is a retrospective cohort study carried out with all the children admitted to the NICU of the Martagão Gesteira Hospital, a reference level III neonatal surgical ICU for surgical congenital malformations in the state of Bahia.

The inclusion criteria were all children admitted to the NICU of the Martagão Gesteira Hospital from June/2015 to November/2017.

The data were collected by reviewing the electronic medical records, relying on information from patient admission to discharge or death.

The independent variables analyzed were: sex, prematurity, low birth weight, days of life upon admission, days of hospitalization, diagnosis at admission, presence of congenital malformation, having undergone surgery, clinical diagnosis of sepsis, blood culture results. The dependent variable considered was death.

The congenital malformations were classified according to the following categories: Malformations of the gastrointestinal tract (GIT), clinical diagnoses, malformations of the central nervous system (CNS), congenital heart defects and others (wall closing defects, urinary tract malformations, and tumors). The patients were classified according to birthweight

as low weight (<2500g) and gestational age in preterm infants (<37 weeks). The pathogens isolated in blood cultures were classified as gram-positive bacteria, gram-negative bacteria, and fungus.

The statistical analysis was performed using the data analysis software Statistical Package for Social Sciences, V 23.0 (SPSS Inc., Chicago, IL, USA). We used the Kolmogorov-Smirnov test to determine the normality of the distribution of continuous variables. For the descriptive analysis, we used means and standard deviation for continuous variables with normal distribution, median and interquartile ranges for continuous variables with non-normal distribution, and proportions for categorical variables. We calculated the odds ratio and confidence interval (95% CI) for all the variables. Univariate analysis was conducted comparing the individuals based on the death outcome using the chi-square test was used for the categorical variables and the Student t-test or Mann-Whitney test for continuous variables, depending on their distribution. Then we carried out a multivariate analysis by logistic regression, including variables that showed a p-value <0.2 in the univariate analysis. Survival analysis was performed by the Kaplan-Meier curve and Log-Rank test with the variables that were statistically associated with death in the multivariate analysis. We adopted a significance level of a=5% and an error B=80%.

This study was carried out after approval by the Research Ethics Committee of the Faculty of Medicine of Bahia CAEE (66804316.3.0000.5577).

RESULTS

During this period, 246 patients were admitted to this service and had their data collected. Of these, most were male, the minority was premature (39.0%), and nearly half had low birth weight (46.6%). The median of days of life on admission was 9 days, which classified the population as late neonates. The vast majority of hospitalized patients had some congenital malformation (77%). The main congenital malformations were: Malformations of the GIT (32%), malformations of the CNS (18.4), and congenital heart diseases (10.7%). (TABLE 1)

Most patients underwent some surgical procedure (67.4%) to correct the congenital malformation. The clinical diagnosis of sepsis was present in little more than half of the cases (50.6%). The blood culture was positive in only 25.2%; and the main pathogens isolated were Gram-positive bacteria (48.4%), mainly Coagulase-negative Staphylococcus, representing almost half of all isolated pathogens (43.5%), followed by gram-negative bacteria (37.1%), mainly Klebsiella sp. (16.1% of all pathogens isolated), and fungi 14.5%, with only Candida sp being isolated. The mean length of hospitalization was 13 days. Death was the outcome in 23.8% of the cases, with a median of 18 days up to this outcome. (TABLE 2)

It was possible to demonstrate through univariate analysis that the variables that were associated with death were low birth weight, diagnosis at admission, diagnosis of sepsis, and blood culture results. The variables that presented a trend of significance

TABLE 1. PATIENT DISTRIBUTION BY EPIDEMIOLOGICAL CHARACTERISTICS. SALVADOR (BA) BRASIL, 2018

	Patients N=246 (%)	Death N=58 (23.8%)	Gross OR (95% CI)	P-value
Sex			1.21 (0.673-2.191)	0.519
Male	133 (54.1%)	29 (22.1%)		
Female	113 (45.9%)	29 (25.7%)		
Prematurity	87 (39%)	22 (25.3%)	1.195 (0.634-2.254)	0.719
Low birth weight	109 (46.6%)	32 (29.4%)	1.946 (1.049-3.609)	0.033
Days of life at admission (median; IQR)	9; 22	119.66[1]	-	0.771
Days of hospitalization (median; IQR)	13;22	136.0[1]	-	0.082
Congenital malformation	188(77%)	46 (24.7%)	1.205 (0.586-2.475)	0.612
Diagnosis at admission				0.002
Clinical diagnosis*	56 (23%)	12(21.4%)	1.0	-
GIT Malformation	78 (32%)	20(25.6%)	1.264 (0.559-2.859)	0.573
CNS Malformation	45 (18.4%)	6 (13.6%)	0.579 (0.198-1.691)	0.318
Congenital heart disease	26 (10.7%)	14(53.8%)	4.278 (1.572-11.639)	0.004
Other malformations	26 (10.7%)	6(24%)	0.688 (0.233-2.026)	0.497

[1] Sum of the Mann-Whitney test rank; *Variable used as reference

TABLE 2. PATIENT DISTRIBUTION BY THE CLINICAL CHARACTERISTICS OF EVOLUTION DURING HOSPITALIZATION. SALVADOR (BA) BRASIL.

	Patients N=246 (%)	Death 58 (23.8%)	Gross OR (IC 95%)	P-value
Surgery	164 (67.2%)	44 (24%)	1.758 (0.897-3.444)	0.098
Diagnosis of sepsis	118 (50.6%)	46 (39.3%)	8.585 (3.824-19.273)	0.000
Blood culture				0.001
Negative*	182 (74.5%)	34 (18.7%)	1.0	-
Gram-positive	30 (48.4%)	15 (50%)	4.353 (1.942-9.755)	0.000
Gram-negative	23 (37.1%)	8 (34.8%)	2.322 (0.911-5.917)	0.078
Fungus	9 (14.5%)	1(11.1%)	0.544 (0.066-4.497)	0.572

* Variable category used as reference

with a p-value <0.2 were days of hospitalization, having undergone surgery. All of these variables were included in the multivariate analysis by logistic regression.

After the completion of the multivariate analysis, it was possible to observe that the only three variables in the model that still demonstrated a significant association with death were the diagnosis of congenital cardiopathy, which resulted in a chance approximately 4.5 times greater of death, the clinical diagnosis of sepsis, with a 8.1 times higher chance of death, and the presence of gram-positive bacteria isolated in the blood culture, with a 3.9 times higher chance of death. (TABLE 3).

The survival curve was drawn with the three variables that remained in the model after multivariate analysis. The median of days until death for the entire population was 18 days (95% CI 11.7-24.2). The clinical diagnosis of sepsis was the only variable that showed statistical difference regarding the number of days until death between the groups in the Log-Rank test, showing that individuals who presented sepsis had a median of 18 days until death (95% CI 11.3-24.6), while those who did not have a clinical diagnosis of sepsis had a median of 13 days (95% CI 0.0-38.6), with a p-value = 0.005 in the Log-Rank test (FIGURE 1).

TABLE 3. RESULTS OF THE LOGISTIC REGRESSION FOR RELATED VARIABLES AND MORBIDITY AND MORTALITY IN PATIENTS FROM THE SURGICAL NICU. SALVADOR (BA) BRASIL, 2018.

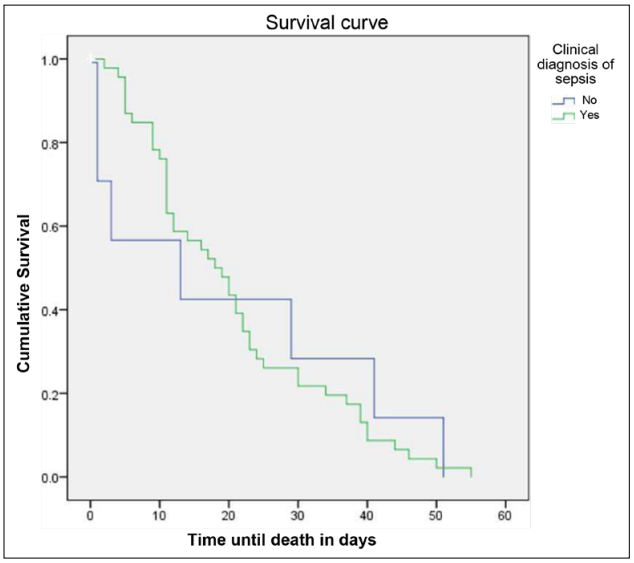
	Adjusted OR (95% CI)	P-value
Diagnosis at admission		
Clinical diagnosis*	1.0	-
GIT Malformation	0.925 (0.317-2.699)	0.389
CNS Malformation	0.557 (0.147-2.108)	0.557
Congenital heart disease	4.5 (1.317-15.432)	0.016
Other malformations	0.656 (0.170-2.533)	0.540
Days of hospitalization	0.979 (0.956-1.003)	0.084
Surgery	2.531 (0.976-6.564)	0.056
Diagnosis of sepsis	8.121 (3.332-19.795)	0.000
Blood culture		
Negative*	1.0	-
Gram-positive	3.958 (1.490-10.513)	0.006
Gram-negative	1.622 (0.546-4.817)	0.384
Fungus	0.395 (0.043-3.583)	0.409

* Variable category used as reference

DISCUSSION

The NICU services not linked to a maternity service usually present different epidemiological profiles and morbidity and mortality characteristics. We can observe that the profile of the patients treated in this service was of neonates with low birth weight, the minority of which was premature (39%), admitted already in the late neonatal period, in their great majority with surgical congenital malformations.

FIGURE 1. SURVIVAL CURVE OF INDIVIDUALS WITH A DIAGNOSIS OF SEPSIS.



These characteristics alone imply a different pattern of morbidity and mortality in this period since maternal and perinatal factors are expected to already have less impact on mortality.[1]

Initially, low birth weight was one of the variables associated with death in the univariate analysis. This finding was already expected since this association is well established in the literature.[7-9] However, in the multivariate analysis, low birth weight was not associated with death, so that it is assumed that, when there is interaction with other factors, perinatal factors demonstrate a lower influence in the late neonatal period in detriment to factors related to hospitalization and the underlying disease.

GIT malformations were the most frequent diagnosis in our population, along with malformations of the CNS, and congenital heart diseases. Whereas the diagnosis of congenital heart disease was the only one associated with death in the univariate analysis and that remained in the final model after the multivariate analysis, presenting a 4.5 times higher chance of death, as corroborated by Stewart et al.[10] That demonstrates that congenital malformations are responsible for 45% of deaths in a NICU in North America, and congenital heart disease is one of the main contributing factors. In addition, this diagnosis in our population showed a high frequency in comparison to the general population, in which the prevalence is approximately 4 to 5 cases per 1000 live births.[11] This greater frequency can be due potentially to the high severity of heart malformations, requiring the assistance of highly specialized services, something that is corroborated by the high mortality rate (53.8%), and this is the diagnosis with the highest rate of lethality in our population.

The univariate analysis failed to demonstrate an association between the diagnosis of congenital malformation and death, as would be expected for the late neonatal period, something that has been demonstrated in several studies on general NICU services.[8,10,12] However, our sample consists of patients from a NICU service that receives mainly surgical patients; thus, almost our entire population has been diagnosed with some type of malformation, which leads to the failure in identifying a difference between the groups.

The clinical diagnosis of sepsis was established in almost half of the individuals in our population and proved to be associated with death in the univariate analysis, remaining in the model after multivariate analysis and increasing the chance of death in around 8 times. However, this was not reflected by positive blood culture results, although this was already expected since it is known that the positivity rate of blood cultures from neonates is usually low, often due to the collection of an insufficient volume of blood, both due to difficulty in puncture and unfavorable hemodynamic conditions of these patients.[13] The pathogens most frequently isolated were similar to those demonstrated in the literature, indicating a higher frequency of agents that usually are not pathogenic in healthy newborns, such as coagulase-negative Staphylococcus and Candida sp.[14,15] In fact, even after the multivariate analysis, the isolation of gram-positive bacteria, among them the most frequent being coagulase-negative Staphylococcus, increased the chance of death in approximately 4 times. In North America, infections by this pathogen are responsible for up to 70% of the cases of neonatal sepsis and are related to longer hospitalizations and, consequently, higher treatment costs, thus burdening the health system. [16]

The survival analyses were carried out with the three variables that remained in the model after multivariate analysis. However, the clinical diagnosis of sepsis was the only variable to present a statistical difference regarding the number of days until death between the groups, demonstrating that the individuals who received a clinical diagnosis of sepsis later died, suggesting that the longer the length of hospitalization, the greater the chance of nosocomial sepsis due to interventions carried out.

Among the limitations of our study, we emphasize that the main one was analyzing a single-center, with retrospective data collection from patient records, which presents a risk of record bias.

CONCLUSION

We conclude that the NICU service outside a maternity service has a different profile of morbidity and mortality, receiving mainly patients with congenital malformations that require surgical repair, and death as an outcome was associated with the diagnosis of congenital heart disease, clinical diagnosis of nosocomial sepsis, and isolation of gram-positive bacteria in the blood culture.

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Author's Contribution

Sofia Oliva-Costa - study design; acquisition, analysis, and interpretation of data; drafting of the manuscript; Samir Nahass - acquisition of data; review and critical analysis of the manuscript; approval of the final version for publication; Andréa Dourado - acquisition of data; review and critical analysis of the manuscript; approval of the final version for publication; Selma Lopes - project concept; design of the study; acquisition, analysis, and interpretation of data; critical review of the manuscript and approval of the final version for publication.

RESUMO

OBJETIVO: *Traçar o perfil de pacientes atendidos em uma Unidade de Terapia Intensiva Neonatal cirúrgica nível III desvinculada de maternidade e analisar fatores de risco para mortalidade nesta população.*

MÉTODOS: *estudo de coorte retrospectivo, avaliando os pacientes internados em um serviço de Unidade de Terapia Intensiva Neonatal cirúrgica nível III de referência no estado no período de junho/2015 a novembro/2017. A análise univariada foi realizada pelo teste de Qui-quadrado e T-student ou Mann-Whitney. Foi realizada a analise multivariada por regressão logística incluindo no modelo as variáveis que apresentaram valor de P <0,2 na analise univariada. Foi realizada curva de Kaplan-Meier e teste Log-Rank com as varáveis que foram estatisticamente associadas ao óbito na análise multivariada. Adotou-se um nível de significância de a=5% e um erro B=80%.*

RESULTADOS: *Neste período, 246 pacientes foram internados neste serviço. Foram a óbito 58 (23,8%) pacientes, com tempo médio de óbito de 18 dias. Metade dos pacientes apresentaram diagnóstico clínico de sepse (50,6%), com hemocultura foi positiva em 25,2% e bactérias gram-positivas (48,4%) foram os principais patógenos isolados. As variáveis que se mantiveram no modelo final após a análise multivariada foram diagnóstico de cardiopatia congênita (OR=4,5; p=0,016), diagnóstico clinico de sepse (OR=8,1; p=0,000), e isolamento de bactéria gram-positiva na hemocultura (OR=3,9; p=0,006).*

CONCLUSÃO: *O serviço de Unidade de Terapia Intensiva cirúrgica nível III não vinculada a maternidade apresenta perfil diferenciado de morbimortalidade, e o óbito esteve associado ao diagnóstico de cardiopatia congênita, ao diagnostico clinico de sepse e ao isolamento de bactérias gram-positivas na hemocultura.*

PALAVRAS-CHAVE: *Mortalidade infantil. Anormalidades congênitas/cirurgia. Unidades de terapia intensiva neonatal.*

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ORIGINAL ARTICLE

Is the COVID-19 disease associated with de novo nephritic syndrome?

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SUMMARY

INTRODUCTION: *This study aims to determine the incidence of de novo nephritic syndrome (NS) in COVID-19 patients and identify its associated factors.*

METHODS: *All ward patients with COVID-19 pneumonia were investigated. After determining the inclusion and exclusion criteria, the study population was identified. The urine dipstick test and urine protein creatinine ratio (UPCR) measurements were performed. Patients with de novo NS findings, nasopharyngeal swab, and urine RT-PCR tests were performed simultaneously*

RESULTS: *This descriptive cross-sectional study was conducted with 21 patients with COVID-19. The mean age of the patients was 42.2±8.8 years, and 71.4% of them were male. The mean duration of follow-up was 28.4±9.3 days. The urine RT-PCR test was positive in one patient (4.8%). Improvements were observed in hematuria by 71.4%, and proteinuria by 85.7% at the end of the follow-up. A significant decrease in the measured UPCR was found in comparison to the baseline(P=0.000). Also, improvements were recorded in the complete blood counts, inflammatory parameters, ferritin, and coagulation tests, compared to the baseline. There was a positive correlation between baseline UPCR and ferritin, and a negative correlation between baseline UPCR and sodium values*

CONCLUSION: *COVID-19-induced de novo nephritic syndrome may occur mainly due to tubulointerstitial involvement and often results in spontaneous remission. However, why these findings were not present in all patients who had no comorbidities is not clear.*

KEYWORDS: *Coronavirus Infections. Hematuria. Proteinuria. Acute kidney injury. Nephritis.*

INTRODUCTION

The Coronavirus (COVID-19) outbreak was recognized as a pandemic in March 2020 by the World Health Organization (WHO). Fever, cough, and shortness of breath are the most common complaints in these patients[1]. According to our knowledge, the respiratory, immune, and coagulation systems are among the major targets of the virus[2]. In terms of organ involvement, acute respiratory distress

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syndrome (ARDS) due to pneumonic infiltration of the lung is the first organ to be affected[3]. Subsequent clinical and autopsy studies showed damage in several extrapulmonary organs, including acute heart and kidney damage, in addition to ARDS[4,5]. The mechanisms of kidney damage in COVID-19 patients and whether the kidney is a hidden viral nest are still unclear. COVID-19 virus has been shown to cause injury in tubulointerstitial areas rather than in the glomeruli of the kidney[6]. In an autopsy study on COVID-19-induced kidney injury, acute proximal tubular and endothelial damage was found. Acute kidney injury (AKI) and proteinuria were shown to develop due to the presence of particles of the virus in the proximal tubule epithelium and podocytes[5]. In the normal population, active urinary sediments may occur due to AKI, sepsis, and multiorgan failure[7]. Proteinuria and hematuria were found to be associated with the risk of AKI and mortality in critically ill patients without COVID-19 disease[8,9]. Microscopic hematuria and proteinuria are common, especially in severe COVID-19 patients in intensive care units (ICU)[8]. The presence of these renal involvements (AKI, hematuria, proteinuria) was shown to increase the risk of COVID-19-induced mortality, compared to patients without renal involvement[7,8]. Conflicting results on COVID-19-induced microscopic hematuria and proteinuria were reported. The symptoms of proteinuria and hematuria detected in the studies may be due to underlying comorbidities, such as hypertension and diabetes mellitus. In addition, due to the low viremia potential of COVID-19, the microscopic hematuria and proteinuria found in particularly severe patients in ICU may develop secondary to AKI, cytokine storm, and sepsis. However, symptoms of de novo nephritic urine, developed in stable patients with no comorbid disease and no AKI or sepsis condition may be associated with COVID-19 disease.

This study aims to determine the incidence of de novo nephritic syndrome in patients with pneumonia due to COVID-19, and to investigate whether urinary findings were associated with COVID-19.

METHODS

All ward but not ICU patients with COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) positivity were detected. Patients >18 and <60 years of age, with proteinuria and/or hematuria detected in their urine, without any chronic disease, such as hypertension, diabetes mellitus, chronic renal failure, glomerular disease, patients who did not receive any antihypertensive medication, and patients without a history of previous microscopic hematuria and/or proteinuria were included in the study. Patients who received a therapeutic or herbal medicine that may cause nephritic syndrome, patients with viral hepatitis, AKI, renal transplant, kidney stones, urinary tract infection, and ICU patients, patients with a urinary catheter, with a history of malignancy, and female patients with menstrual bleeding were excluded from the study. The urine dipstick test positivity detected on the first day of hospitalization was repeated on the first morning using the dipstick test, and urine protein creatinine ratio (UPCR) was measured. Patients' biochemical parameters were recorded at admission and after discharge. The study was carried out upon receiving approval by the Ethics Committee of the Sakarya University Faculty of Medicine (No:71522473/050.01.04/248).

Statistical analysis: Quantitative data were expressed as mean values ± SD, medians, and ranges. Qualitative data were expressed as numbers and percentages. The assumption of normality was tested by the Shapiro-Wilk test. Paired Samples T-test and Wilcoxon Signed Rank tests were used when appropriate. The Spearman correlation coefficient was used to evaluate the degree of correlation between the parameters. P-values <0.05 were considered statistically significant. Analyses were performed by using Statistical Package for the Social Sciences version 20.0 (IBM SPSS Statistics; Armonk, NY, USA).

RESULTS

A. General characteristics

A total of 1669 COVID-19 patients were investigated in this descriptive cross-sectional study between March 15th and April 20th, 2020. The study was conducted with 21 patients (1.26%) who met the criteria for inclusion in the study and had de novo microscopic hematuria and nephritic proteinuria, according to urine tests and a history of comorbidities. The mean age of the patients was 42.2±8.8 years, and 15 (71.4%) were male. The mean body mass index and duration of the follow-up period were 23.6±5.0 kg/m2 and 28.4±9.3 days, respectively.

B- Urine analysis and laboratory outcomes

Two consecutive results of more than trace or 1+ of protein on the dipstick test were considered as positive proteinuria (1+ in 8 patients, 2+ in 5 patients, 3+ in 8 patients). Two consecutive results of more than trace or 1+ of blood on the dipstick test were considered as positive hematuria (1+ in 9 patients, 2+ in 7 patients, 3+ in 5 patients). Two consecutive results of random UPCR were measured and >300 mg/g creatinine was considered as abnormal proteinuria.

Just one patient (4.8%) had positive urine COVID-19 RT-PCR test results. Hematuria and proteinuria were found to be improved by 71.4% and 85.7%, respectively. In addition, there was a significant decrease in the measured UPCR compared to the baseline (409.1±218.6 vs 109.1±218.6 mg/g creatinine, P=0.000) (Table 2). The complement, antinuclear antibody, anti-neutrophil cytoplasmic antibody, and Anti-ds-DNA antibodies were negative at admission. As the treatment for COVID-19, 21 (100%) of the patients received hydroxychloroquine, 10 (47.6%) received oseltamivir, 8 (38%) received azithromycin, and 5 (23.8%) received favipiravir. At the end of the follow-up, complete blood counts, CRP, procalcitonin, serum albumin, eGFR, ferritin, and coagulation parameters were found to be significantly improved compared to the baseline values (P<0.05) (Table 3). There was no significant correlation between baseline hematuria and proteinuria and other parameters. However, there was a moderately positive correlation between basal UPCR and baseline ferritin (r=.0.47 p=0.037), and a moderately negative correlation between baseline UPCR and baseline Na (r=-0.45 p=0.042).

TABLE 1. BASELINE CHARACTERISTICS OF COVID-19 PATIENTS

Items	Outcome
Age (years)	42.2 y 1l ± 8.8
Sex M/F (no) (%)	15/6 (71.4/28.6)
BMI (kg/m2)	23.6 ± 5.0
Duration of follow up (days) mean values ± SD (min.-max.)	 28.4 +/- 9.3 (17- 24- 44)
Complaints (no) (%) Fever Cough Shortness of Breath Myalgia Diarrhea Sore throat Anosmia	 16 (76.2) 16 (76.2) 8 (38.1) 6 (28.5) 3 (14.2)2 2 (9.5) 1 (4.8)
Radiologic findings No involvement (no) (%) Unilateral involvement (no) (%) Bilateral involvement (no) (%)	 2 (9.5) 2 (9.5) 17 (80.9)
Urine RT-PCR (no) (%)	1 (4.8)

M: male, F: female, BMI: Body mass index, RT-PCR: reverse transcription-polymerase chain reaction.

DISCUSSION

In this study, we investigated 1669 COVID-19 patients with de novo nephritic syndrome. Spontaneous remission was found in 85.7% and 71.4% of the patients' proteinuria and hematuria findings, respectively. In addition, there was a statistically significant remission in random UPCR. Recently, the incidence of proteinuria and hematuria in COVID-19 patients were found to be 65.8% and 41.7%, respectively. By using dipstick tests, the reduction ratio of proteinuria and microscopic hematuria were 68.5% and 43.1%, respectively. Moreover, a greater incidence of proteinuria (81.2% and 85.7%, respectively, versus 43.8%) and hematuria (39.1% and 69.6%, respectively, versus 33.3%) were demonstrated in severe or critically ill COVID-19 patients. The prevalence of hypertension and diabetes mellitus was 32.2% and 22.9%, respectively. In our study, however, the random UPCR was also measured in addition to the urine dipstick test. As our patients did not have any chronic illness, this suggests that the COVID-19 virus itself directly causes renal involvement. To our knowledge, for the first time, we demonstrated de novo nephritic syndrome in COVID-19 patients. The reversibility of most of the findings in patients suggests that it may be due to tubulointerstitial nephritis (TIN) caused by the virus. However, eosinophilia and eosinophiluria are expected in addition to microscopic hematuria and nephritic proteinuria as TIN due to certain

TABLE 2. CHARACTERISTICS OF URINE FINDINGS AND COVID-19 TESTS

Variable	Baseline value	End of follow up value	P
Hematuria frequency (no) (%)	21/21 (100.0 %)	6/21 (28.6 %)	*
Proteinuria frequency (no) (%)	21/21 (100.0 %)	3/21 (14.3 %)	*
UPCR (mg/g creatinine) mean values ± SD (min.-max.)	409.1 ± 218.6 (77.7 – 935.0)	109.1 ± 218.6 (47.7 – 311.0)	0.000**
NP swab RT-PCR positivity (n) (%)	21/21 (100.0 %)	--	--
Urine RT-PCR positivity (n) (%)	1/21 (4.8 %)	--	--

* McNemar Test was not calculated. ** Wilcoxon Signed Rank Test was used.

UPCR: Urine protein creatinine ratio, NP: Nasopharyngeal, RT-PCR: reverse transcription-polymerase chain reaction

TABLE 3. DEMOGRAPHIC LABORATORY PARAMETERS OF PATIENTS AT BASELINE AND END OF FOLLOW-UP

Variable	Baseline value mean values ± SD (min.-med.-max.)	End of follow up value mean values ± SD (min. med. max.)	P
White Cell Count NV: 5.6-10.2 (K/uL)	6.97 ± 3.14 (2.95 – 16.20)	6.05 ± 1.62 (3.14 – 10.80)	0.205*
Lymphocyte Count NV: 0.6-3.4 (K/uL)	1.41 ± 0.43 (1.40 – 12.40)	2.03 ± 0.47 (1.40 – 3.62)	0.000**
Eosinophil NV: 0.0-0.7 (K/uL)	0.066 ± 0.110 (0.000 – 0.390)	0.151 ± 0.100 (0.010 – 0.400)	0.000*
Neutrophil/ Lymphocyte ratio	3.79 ± 2.48 (1.03 –10.71)	1.56 ± 0.49 (0.65 – 2.81)	0.000*
Eosinophil/Lymphocyte ratio	0.039 ± 0.110 (0.000 – 0.200)	0.074 ± 0.100 (0.000 – 0.180)	0.001*
Platelet Count NV: 142-424 (K/uL)	190.7 ± 58.3 (103.0 – 340.0)	252.4 ± 52.7 (182.0 – 364.0)	0.000**
INR NV: 0.8-1.3	1.10 ± 0.12 (0.94 – 1.31)	1.02 ± 0.12 (0.80 – 1.33)	0.020*
Serum Creatinine NV: 0.67-1.17 (mg/ml)	0.73 ± 0.19 (0.27 – 1.10)	0.67 ± 0.14 (0.39 – 0.90)	0.175**
e-GFR NV: 90-120 (ml/dk/1.73m2)	107.0 ± 11.7 (89.0 – 138.0)	113.3 ± 10.4 (99.0 – 135.0)	0.003**
Uric acid NV: 3.5-7.2 (mg/ml)	4.8 ± 1.2 (3.3 – 8.3)	5.1 ± 1.1 (3.8 – 7.2)	0.254*
Sodium NV:136-146 (mmol/L)	137.4 ± 2.9 (132.0 – 142.0)	139.5 ± 2.1 (135.0 –– 142.0)	0.005*
C-Reactive Protein NV: 0-5 (mg/L)	74.5 ± 69.1 (2.5 – 260.0)	5.2 ± 6.9 (2.0 – 34.8)	0.000*
Procalcitonin NV: 0.5 (ng/ml)	0.61 ± 0.78 (0.01 – 2.10)	0.04 ± 0.01 (0.02 – 0.06)	0.000*
D-Dimer NV: 0-500 (ug/L)	1045.0 ± 1383.4 (22.0- 4620.0)	225.6 ± 168.8 (32.0 – 630.0)	0.002*
Ferritin NV: 21.81-274.66 (mcg/L)	432.3 ± 417.5 (15.0 – 1292.0)	99.8 ± 98.6 (10.0 – 442.0)	0.000*
Fibrinogen NV: 200-400 (mg/ml)	463.1 ± 117.8 (290.0 – 720.0)	278.1 ± 52.3 (183.0 – 409.0)	0.000**
Serum Albumin NV: 3.2-4.6 (gr/dl)	37.0 ± 4.6 (30.2 – 46.0)	39.9 ± 8.6 (4.0 – 48.8)	0.006*
Lactate Dehydrogenase (LDH) NV: 0-248 (U/L)	340.7 ± 149.3 (179.0 – 653.0)	180.5 ± 37.7 (118.0 – 271.0)	0.000**

* Wilcoxon Signed Rank Test was used. ** Paired Samples T-Test was used. INR: İnternational normalized ratio

viral infections and drugs[10,11]. In contrast, there have been studies reporting eosinopenia during the active period of the COVID-19 disease[12]. In our study, a significant improvement in the median eosinophil count and ENR was recorded at baseline. Although the pathophysiology of the detected eosinopenia is not fully understood, eosinopoesis inhibition in the bone marrow during the active period of the disease may develop due to eosinophil apoptosis and decreased expression of chemokine receptor/adhesion factors[13,14]. The postmortem autopsy results of 26 recent COVID-19 cases showed virus particles in the proximal tubule epithelium and podocytes, rather than the glomeruli of the kidney. Also, hemosiderin granules were detected in the tubular epithelium of four patients with hematuria detected by the dipstick test. Some patients have been shown to have erythrocyte plugs in their microvascular structures, followed by endothelial damage[4]. All of these patients had high cytokine storm and multi-organ failure. For these reasons, we believe that COVID-19 plays a significant role in the emergence of severe renal findings in postmortem results. However, due to the low viremia potential of COVID-19, renal involvement in mild-moderate patients may result in mild or transient symptoms.

The results of our study showed significant improvement in complete blood counts, kidney function tests, hypoalbuminemia, ferritin levels, infection, and coagulation parameters at the end of the follow-up period ($P<0.05$). According to the evaluations performed using the Spearman correlation coefficient, there was a positive correlation between baseline UPCR and basal ferritin ($r=.0.47$ $p=0.037$), and negative correlation between baseline UPCR and baseline Na ($r=0.45$ $p=0.042$). Under normal conditions, it is known that the majority of sodium and iron filtered from the glomeruli are absorbed from the proximal tubule of the kidney[15]. High expression of ferritin in the proximal epithelial cells was shown in mice study models related to renal iron metabolism[16]. Particularly the iron regulator protein-1 and iron regulator protein-2 (IRP1, IRP2) were shown to be expressed in high amounts in the proximal tubule[17,18]. These proteins regulate the expression of both the heavy (H) and light (L) chains of ferritin, transferrin receptor-1 (TfR1), and multiple other iron proteins. IRPs are cytosolic proteins that sense cytosolic iron levels and bind to RNA stem-loop motifs, which are found in the mRNA transcripts of iron metabolism genes. The IRP1 dysregulation causes hypoxia in the proximal tubule, while the IRP2 dysregulation causes tissue iron metabolism degradation and ferritin elevation[16,19]. COVID-19 may have caused more damage to the proximal tubule, thus causing deterioration in the reabsorption mechanisms of sodium and ferritin. As a result, excessively high acute-phase reactants during the active phase of the disease decrease in sodium and eGFR values,

and subsequent spontaneous remission may be due to reversible damage of the proximal tubule caused by the viral load (Table-3).

The main limitation of our study was the small sample size of participants. Moreover, we were unable to assess eosinophiluria as it could not be measured at the beginning. The histopathological examination could not be performed because of the lack of indications of kidney biopsy. We did not perform a renal biopsy in our patients, nor did we demonstrate the virus directly within the renal tubule cells in the renal tissue, nor were we able to show the immune response-related damage due to the virus.

In conclusion, the incidence of nephritic urine findings due to COVID-19 is low. Perhaps, the proteinuria and hematuria detected may be related to fever and systemic inflammatory associated with COVID-19 in the early stages. The recovery of symptoms and of renal involvement can confirm these results. We believe that renal involvement from COVID-19 needs to be verified with advanced biomarker and immunohistochemical studies.

Author's Contribuitions

Dheir H. and Karabay O. conceived the presented idea. Dheir H. Yaylaci S., Genc A.C., and Genc Turkoglu F. developed the theory and conducted the computations. Genc A.B., Guclu E., Muratdagi G., and Toptan H. verified the analytical methods. Dheir H and Sipahi S supervised the findings of this work. All authors discussed the results and contributed to the final manuscript

RESUMO

INTRODUÇÃO: *Este estudo tem como objetivo determinar a incidência da síndrome nefrítica de novo (SN) em pacientes com COVID-19 e identificar os fatores associados.*

MÉTODOS: *Todos os pacientes da enfermaria com pneumonia por COVID-19 foram investigados. Após a determinação dos critérios de inclusão e exclusão, a população do estudo foi identificada. Foram realizadas medições do teste da vareta da urina e da razão da creatinina das proteínas na urina (UPCR).*

RESULTADOS: *Este estudo transversal descritivo foi realizado com 21 pacientes com COVID-19. A idade média dos pacientes foi de 42,2±8,8 anos e 71,4% dos pacientes eram do sexo masculino. A duração média do seguimento foi de 28,4±9,3 dias. O teste de RT-PCR na urina foi positivo em um paciente (4,8%). Houve melhorias observadas na hematúria em 71,4% e na proteinúria em 85,7% no final do acompanhamento. E uma diminuição significativa na UPCR medida em comparação à linha de base (p=0,000). Além disso, foram registradas melhorias nas contagens sanguíneas completas, nos parâmetros inflamatórios, nos testes de ferritina e de coagulação, comparados aos valores basais. Houve correlação positiva entre UPCR basal e ferritina, e correlação negativa entre os valores basais de UPCR e sódio.*

CONCLUSÃO: *A síndrome nefrítica de novo induzida por COVID-19 pode ocorrer principalmente devido ao envolvimento túbulo-intersticial e frequentemente resulta em remissão espontânea. No entanto, a questão de por que esses achados não se apresentaram em todos os pacientes que não apresentavam condição comórbida não é clara.*

PALAVRAS-CHAVE: *Infecções por coronavírus. Hematúria. Proteinúria. Lesão renal aguda. Nefrite.*

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ORIGINAL ARTICLE

Knowledge of medical students on organ donation

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SUMMARY

OBJECTIVE: *To analyze the spontaneous knowledge of medical students about organ donation.*

METHODS: *518 students of a medical school in Sao Paulo city, from the first-year to internship, answered an objective questionnaire applied through electronic media to assess their spontaneous theoretical knowledge and organ donation awareness.*

RESULTS: *Organs that can be donated after brain death, such as the cornea, kidneys, heart, liver, and lung were mentioned by the students. Regarding in-life transplantation, they answered it was possible to donate mainly the kidney (91.3%), part of the liver (81.1%), and bone marrow (79.7%). Although it was not expressive, we also noted that their knowledge gradually increased as they reached the end of the course.*

CONCLUSIONS: *Medical students knowledge on organ donation in life and after death was a little superior to 60%. The students had limited exposure to this subject during the course (<40% of them before the internship). The authors suggest that students should be more exposed to the theme of "organ donation" in the medical curriculum.*

KEYWORDS: *Tissue and organ procurement. Students, medical. Health personnel. Education, medical. Transplantation.*

INTRODUCTION

Transplantation, oftentimes, is the only option for patients with functional failure of certain organs. There is a lack of clarification and permanent programs on donation awareness, which generate waiting lists for organs and tissues, some of which can be derived from individuals alive or dead.

The potential donor needs to be identified, and the family of the donor must agree to the donation. If the health professionals and families do not have prior information on the subject, or if the deceased person never expressed their opinion on this matter, a negative answer becomes more common, considering the difficult moment experienced by the family[1].

The criteria for the diagnosis of brain death, according to the Brazilian Federal Council of Medicine Resolution number 1.480/1997, are rigorous and involve

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neurological and complementary examinations[2]. After the diagnosis, the family goes through an interview with the purpose of providing them with objective and clear information on the possibility of the organs being donated for transplant. Once the donation is approved, the transplantation process begins with the harvesting of only the organs or tissues authorized by the family[1].

According to the Brazilian Ministry of Health[1], the organs/tissues that can be donated after brain death are:

- Heart
- Lungs
- Kidneys
- Liver
- Pancreas
- Intestine
- Skin
- Bones
- Corneas
- Cartilages
- Tendons
- Menisci
- Muscle fascia
- Heart valves
- Vessels
- Pericardium
- Bone marrow

Multivisceral transplantation is also possible, and it consists of implanting the liver, pancreas, stomach, duodenum, and small intestine in the same individual. There are reports on transplantation of limbs, face, larynx, and trachea, among other things, but these are not carried out in Brasil[2].

Living donor transplantation is also possible. A lot of care is taken to prevent any injury to the donor. The organs and tissues that can be donated by living individuals are[3]:

- One of the kidneys
- Part of the lung
- Part of the liver
- Part of the pancreas
- Bone marrow

The Brazilian Public Health System (SUS) has the largest public program of transplants worldwide and is responsible for 87% of all organ transplantations in Brasil[4]. Currently, in Brasil, in order to be an organ and tissue donor, it is necessary to warn one's family about this wish. However, donation refusal is much greater than acceptance[1]. This is due to several factors, among them the lack of information on the importance of donation, the approach of health professionals with the families, sensationalist news stories about organ trafficking, among others[2].

In a survey conducted in São Paulo, in 2017, considering 2,880 potential donors notified, among the causes for the donation does not being materialized, the most frequent (37%) was the refusal by the family during the interview[4]. This is one of the reasons why it is so important for health professionals to know about organ donation since they will be the ones who will pass the information along to those responsible for the donation.

METHODS

This is a cross-sectional study conducted with medical students from the 1st to the 6th-year of a faculty of medicine in the city of São Paulo (FM-SP). The subjects answered to a multiple-choice web-based questionnaire to evaluate their theoretical knowledge and investigate their awareness on organ donation. After responding the survey, informative material was sent to participants clarifying the aspects covered in the questionnaire.

The research project was submitted for consideration and approval by the Human Research Ethics Committee, and the subjects who participated signed the Informed Consent Form digitally.

The information collected in this survey were analyzed descriptively through their absolute and relative frequencies (percentage).

RESULTS

All the participants were students of a faculty of medicine in the city of São Paulo (FM-SP). The 518 students answered to a multiple-choice questionnaire, which was sent to 1,057 students whose contacts were available at the time of the application of the questionnaire. We obtained more answers from students who were in the years of the medical course, i.e., 30.9% in the 1st year, 22.2% in the 2nd year, 11.8% in the 3rd year, 19.7% in the 4th year, 8.5% in the 5th year, and 6.9% in the 6th year.

Most respondents were females (74.1%). The predominant age group was 20-25 years (57.53%), followed by those younger than 20 years (26.6%), 25-30 years (10.2%), and over 30 years (5.6%).

Regarding ethnicity, there was a predominance of whites (84.4%), followed by other ethnicities as follows: brown (9.8%), yellow (4.2%), black (0.8%), and indigenous (0.2%). These individuals were predominantly Catholic (48.3%), followed by those without religion (17.4%), Evangelical (14.5%), Spiritualists (12.7%), others (6.4%), and Jews (0.6%).

Most participants had no prior experience/exposure to situations of organ donation, corresponding to 73.5% of those who answered the questionnaire. Among those who had (26.4%), 18.5% reported that this exposure was theoretical, 1.3% that it was practical, 4.3% had practical/theoretical exposure, 0.8% had a role-play experience, and 4.6% went through any real situation. Among the students of the 1st year, 17% answered that they had already had some exposure/experience related to organ donation; that figure was 16% in the 2nd year, 21% in the 3rd year, 38% in the 4th year, 36% in the 5th year, and 67% in the 6th year, as shown in Figure 1.

Regarding the question about which organs can be donated *after brain death*, we found that most students knew that it is possible to donate the cornea (92.7%), kidneys (89.2%), and heart (89.8%), followed by liver (84.6%) and lung (79.2%). The frequency with which the participants indicated other organs can be seen in Table 1.

Regarding the organs that can be donated *in life*, students answered that it was possible to donate mostly kidney (91.3%), part of the liver (81.1%), and bone marrow (79.7%). The frequency of other donations can be seen in Table 1.

However, students were wrong in assuming that organs/tissues such as part of the pancreas (33.2%), cornea (20.8%), cartilage (18.1%), liver (12.4%), lung (11.6%), muscle (10.2%), heart (9.8%), bones (9.7%), pancreas (7.5%), valve (5.6%), multivisceral (3.9%), and the skin (0.6%) could be donated in life.

Overall, 63.7% of the students gave right answers regarding the organs that could be donated *in life* and 61.8% *after brain death*.

TABLE 1. ANSWERS PROVIDED BY MEDICAL STUDENTS TO THE QUESTIONNAIRE ON ORGANS THAT CAN BE DONATED.

Organs that can be donated after death, n(%)			p-value[a]
Cornea	480	(92.7%)	0.00
Heart	465	(89.8%)	0.58
Kidney	462	(89.2%)	0.86
Liver	438	(84.6%)	0.31
Lung	410	(79.2%)	0.34
Skin	397	(76.6%)	0.52
Pancreas	354	(68.3%)	0.08
Part of the liver	302	(58.3%)	0.12
Bone marrow	268	(51.7%)	0.17
Bones	226	(43.6%)	0.00
Part of the lung	213	(41.1%)	0.39
Valve	213	(41.1%)	0.00
Part of the pancreas	182	(35.1%)	0.03
Cartilage	162	(31.3%)	0.05
Multivisceral	148	(28.6%)	0.13
Muscle	136	(26.3%)	0.01
Organs that can be donated in life, n(%)			
Kidney	473	(91.3%)	0.48
Part of the liver	420	(81.1%)	0.06
Bone marrow	413	(79.7%)	0.00
Part of the lung	173	(33.4%)	0.00
Part of the pancreas	172	(33.2%)	0.17

[a]Pearson's chi-square test.

FIGURE 1. REPORT OF THE MEDICAL STUDENTS ABOUT EXPOSURE TO THE ORGAN DONATION TOPIC.

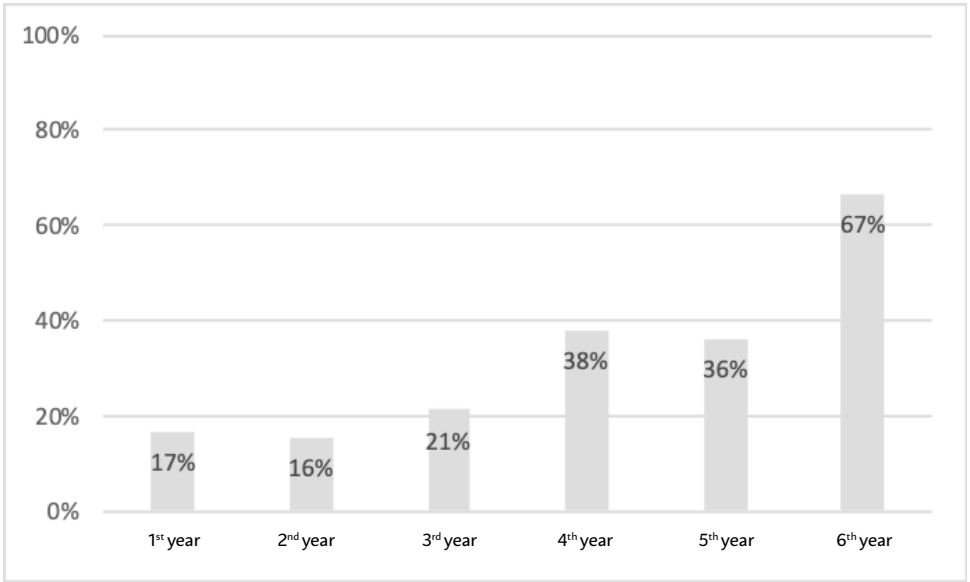
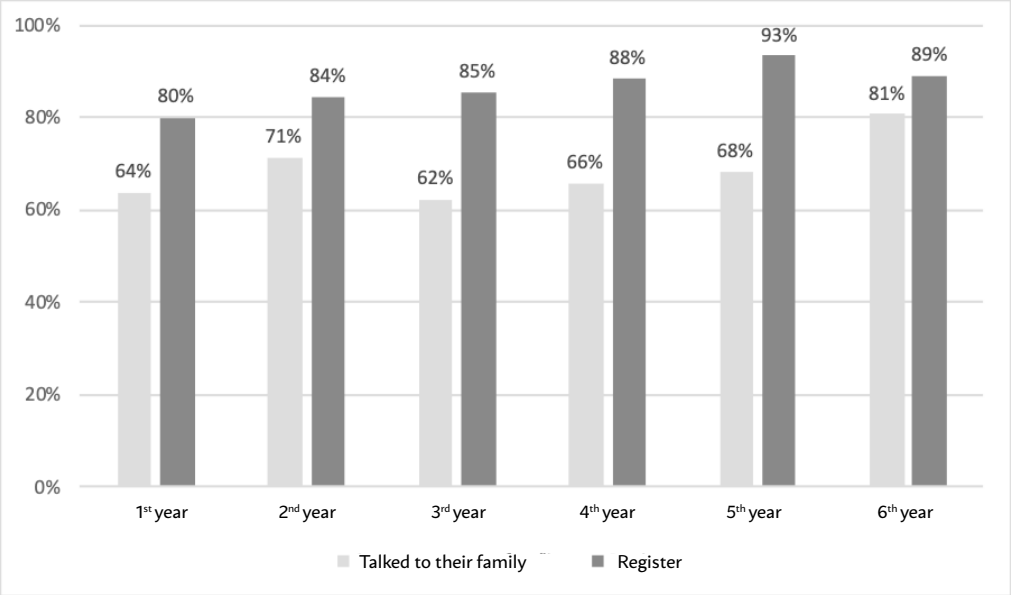


FIGURE 2. PERCENTAGE OF AFFIRMATIVE ANSWERS OF STUDENTS WHEN ASKED IF THEY HAD ALREADY TALKED TO THEIR FAMILIES ABOUT ORGAN DONATION *VS.* IF THEY WOULD REGISTER AS ORGAN DONORS.



The percentage of students who said they would be able to explain to the relatives of a potential donor what is brain death was 82.6%. According to them, the main challenge in organ donation currently is the fear of mutilation/deformation (33.6%); in second place would be the understanding of brain death (26.6%), followed by religious beliefs (22.2%), no communication of the desire in life (15.4%), discrediting of the health system (1.3%), and others (0.8%), among which were "prejudice", "remembrance of the deceased," "indiscriminate trade of organs," and the regulations that define who is the "representative" of the will of the deceased.

In addition, 67.2% of the participants stated that they have already talked to their families about organ donation (Figure 2) and, if there was an official record to become a donor after death, 84.9% would register themselves in it, 1.3% would not register, and 13.7% answered that they are not ready to make this decision.

DISCUSSION

In this study, the students of the 1st to 4th year of the medical course had greater participation than those of the 5th and 6th years. The authors consider that the low participation rate of the last two years may be due to the fact that these students are in an internship, with interests and obligations related to the practical activities of this period. The greater participation in the first years of the program certainly had an influence on the predominant age in this research, i.e., individuals from 20 to 25 years, followed by those younger than 20 years.

Caucasian and Catholic individuals were also predominant. The Instituto Brasileiro de Geografia e Estatística (IBGE) describes that 44.2% of the Brazilian population is composed of white individuals[5] and 64.6% of Catholics[6]; thus, this distribution would be in line with the overall composition of our sample.

In Brasil, no religion is contrary to the donation of organs and tissues[7]. People, oftentimes, have their own interpretations of the doctrines imposed and use them as a justification for the refusal to donate[8].

The questionnaires were sent to approximately 1,057 students of the medical course, and the response rate was 49%. This rate is much than the rate of expected responses to online surveys, which is around 20%, reinforcing the representativeness of this sample of students who participated in our study[9].

Most students (73.55%) had no previous experience with organ transplantation, and when there was exposure to the topic, it was mainly of a theoretical nature, related to lectures on the subject. When comparing the students who had exposure to the topic of organ donation, we noticed there was a relative increase along the

years of study (Graph 1), although it was less than 40% up until the 5th year.

Considering there was significant participation of students in this study, the topic does not appear to have been widely addressed during the medical program. This type of result is not surprising and is one of the reasons for the present study since medical students, future physicians, are essential in the guidance regarding organ donation in any area in which they will exercise their activities after having graduated.

No one got 100% of the answers right regarding the organs that could be donated. It is worth mentioning, however, that the questionnaire contained more rare alternatives for donation, such as multivisceral donation, because we considered that one of the functions of this study was to promote information about the various possibilities of donation. Students had greater knowledge about corneal, kidney, and heart donations. We also noticed that the knowledge gradually increased over the medical course, but not expressively, which shows the need for greater exposure of medical students to information about organ donation.

We emphasize that after obtaining the answers for all questionnaires, the students received a feedback message from the researchers containing information about the correct answers, thus increasing their knowledge on the subject.

The main challenge for organ donation, in the opinion of most students, was fear of mutilation. However, studies in this area show that the biggest problem in a transplantation program such as the Brazilian one is that people do not communicate their desire to donate their organs to their families during life.

We noticed that most participants had not yet talked to their families about the intention of becoming organ and tissue donors after death. It is known that such a simple attitude makes a huge difference in the moment relatives decide whether or not to allow the donation. On the other hand, it was interesting to observe that students said they would register as donors, and this answer was more frequent than the report of having already talked with their families about the subject; this same pattern was observed from the 1st to the 6th year (Figure 2).

The authors consider that the type of approach used in the present study has an educational role. It is important in disseminating information about organ donation, raising awareness about the problem of the shortage of organs and tissues for patients who need transplantations, and about the importance of this therapeutic resource to save or improve the quality of life of the patients who need them.

In other publications related to the knowledge of medical students about organ donation, we could not find any studies that evaluated the knowledge about which organs could be donated in life and after brain death. In addition, the number of participants in the present study was higher than any other research in the field. Some of these studies addressed issues related to general knowledge and beliefs about organ donation, understanding of brain death, and possible factors contrary to the donation[7,10,11].

It is worth mentioning that the scarcity of information about organ donation is not something observed exclusively in Brasil. Studies have been conducted in Mexico, Canada, Hong Kong, and Turkey which also affirm the importance of improving the approach to the subject in medical schools[12-15].

CONCLUSION

We consider that the knowledge of undergraduate medical students about organ donation was slightly above 60% regarding which organs and tissues could be donated in life and after death. The exposure of students to the topic during the medical course was low (involving less than 40% of them up until the 5th year).

The results presented suggest that we should revise the curriculum of medical schools to increase information about organ donation during the course, preferably early on, in addition to teach medical students about the protocol for the diagnosis of brain death, which may optimize not only the training of health professionals but the participation of each individual as a multiplier of information in their daily lives, and, possibly, as a potential declared organ donor.

Author's Contribution

Jessica Escribano Sampaio: preparation of the project, recruitment of subjects, data collection, drafting of the paper.

Danilo Euclides Fernandes: data tabulation and analysis, support in the project management and methodology.

Gianna Mastroianni Kirsztajn: supervision of the project, drafting of the paper, formal analysis, methodology, analysis, and discussion of the data.

RESUMO

OBJETIVOS: *Analisar o conhecimento espontâneo dos graduandos de medicina sobre doação de órgãos.*

MÉTODOS: *A pesquisa foi realizada com 518 graduandos de medicina do 1º ao 6º ano de uma faculdade de medicina da cidade de São Paulo (FM-SP). Os indivíduos responderam a um questionário de múltiplas alternativas aplicado por mídia eletrônica, para avaliar o conhecimento teórico espontâneo e o grau de conscientização sobre doação de órgãos.*

RESULTADOS: *Órgãos que podem ser doados após a morte encefálica, como a córnea, rins, coração, fígado e pulmão foram, em sua maioria, de conhecimento dos estudantes. Em vida, os alunos responderam que era possível a doação sobretudo de rim (91,3%), parte do fígado (81,1%) e medula óssea (79,7%). Pudemos notar também que o conhecimento aumentou gradualmente no decorrer do curso, mas não de forma expressiva.*

CONCLUSÕES: *O conhecimento dos graduandos sobre doação de órgãos em vida e após a morte foi pouco superior a 60%. A exposição dos alunos ao tema foi baixa durante o curso (<40% deles até o 5º ano). Os autores sugerem que deveria haver maior exposição dos alunos ao tema "doação de órgãos" na grade curricular do curso médico.*

PALAVRAS-CHAVE: *Obtenção de tecidos e órgãos. Estudantes de medicina. Pessoal de saúde. Educação médica. Transplante.*

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ORIGINAL ARTICLE

Evaluation of treatment of the exacerbation of asthma and wheezing in a pediatric emergency department

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SUMMARY

OBJECTIVES: *To evaluate the treatment of wheezing and exacerbation of asthma in a pediatric emergency unit (ED), comparing it to that recommended by the guidelines for this purpose.*

METHODS: *Descriptive cross-sectional study through medical records survey of children and adolescents (0–15 years of age) who received medication for wheezing or asthma exacerbation from January to April 2015 in the ED. The selected treatment was compared to that recommended by the guidelines, being analyzed the variables related to the medication (number and dose of short-acting β2 agonist, associated or not with anticholinergic, oral or parenteral corticosteroid) and the length of stay in ED (≤1 h, ≥8 h and hospital admission).*

RESULTS: *One-thousand eleven patients were selected with 56.7% between 3 and 15 years and 56% male. Although the selected drugs were in accordance with what was recommended, errors were observed in relation to dose, drug of choice, and method and time of use with the most frequent finding being incorrect dose (short-acting β2 agonist: 66% and ipratropium bromide: 95.2%).*

CONCLUSION: *The level of use of the measures recommended by the guidelines was low but compatible with other studies, leading to an increased risk of treatment failure and higher costs. Despite wide dissemination, the established concepts have not been sufficiently incorporated into clinical practice, suggesting the need for more effective educational actions for this process to occur.*

KEYWORDS: *Asthma. Respiratory sounds. Child. Adolescent. Emergency treatment.*

INTRODUCTION

Asthma affects 1.8%–36.7% of the population in different countries.[1,2] An international multicenter study showed a 16.6% prevalence of recurrent wheezing with 72.7% requiring emergency consultations. In Brasil, the registered rates were high and varied between 11.8% and 21.7%.[3] In Santo André, asthma was observed in 24.3% of children aged 6–7 years and in 19% of adolescents aged 13–14 years[4] and 60.7% of emergency visits.[5]

Asthma is still a frequent cause of hospitalization, morbidity, and high financial burden for families and the healthcare system.[6] The current literature is controversial with regard to the explanation for the increase in emergency visits in recent decades,

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suggesting a possible relationship to urban growth in developing countries.[7]

In Brasil, a reduction in mortality in the more developed regions is occurring, and an increase in others in which low socioeconomic status, inadequate treatment, irregular follow-up, and less access by the population to the health system prevail. In most of these cases the ED is the only gateway in which prescriptions for inhaled corticosteroids (IC) and referral to specialists are low.[7–9]

Asthma crisis or exacerbation (AE) is an acute or subacute worsening of symptoms and lung function in relation to the patient's usual state and demonstrates inadequate control of the disease. Effective treatment is related to the rapid and accurate assessment of severity with a medical approach immediate, effective, and improved oxygenation.[7–11]

The literature describes several risk factors for hospitalization and readmission: (1) age group (< 2 years), (2) severity (moderate and severe persistent forms), (3) low socioeconomic status, (4) maternal education, (5) inadequate prophylactic treatment, and (6) most importantly, repeated consultations in the ED (≥ 2 x/month) in addition to asthma in close relatives, absence of follow-up, passive smoking, male gender, and school attendance of these patients.[12,13]

The objective of the study was to describe the treatment used and to assess whether the measures applied by pediatricians in the ED are in accordance with the guidelines for the proper management of AE and wheezing.

METHODS

This study was a cross-sectional descriptive study with data collection at the Bangu Emergency Care Unit, in Santo André, SP, which serves an urban population and users of the Unified Health System (SUS).

The medical records of children and adolescents from January to April 2015, were surveyed and included after fulfilling the inclusion criteria of age (zero and incomplete 15 years), with AE and/or wheezing, and who received a short-acting β2 agonist (B2CA). Medical records showing failure to complete, doubtful diagnosis, and pathology in which the use of B2CA was not justified were excluded (Image 1). The length of stay was considered from the patient's arrival to the last medical or nursing note.

The unit of analysis was the visit to the ED as each visit represented an occasion for independent treatment.

To assess the adequacy of the treatment, we used the Global Initiative for Asthma (GINA) 2014[10] and Guidelines of the Brazilian Society of Pulmonology and Tisiology for Asthma Management, 2012[11] as the guidelines for treatment assessment.

The variables that were analyzed related to medications were number of inhalations and dose of B2CA, isolated or associated with anticholinergic, use of corticosteroids and those related to the outcome included length of stay in PE ≤ 1h and prolonged stay ≥8h.

The drugs available at the time of the study were fenoterol, ipratropium bromide, corticosteroids (prednisone, prednisolone, hydrocortisone, methylprednisolone, and dexamethasone), magnesium sulfate, and aminophylline.

The ED did not have a peak expiratory flow meter.

To characterize the sample, descriptive statistical methods were used, and the results were transferred to a database, prepared in Excel (Microsoft), and analyzed with the STATA version 11.0 program. Qualitative variables were presented as absolute numbers and percentages. The level of significance was 5%.

The study was approved by the Research Ethics Committee of the Faculdade de Medicina do ABC (Opinion Number: 2,647,797).

RESULTS

The consultations (12,038) were carried out in the evaluation period with 1,497 patients receiving B2CA but only 1,011 diagnosed with AE or wheezing.

There was a predominance of males (573/1011; 56.7%) and the age group of 3 to 15 years (567/1011; 56%). They were divided according to the presentation of isolated wheezing (609/1011; 60.2%), wheezing associated with viral disease (217/1011; 21.5%) and wheezing associated with bacterial disease (185/1011; 18.3 %) (Table 1).

Although the selected drugs were in accordance with the recommended guidelines, with the exception of aminophylline, which was used in 14 (1.4%) children, and magnesium sulfate, recommended in the most severe and refractory cases, was used only once,[6,8–10,12] inconsistencies were observed regarding the form of use, dose, and length of stay:

IMAGE 1. SELECTION OF MEDICAL RECORDS UNTIL SAMPLE IS OBTAINED.

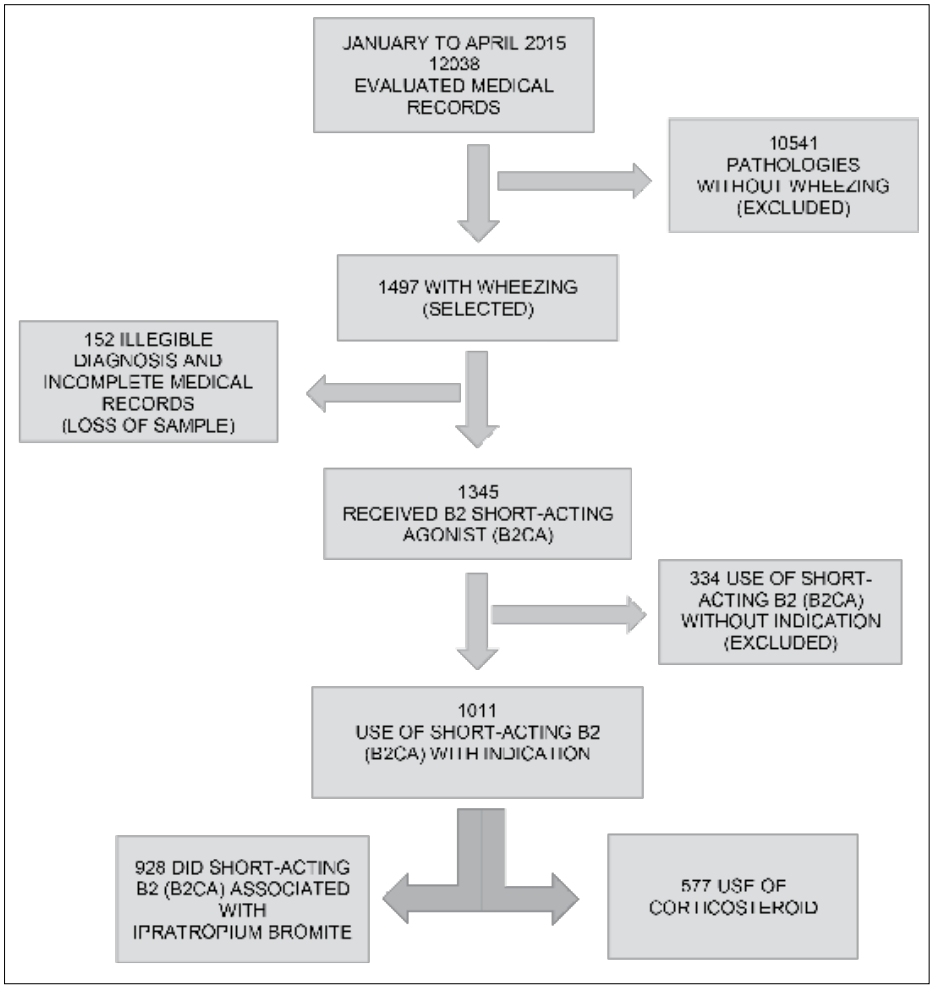

TABLE 1. DIAGNOSIS OF ADMISSION TO THE EMERGENCY DEPARTMENT (ED) ACCORDING TO AGE, RECOMMENDATIONS ABOUT THE USE OF THE SHORT-ACTING β2 AGONIST, IPRATROPIUM BROMIDE, AND INADEQUATE NUMBER OF INHALATIONS (N=1011).

DIAGNOSIS	< 3 years old		3 to 10 years old		> 10 years old		TOTAL	
	n	%	n	%	n	%	n	%
Wheezing + bacterial infection	98	53.0	64	34.6	23	12.4	185	18.3
Wheezing + viral infection	126	58.0	65	30,0	26	12.0	217	21.5
Isolated wheezing	220	36,1	291	47.8	98	16.1	609	60.2
TOTAL	444	44	420	41.5	147	14.5	1011	100

DRUG	Recommended		Not Recommended				Inadequate No of inhalations	
			Higher Dose		Lowest Dose			
	n	%	n	%	n	%	n	%
B2 short-acting agonist (N=1011)								
< 3 years old	199	43.6	63	13.8	176	38.5	19	4.1
3 to 10 years old	129	31.3	36	8.7	222	53.9	25	6.1
> 10 years old	16	11.3	0	-	115	81	11	7.7
TOTAL	344	34	99	9.9	513	50.7	55	5.4
Ipratropium bromide (N=928)								
< 3 years old	14	3.3	0	-	396	93.6	13	3.1
3 to 10 years old	18	4.7	0	-	356	93.2	8	2.1
> 10 years old	13	10.6	0	-	94	76.4	16	13
TOTAL	45	4.8	0	-	846	91.2	37	4

a. B2 short-acting agonist (B2CA): Fenoterol was the selected B2CA via nebulization with O_2 being the vehicle with 0.9% saline volume of 5 ml without reference to the flow.
   For this variable, 1011 (67.5%) of the 1.497 patients were eligible because 152 (10.2%) of the medical records were inadequate and 334 (22.3%) of the children did B2CA without indication; of these eligible children, 344/1011 (34%) received the doses that were recommended in the guidelines. Of the changes not recommended, we found low dose 513/1011 (50.7%), above dose in 99/1011 (9.9%), and inadequate inhalation number with 55/1011 (5.4%).
   We then observed that 66% of the children received inadequate doses of B2CA (Table 1).
b. Ipratropium bromide: In the study, 928/1011 (91.8 %) received anticholinergic associated with B2CA although the recommendations in the guidelines state it should be used only in severe cases in the first three inhalations; of these 45/928 (4.8%) received recommended doses, and for the vast majority 883/928 (95.2%), there were errors regarding dose, severity, and/or number of inhalations (Table 1).
c. Corticosteroids: In the study 577/1011 (57%) children received some corticosteroids, which were more frequent in the group of isolated wheezers 360/609 (59.1%). Hydrocortisone was the most used with the preferred route being intravenous followed by the intramuscular route (Table 2).
d. Length of stay in the ED: Regarding the 1497 children who received β2CA, two evasions (0.1%), 101 (6.7%) medical records without information about the medication schedules were noted. It was possible to analyze 1394 medical records regarding the length of stay. We found 502/1394 (36%) who stayed < 1 h throughout their service, 496/1394 (35.6%) from 1 to 2 h, 367/1394 (26.3%) from 2 to 8 AM, and 29/1394 (2.1 %) > 8 h. The vast majority (71.6%) remained < 2 h in their care.

DISCUSSION

AE and wheezing are currently among the most frequent causes of visits to ED and hospitalization in the pediatric age group.[2,4,6,7,9–11] This reality contrasts with implementation in the last decades of guidelines whose purpose is to update, guide, and standardize diagnostic and treatment procedures and consequently, obtain better control of the disease.[6,9–13]

The disclosure of guidelines, however, is not always sufficient to lead to their use in daily practice; therefore, there is a gap between the management of patients and the one recommended by the guidelines occurs.[8,14,19,20] The recommendations are not even followed by doctors who understand them, which contributes to the occurrence of poor treatments, prescription errors, and poor maintenance of disease morbidity.[14–18]

Inadequate control and management in asthma attacks are associated with significant morbidity and economic impact. [8,11,21,22] Analyzing and changing these barriers to adherence to the management and treatment guidelines are essential to improve disease management.[4,10,11,15]

In wheezing, treatment, including B2CA, ipratropium bromide, IC, oral corticosteroid (OC), magnesium sulfate, and occasionally adrenaline in addition to theophylline within the scope of intensive care is recommended. [9,10,12] At the time of the study, salbutamol and IC recommended by the guidelines were not available in the ED, despite being provided free of charge by the Popular Pharmacy Program of the Ministry of Health/2012.[9,11,23,24]

The present study showed a predominance of isolated wheezing in all age groups, a finding that was not compatible with the literature, which reports a higher incidence of viral and bacterial associations, especially in younger children. These data may be a consequence of the selected model, which did not allow patient follow-up and subsequent verification of the association in addition to the absence of supporting tests.[10,19]

TABLE 2. USE OF CORTICOSTEROIDS ACCORDING TO THE DIAGNOSIS OF PATIENTS.

Corticosteroid	Wheezing + bacterial infection		Viral Wheezing		Isolated Wheezing		TOTAL	
	n	%	n	%	n	%	n	%
None	74	17	111	25.6	249	57,4	434	43
Oral Route	39	18.5	42	19.9	130	61.6	211	20,9
Intravenous Route	29	14.6	31	15.6	138	69.8	198	19.5
Intramuscular Route	43	25.6	33	19.6	92	54.7	168	16.6
TOTAL	185	18,4	217	21,5	609	60,1	1011	100

Several authors have observed the use of insufficient doses of B2CA in the ED.[11,12,17,21] As in most public EDs in Brasil, fenoterol, rather than salbutamol, was available. Fenoterol is practically not mentioned in the current literature, whereas salbutamol has been widely used and studied in recent years.[9–11,22]

Corticosteroids are the gold standard for the treatment of AS and wheezing, and should be used in the first hour, being a well-documented fact that their use decreases visits to ED (25%),[17,19,22] hospitalizations, re-consultations, and severity.[6,10,11] Its use is recommended orally as early as possible because regardless of the route chosen, it requires at least 4 h to observe clinical improvement.[11,12,15,24,25] At the time of the study (2014/15) its use, route, and doses were well established.[6,9–11] However, in this study, the preferred routes were intravenous and intramuscular, determining an increase on invasive procedures, material costs and hours of nursing, despite not having been reported clinical data that supported their prescription, such as vomiting or severity of the case.[6,9–11] Oral prednisolone, recommended in the guidelines, was used in 211/576 (36.6%), and intramuscular dexamethasone in 58/576 (10%). The prescribed dose was not analyzed due to the frequent lack of weight registration in the medical records, which was probably calculated by formulas.[6,9–11] Although studies have shown that the dose does not have a big impact on emergency treatment,[18] the use of recommended doses is of paramount importance when considering its adverse effects.[6,9–11]

Ipratropium bromide is an inhaled anticholinergic that when administered with B2CA decreases the risk of hospitalization in children with EA.[23] Its use is well endorsed in EDs, especially in severe crises but not in hospitalized patients and in mild crises[24] because it does not improve the severity of the case or decrease the length of hospital stay and generates unnecessary expense (three times greater than that of fenoterol).[15,22–24] The combination of ipratropium bromide and B2CA produces marked and prolonged bronchodilation thus causing a decrease in secretions and edema in AE and wheezing.[23,24] With regard to this variable, the greatest inconsistencies were found, demonstrating that there are barriers preventing guidelines from being used in clinical practice. It is worth mentioning that these drugs are the ones that suffered the most changes in the latest guidelines.[8–11,23,24]

The length of stay in the ED was difficult to assess due to the few information found in the medical records. It is also important to mention the impossibility of quantifying the waiting time to fill the form, screening by the nurse, and medical care, thus enabling the risk of bias. However, it is important to note that the early discharge of ED is known to be one of the main causes for re-consultations and complications, and this subject deserves further studies.[15] A length of stay < 2 h for all care is considered as high risk for not following the protocols as studies recommend the observation of at least 1 h after adequate response to treatment to consider the condition stable and opt for discharge.[10,11,15]

According to the medical records, 998/1394 (71.6%) children could have an unfavorable prognosis due to the short observation period. However, the shorter time in ED suggests that AE were considered mild or moderate when the number of inhalations would be less than three or that there was an error in the diagnosis or classification. These findings are in line with the literature in which it is reported that mild crises are the most neglected with the need to emphasize the recommendations for valuing symptoms and early identification of warning signs and worsening as reported by the family.[8–11]

Studies show that knowledge about AE is insufficient and is worrying among ED professionals[19,20] and point to flaws and barriers in adhering to the guidelines with underuse of medications and misguided clinical conduct that increase the risk of serious and fatal crises. In addition, attitudes are incorporated into clinical practice that hinder the applicability of guidelines in addition to the lack of appropriate drugs and structural and functional changes in the public service.[14,17,18]

In Brasil, nebulization is still the most widely used form of inhaled drug administration. Studies have demonstrated equivalence or advantages of aerosols, associated or not with spacers, which lead to rapid onset bronchodilation (1–5 min) with lasting therapeutic effects of 2 to 6 h, ease of administration, less side effects, better lung deposition, faster preparation and administration (Nebulization = ±13.8 min; ID = ±3.4 minutes), and lower cost (Nebulization = ±R $ 15.7; ID = ±R$ 4,7), representing 30.3% of the cost of nebulization, but this comparison did not take into account the disinfection cost for reusing the spacers that would be necessary in the emergency room.[8–11,15,19,22]

As for the cost of prophylactic treatment with inhaled corticosteroids and clinical follow-up (6 consultations/year) in Brasil, it is equivalent to a single hospitalization (U$ 120,00), considering only the direct cost.[14]

In the present study, the use of B2CA and non-recommended ipratropium bromide was observed, especially with doses below the recommended ones, corticosteroids by non-recommended routes, use of aminophylline to the detriment of magnesium sulfate, and remaining under observation for a shorter time than indicated, facts that can determine unfavorable consequences.

Aiming at reducing AE and wheezing related morbidity, current knowledge highlights the importance of adopting a set of prophylactic measures, such as: exclusive breastfeeding, avoiding exposure to viruses, at least in the first three months of life (maternity leave), adequate vaccination; assistance: adequate and judicious use of drugs with procedures adapted to our actual situation; managerial: reduction in treatment costs, impact on the drug-based economy and educational aspects with the implementation of teaching strategies for caregivers and health professionals in prevention, diagnosis, treatment and dissemination of this knowledge.[8,9,17]

CONCLUSION

The level of use of the measures recommended by the guidelines was low and compatible with other studies, leading to an increase in the risk of treatment failure and higher cost.

It is concluded that there is a need to promote effective and continuous education of health professionals in the ED for better understanding and adherence to the recommendations elaborated by the guidelines, which despite their wide dissemination, are poorly implemented in clinical and daily practice.

Author's Contribution

All authors have contributed equal to work.

RESUMO

OBJETIVOS: *Avaliar o tratamento da sibilância e da exacerbação da asma em unidade de emergência pediátrica (DE), comparando-o ao recomendado pelas diretrizes para esse fim.*

MÉTODOS: *Estudo descritivo transversal, por meio do levantamento de prontuários de crianças e adolescentes (0 - 15 anos de idade) que receberam medicação para sibilância ou exacerbação da asma, no período de janeiro a abril de 2015, em DE. O tratamento empregado foi comparado ao preconizado pelas diretrizes sendo analisadas as variáveis referentes à medicação (número e dose de β2 agonista de curta ação, associado ou não a anticolinérgico, corticosteroide oral ou parenteral) e ao tempo de permanência na DE (≤1 h, ≥8 h e internação hospitalar).*

RESULTADOS: *Foram selecionados 1011 pacientes, 56,7% com idades entre 3 e 15 anos e 56 % do sexo masculino. Embora os fármacos utilizados estivessem de acordo com o preconizado, foram observados erros com relação a dose, droga de escolha, forma de utilização, tempo de uso, sendo dose incorreta o achado mais frequente (β2 agonista de curta ação: 66% e brometo de ipratrópio: 95,2%).*

CONCLUSÃO: *O nível de utilização das medidas recomendadas pelas diretrizes foi baixo e compatível com outros estudos, levando a risco aumentado de falha no tratamento e maior custo. Apesar da ampla divulgação, os conceitos estabelecidos não são suficientemente incorporados à prática clínica, sugerindo a necessidade de ações educativas mais efetivas para que isso ocorra.*

PALAVRAS-CHAVE: *Asma. Sons respiratórios. Criança. Adolescente. Tratamento de emergência.*

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REVIEW ARTICLE

Discriminant indexes to simplify the differential diagnosis between iron deficiency anemia and thalassemia minor in individuals with microcytic anemia

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SUMMARY

INTRODUCTION: *Microcytic anemias are very common in clinical practice, with iron deficiency anemia (IDA) and thalassemia minor (TT) being the most prevalent. Diagnostic confirmation of these clinical entities requires tests involving iron metabolism profile, hemoglobin electrophoresis, and molecular analysis. In this context, several discriminant indices have been proposed to simplify the differential diagnosis between IDA and TM.*

OBJECTIVE: *The aim of this paper was to demonstrate the clinical relevance of the use of discriminant indices in individuals with microcytic anemia to simplify the differential diagnosis between iron deficiency anemia and minor thalassemia.*

METHODS: *A bibliographic and cross-sectional search was performed in the PubMed, SciELO and LILACS databases, using the following descriptors: iron deficiency anemia, thalassemia minor, and differential diagnosis.*

RESULTS: *More than 40 mathematical indices based on erythrocyte parameters have been proposed in the hematological literature in individuals with microcytosis. Green & King indexes (IGK), Ehsani index, and erythrocyte count (RBC) had excellent performances, especially when their efficacy was observed in adults and children.*

CONCLUSIONS: *Confirmatory tests for differential diagnosis between IDA and TM require time-consuming and costly methods. Despite the excellent performances of IGK, Ehsani index, and RBC, none of them presented sufficient sensitivity and specificity to establish a diagnosis. However, they can provide a powerful additional tool for diagnostic simplification between IDA and TM.*

KEYWORDS: *Anemia, iron-deficiency. Beta-thalassemia. Diagnosis, differential.*

INTRODUCTION

Anemia is a global public health problem that affects both the developed and developing countries and has major consequences for human health, as well as for social and economic development, affecting 24.8% of the world population[1]. Regarding the definition of anemia, most of the medical-scientific studies adopt the criteria proposed by the World Health Organization (WHO), which are: values of circulating

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hemoglobin less than 13 g/dL for men (aged 15 years or older); 12 g/dL for women (aged 15 years or older, non-pregnant), teenagers, and children aged 12 to 14 years; 11.5 g/dL for children aged 5 to 11 years; and 11 g/dL for pregnant women and children aged 6 months to 4 years[2]. The most common causes of anemia are iron deficiency (IDA) and thalassemia minor (TM), microcytic anemias characterized by the insufficient synthesis of hemoglobin (Hb) on erythroid precursors, causing a reduction in the mean corpuscular volume (MCV) of erythrocytes[3].

The causes of IDA include inadequate iron intake, chronic blood loss in the gastrointestinal tract, and prolonged menstrual bleeding. Thalassemia minor (TM) is the result of ineffective erythropoiesis due to an imbalance in the synthesis of globin chains, caused by a genetic abnormality in the hemoglobins[4].

The differential diagnosis of microcytic anemias is of great clinical relevance since their prognosis and treatment are different. The first step to diagnose microcytic anemias is to analyze blood smear samples and determine the erythrocyte indexes using cell counters[5]. Currently, diagnosis confirmation of these diseases is obtained through exams that assess iron metabolism, hemoglobin electrophoresis, and molecular investigations. All of these methods require significant financial and time resources to confirm the diagnosis. Therefore, with the goal of simplifying the differential diagnosis between IDA and TM, several indexes based on erythrocyte parameters have been suggested[6,7]. The objective of this paper was to demonstrate the clinical relevance of discriminant indexes in individuals with microcytic anemia to simplify the differential diagnosis of iron deficiency anemia and thalassemia minor.

METHODS

This bibliographic and transversal study was carried out using the descriptors: iron deficiency anemia, thalassemia minor, and differential diagnosis. The descriptors used allowed for a comprehensive search on the subject on the following databases: PubMed, SciELO, and Lilacs. The descriptors used for searching all the databases were: iron deficiency anemia, beta-thalassemia, and differential diagnosis. The inclusion criterion was the presence of the keywords in the title or abstract of the papers, without any date restrictions. There was a restriction on language, and only papers in English or Portuguese were considered.

RESULTS

A total of 149 articles were obtained through the combined use of the descriptors, of which 106 were irrelevant to the topic or were in other languages. Thus, only 43 articles remained to be analyzed, of which 25 were used in this study, taking into account those that used patients and had more significant statistical results.

DISCUSSION

Microcytic anemia, characterized by the insufficient synthesis of hemoglobin (Hb) on erythroid precursors and by a reduction in the mean corpuscular volume (MCV) of erythrocytes, is often a consequence of IDA and TM[3,8]. Other less common causes that should also be considered include chronic disease/inflammation anemia and sideroblastic anemia[5].

IDA is a very frequent finding not only in developing countries due to a poor nutritional status, but also in the western world, where women of childbearing age are often diagnosed with IDA due to intermittent blood loss associated with inadequate iron intake[8]. Iron deficiency develops, most of the time, slowly and progressively, and, for didactic purposes, can be divided into three stages: depletion of iron reserves, iron-deficient erythropoiesis, and IDA. Mean values of Hb of 10.0 g/dL (9.3 to 10.7), MCV of 73 fL (67 to 76), mean corpuscular hemoglobin (MCH) of 22.7 pg (20.8 to 24.1), and Red Blood Distribution Width (RDW) of 17.9% (16.6 to 19.4) are usually found. The erythrocyte, Red Blood Cell (RBC), count is usually normal or decreased, and the reticulocyte count is normal or reduced[5,6,9].

Thalassemia, traditionally, is highly prevalent in the Mediterranean region, Middle East countries, the Arabian Peninsula, and Southeast Asia, but population migration has currently spread the genes of thalassemia almost throughout the world[8]. Thalassemias are inherited anemias caused by a partial or complete deficiency of globin chain synthesis and are the most common genetic disorders worldwide, constituting a major public health problem[10]. TM is a clinical definition applied to heterozygous, asymptomatic patients. Its most common types are alpha thalassemia minor and beta-thalassemia minor, in which the subunits of alpha-globin and beta-globin are decreased, respectively[11]. Mean values of Hb of 10.9 g/dL (10.5 to 11.8), MCV of 63.8 fL (61.6 to 68.5), MCH of 20.4 pg (19.7 to 21.6), and RDW of 15.9% (15.3

to 16.9) are generally found in both alpha and beta TM. RBC is usually increased and the reticulocyte count is normal or increased[5,6,9,12].

The diagnosis of IDA is obtained through measurements of serum iron, total iron-binding capacity (TIBC), transferrin and serum ferritin saturation, whereas the diagnosis of beta TM is usually by hemoglobin electrophoresis and levels of Hb A_2 greater than 3.5% (Table 1)[5,6,13]. On the other hand, the diagnosis of alpha TM requires molecular investigations of the alpha gene, since the levels of Hb A_2 are reduced (<2.5%)[5,7,12].

Differentiating IDA, mild or moderate, from TM (alpha and beta) can be a diagnostic dilemma since both conditions are microcytic anemias and share many characteristics. Evidently, a correct diagnosis in patients with microcytic anemia is important: it can provide an indication of iron supplementation for patients with IDA, avoid unnecessary iron therapy for patients with TM, and, of course, prevent severe and lethal forms of thalassemia syndromes through instruction in areas of high prevalence[3,8,12].

Despite its great usefulness, confirmatory tests for diagnosing microcytic anemias involve methodologies that are time-consuming, high-cost, and inaccessible to poor populations[5]. In an attempt to simplify the differential diagnosis between IDA and TM, more than 40 mathematical indexes based on erythrocyte parameters have been proposed in the hematologic literature for patients with microcytosis[5,8]. These indexes use formulas that incorporate, in various combinations, at least two erythrocyte parameters provided by automated hematology analyzers. Most indexes incorporate MCV, MCH, RBC, Hb, and RDW, in various combinations, to amplify the differences of unique parameters for both anemias[14].

TABLE 1. DIFFERENTIAL DIAGNOSIS BETWEEN IRON DEFICIENCY ANEMIA AND BETA THALASSEMIA MINOR13

Variable	Iron deficiency anemia	Beta thalassemia minor
Number of red blood cells	dec.	normal or inc.
Hb	dec.	dec. or normal
MCV	dec.	dec.
RDW	inc.	inc.
Reticulocyte count	Normal or dec.	normal or inc.
Peripheral blood morphology	Hypochromia	microcytosis, basophilic stippling
Transferrin saturation	dec.	normal or inc.
Ferritin (ng/mL)	dec.	normal or inc.
Hb electrophoresis	Normal Hb A_2	inc. Hb A_2.
Therapeutic test with iron	positive	Negative

Legend: Hb, hemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width; dec., decreased; inc, increased.

England et al.[15], in 1973, found that RBC alone can differentiate IDA from beta TM. However, in 72 patients with microcytosis, a simple discriminant function derived from MCV, RBC and Hb (MCV-RBC-(5xHb)-3.4) correctly identified all except one of the cases studied (99%). In another study involving 103 individuals with microcytosis, Mentzer[16], in 1973, demonstrated that a discriminant function (MCV/RBC) had similar efficacy to that proposed by England et al.[15]. A study conducted by Bessman et al.[17], in 1979, aiming to quantify the degree of anisocytosis (RDW) in patients with IDA and TM (alpha and beta), showed a marked difference between IDA and TM. Fifty-three individuals with IDA had increased RDW, while 25 with beta TM had normal or slightly increased RDW.

In a study involving 102 patients with IDA and 33 with beta TM, Green & King[18], in 1989, compared a new discriminant function (MCV^2× RDW/Hbx100) with six other discriminant indexes and concluded that the use of this discriminant function that incorporates RDW resulted in greater accuracy to distinguish IDA from TM. In another study involving 284 patients (130 with IDA and 154 with beta TM), Ehsani et al.[19], in 2009, compared a new index (MCV-10xRBC) with four other indexes (England-Fraser, Mentzer, Srivastava, and RBC) and demonstrated that the new index was able to identify 263 individuals (92.96%), inferior only to the Mentzer index, that correctly diagnosed 269 individuals (94.71%). Despite that, its calculation simplicity makes it acceptable.

More recent studies involving new hematological parameters, such as the percentage of microcytic and hypochromic erythrocytes (M/H ratio), have demonstrated to be useful in detecting small changes in the number of erythrocytes with inadequate hemoglobinization in patients with IDA and TM[20].

In a meta-analysis conducted by Hoffmann et al.[8], in 2015, 12 discriminant indexes were selected from the literature to differentiate between IDA and TM in patients with microcytosis (Table 2). It is widely accepted that none of these indexes is 100% sensitive and specific. Even more complex approaches,

TABLE 2. DISCRIMINANT INDEXES (CALCULATIONS, CUT-OFF, SENSITIVITY, AND SPECIFICITY)[8]

Discriminant indexes	Calculations	Cut-of	Sensitivity	Specificity
M / H ratio	% Microcytes/ % Hypochromic	3.7	0.92 (0.87 - 0.98)	0.86 (0.81 - 0.91)
RBC	RBC	5.0	0.85 (0.80 - 0.88)	0.90 (0.86 - 0.93)
Sirdah	MCV - RBC - (3 X Hb)	27.0	0.83 (0.75 - 0.89)	0.90 (0.83 - 0.95)
Ehsani	MCV - (10 X RBC)	15	0.91 (0.85 - 0.94)	0.82 (0.76 - 0.87)
England and Fraser (E&F)	MCV - RBC - (5 x Hb) - 3.4	0	0.75 (0.70 - 0.79)	0.92 (0.90 - 0.94)
Green and King (G&K)	MCV^2 x RDW / 100 x Hb	65	0.79 (0.73 - 0.83)	0.89 (0.85 - 0.92)
Jayabose (RDW índex)	MCV / (RBC x RDW)	220	0.83 (0.78 - 0.88)	0.85 (0.81 - 0.88)
Mentzer	MCV / RBC	13	0.82 (0.79 - 0.86)	0.85 (0.82 - 0.88)
Shine and Lal (S&L)	MCV^2 x MCH	1.53	0.96 (0.93 - 0.97)	0.41 (0.27 - 0.56)
Ricerca	RDW / RBC	4.4	0.93 (0.88 - 0.97)	0.52 (0.36 - 0.67)
Srivastava	MCH / RBC	3.8	0.78 (0.72 - 0.82)	0.81 (0.77 - 0.85)
Bessman	RDW	15	0.62 (0.61 - 0.63)	0.66 (0.65 - 0.68)

Legend: RBC, erythrocyte count; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; RDW, red cell distribution width; Cut-off, cutoff point.

including different combinations of simple indexes or multivariate discriminant analysis, are incapable of achieving absolute sensitivity and specificity. However, these indexes can be effective as a preliminary screening tool when an adequate cut-off is chosen[8,14].

Matos et al.[21], in 2013, evaluated the discriminative power of seven indexes to differentiate between IDA and beta TM in the Brazilian population and reported that the Green & King index and RDW had the highest reliability. A study conducted by Miri-Moghaddam et al.[9], in 2014, to assess the effectiveness of discriminant mathematical formulas and their cut-offs concluded that the Green & King index had the highest efficiency and suggested that the cut-off should be determined, for all formulas, in different populations. In a large study with 2,664 individuals with microcytic anemia - 1,259 with IDA, 1,196 with TM (877 with beta TM and 319 with alpha TM), 150 with TM with IDA or concomitant chronic disease, and 36 with other diseases, Urrechaga et al.[22], in 2017, investigated the performance of 25 discriminant indexes that only use parameters available in all automated hematology analyzers and demonstrated that the Green & King index had an excellent performance, behind only the Jayabose and Janel 11T indexes.

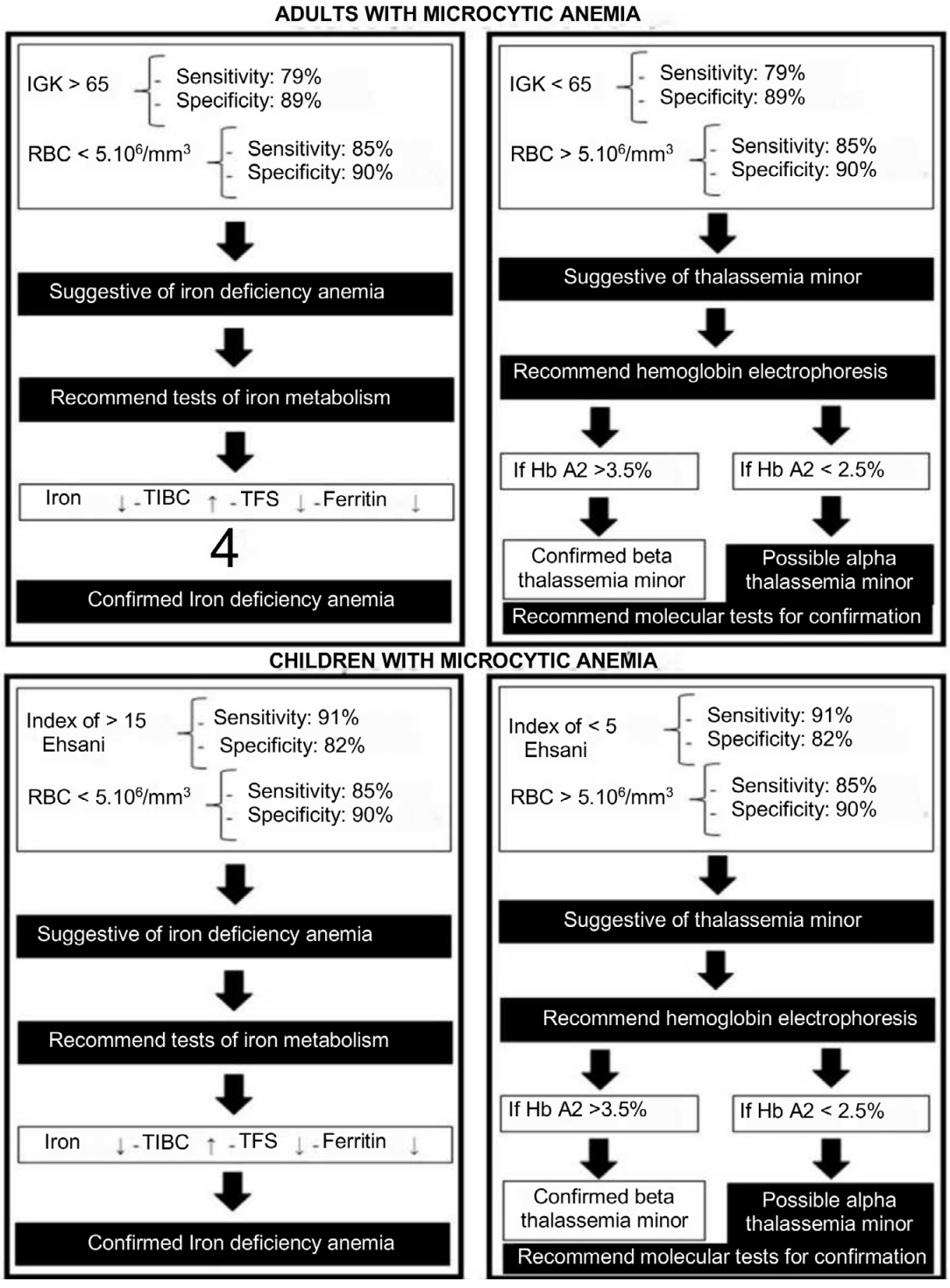
Hoffmann et al.[8], in 2015, demonstrated that the age group (adult or child) and the geographic region, but not the type of hematological analyzer nor the Cut-off, are important factors to determine the diagnostic usefulness of discriminant indexes. The only situation in which more heterogeneity can be expected is for discriminant indexes that incorporate RDW since this parameter is not well standardized and presents considerable differences between different analyzers. However, some discriminant indexes that incorporate RDW (Green & King and Jayabose) combine it with multiple other parameters and, thus, mitigate the possible influence of RDW in their performance[22].

Overall, the more recent indexes seem to be able to make this distinction better than the more traditional formulas. However, when evaluated in more detail, older indexes (England & Fraser, Mentzer, and Green & King) performed better in adults. In contrast, some more recent discriminant indexes (Jayabose, Sirdah, and Ehsani) performed much better in children. The M/H ratio, up until now, has only been investigated in adult populations; therefore, how this discriminant index behaves in children remains to be observed[8].

Erythrocytosis (increased RBC) and mild anemia are characteristics of TM, and the erythrocytes are usually more microcytic (reduced MCV) than in IDA; whereas in IDA, the level of anisocytosis (RDW) is greater, along with lower Hb levels when compared with those of TM[6,9,12,14]. According to the meta-analysis conducted by Hoffmann et al.[8], in 2015, the Green & King, Jayabose, Ehsani, Sirdah, and RBC indexes had excellent performances, behind only that of the M/H ratio (restricted to a few hematologic counters) 20. Based on the superiority of the Green & King index found in most studies and on its highest performance in adults, along with the high performance of the Ehsani and RBC indexes in children, a simplification is proposed for the differential diagnosis between IDA and TM, based on discriminant indexes (Figure 1).

For patients with beta TM and concomitant IDA, Hb levels A_2 may be reduced, leading to diagnostic difficulties. Therefore, due to the possibility of these

FIGURE 1. SIMPLIFICATION OF THE DIAGNOSIS OF IRON DEFICIENCY ANEMIA AND THALASSEMIA MINOR, IN ADULTS AND CHILDREN, USING DISCRIMINANT INDEXES.



Legend: RBC, Red Blood Cell; Hb, Hemoglobin; MCV, Mean Corpuscular Volume; IGK, Index of Green & King; TIBC, Total Iron-Binding Capacity; TFS, Transferrin Saturation; Hb A2, Hemoglobin A2. * Hb and MCV decreased according to age and sex.

two entities coexisting, the diagnosis of beta TM can be confused by reduced levels of Hb A_2. Thus, the iron deficiency must be identified and corrected for patients with a high suspicion of beta TM, particularly if the levels of Hb A_2 are within the normal range (2.5 - 3.5%)[23]. Another limitation in the use of discriminant indexes is the presence of alpha TM in patients with IDA; thus, individuals with reduced levels of Hb A_2 need to undergo molecular analyses for diagnostic confirmation[5,12].

CONCLUSION

Despite its great usefulness, confirmatory tests for a differential diagnosis between IDA and TM require methods that are time-consuming and costly. In this context, the use of discriminant indexes that use erythrocyte parameters can provide a powerful tool to simplify the diagnosis of IDA and TM. The IGK, Ehsani, and RBC indexes had excellent performances; however, none of them were sufficiently sensitive and specific to establish a diagnosis. Despite that, they are of great value to identify, in particular, individuals with microcytic anemia, in whom diagnostic tests are indicated for confirmation of TM.

RESUMO

INTRODUÇÃO: *Anemias microcíticas são muito comuns na prática clínica, sendo a anemia ferropriva (AF) e a talassemia menor (TM) as mais prevalentes. A confirmação diagnóstica dessas entidades clínicas requer testes que envolvem o perfil do metabolismo do ferro, eletroforese de hemoglobinas e análises moleculares. Nesse contexto, vários índices discriminantes têm sido propostos para simplificação do diagnóstico diferencial entre AF e TM.*

OBJETIVO: *O objetivo deste artigo foi demonstrar a relevância clínica da utilização de índices discriminantes em indivíduos com anemia microcítica, para simplificação do diagnóstico diferencial entre anemia ferropriva e talassemia menor.*

MÉTODOS: *Foi realizada uma pesquisa bibliográfica e transversal nas bases de dados PubMed, SciELO e Lilacs, utilizando-se os seguintes descritores: anemia ferropriva, talassemia menor e diagnóstico diferencial.*

RESULTADOS: *Mais de 40 índices matemáticos baseados em parâmetros eritrocitários foram propostos na literatura hematológica em indivíduos com microcitose. Os índices de Green & King (IGK), o índice de Ehsani e a contagem de eritrócitos (RBC) obtiveram excelentes desempenhos, especialmente quando sua eficácia foi observada em adultos e crianças.*

CONCLUSÕES: *Testes confirmatórios para o diagnóstico diferencial entre AF e TM demandam métodos que consomem bastante tempo e alto custo. Apesar dos excelentes desempenhos do IGK, do índice de Ehsani e do RBC, nenhum deles possui sensibilidade e especificidade suficientes para firmar diagnóstico. No entanto, podem fornecer uma poderosa ferramenta adicional para simplificação diagnóstica entre AF e TM.*

PALAVRAS-CHAVE: *Anemia ferropriva. Talassemia beta. Diagnóstico diferencial.*

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REVIEW ARTICLE

Pharmacological therapy and cardiovascular risk reduction for type 2 diabetes

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SUMMARY

The pharmacological therapy for type 2 diabetes mellitus has presented important advances in recent years, which has impacted the treatment of patients with established cardiovascular disease or with high cardiovascular risk. In this scenario, two drug classes have emerged and demonstrated clear clinical benefits: SGLT-2 inhibitors and GLP-1 agonists. The present review discusses the pharmacology, adverse effects, and clinical trials that have demonstrated the benefits of these medications in reducing cardiovascular risk.

KEYWORDS: *Diabetes mellitus, Hypoglycemic agents, Heart disease.*

INTRODUCTION

Type 2 diabetes mellitus (DM-2) is a prevalent condition that affects approximately 450 million people worldwide. It is expected that approximately 640 million people will be affected in 2040. Until recently, scientific evidence has indicated that pharmacological therapy for DM would be able to reduce only microvascular complications (retinopathy, nephropathy, and neuropathy). However, in 2008, after 10 years of follow-up, the UK Prospective Diabetes Study (UKPDS) observed potential for reducing cardiovascular events, including death, by improving the glycemic control of DM-2[1]. These observations were a milestone in cardio-diabetology since cardiovascular disease (CVD) is the main cause of death among diabetics.

In 2007, the results of a meta-analysis raised great concern about the use of oral antidiabetics by demonstrating a higher risk of acute myocardial infarction and mortality with the use of rosiglitazone[2]. Since then, the Food and Drug Administration and the European Medicines Agency have become concerned about the cardiovascular risk associated with new therapies for DM and have established that new drugs for the treatment of DM-2 should be tested in randomized, prospective, and controlled studies. Two classes of drugs, sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, have shown not only safety but also great potential for reducing macrovascular events.

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For decades, two key ways of treating diabetes were sulfonylureas,[3] which have controversial safety, and DPP-4 inhibitors, which are neutral in terms of cardiovascular endpoints. These characteristics were shown in the EXAMINE[4] and CAROLINA[5] studies. The only therapeutic target was glycemic control, and not the reduction of cardiovascular clinical events.

SGLT2 inhibitors

SGLT-2 transport protein inhibitors are the first class of medication for DM-2 therapy that has demonstrated a reduction in cardiovascular risk. SGLT-2 is a protein found in the proximal convoluted tubules of nephrons and is responsible for the reabsorption of 90% of the filtered glucose in the glomerulus. Another carrier protein found in nephrons is SGLT-1, which reabsorbs the remaining 10% of filtered glucose. Through this mechanism of action, SGLT2 inhibitors are able to reduce glycated hemoglobin (HbA1c) levels by 0.5-1%, in addition to reducing systolic (± 4-6 mmHg) and diastolic blood pressure (± 1-2 mmHg). The latter effect is due to greater osmotic diuresis and possibly also the promotion of nephron remodeling, improvement of endothelial function, reduction in arterial stiffness, and weight loss due to the caloric loss caused by glycosuria[6-10].

The SGLT2 inhibitors available so far are empagliflozin, canafliflozin, dapagliflozin, and ertugliflozin (table 1). All of these drugs are administered once a day due to their prolonged half-life. Furthermore, they have similar pharmacokinetic and pharmacodynamic characteristics except for the degree of selectivity of blocking SGLT-2 receptors in relation to SGLT-1 receptors (empagliflozin> ertugliflozin> dapagliflozin> canagliflozin). Among these, ertugliflozin is the only one with no studies demonstrating a reduction in cardio-vascular events thus far.

TABLE 1

SGLT-2 inhibitor	Doses available
Empagliflozin	10-25 mg once daily
Dapagliflozin	5-10 mg once daily
Canagliflozin	100-300 mg once daily
Ertugliflozin	5-15 mg once daily

The EMPA-REG OUTCOME study was the first large study to demonstrate a reduction in CV risk. This study tested the administration of empagliflozin in patients with DM and established CVD. After a 3.1-year follow-up, there was a 14% reduction in the incidence of the primary composite outcomes in the form of major adverse cardiac and cerebrovascular events (MACCE), which include cardiovascular death, stroke, and acute myocardial infarction (AMI). Emphasis was placed on the 38% reduction in the general mortality rate and the 32% reduction in the cardiovascular mortality rate. In addition, a 35% reduction in hospitalizations for heart failure has been reported, suggesting that the benefit of this class of drug is mainly due to its hemodynamic effects[7].

In 2017, the CANVAS study on canagliflozin was published. Unlike the EMPA-REG OUTCOME study, the CANVAS study included a mixed population of patients with DM-2 and CVD or without CVD, as well as multiple risk factors. Canagliflozin therapy reduced the primary endpoint composed of MACCE by 14%, but unlike the EMPAREG-OUTCOME study, there was no difference in the isolated analysis of mortality. Hospitalization rates for heart failure were also reduced by 33%[6]. The use of canagliflozin was also evaluated in patients with DM-2 and chronic kidney disease by the CREDENCE study. This study was conducted because of the possible benefits of SGLT2 inhibitors in reducing the progression of diabetic nephropathy. After an average follow-up of 2.6 years, a 39% reduction in hospitalization for heart failure and a 20% reduction in the outcome rates of MACCE were demonstrated, in addition to benefits in reducing the progression of diabetic nephropathy[11].

The DECLARE-TIMI 58 study published in 2019 analyzed the use of dapagliflozin in a mixed population with less severe conditions compared to previous studies. The population was composed of patients with CVD and DM-2 (40%) or with DM-2 and multiple risk factors. The results of 4 years of follow-up showed a 17% reduction in cardiovascular death and hospitalization for heart failure, which were mainly driven by a 27% reduction in hospitalization for heart failure. However, there was no significant decrease in cardiovascular death or the primary composite outcome[12].

An important difference is apparent in the reduction of clinical events among these four studies: a significant reduction in cardiac death was only observed in EMPAREG-OUTCOME. This could possibly be explained by the different populations included in each of these trials. EMPAREG-OUTCOME included only patients with established CVD, while the other three included heterogeneous populations of patients with or without CVD and different high risk factors.

The most recent major study to demonstrate the cardiovascular benefits of ISGLT2 is the DAPA-HF study. This study looked at the use of dapagliflozin in an exclusive population of patients with heart failure and reduced left ventricular ejection fraction (≤40%). The motivations for this study were the previous results demonstrating a significant reduction in the occurrence of hospitalization for heart failure and the biological mechanisms that could justify the use of this class of medication in patients with heart failure. It is important to highlight that the presence of DM-2 was not mandatory for inclusion in this trial and was not diagnosed in 58.2% of the participants. After a follow-up of only 18 months, dapagliflozin reduced hospitalization for heart failure by 30%, cardiovascular death by 18%, and all-cause mortality by 17%. Additionally, there was a symptomatic improvement in heart failure assessed by the Kansas City Cardiomyopathy Questionnaire[13].

Despite the clear documented benefits of the use of SGLT2 inhibitors, especially in a population with established CVD, some major side effects should be discussed. The glycosuric effect of this class of drugs causes an increased risk of infections of the genital tract, especially urinary infections and vulvovaginal candidiasis[14]. Osmotic diuresis with a consequent contraction of intravascular volume can trigger arterial hypotension in more susceptible patients[15]. Another adverse effect reported is the risk of lower limb amputations, particularly with the use of canagliflozin in the CANVAS study. This means that patients using SGLT2 inhibitors should be monitored and adequately oriented about foot care[6]. The CANVAS study also identified higher rates of bone fracture with canagliflozin, which seems to be explained by greater bone loss with this SGLT2 inhibitor[6]. Finally, there are reports of cases of diabetic euglycemic ketoacidosis[16, 17].

GLP-1 receptor agonists

In addition to pancreatic hormones (insulin, glucagon, and amylin), blood glucose homeostasis depends on gastrointestinal peptides, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). The production of these substances illustrates incretins' effect of greater stimulation of insulin secretion with an oral supply of glucose than an equivalent dose intravenous infusion[18]. GLP-1 is produced by L cells in the ileum and colon in response to hyperglycemia after caloric intake. After binding to its specific receptor, the peptide acts on various tissues, with the effect being greater on pancreatic beta cells. This leads to glucose-dependent insulin secretion and inhibits the release of glucagon. However, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP4)[19].

Synthetic analogues are resistant to the action of DPP4 and accentuate pleiotropic events that favor weight loss, such as delayed gastric emptying and reduced appetite. Defects in this regulation are possibly associated with the development of diabetes. Currently, six drugs have been approved for the treatment of DM2: exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide, and semaglutide. All of them cause a significant reduction in glycated hemoglobin (0.55 - 1.21%), and long-acting ones are usually more effective in glycemic control[20]. One factor that can hinder adherence is the route of administration, since all of these medications are administered subcutaneously except for semaglutide, which can be taken orally (table 2).

TABLE 2

GLP-1 receptor agonists	Doses available
Ezenatide	5-10 mcg twice daily or 2 mg 1 once a week
Liraglutide	0.6-1.8 mg once daily
Lisenatide	10-20 mcg once daily
Albiglutide	30-50 mg once a week
Dulaglutide	0.75-1.5 mg once a week
Semaglutide	Subcutaneous: 0.25-1 mg once a week Oral: 7-14 mg once daily

Initial evidence has shown conflicting results regarding the reduction of CV risk. Only liraglutide and semaglutide have demonstrated superiority to standard therapy. The LEADER study published in 2016 showed a significant reduction (13%) in the primary outcomes (MACCE) when comparing the administration of liraglutide at 1.8 mg (or the maximum tolerated dose) over an average follow-up of 3.8 years[21]. This result was mainly driven by a reduction in CV death (22%), and unlike ISGLT2, there was no significant reduction in hospitalization rates for heart failure. The SUSTAIN-6 study tested semaglutide and showed an even more expressive reduction in the same composite outcome, with a 26% reduction in comparison to the control group. This result was mainly driven by stroke. However, there was no significant decrease in CV mortality or AMI[22]. The difference between these two studies may have occurred due to the shorter follow-up period (2.1 years) and the

lower number of participants in SUSTAIN-6. Both studies included patients with high cardiovascular risk, and 80% of them had established CVD and an average HbA1c of 8.7%.

Despite the encouraging results of the trials mentioned, other studies have failed to find a significant reduction in cardiovascular events with GLP-1 receptor agonists, and only the cardiovascular safety has been proven for some of these new drugs in comparison to a placebo. These studies were EXSCEL, which randomized 14,752 patients to use exenatide weekly; PIONEER 6, which examined oral semaglutide; and ELIXA, which included patients in a secondary prevention scenario for the evaluation of lixisenatide, and hospitalization for angina was part of the primary composite outcome[23-25].

More recently, the class effect theory for protection from cardiovascular events has gained strength since the publication of the HARMONY and REWIND studies[26, 27]. The first of these studies assessed albiglutide and demonstrated a 22% reduction in MACCE, which even led to the resumption of production of this medication, which had previously been discontinued. The REWIND study observed a reduction of only 12% in MACCE driven by stroke, but it included most patients in primary prevention, and only 31.5% had evidence of established atherosclerotic disease.

A meta-analysis published in 2019 demonstrated that GLP-1 RA reduces MACCE (NNT 75) and its individual components, in addition to reducing the risk of hospitalization for heart failure and worsening renal function (mainly by reducing macroalbuminuria). These benefits were achieved without increasing the risk of severe hypoglycemia[28]. It is important to highlight the relevant association between obesity and CVD, as well as the average weight loss of 2.9 kg that occurs when taking this class of drug[29].

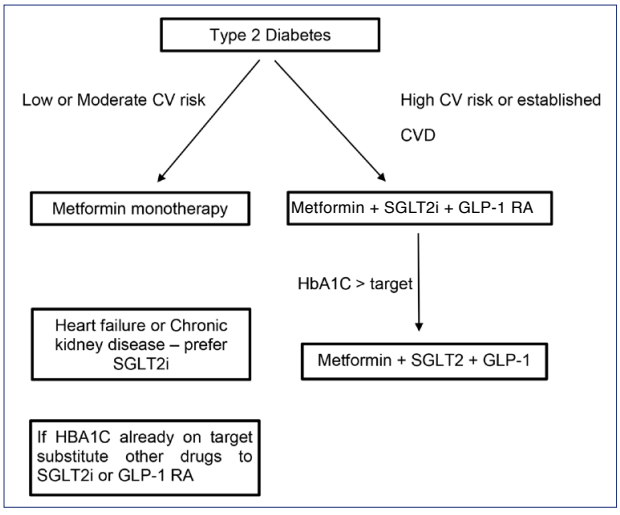
GLP-1 RA slows the progression of kidney disease and the possible dysfunction of incretins in type 1 DM, but it should not be used in patients with terminal CKD or type 1 DM[30]. The adverse effects are mainly related to the gastrointestinal tract, particularly nausea, which tends to improve with time of use or with dose reduction. Increased progression of retinopathy was observed in SUSTAIN-6 but has not been reproduced in other trials and may be the result of type I error or associated with significant glycemic reduction[31, 32]. After reports of acute pancreatitis in users of GLP-1 RA, there was an initial concern that has not been confirmed in prospective and randomized studies, and a relationship has only been reported with calculous cholecystopathy. Despite this, GLP-1 RA should not be prescribed for patients with a history of pancreatitis[33]. Another raised concern is the action of AR-GLP1 on C cells of the thyroid based on experiments on animal models, which has led to it being banned for use in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2A or 2B[34-37].

Present Recommendations

The studies mentioned show a clear benefit of using SGLT2 inhibitors and GLP-1 RA to reduce cardiovascular events. Since the dissemination and wide discussion of these studies, there have been changes in the recommendations of guidelines for first-line medical therapy for DM. The 2019 European Society of Cardiology (ESC) guidelines recommend monotherapy with SGLT2 inhibitors or GLP-1 RA for the initiation of treatment in patients with CVD or high-risk CV. If a patient is already using metformin, the addition of one of these classes is advised if HbA1c ≥ 7.0%.

On the other hand, the American Academy of Diabetes (ADA) favors metformin as an initial therapy for all patients, given its wide availability and low cost. However, it points out that in patients with CVD, chronic kidney disease, heart failure, or indicators of high CV risk (> 55 years of age with ventricular hypertrophy or stenosis > 50% in coronary, carotid, or peripheral vascular territory), it is recommended that treatments include an SGLT2 inhibitor or GLP-1 RA with proven cardiovascular benefit, with a preference for SGLT2 inhibitors in patients diagnosed with heart failure, regardless of glycated hemoglobin levels (Figure 1).

FIGURE 1



We are even considering replacing medications that have a neutral cardiovascular effect with drugs that have proven prognostic benefit in patients with established CV disease, even among those with good glycemic control.

CONCLUSION

DM treatment has changed substantially in recent years. Evidence supporting a transition from glycemic control as a therapeutic target to the reduction of cardiovascular events has been demonstrated in various clinical studies and must be reflected in clinical practice. Therapeutic inertia should be avoided with the use of medications that are known to be associated with the reduction of clinical events in populations with established CVD or high cardiovascular risk. This approach appears to be not only reasonable but also the most appropriate approach based on the available evidence.

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None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

EBM and EGL conceived, wrote, and revised the entire final manuscript, FGP wrote the introduction and revised the final manuscript, LNSC wrote and revised the GLP-1 analogue section, TDQ wrote and reviewed the section on GLP-1 analogs, and CVSJ reviewed the final manuscript and participated in the conception.

RESUMO

A terapia farmacológica do diabetes mellitus tipo 2 apresentou avanços importantes nos últimos anos, impactando principalmente o tratamento dos pacientes com doença cardiovascular estabelecida ou com alto risco cardiovascular. Nesse cenário, surgiram duas classes de fármacos com claros benefícios clínicos; os inibidores da SGLT-2 e os agonistas do GLP-1. Na presente revisão os autores discutem desde a farmacologia, efeitos adversos e também os estudos clínicos que demonstraram os benefícios dessas medicações na redução de risco cardiovascular.

PALAVRAS-CHAVE: *diabetes mellitus, hipoglicemiantes, cardiopatias.*

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REVIEW ARTICLE

Review and pictorial essay on complications of bariatric surgery

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SUMMARY

Obesity is a chronic disease characterized by excess fat in the body and a real public health problem. Bariatric surgery, in recent decades, has gained space in its treatment due to the efficiency obtained in weight loss and significant reduction of the related comorbidities. The most commonly performed bariatric procedures include Roux-en-Y gastric bypass, adjustable gastric band, and laparoscopic sleeve gastrectomy. Possible complications described include fistulas, dehiscence, marginal ulcers, intestinal obstruction, internal hernias, and anastomotic stenosis. These complications may have unfavorable clinical outcomes since symptoms are often nonspecific. Abdominal computed tomography (CT) is an important tool in the evaluation of postoperative complications, both in the immediate and late postoperative status of patients undergoing such a procedure. We analyzed the most illustrative tomographic findings of the different complications after reducing gastroplasty in 203 patients without distinction of age or gender. Correct interpretation requires radiologists to understand the surgical technique since postoperative anatomy and surgery-specific complications may be obstacles to proper interpretation.

KEYWORDS: *Gastroplasty. Bariatric surgery. Postoperative complications. Tomography, X-ray computed.*

INTRODUCTION

Obesity is a chronic disease characterized by excess adipose tissue in the body. It has reached epidemic proportions, making it a public health problem. Over the last decades, bariatric surgery has gained space for the treatment of morbid obesity and the substantial reduction of comorbidities, mainly due to unsatisfactory results from the conventional clinical treatment[1,2].

The most commonly performed bariatric procedures include the laparoscopic Roux-en-Y gastric bypass, the laparoscopic adjustable gastric banding, and the laparoscopic vertical sleeve gastrectomy -[3-5]. Among the possible complications described in the literature are fistulas, dehiscences, marginal ulcers, intestinal obstruction, internal hernias, and anastomotic stenosis[6-8]. These complications may present

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unfavorable outcomes since the clinical symptoms are often nonspecific and include: abdominal pain and distension, nausea, and vomiting.

Postoperative imaging studies, CT in particular, for bariatric procedures are typically carried out to identify the integrity and patency of the anastomosis and to identify such complications[3,4]. An adequate evaluation requires radiologists to understand the surgical technique since the complex post-surgical anatomy and the specific complications from surgery make the interpretation more difficult. Finally, the unfavorable outcomes of such complications can be minimized, particularly through an early evaluation by imaging studies, therefore better management is obtained through a prompt assessment by a radiologist.

METHODS

The objective of this study was to review the main complications and their radiological aspects found post-operatively in patients who underwent Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding, laparoscopic vertical sleeve gastrectomy. We analyzed, retrospectively, the abdomen computed tomography images that were most illustrative of different complications after bariatric procedures completed in 203 patients from August 2012 to July 2019. The analysis was carried by a physician of the Radiology and Imaging Diagnosis Department of the Rede Mater Dei. The images were stored in the PACS (Picture Archiving and Communications System) and obtained from a multislice/helical computed tomography device without or without injection of intravenous non-ionic iodinated contrast and/or associated with the ingestion of iodinated contrast diluted in water. The main complications observed were: internal hernias, adherence or bridles, twisting of the root of the mesentery, intestinal intussusception, fistula, and anastomotic stenosis.

DISCUSSION

Obesity and its related health complications have reached epidemic proportions[2-6]. The association between obesity and diabetes type II, increased cardiovascular risk for hypertension, hypercholesterolemia, sleep apnea, osteoarthritis, and other complications such as “metabolic syndrome” and cancers is well established. Such an increase in the incidence of the obese population, in addition to increasing rates of morbidity, is related to higher health-related costs, both in direct spending for the treatment of obesity and in indirect costs due to the decrease in productivity and absenteeism at work[1].

It has been demonstrated that weight reduction, even at a small level, is beneficial. The patients who are candidates for surgical treatment are those with a body mass index (BMI) greater than 40 kg/m^2, BMI greater than 35 kg/m^2 associated with comorbidities such as those described above, in addition to failure in the clinical treatment. Bariatric surgery has demonstrated superiority over non-surgical treatments, producing lasting weight loss in comparison to changes in lifestyle and with a greater impact on obesity-related comorbidities.

Roux-en-Y gastric bypass is currently one of the most used procedures, and it can be accomplished through laparoscopy or open surgery. The gastric bypass, in this technique, consists in reducing the extent of the gastrointestinal tract, excluding from the food transit part of the stomach, the duodenum, and usually about 40 cm from the proximal jejunum - corresponding to biliopancreatic or afferent loop. This loop measures, generally, around 75 cm (75-150 cm linearly in the largest BMIs) and is distally anastomosed to the jejunum - with a retro- or antecolic route - with the segment that allows the food transit, the efferent or Roux loop. This segment is composed of a superior, vertical or horizontal, small gastric pouch with an approximate volume capacity of 25 mL (20-40), which is anastomosed proximally to the jejunum segment sectioned near its origin. Weight loss occurs mainly through a restrictive mechanism since the small gastric pouch and the narrow gastrojejunal transit create early and prolonged satiety. Malabsorption contributes to a lesser degree to the weight loss due to the bypass of the duodenum and the variable length of the proximal jejunum. These anastomoses can be associated with the emergence of internal hernias, as Petersen hernias and transmesenteric hernias, which may be favored by retrocolic anastomosis.

Vertical sleeve gastrectomy, in turn, is an essentially restrictive procedure performed in patients with morbid obesity as a first procedure before the advent of RYGB. Due to its ease of execution and no consequential anastomoses, in addition to providing satisfactory rates of weight loss, it was once the main procedure for bariatric surgery in the United States and worldwide. Technically, it consists of longitudinally dividing, via laparoscopic route and with the

irreversible exclusion of curvature, the gastric fundus, body, and proximal antrum, an area that corresponds to approximately 70% to 80% of the stomach.

Regarding the immediate postoperative radiographic evaluation of these patients, the goal is usually to evaluate the possibility of leaks or obstructions in order to determine, for example, whether there is a need for urgent reexploration, or if there are any fistulas. The patency of gastrojejunostomy and jejunojejunostomy are analyzed, as well as the proper progression of the oral contrast material before the patient is discharged (usually 24-72 hours after surgery). The tomographic study also allows to assess late complications and is determinant in the detection and characterization of obstructions of the small intestine, due, for example, to twisting of the mesenteric root and internal hernias.

The technique for image acquisition by computed tomography is similar to that used in conventional exams for abdomen analysis.

The mAs factor is obtained automatically and the tension (KV) is adjusted to provide the optimum picture quality, limiting the radiation dose. The intravenous (IV) contrast is administered based on weight, similarly to patients of non-bariatric surgery, with a standard delay of approximately 70 seconds, which is the preferred and assists, in particular, in the detection of vascular complications and abscesses[4,8].

The oral contrast assists in the detection of complications such as leakages and fistula routes. Given the reduction of functional gastric volume, usually, a smaller quantity of the oral contrast agent soluble in water should be used - approximately 60 ml ingested immediately before the scan. The goal is to opacify the gastric pouch, as well as the adjacent output (proximal efferent loop) and not the entire length of the intestinal transit. The images are obtained through thin sectional slices, which are then reconstructed on the axial, coronal, and sagittal planes with a section approximately 3.0 mm thick. It is important to emphasize that the use of thin slices is fundamental to allow high-resolution multiplane reconstructions, assisting in the evaluation of the causes of obstruction of the small intestine and in the identification of findings of internal herniae, such as architectural distortion of the mesentery and adjacent vessels[4,8,9].

Fistulas

The anastomotic leaks are early postoperative complications that can occur, generally, within ten days after the surgery in 6% of patients, requiring emergency surgical reexploration in 80% of the cases[10]. Most postoperative leaks after RYGB extend to the upper left quadrant, to the left of the gastrojejunal anastomosis, but can also be present in the jejunojejunal anastomosis[11]. Leaks may be small and self-limited, present in asymptomatic patients or in those with nonspecific symptoms, such as tachycardia, fever, and abdominal pain or even sepsis. More commonly observed after the gastric sleeve, 1% to 8% of the cases,

FIGURE 1.

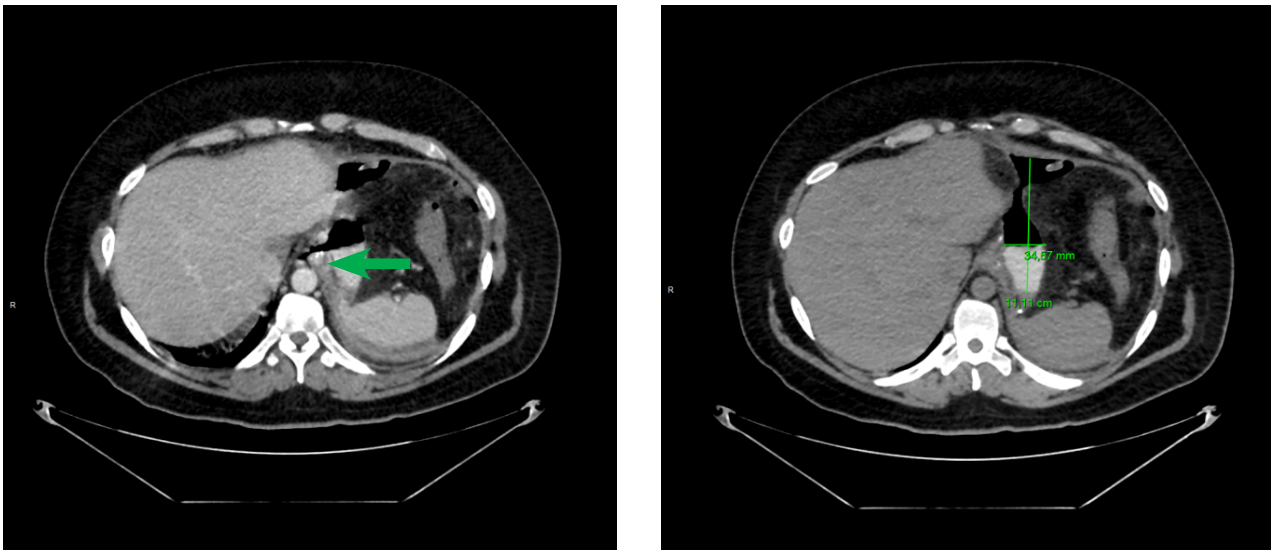

Image A - Collection (estimated measurement between the green calipers) located laterally to the gastric pouch , containing liquid and gas. There is a fistulous route (green arrow) between the gastric pouch and the collection, with extravasation of the contrast media administered orally.

FIGURE 1.

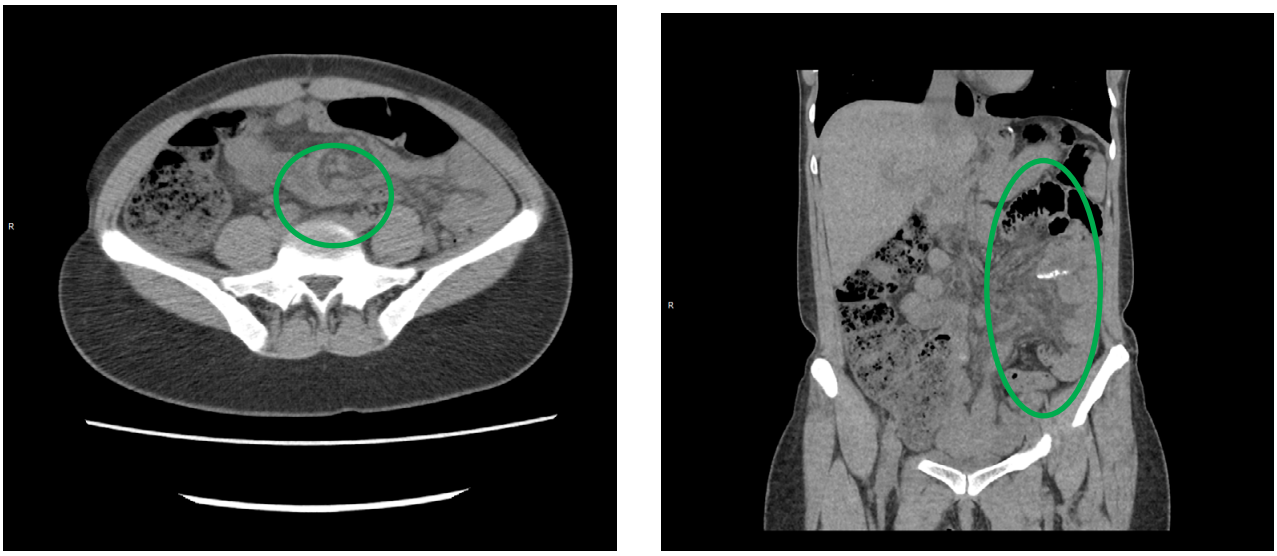

Image B – Internal hernia – axial and longitudinal cuts – twisting of the root of the mesentery, with "whirlpool sign" (circle) and "mushroom sign" (ellipse). Twisting of the axial mesentery in the epigastric region, with rotation of vessels, peritoneal adipose tissue and small intestine loops without significant distension or thickening of the walls.

and leading to significant morbidity, it is also possible after RYGB[11,12]. Therefore, early detection is essential to reduce this risk. Leaks occur most commonly in the proximal row of staples of the gastroesophageal junction (Figure 1) and may be caused by mechanical failure or ischemia. The CT may also show hematomas in the topography of the procedure or abscesses related to the fistulas[6,8].

SMALL INTESTINE OBSTRUCTION

Obstructions of the small intestine are a relatively common complication after RYGB. Their incidence varied from 0.4% to 7.45% in a review of the subject[11]. Such obstruction may be caused by different mechanisms, such as: adhesions, internal hernias, hernias of the abdominal wall, anastomotic stenosis, and hematomas. The tomographic findings include dilated bowel loops upstream from the point of transit narrowing concomitant to the presence of distally collapsed loops[4,9,11].

Such findings have a high correlation with the presence of internal hernias in patients post-RYGB.

Internal hernias can present both acutely and in the late postoperative period, occurring due to flaws in the mesentery, and the small intestine it thus herniated because of these flaws, usually toward the upper left abdomen, which predisposes to the occurrence of obstruction, ischemia, infarction, and even perforation. Internal hernias occur in about 3% of patients post-RYGB and can be potentially fatal, occurring in both the early and late post-surgery period; however, they are more common in the latter[1,10,12]. There are three different types of internal hernias that can occur after RYGB: 1 - through the mesocolon; 2 - in a potential mesenteric defect adjacent to the jejunojejunal anastomosis; and 3 - as Petersen hernias. Some characteristic defects of the mesentery may serve as potential sites for the development of internal hernias, among them: the defect created in the transverse mesocolon with the retrocolic Roux loop - which, despite minimizing tension on the anastomosis, is the most common site of occurrence of hernias -, the defect that develops adjacent to the jejunojejunal anastomosis, and the defect between the caudal margin of the mesocolon and the mesentery of the Roux loop, also called Petersen hernia[1,3,9,12].

The best sign isolated for detecting an internal hernia was the "mesenteric whirlpool" sign[9,13], which refers to the centripetal curvilinear appearance of the mesenteric vessels and fat in the mesenteric root of the small intestine. A greater correlation was obtained by the combination of this latter finding with the "mushroom" sign, which refers to the shape of the hernial content when it protrudes through the relatively narrow opening between the vessels and the mesenteric root. After crossing this narrowing, the content expands toward the left hypochondrium (Figure 1). Another finding that can assist in the identification of internal hernias is the displacement of the

jejunojejunal anastomosis from its typical location, which would be on the left middle abdomen. As for the Petersen hernia (Figura 2), the herniated loop is characteristically found in the upper left quadrant of the abdomen, above the level of the stomach. Other findings that have also been described include: the displacement of the angle of Treitz anteriorly and to the right, as well as the presence of ileal loops with a descending route, originating in the upper left quadrant. The whirlpool and mushroom signs may be present but are less specific[9,13].

Intussusception

Intussusceptions in the small intestine may be transient or fixed and are a rare cause of obstruction after gastric bypass surgery. They typically occur in the very jejunojejunal anastomosis or adjacent to it, with the line of staples presumably acting as the starting point for intussusception[4]. Reduced intestinal peristalsis or even ectopic peristaltic stimulation in the jejunum post-surgery can trigger dysfunctional retrograde contractions close to the anastomosis and operate as a contributing factor (Figure 2)[4,8].

FIGURE 2.

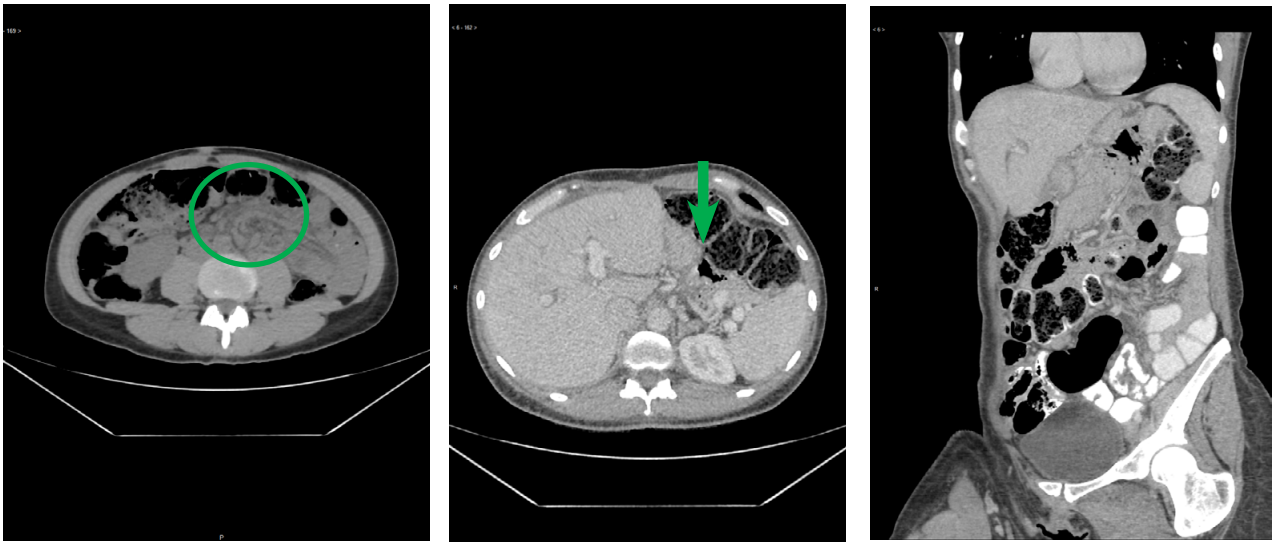

Image C - Petersen Hernia - axial planes and oblique sagittal reformatting: whirlpool sign - twisting of the root of the mesentery with a spiral effect of the vessels - circle. Internal hernia with small intestine loop interposed between the stomach and the colon (arrow and ellipse).

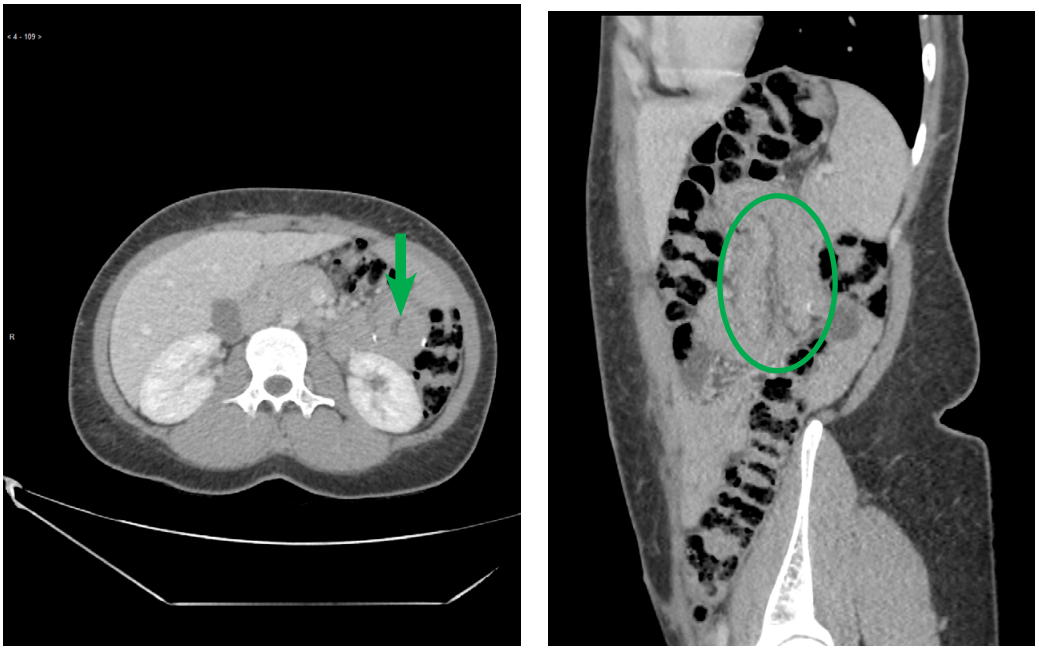

Image D - intestinal intussusception after gastric bypass - axial reformatting and in the oblique sagittal plane. Enlargement of the enteric anastomosis, with protrusion of the jejunal loops towards the inside, characterizing intestinal invagination - target aspect (arrow). Reformatting in the sagittal plane to assess the intussusception (ellipse).

Anastomotic stenosis

Another complication that can also lead to obstruction and that was observed in our study was anastomotic stenosis. The anastomotic narrowing can be the result of reactional edema in the perioperative period and circular stapling of the jejunojejunal anastomosis, or it can manifest late, resulting from ischemia, bridles, or adhesions[1,2,5,6]. The obstruction of the afferent loop is potentially fatal since a closed loop is created, in which there are no natural means for decompression of the segment, which can lead to gastric perforation and/or necrosis. Jejunojejunal anastomotic stenosis usually requires re-operation; however, it is much less common than gastrojejunal anastomotic stenosis (3% to 9%), occurring in <0.9% of the cases and with the possibility of leading to small intestine obstruction[1,3,10,12]. This narrowing in the anastomosis presents in the CT as distending loops upstream the Roux segment, the biliopancreatic loop, or both[1,4]. CT may be particularly advantageous to

FIGURE 3.

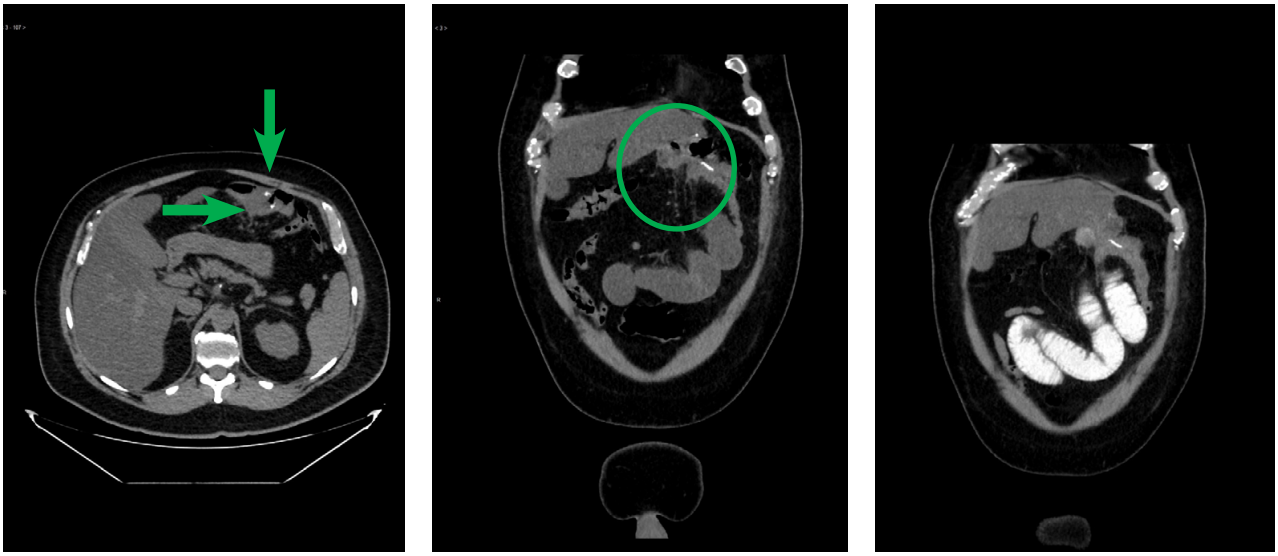

Image E - Jejunojejunal anastomosis with uppward displacement up until near the epigastric region (head of arrow). It is associated with light densification of adjacent adipose planes in this topography (arrow). It is possible to see moderate focal dilatation of the jejunal loops upstream of the anastomosis (circle). After opacification of the digestive tube with the oral contrast, the focal dilatation of the jejunal loops is maintained upstream the anastomosis, without progression of the oral contrast beyond this level (ellipse). The aspect is compatible with intestinal obstruction, possibly related to birdles or adhesions.

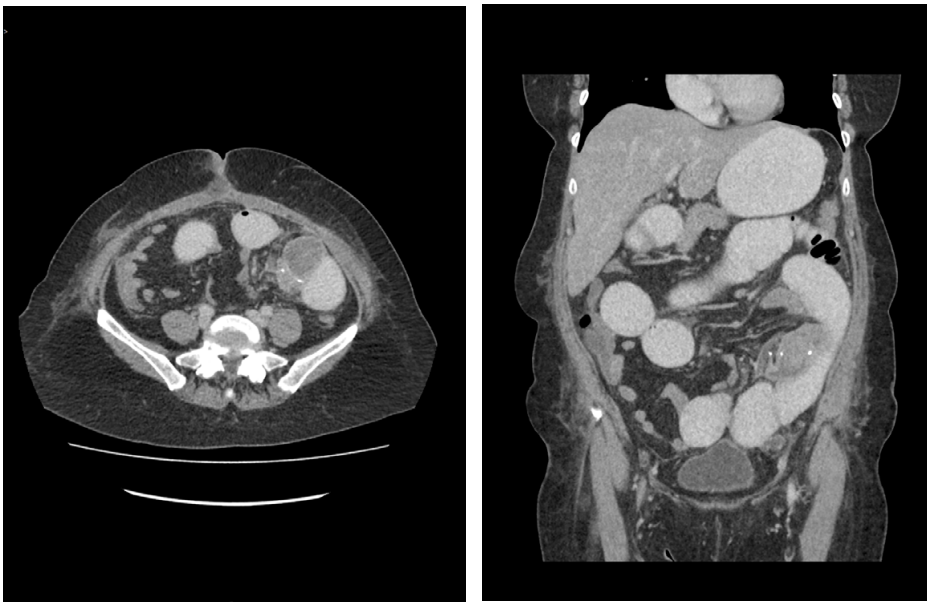

Image F - Jejunojejunal anastomotic stenosis. Distending small intestinal loops, with envolvment of the jejunal segments, distended by air-fluid content, with fecalization of its content in the distal third of the distension. A small focal/segmental area stands out with luminal narrowing in the enteroenteric anastomosis (arrow), without areas of significant parietal thickening identifiable with the method. Consequent absence of fecal and gas content in the colon (intestinal obstruction). There was no progression of contrast material beyond the anastomosis (circle).

evaluate jejunojejunal anastomosis because it allows excellent evaluation of the biliopancreatic/afferent loop (Figure 3)[1,7,10].

Adjustable gastric banding / gastric ring

The placement of the adjustable gastric bands/rings generally is done laparoscopically and constitutes the placement of a ring around the proximal region of the stomach, sutured to the abdominal wall, usually 5 cm below the hemidiaphragm to restrict the passage of ingested food[2,11]. CT assists in the assessment of the correct positioning of the band and its possible shifting/migration due to the possible weakening or breakage of the sutures[11]. Other possible, but less frequent complications would be erosion and infection[3,4].

CONCLUSION

Bariatric surgery has been increasingly prevalent in response to the obesity epidemic. Various techniques for surgical management are available for surgeons, and the role of radiologists is to be familiar with such procedures. Knowledge of the expected postoperative anatomy, major complications, and main image signs are fundamental for a precise diagnosis and to optimize patient care.

Author's Contribution

Raspante, L.B.P.; Barquette, A.C.; Motta, E.G.P.C, Ribeiro, M.A; Moreira, W.; Ramos, L.F.M.; contributed to the design and implementation of the research, to the analysis of the images, and to the writing of the manuscript.

RESUMO

A obesidade é uma doença crônica caracterizada pelo excesso de tecido adiposo no organismo e um verdadeiro problema de saúde pública. A cirurgia bariátrica, nas últimas décadas, ganhou espaço no seu tratamento devido à eficiência obtida na perda ponderal e redução importante de comorbidades relacionadas. Os procedimentos bariátricos mais comumente realizados incluem o bypass gástrico em Y-de-Roux, a banda gástrica ajustável e a gastrectomia vertical — Sleeve — por via laparoscópica. Entre as complicações possíveis descritas podem ser citadas: fístulas, deiscências, úlceras marginais, obstrução intestinal, hérnias internas e estenose de anastomoses. Essas complicações podem apresentar desfechos clínicos desfavoráveis, uma vez que os sintomas são frequentemente inespecíficos. A tomografia computadorizada de abdome (TC) constitui uma importante ferramenta na avaliação de complicações pós-operatórias, tanto no status pós-cirúrgico imediato quanto tardias, de pacientes submetidos a tal procedimento. Foram analisados os achados tomográficos mais ilustrativos das diferentes complicações pós-gastroplastia redutora ocorridas em 203 pacientes sem distinção de idade ou gênero. A correta interpretação requer que os radiologistas compreendam a técnica cirúrgica, uma vez que a anatomia pós-cirúrgica e as complicações específicas da cirurgia podem ser obstáculos para a adequada interpretação.

PALAVRAS-CHAVE: *Gastroplastia. Cirurgia bariátrica. Complicações pós-operatórias. Tomografia computadorizada por raios X.*

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REVIEW ARTICLE

Ocular manifestations of COVID-19: a literature review

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SUMMARY

Coronavirus disease 2019 (COVID-19) caused by the highly pathogenic SARS-Cov-2 virus, was declared as a pandemic by the World Health Organization (WHO) in March 2020. Its main clinical manifestations are related to airway involvement; however, there is extrapulmonary impairment in some cases. Given this context, this literature review aims to identify the ophthalmological conditions caused by infection with the novel coronavirus. Although ocular findings do not include the standard clinical presentation of the disease, there are reports of some ophthalmological changes in COVID-19 patients, and conjunctivitis is the most common among these.

KEYWORDS: *Coronavirus Infections. Pandemics. Signs and Symptoms. Ophthalmology. Conjunctivitis.*

INTRODUCTION

Viruses circulate in humans, birds, and other animals causing epidemics and pandemic outbreaks throughout history, as was the case with H1N1 (Spanish flu) and H3N2 (Hong Kong fever), in 1968, which resulted in over 1 million deaths[1].

On 11 March 2020, the World Health Organization (WHO) declared a pandemic caused by novel coronavirus NCOV-19, which causes Sars-COV-2, Severe Acute Respiratory Syndrome with systemic repercussions, such as organ failure and septic shock[2,3]. Since the pandemic was announced, the number of new COVID-19 cases (Coronavirus disease) has increased dramatically outside the Chinese territory, with 143 countries reporting infections by NCOV-19 to the WHO[4].

The first cases of the disease were reported in the city of Wuhan, in the Hubei province of China, where the patients had symptoms such as dry cough, dyspnea, fever and bilateral pulmonary infiltrates in imaging examinations. In addition to these signs and symptoms, after a more detailed analysis through nasopharyngeal swabs, the causal agent was identified by the Chinese Center for Disease Control and Prevention as Sars-CoV-2[3].

Sars-CoV-2 is a single-stranded RNA virus with immunological characteristics similar to Sars-CoV-1[5]. This pathogen is part of the beta-coronavirus family and has a great diversity of non-structural proteins and spike proteins that interact heavily with the

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receptors of angiotensin-converting enzyme 2 (ACE2) in the human body[5]. ACE2 is more concentrated in the lung, heart, renal and intestinal tissue[6]. In the lung, the receiver is expressed in epithelial cells, which suggests a relationship between ACE2 and the characteristic alveolar damage of COVID-19 patients[7.8].

The immune response to the virus is mediated by T-lymphocytes through antigen-presenting cells and alveolar macrophages, which have ACE2 receptors. Thus, there is an inflammatory phenomenon perpetuated by CD-4 and cellular destruction mediated by cytotoxic CD8[7].

The ocular tissue is also a site of ACE2 expression, which is present in the cornea and in the conjunctiva epithelial cells[9.10]. This receptor is associated with the maintenance of intraocular pressure and presents an important role in the physiopathology of COVID-19[11].

Since the ocular surface can serve as a gateway to various pathogens, it is believed that this includes the coronavirus[12]. Considering this is an ideal environment for the virus adhesion due to its tropism related to the surface receptor, some authors postulate that the contact of the ocular surface with objects and hands contaminated by the virus can serve as the initial site of infection, which then spreads[12.13].

The existence of ACE2 in the corneal limbus allows the beta-coronavirus to cross the ocular surface and spread to other parts of the body, either through the hematogenic route or the nervous system, through the trigeminal nerve[14].

The presence of eye signs and symptoms and the possibility of NCOV infection-19 through contaminant droplets in the conjunctiva have aroused the interest of medical institutions. The adoption of preventive measures for individual eye protection and the early recognition of ocular symptoms in patients with suspected COVID-19, thus, have been identified as essential[13.15].

Although this is a very current scenario, there are some reports of ocular manifestations in patients with a diagnosis of COVID-19[15]. The most frequent finding of ocular involvement is viral conjunctivitis, presenting redness, lacrimation, and foreign body sensation from the 13th day of the disease or as the first sign of infection[16-18].

Although conjunctivitis is not a classical or standard presentation of the novel coronavirus, physicians and ophthalmologists should be aware of patients complaining of this symptoms[8]. This study aims to identify and analyze the main ocular complaints resulting from viral infection by Sars-Cov-2.

METHODS

The current work is a literature review of the main ocular manifestations found in COVID-19 patients. A search was carried out in the PubMed, SciELO, and Lilacs databases using keywords such as *Ocular findings and COVID-19, as* well as *ocular manifestation and coronavirus.* As a result, we found some initial studies from 2019-2020 and selected those that fit into the proposed theme; eight works remained for analysis.

RESULTS AND DISCUSSION

The acute respiratory disease caused by the novel coronavirus spread beyond the Chinese territory and drew attention worldwide. NCOV-19 uses ACE2 to attach, in particular, to the respiratory epithelium and achieve systemic circulation in the host[19].

Recognizing the ocular manifestations in patients infected by the coronavirus is necessary in order to understand the role of ophthalmology at the frontline. Since viral RNA has already been found in the conjunctiva[9.10], ophthalmologists have a relevant role in combating this pandemic, i.e., predicting the risk of clinical complications in patients and clarifying the importance of the ocular surface in the transmission of the disease, since there are few studies published on this subject[20].

A study conducted in February 2020 in the Yichang Central People's Hospital made a retrospective analysis of 38 patients hospitalized due to COVID-19. Of these, only two had positive nasopharyngeal and conjunctival swabs, and 12 (31%) presented ocular manifestations such as conjunctival hyperemia, increased secretion, and epiphora[15].

In this study, it was observed that 50% of the cases of the novel coronavirus with ocular symptoms occurred in patients classified as severe and critical, based on the Guideline for the Prevention and Control of COVID-19[15.21]. Added to this, in laboratory findings, there was a greater count of white blood cells, neutrophils, lactic dehydrogenase, and C-reactive protein when compared to patients without visual complaints[15].

Parallel to this study, 535 patients were recruited by the Optical Valley and Tongji Hospital of the University of Science and Technology of Huazhong in WuHan, China. Of the total number of patients, about 20% had dry eye, 12% blurred vision, 11% foreign body sensation,10% epiphora, and 9% increased ocular secretion[11].

Among the complaints reported, dry eye, blurred vision, and foreign body sensation were symptoms compatible with those of the patients analyzed in the study by the Yichang Central People's Hospital[11,15]. In addition, it was concluded that conjunctival congestion is not common (only 5% of patients) and that the ocular manifestations generally occur early in COVID-19[11].

Since the symptoms reported by coronavirus patients are common complaints in ophthalmology, ophthalmologists can be the first professional sought by patients with COVID-19[22]. Thus, it is essential, in these cases, that patients perform an active search for other signs and symptoms, particularly those related to the respiratory system, bearing in mind the current epidemiological context[23].

In Thailand, a study with 48 patients positive for COVID-19 used direct ophthalmoscopy and corneal scraping in patients with suspected cases of conjunctivitis. Of the individuals examined, no eye problems were reported. However, the author emphasized that ocular manifestations are often ignored by the Thailandese[23]. In addition, ophthalmological symptoms of the disease can go easily unnoticed since they initially present as nonspecific manifestations[24].

At the hospital of the University of Zhejiang, an interview was carried out with 56 hospitalized patients diagnosed with COVID-19. A questionnaire was applied with these patients in order to evaluate the quality of their ocular surface, based on the Ocular Surface Disease Index, before and after the disease[24].

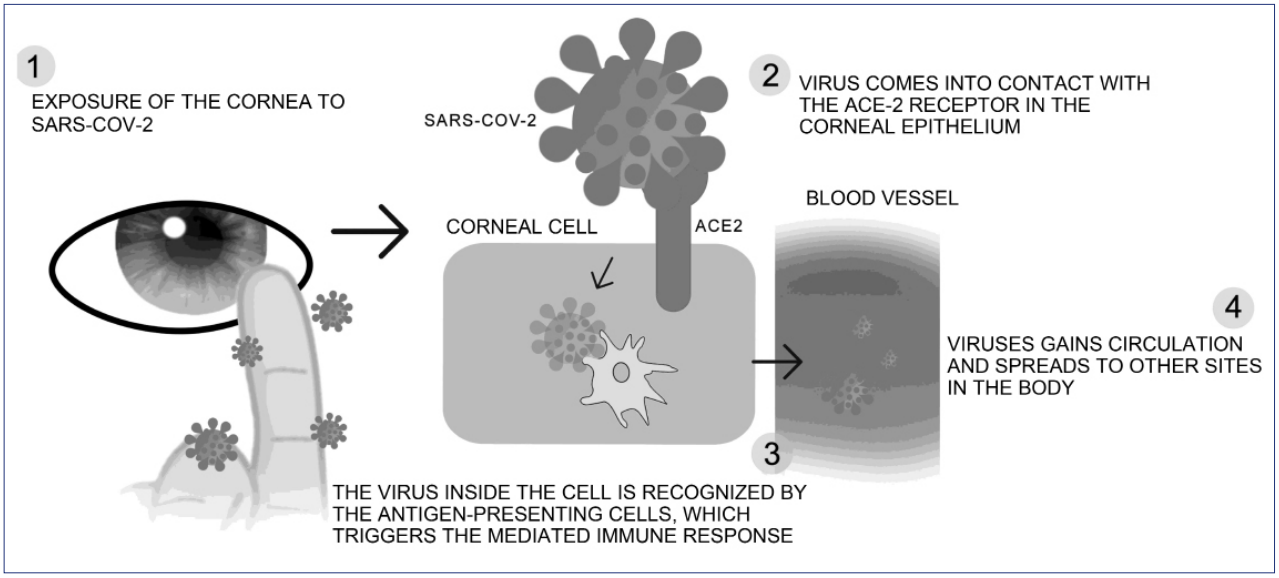
The main ophthalmic complaints of patients were increased secretion, foreign body sensation, dry eye, and red-eye, and these findings are compatible with those of other studies[11,15,24]. Regarding the time of onset of ocular signs and symptoms, in most cases they preceded the respiratory symptoms in a few days, emphasizing the importance of giving proper value to these complaints in the current situation[24].

In addition, it was noted that the dry eye score pf patients before the novel coronavirus was compatible with the average indices of the Chinese population; however, there was a significant increase in it after the infection, suggesting that the dry eye can be an extrapulmonary manifestation of the disease[24].

In Italy, a study involving five patients with nasopharyngeal swab positive for COVID-19, in April 2020, reported that all individuals analyzed presented acute conjunctivitis as the only manifestation of the disease[25]. The complaints of the patients included hyperemia, increased secretion, epiphora, and photophobia, in the absence of other systemic symptoms, and this was less common symptomatology in comparison to the findings of most studies involving ocular symptoms secondary to infections by the new coronavirus[25].

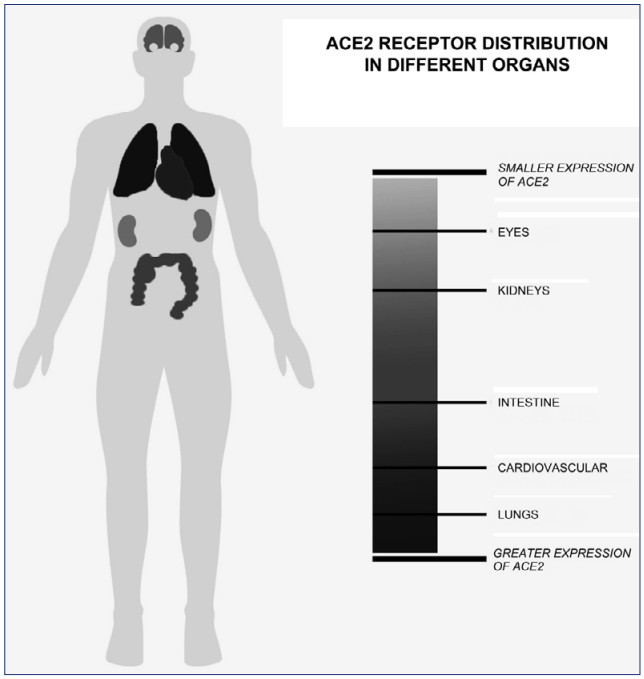
A case report of a 27-year-old patient demonstrates viral conjunctivitis as an initial symptom of severe COVID-19[18]. The study depicts an Argentinian individual who developed a foreign body sensation and evidence of swollen eyelid, conjunctival hyperemia, and red-eye, evolving after 12 hours into a fever with sudden dyspnea[18].

FIGURE 1. PROBABLE PHYSIOPATHOLOGICAL MECHANISM OF THE SARS-COV-2 INFECTION THROUGH THE OCULAR SURFACE.



Source: Cunha CEX, 2020. This figure was designed using Freepik.com resources (https://br.freepik.com/). The physiopathology illustrated was described by Napoli et al.[12].

FIGURE 2. ACE2 RECEPTOR DISTRIBUTION IN DIFFERENT ORGANS OF THE HUMAN BODY.



Source: Cunha CEX, 2020. This figure was designed using Freepik.com resources (https://br.freepik.com/). Distribution of the ACE2 receptor in different tissues of the body as presented by Amesty et al.[9].

TABLE 1. MAIN OCULAR MANIFESTATIONS OF COVID-19.

Main ocular manifestations of COVID-19
Conjunctival hyperemia
Foreign body sensation
Dry eye
Photophobia
Epiphora
Blurred vision
Eyelid swelling
Increased secretion

Main ocular manifestations described in articles reviewed for this study.

CONCLUSION

In the abovementioned reports it is possible to see that, despite the very recent context, studies demonstrate that ocular manifestations may present as the initial or exclusive complaints from the novel coronavirus, even though this is not the most common and standard presentation. Among these ophthalmologic findings is viral conjunctivitis, which may evolve with hyperemia, foreign body sensation, swollen eyelid, epiphora, increased secretion, in addition to dry eye, and blurred vision.

Therefore, it is necessary to broaden our understanding of this new pathology and identify its extrapulmonary manifestations to fully evaluate patients so that we can understand the role of ophthalmology at the frontline. In addition, since viral RNA has been found in the conjunctiva in some studies, the role of health care professionals is shown to be important in guiding the population regarding the care in handling the ocular surface[9,10].

Author's Contribution

All authors contributed equally to this work.

RESUMO

A doença do coronavírus 2019 (COVID-19) causada pelo vírus, altamente patogênico, Sars-Cov-2, foi declarada como uma pandemia pela Organização Mundial da Saúde (OMS) em março de 2020. As principais manifestações clínicas se relacionam com o acometimento da via aérea; no entanto, há em alguns casos comprometimento extrapulmonar. Perante esse contexto, esta revisão de literatura objetiva identificar as condições oftalmológicas resultantes da infecção pelo novo coronavírus. Apesar de os achados oculares não contemplarem o quadro clínico padrão da doença, há relatos de algumas alterações oftalmológicas em pacientes com COVID-19 positivo, sendo a conjuntivite a mais comum entre estas.

PALAVRAS-CHAVE: *Infecções por coronavírus. Pandemias. Sinais e sintomas. Oftalmologia. Conjuntivite.*

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REVIEW ARTICLE

Hypofractionated and hyper-hypofractionated radiation therapy in postoperative breast cancer treatment

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SUMMARY

INTRODUCTION: *Radiation therapy is widely used as adjuvant treatment in breast cancer patients. In the last decades, several studies have been designed to evaluate the safety and efficacy of hypofractionated breast radiation therapy. More recently, even shorter regimens with doses above 4 Gy (hyper-hypofractionation) have also been proposed. This study aims to present a narrative review of the various hypofractionation protocols used to treat breast cancer patients with a focus on clinical application.*

RESULTS: *Long-term results from several phase III randomized controlled trials demonstrated the safety and efficacy of hypofractionated breast radiation therapy using 15 or 16 fractions for early and locally advanced disease. The results of the initial clinical trials of hyper-hypofractionation are also encouraging and it is believed that these regimens may become routine in the indication of adjuvant radiation therapy treatment after the ongoing studies on this subject have matured.*

CONCLUSIONS: *The idea that normal tissues could present high toxicity at doses above 2 Gy was opposed by clinical trials that demonstrated that moderate hypofractionation had similar results regarding oncological and cosmetic outcomes compared to conventional fractionation. Cosmetic and toxicity results from hyper-fractionation studies are in principle favorable. However, the long-term oncological results of studies that used hyper-hypofractionation for the treatment of breast cancer patients are still awaited.*

KEYWORDS: *Radiation therapy. Breast neoplasms. Radiation dose hypofractionation.*

INTRODUCTION

Radiation therapy (RT) is one of the main modalities for adjuvant treatment of breast cancer, performed in approximately 87% of the cases since it brings positive results in local control and overall survival in patients with early and locally advanced disease[1,2].

The most used standard dose of RT for decades was 50 Gy/50.4 Gy, prescribed in 25-28 sessions of 1.8-2 Gy daily, i.e., conventional fractionation (CF). This scheme was based on the assumption that daily doses above 2 Gy could increase the side effects of the treatment[3]. However, in recent decades several studies were designed to evaluate the safety and efficacy of hypofractionated radiation therapy for breast cancer.

The objective of the present study is to present a

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narrative review of the several protocols for hypofractionated radiation therapy for the treatment of breast cancer, with a focus on clinical application.

MODERATE HYPOFRACTIONATION-RANDOMIZED CLINICAL TRIALS

A Canadian study randomized 1,234 women diagnosed with early-stage cancer submitted to breast-conserving surgery to receive 42.5 Gy in 16 fractions, or 50 Gy in 25 fractions[4]. The risk of local recurrence in ten years was 6.7% for the standard irradiation in comparison with 6.2% among the 622 who received hypofractionation. After ten years, 71.3% of the women in the control group, in comparison with 69.8% of the women in the hypofractionated group, had a good or excellent cosmetic result[5].

A pilot study conducted in UK randomized 1,410 patients between 1986 and 1998 after conservative breast surgery into three groups: a control group with a dose of 50 Gy in 25 sessions of 2 Gy daily, and two other groups with schemes hypofractionated into 13 sessions: 39 Gy in 13 sessions of 3.0 Gy daily, and 42.9 Gy with 3.3 Gy daily. The primary outcome of this study was the late effect in normal tissue, and the secondary outcome was local control. After a minimum follow-up period of five years, the risk of emergence of any changes in the appearance of the breast after 50 Gy, 39 Gy, and 42.9 Gy was 39.6%, 30.3%, and 45.7%, respectively. Ipsilateral tumor recurrence in the tested fractionations was similar to the conventional fractionation of 50 Gy[6]. After ten years of follow-up, the risk of ipsilateral recurrence was 12.1% (95% CI 8.8 - 15.5) in the 50 Gy group, 14.8% (11.2 - 18.3) in the 39 Gy group, and 9.6% (6.7 - 12.6) in the 42.9 Gy group, respectively. Based on the pilot study described previously, two randomized clinical trials were developed in parallel by the UK group: Start A and Start B. The first virtually kept the design of the pilot study, only correcting the dose of one of the groups to 41.6 Gy into 13 sessions of 3.2 Gy[7]. Whereas Start B randomized the patients into two groups: a control group with the standart fraction, 50 Gy into 25 fractions of 2 Gy daily, and a second group with fractionation of 15 sessions of 2.67 Gy daily[8]. In total, 1,105 women were assigned to the 50 Gy group, and 1,110 to the 40 Gy group. After a mean follow-up of six years (IQR 5.0 - 6.2), the locoregional recurrence rate in five years was 2.2% (95% CI 1.3 to 3.1) in the 40 Gy group, and 3.3% (95% CI 2.2 to 4.5) in the 50 Gy group, representing an absolute difference of 0.7% (95% CI -1% to 0.9%). Photographic and patients' self-assessments showed lower rates of late adverse events after 40 Gy than after 50 Gy. The update of the UK studies proved the effectiveness and safety of the hypofractionated treatment with a long follow-up period[9].

Wang et al.[10] randomized women (cT3-cT4 or with at least four compromised lymph nodes), post-mastectomy to receive 50 Gy into 25 fractions (n=414), or 43.5 Gy into 15 fractions (n=406) in the chest wall and lymphatic drainage. The cumulative incidence in five years of locoregional recurrence was 8.3% (95% CI 5.8 to 10.7) in the hypofractionated RT group, and 8.1% (90% CI 5.4 to 10.6) in the of conventional fractionation group (absolute difference of 0% to 2%, 90% CI -3.0 to 2.6; hazard ratio 1.10, 90% CI 0.72 to 1.69; p<0.0001 for noninferiority). There were no significant differences between the groups regarding

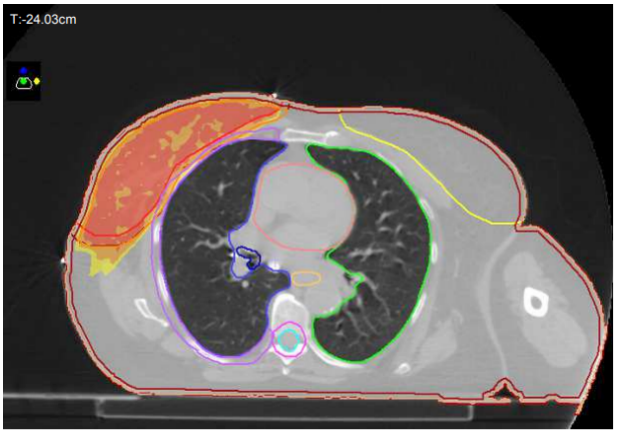

FIGURE 1. TOMOGRAPHIC PLANE WITH ISODOSE CURVES FOR HYPER-HYPOFRACTIONATION PLANNING.

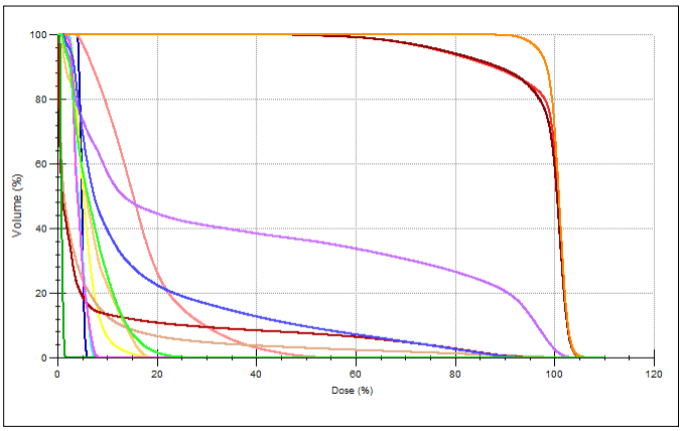

FIGURE 2. DOSE HISTOGRAM *X* HYPER-HYPOFRACTIONATED TREATMENT PLAN VOLUME.

acute and late toxicities, except for grade 3 acute skin toxicity, which was higher in the RT group with conventional fractionation (14 [3%] HF-M *versus* 32 [8%] CF; p<0.0001). There was no significant difference in the overall survival or disease-free survival between the groups.

Although some countries and specialized centers use routine moderate hypofractionated RT for the treatment of all breast cancer patients, regardless of the staging and type of surgery performed, this recommendation is not employed by many in clinical practice, particularly in patients with advanced disease who require wider radiation fields involving the lymphatic drainage[11].

Table 1 summarizes the various treatment regimens employed in randomized clinical trials published on moderate hypofractionated RT.

HYPER-HYPOFRACTIONATION- RETROSPECTIVE AND PROSPECTIVE STUDIES

Currently, with the advance in RT treatment techniques, fractionations with high daily doses (hyper-hypofractionation) and fewer days of treatment have been used in some new clinical trials. However, these fractionations have been the object of studies for over 30 years, mainly in elderly patients, since this population presents greater difficulty in treatment adherence due to multiple comorbidities[12-16].

In a pioneer publication in 1987 by Roston et al.[17], 84 elderly patients with breast carcinoma were treated with once-a-week regimens using 6.5 Gy in a total of six fractions. The mean age of the patients was 69.2 years. The treatment was well tolerated by all patients, and the initial results of local control were encouraging.

During the same period, between 1987 and 1999, 150 patients with a median age of 78 years who had non-metastatic breast tumors were treated with surgery and then hyper-hypofractionated adjuvant RT. Radiation therapy was performed once a week, in five fractions of 6.5 Gy, to a total dose of 32.5 Gy (boost dose to the tumor bed in 33%). The acute toxicity of all degrees totaled 26.5%, and the rate of all late reactions was 45.5%, in most cases grade I and grade II. The rate of local recurrence in the long term was 2.3% and disease-free survival at five and ten years was 80% and 71.5%, respectively[18].

In a retrospective series, Kirova et al.[19] concluded that the hyper-hypofractionated treatment is an acceptable alternative. Three hundred and sixty-seven women aged 70 years or more, with clinical stages I or II, treated with conservative breast surgery and adjuvant RT at the Institut Curie received a schedule for normofractionated radiation therapy (50 Gy into 25 fractions with or without a boost dose at the tumor bed) or a hyper-hypofractionated scheme (32.5 Gy into five fractions of 6.5 Gy, once a week). A total of 317 patients were on the normofractionated group, and 50 were in the hyper-hypofractionated group. The survival rates were similar between the two groups (93% and 91% for locoregional-recurrence-free survival, and 92% and 93% for metastasis-free survival, respectively).

Monten et al.[20] published, in 2017, a phase II study that investigated the feasibility and safety of the hyper-hypofractionated treatment in women over 65 years with five fractions of doses between 5.7 Gy and 6.5 Gy daily. Clinically relevant dermatitis was observed in 11.6% of the patients and occurred only in the boost dose subgrup (17.5% grade 2-3 *versus* 0% in the group without boost dose). The authors concluded that the treatment is technically feasible and resulted in low acute toxicity.

Dragun et al.[21] published the first results of a prospective phase II trial. Patients who underwent conservative breast surgery in stages 0, I, or II with negative surgical margins received radiation therapy for 30 or 28.5 Gy into five once-weekly fractions with or without a boost dose at the tumor bed. One hundred and fifty-eight eligible patients were submitted to whole-breast hyper-hypofractionated RT once-weekly. Disease-free survival after three years and the overall

TABLE 1. PROSPECTIVE STUDIES ON MODERATE HYPOFRACTIONATED RADIATION THERAPY

Study	N	FRACTIONATION
Whelan et al., 2002[4]	1,234	50 Gy - 2 Gy/fraction, 35 days, versus 42.5 Gy - 2.65 Gy/fraction, 22 days
Yarnold et al., 2005[6]	1,410	50 Gy into 25 fractions; 39 Gy into 13 fractions, or 42.9 Gy into 3.3 Gy/fraction
Haviland et al., 2013[9]	2,236	Start A: 50 Gy; 2 Gy fractions versus 41.6 Gy into 13 fractions 3.2 Gy Start B: 50 Gy into 25 fractions; versus 40 Gy into 15 fractions,
Wang et al., 2019[10]	820	50 Gy into 25 Gy/fractions versus 43.5 Gy into 15 Gy/fractions Note: Post-mastectomy.

TABLE 2. AVAILABLE STUDIES ON HYPER-HYPOFRACTIONATION.

Study	TYPE OF STUDY	N	FRACTIONATION	Note
Rostom et al., 1987[17]	Retrospective	84	6.5 Gy x 6 fractions	Weekly
Ortholan et al., 2005[18]	Prospective single-arm study	150	6.5 Gy × 5 fractions; FSC 5.5 Gy × 5 fractions	Weekly Supplementation of dose 6.5 Gy × 1 or 2 fractions
Kirova et al., 2009[19]	Retrospective	367	50 Gy x 25 fractions 32.5 Gy x 5 fractions x 6.5 Gy	Weekly N(50 Gy) 317 x (32.5 Gy) 50
Monten et al., 2017[20]	Prospective phases I and II	95	28.5 Gy to 5.7 Gy breast or chest wall; 27 Gy/5.4 Gy FSC; 32.5 Gy/6.5 Gy to 34.5 Gy/6.9 Gy SIB at the tumor bed	Alternate days SIB associated with higher toxicity
Dragun et al., 2017[21]	Prospective single-arm study	41	6 Gy x 5 fractions	SIB with more toxicity
Rebouças et al., 2019[22]	Prospective single-arm stage II study	44	30 Gy x 5 fractions of 6.0 Gy	Weekly Preliminary results
Agrawal et al., 2011[24]	Prospective randomized	915	40 Gy into 15 fractions (control), 28.5 Gy into 5.7 Gy, or 30 Gy (6 Gy x 5 1 x weekly)	Weekly

SIB = Simultaneous Integrated Boost.

survival rates were 97.5% and 96.2%, respectively. The most commonly observed acute toxicities of grade 1 or 2 were chest pain, radiodermatitis, and fatigue. Excellent or good cosmesis was 82.3%, and 17.7% was average or poor.

Rebouças et al.[22] presented the initial results of toxicities for a prospective phase II study. The prescribed dose was 30 Gy into five fractions of 6.0 Gy, one fraction weekly, without a supplementary dose at the tumor bed. Skin erythema was the most common acute adverse event observed. At the end of the treatment, 30 patients (68.2%) presented some degree of dermatitis due to radiation. Regarding the cosmetic appearance, there was no significant difference between the pre-treatment and one-year assessment. The overall survival after two years and disease-free survival were, respectively, 96.8% and 97.7%.

In an UK phase III multicenter, randomized trial (Fast-Forward), the participants were randomized into three different groups: 40 Gy into 15 fractions (control), 28.5 Gy into five fractions, and 30 Gy into five fractions. Grade 3 RTOG toxicities were: 40 Gy 6/44 (13.6%); 27 Gy 5/51 (9.8%); 26 Gy 3/52 (5.8%). There were no toxicities grade 4 or 5. The patients with grade 3 CTCAE toxicity were: 40 Gy 0/43; 27 Gy 1/41 (2.4%); and 26 Gy 0/53. In conclusion, the acute skin toxicity in patients enrolled in the Fast-forward study was acceptable. However, for this hyper-hypofractionation scheme to be used in clinical practice, the formal publication of the study with long-term clinical follow-up is expected[23].

Table 2 summarizes the various treatment regimens employed in the retrospective and prospective studies published on hyper-hypofractionated RT.

IMPLICATIONS FOR CLINICAL PRACTICE

Adjuvant RT after breast surgery carried out in five to seven weeks was, for decades, the gold standard in the treatment of early breast cancer with widely recognized oncologic and cosmetic results. The idea that normal tissues could present high toxicity with doses above 2 Gy and, consequently, the fear of radio-oncologists in using shorter treatment regimens was pioneeringly countered by the Canadian OCOG[4] study and the British Studies[7,8]. The long follow-up results of these studies have proven that the moderate hypofractionated treatment showed similar results regarding oncologic and cosmetic outcomes and quality of life when compared to conventional fractionation. These results also encouraged the change of the understanding of ASTRO, in 2018[25], in comparison to the previous understanding of 2011[26], making it possible to use the moderate hypofractionated regimen more widely in the early stages.

The Chinese phase III randomized trial with more

than 800 patients[10], despite its limitations, evaluated the use of moderate hypofractionation post-mastectomy in the chest wall and lymphatic drainage, paving the way for the use of this treatment regimen in patients with more advanced disease staging. In addition, the analysis of the subgroup of patients who received irradiation of the lymph node chain, as well as post-mastectomy in British studies[6-8], also did not demonstrate worse results in these patients in relation to rates of local control, survival, and side effects.

The evolution in the concepts of radiobiology and, in particular, the evolution in the delivery of radiation over the last two decades has allowed healthy tissues to be increasingly spared from doses and, consequently, paved the way for studies with even shorter schemes of RT, i.e., hyper-hypofractionation with doses above 4 Gy. The cosmetic and toxicity results of hyper-hypofractionation studies have been, in principle, favorable[20,24]. However, we still wait for the long-term oncological results of patients treated with hyper-hypofractionation schemes for its application in clinical practice.

FINAL CONSIDERATIONS

Moderate hypofractionated RT schemes for adjuvant treatment of breast cancer have become a real option in recent years. The worries regarding acute and late toxicities, as well as regarding the oncologic control, are no longer reasons for not indicating moderate hypofractionated RT. Despite this, there is still a reluctance to employ this scheme without restrictions in clinical practice, mainly in patients who underwent a mastectomy, who need to receive treatment of the regional lymph node chains, and who were submitted to surgical reconstruction.

Hyper-hypofractionation is being studied and, apparently, shows encouraging results. It is believed that, in the future, such schemes may become routine in the indication of adjuvant treatment with RT for locally advanced early tumors. More prospective randomized studies are needed to prove the efficacy and safety of hyper-hypofractionation.

Author's Contribution

All authors contributed equally to this work.

RESUMO

INTRODUÇÃO: *A radioterapia é amplamente utilizada como tratamento adjuvante nas pacientes com câncer de mama. Nas últimas décadas, diversos estudos foram desenhados para avaliar a segurança e a eficácia da radioterapia hipofracionada moderada de mama. Mais recentemente, esquemas ainda mais curtos, com doses acima de 4 Gy (hiper-hipofracionamento), foram também propostos. Este estudo tem o objetivo de apresentar uma revisão narrativa dos diversos protocolos de hipofracionamento utilizados no tratamento do câncer de mama com o foco na aplicação clínica.*

RESULTADOS: *Os resultados de longo prazo de diversos ensaios clínicos randomizados fase III demonstraram a segurança e a eficácia da radioterapia hipofracionada moderada utilizando 15 ou 16 frações para doença inicial e localmente avançada. Os resultados dos ensaios clínicos iniciais de hiper-hipofracionamento são também animadores e acredita-se que esses esquemas poderão se tornar rotina na indicação do tratamento adjuvante com radioterapia após a maturação dos estudos em andamento sobre esse tema.*

CONCLUSÕES: *A ideia de que os tecidos normais poderiam apresentar toxicidade elevada com doses acima de 2 Gy foi pioneiramente contraposta por ensaios clínicos que comprovaram que o hipofracionado moderado apresentava resultados semelhantes em relação aos desfechos oncológicos e cosméticos quando comparados ao fracionamento convencional. Os resultados cosméticos e de toxicidade dos estudos de hiper-hipofracionamento são, em princípio, favoráveis. Todavia, ainda se aguardam os resultados oncológicos de longo prazo dos estudos que aplicaram o hiper-hipofracionamento para o tratamento das pacientes com câncer de mama.*

PALAVRAS-CHAVE: *Radioterapia. Neoplasias da mama. Hipofracionamento da dose de radiação.*

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COMMENTARY

Comment on "Aerobic exercise effects in renal function and quality of life of patients with advanced chronic kidney disease"

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Dear Editor,

We read with great interest the study by Calvo-Lobo et al.[1] in which they demonstrated that aerobic exercise may cause improvements in renal function and in the quality of life of patients with advanced chronic kidney disease. This study further pointed out that protocols specifically for patients with advanced stages of chronic kidney disease should be carried out in order to study their effectiveness and safety. However, some concerns should be addressed.

To begin with, control subjects were not recruited in this study. In my view, there should be two groups, one group to complete the exercises and another group that is exercise-free. Additionally, the small sample is also a limitation of this study.

The description of statistical analysis should also be revised. In the results section, the author described that "the other renal function parameters did not show any statistically significant differences". The sentence should be revised as "no statistically significant was found for the other renal function parameters". Because "statistically significant difference" and "no statistically significant was found for difference" have different meanings.

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COMMENTARY

Comment on "Preoperative anxiety induces chronic postoperative pain by activating astrocytes in the anterior cingulate cortex region"

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Dear Editor,

We read with great interest the study by Gu et al.[1] in which they demonstrated that anxiety plays a key role in the development of chronic pain. This study offers new guidance for improving chronic postoperative pain. However, some concerns should be raised.

To begin with, we support the comments by Xue et al.[2] that more methods for the model of anxiety were necessary. Additionally, it is also important for a clinical study to explore the relationship between anxiety and the risk of chronic postoperative pain. Nerve injury and inflammation promote chronic postoperative pain. Thus, the authors could determine the inflammation response of the mouse. Single-prolonged stress modeling and hysterectomy should be used as a reference. The definition of a successful model of single-prolonged stress should be addressed in detail.

Secondly, more experiments were needed to confirm the relationship between the activation of astrocytes and chronic pain. The activation of astrocytes may be the result of chronic pain but not the cause. Thus, improving the lifestyle may be an effective way to reduce the duration of chronic postoperative pain.

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COMMENTARY

Comment on "Tuberculosis in Northeastern Brasil (2001-2016): trends, clinical profile, and prevalence of risk factors and comorbidities"

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Tuberculosis (TB) is an infectious disease caused by any of the species that make up the *mycobacterium tuberculosis* complex. Historically it represents a phenomenon that has affected illustrious figures such as writers, poets, artists, and kings. Thus, since ancient times, the disease has represented a public health problem difficult to be fought. Currently, it represents one of the 10 leading causes of death and the leading cause when a single infectious agent is considered, more than HIV/Aids[1].

Global estimates indicate that approximately 10 million people have fallen ill due to TB only in 2018 alone, with a varying disease burden between countries[2]. In that same year, the disease caused 1.2 million deaths among HIV-negative individuals and over 251,000 among those who are HIV-positive[3]. It is worth highlighting that these numbers, at a global level, have remained stable in recent years.

The burden of disease worldwide led the World Health Organization to define, for 2016-2020, three lists of priority countries, each one comprising 30 nations: 1. Countries with the highest burden of disease; 2. Priority countries for multiple drug resistance; and 3. Priority countries due to coinfection by HIV (TB-HIV). Brasil was included in two of these lists: In the 20th position regarding the burden of disease, and in the 19th position regarding TB-HIV coinfection[4].

In 2018 alone, the country registered nearly 72,788 new cases of the disease, with an incidence rate of 34,8/100 thousand inhabitants. Of these, 19,075 cases were in the Northeast region of Brasil, which ranked in second regarding the absolute number of new cases, third in incidence coefficient (33.1/100,000), second in postneonatal mortality due to the disease (2.6/100,000), and third in retreatment (15.9%)[4].

This scenario demonstrates the need for constant surveillance of tuberculosis in the Northeast of Brasil, both at the municipal[5], state,[6], and regional[7] levels. In the study by Souza et al.[7], the authors analyze the temporal trend of the disease and the prevalence of associated comorbidities and factors. One should emphasize the reduction in the incidence rate of the disease in 2001-2016, with an annual decrease

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of -2.3% (44.8/100,000 in 2001 and 30.92/100,000 in 2016).

In addition, in the study in question rates are substantially in the male population, whose annual percentage of reduction is much lower than that observed in the female population (-2.37% and 4.18%, respectively), which makes us reflect on the importance of the males in maintaining the chain of transmission of the disease in the region, accounting for 63.53% of the cases registered in 2001-2016[7].

But what should we expect in the coming years? Which factors may be associated with an increased number of patients starting from 2016 in Brasil? Was is it the context of economic crisis? The expanded offer of diagnosis? More services available? These and other questions deserve the attention of Brazilian researchers.

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COMMENTARY

Comment on "The importance of physical exercise during the coronavirus (COVID-19) pandemic"

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SUMMARY

Currently, many people have been infected by the Coronavirus disease (COVID-19) and presented cardiorespiratory symptoms caused mainly by the host immune system response and respiratory tract inflammation. So far, there is no effective treatment to fight off COVID-19 and, despite many daily speculations about new treatments and vaccines, in this article, we discuss the effectiveness of a cheap and scientific proven technique to treat and prevent several diseases. Many studies have shown the benefits of physical exercise in individuals who have practiced it routinely. This approach is a great strategy to improve people's cardiorespiratory capacity, inflammation system, and immune response. Due to the quarantine period, the practice of physical exercise at home can also be used to fight off COVID-19 and must be inserted into people's routines.

KEYWORDS: *Coronavirus Infections. Betacoronavirus. Exercise.*

INTRODUCTION

Coronavirus disease (COVID-19) has been spreading significantly worldwide. However, currently, several countries have presented a decrease in deaths and infections.[1] Although mortality and contamination curves have been reducing, there are still many symptomatic people presenting arthralgia, myalgia, pain, headache, cough, hypotension, and cardiological malfunction.[2,3]

To fight off infection and symptoms generated by COVID-19 many clinical trials have been developed to test drugs[4], such as hydroxychloroquine,[5] lopinavir-ritonavir,[6] and corticosteroid,[7] but no differences were found beyond standard care regarding mortality and time of symptomatology. Nevertheless, a recent study showed that remdesivir shortens the recovery time of adults infected by COVID-19[8]. It is important to mention that some side effects have been reported on people infected by COVID-19, mainly on cardiovascular function, leading to congestive heart failure, acute heart failure, syncope,[9] and anemia.[8] The biggest multicentric study about COVID-19 published presented that hydroxychloroquine or chloroquine used alone or associated with macrolide decreased survival and increased arrhythmias[10].

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The main mechanism involved in COVID-19 pathogenesis is respiratory tract inflammation and host immunity system response.[11] Patients infected by COVID-19 commonly have lymphopenia, neutrophilia, thrombocytopenia, high systemic immune inflammation, and increased protein C and interleukin 6 levels. The initial condition of the patient and their immune response seem to be important factors that can harm organs' functioning.[12] Thus, as COVID-19 immunological and physiological processes have been elucidated, preventive strategies must be discussed to decrease the duration of symptoms and mortality in infected people.

Physical exercise emerges as a strategy to improve cardiorespiratory variables and endurance in people infected by COVID-19,[13] and in those who are not infected.[14] It is emphasized that individuals engaged in physical exercise programs have an increase of their cardiorespiratory levels, which is considered an important variable to protect against the emergence of several clinical conditions/diseases, such as hypertension, diabetes, and serious heart conditions.[14] People with these characteristics are at higher risk of severe COVID-19 illness.[15]

Besides, older people, which are part of the risk group, present an increase of inflammatory cells, such as cytokines and interleukins 6.[16] It has been shown that physical exercise may modulate the response of several inflammatory mediators.[17-21] Adaptations in exercise parameters play an important role in generating benefits on immunity and inflammation systems.[22] It is also highlighted that aerobic training has been used to prevent and reduce the risk of several conditions, such as endothelial dysfunction, obesity, diabetes, and high blood pressure.[23] As a result, we believe that this protective nonpharmacological approach can be an important strategy for decreasing symptoms and deaths caused by COVID-19.

Telehealth exercise protocols have been developed to help people who present different conditions.[24,25] Besides, the use of video games to insert people in an immersive environment and stimulate them to practice exercise to improve quality of life has been used in older adults[26], children,[27] and individuals with different physical limitations.[28] These approaches could also be applied during the COVID-19 pandemic period because people worldwide must be in quarantine to avoid virus spreading[29,30]. The social isolation period has been traumatic in different ways,[31] stress,[32] anxiety, and depression[33] have been experienced by several people. Exercise can be excellent to improve these symptoms[34] and should be stimulated to be performed at home during this tough time. Considerations about the opening of gyms and public spaces for the practice of exercise must be done with caution because there can be an increase in infections.

Although there is no vaccine to fight off COVID-19, thinking in the long term, since physical exercise has also been related to improving the effects of the vaccine,[35] it would be important to start preparing for this time, improving antibody response by exercising. Physical exercise must be considered a preventive strategy to fight off COVID-19.

CONCLUSION

Many people have been suffering because of the routine changes caused by the quarantine, deaths reported on TV, speculations about new treatments, risk of losing their jobs, and no prediction about the end of the pandemic. Physical exercise is a cheap and easy strategy that should be encouraged during the COVID-19 pandemic because it has been worthy to treat and prevent many cardiorespiratory and physical manifestations developed by people.

RESUMO

Atualmente, muitas pessoas ainda têm sido infectadas pelo Coronavírus (COVID-19) e apresentado sintomas cardiorrespiratórios gerados principalmente pela resposta do sistema imune do hospedeiro e inflamação do trato respiratório. Até agora, não existe nenhum tratamento efetivo para combater o COVID-19 e apesar de muitas especulações diárias sobre novos tratamentos e vacinas, neste artigo, nós discutimos sobre a efetividade de uma técnica barata e cientificamente comprovada para tratar e prevenir diversas doenças. Muitos estudos têm demonstrado os benefícios do exercício físico em indivíduos que tem praticado de forma rotineira. Esta abordagem é uma excelente estratégia para melhorar a capacidade cardiorrespiratória, sistema inflamatório e resposta imune. Devido ao período de quarentena, a prática de exercício físico em casa pode também ser usada para combater o COVID-19 e deve ser inserida na rotina das pessoas.

PALAVRAS-CHAVE: *Infecções por Coronavirus. Betacoronavirus. Exercício físico.*

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