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COVID-19 experience among Brasil's indigenous people

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As evidence accumulates of the disproportionate impact of COVID-19 on some ethnic minority groups, there is emergent evidence of the vulnerabilities of indigenous ethnic groups to COVID-19. On 1st April, the first COVID-19 case in Brasil's 734,000 indigenous population was confirmed[1]. She was an Indigenous Health Worker, 20 years old, of *Kokama* ethnicity, and from the Amazonas who had contact with a doctor diagnosed with COVID-19[2]. As of 25th June, the Ministry of Health reported 4769 COVID-19 cases and 128 deaths among Indigenous peoples. Brasil has 34 Indigenous Sanitary Districts (DSEIs) and 32 have reported positive cases (Table 1)[3]. Globally, Brasil ranks second in infections and mortality and the country is embroiled in a political crisis over COVID-19 management[4]. As with many indigenous populations worldwide, historic socio-environmental, governance, and access to health care issues make Brasil's Indigenous populations disproportionately vulnerable to poor COVID outcomes. We report on current challenges for implementing COVID-19 response measures and early indigenous-led protection initiatives.

The Brazilian Indigenous health subsystem districts, a branch of the National Health System, is located according to geographic, epidemiologic, and ethnographic factors which do not align with the geographic boundaries of the 26 states of Brasil. This creates challenges for the governance and resourcing of the Indigenous health subsystem. The subsystem is ill-prepared for pandemics with the absence of health teams in many villages, long distance to the nearest *Polo Base* (primary care health unit), shortage of beds for inpatients, and difficulties transporting patients to the nearest intensive care unit. These challenges are particularly problematic for communities that are far from urban centers. Living near to or in urban centers, however, carries a high risk of transmission from social vulnerability due to the lack of recognition of borders of indigenous territories and ineligibility for support from government programs for indigenous

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TABLE 1. NUMBER OF INDIGENOUS TESTED FOR COVID-19 CONFIRMED, INFECTED, RECOVERED, AND DEATHS IN BRASIL.

Brazilian indigenous sanitary districts	Confirmed	Infected	Recovered	Death
Alagoas and Sergipe	46	16	27	2
Altamira	67	36	31	0
Alto Rio Juruá	112	86	25	1
Alto Rio Negro	289	131	147	10
Alto Rio Purus	138	74	60	3
Alto Rio Solimões	555	107	423	24
Amapá and Norte do Pará	246	114	131	0
Araguaia	0	0	0	0
Bahia	34	2	31	1
Ceará	289	129	156	4
Cuiabá	3	2	0	1
Guamá-Tocantins	417	160	247	10
South Interior	242	157	80	5
Kaiapó from Mato Grosso	5	0	5	0
Kaiapó from Pará	192	173	12	5
East of Roraima	247	187	48	11
South coast	51	36	14	1
Manaus	204	12	181	7
Maranhão	493	225	257	10
Mato Grosso do Sul	136	39	96	1
Minas Gerais and Espírito Santo	15	11	4	0
Middle Rio Purus	21	3	18	0
Middle Rio Solimões and Affluents	117	52	58	7
Parintins	44	9	33	2
Pernambuco	84	3	74	6
Porto Velho	65	25	38	2
Potiguara	69	62	7	0
Rio Tapajós	305	254	41	9
Tocantins	7	6	1	0
Vale do Javari	74	13	61	0
Vilhena	0	0	0	0
Xavante	52	49	1	1
Xingu	3	2	0	1
Yanomami	147	114	29	4
Total	4769	2289	2336	128

Source: http://www.saudeindigena.net.br/coronavirus/mmapaEp.php. Accessed on June 25th, 2020.

peoples who live outside of recognized territories[5,6]. The implementation of containment measures to prevent transmission is complicated by the extensive invasion of indigenous lands by "*grileiros*" (land invaders) and miners who may be infected with the virus. For example, *Yanomami* Indigenous Lands are regularly invaded by prospectors, and one of the first few COVID-19 cases was a 15-year-old *Yanomami* from *Aldeia Rehebe* in Roraima[7]. Ancestral and widespread cultural habits also create additional risks. For example, in the State of Mato Grosso do Sul a widely-spread habit among indigenous and non-indigenous people is to share an icy infusion of the herb Ilex paraguariensis in conversation circles using the same metal straw ('*bomba*'). These rituals remain active despite campaigns against sharing personal items.

R$10.84 million (~£1.7 million) in emergency resources have been allocated for the protection of indigenous people against COVID-19[9]. This covers the implementation of containment measures by local health practitioners, emergency transfers of symptomatic cases from villages to the nearest city with specialized care units, including hospitals with ICUs, purchase of food and hygiene items, removal of invaders from villages, and culturally accessible information[8]. Indigenous leaders, however, have reported delays in the receipt of these funds from Federal agencies. Several indigenous ethnic groups have created a support network to disseminate information in indigenous languages and have launched financial and food collection campaigns to guarantee basic items for the villages[10]. Indigenous students at the State University of Mato Grosso do Sul have developed short videos that have been disseminated via the internet to the Indigenous communities (https://youtu.be/MTguI3bqluk)[11]. Some communities (e.g. *Tereré*, *Tremembé*, *Potiguara*) have created physical barriers that are manned by volunteers, and passersby are subject to symptom and temperature checks. Suspected cases are referred to the local primary health care facility. Crucially, there have been no new COVID cases in these villages since the barricades were created, thus demonstrating the importance and impact of bottom-up leadership among indigenous communities. The Group of Friends of Indigenous Peoples, a multi-regional group of 20 countries, emphasized that it is crucial that indigenous peoples participate in the design, implementation and evaluation of COVID-19 response strategies. With 305 tribes speaking 274 languages, over 100 isolated indigenous groups in the Amazon, and lack of adequate surveillance systems, participatory governance is essential for the effective and equitable implementation of COVID-19 response strategies in these fragile contexts[12].

Author's Contribution

PTCJ, IMAVD, AJG, MO, PD, SH contributed to the interpretation of the data, article writing, relevant critical review of intellectual content and approval of the final version to be published.

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Should kidney transplants during the COVID-19 pandemic be canceled or maintained?

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COVID-19 is the disease caused by the new coronavirus (SARS-CoV-2) and constitutes a pandemic that has not been previously recorded. There are currently more than 3.5 million cases confirmed in more than 200 countries and more than 100 thousand cases in Brasil. Thus, there has been a shift in the priorities of healthcare services, with material and human resources directed towards the treatment of the infected population[1]. This has been particularly detrimental to patients with chronic diseases.

Chronic kidney disease is closely related to arterial hypertension and diabetes, both risk factors for a worse prognosis of COVID-19. Special attention should be given to this population regarding the measures of individual protection and social isolation recommended by healthcare authorities. Kidney transplants require special care, as such patients are highly susceptible to this infection.

According to the American Society of Transplantation[2], transplants with a live donor are not recommended during the pandemic and epidemiological, clinical, and laboratorial investigations should be performed for deceased donors. Regarding the recipients, the risk-benefit ratio of the procedure should be weighed, as both patients and the surgical team currently run the risk of infection by the new coronavirus[2]. Moreover, infection by COVID-19 may not be diagnosed in donors and recipients due to the low sensitivity of the PCR analysis. An analysis of the bronchoalveolar lavage of the recipient can increase the accuracy of the test, but the time between the notification and execution of the transplantation may render this diagnostic test unfeasible[3].

Challenges for transplant services and patients on dialysis during the pandemic include scarcity of financial resources, lack of beds and respirators, exhaustion of health professionals, and difficulty in performing social distancing due to visits to dialysis centers three times per week. Factors that were already problematic in developing countries are now worse with the imminent collapse of the healthcare system. Patients in need of a transplant are more susceptible to COVID-19 due to

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exposure to the hospital setting, the use of immunosuppressants, and the presence of chronic comorbidities.

There are not yet recommendations for an optimized approach regarding infected immunosuppressed patients. Kidney transplant patients affected by COVID-19 exhibit a broad clinical-laboratorial spectrum of the disease[4]. There is no evidence to consider kidney transplant a completely safe procedure in areas affected by the pandemic.

Brasil is a large country with different stages of the epidemiological curve of the disease. Thus, each case should be considered according to the characteristics of the recipient, geographic location of the transplant center, and incidence of infection by COVID-19 in order to minimize the risks for the patient and medical team. There are currently about 6000 kidney transplants performed annually and nearly 9000 patients on the waiting list[5]. Suspension of these surgeries will lead to an accumulation of patients on the waiting list for dialysis, as resources at dialysis centers are limited. Despite so many uncertainties, kidney transplants should be maintained as long as the healthcare system permits in order to avoid the loss of donated organs and an increase in morbidity and mortality rates of patients on the waiting list.

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PALAVRAS-CHAVE: *Infecções por Coronavirus. Pandemias. Transplantes de rim.*

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Information on occupation of patients with Covid-19: Literature review

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Dear Editor,

Covid-19 was recorded for the first time in Wuhan, the capital of the Hubei province, in China, in December 2019. The disease is caused by a new coronavirus (Sars-COV-2) and transmitted by the sharing of aerosols[1]. From its origin until the 21st of April of 2020, the disease had already caused the death of more than 175,000 people worldwide. There had been more than 2.5 million confirmed cases on this date[2].

The World Health Organization (WHO) declared Covid-19 a pandemic on 11 March 2020[3] and, since then, has been, along with its member countries, seeking mechanisms to control the disease. Since this is a new disease, scientists have been working hard to develop research that allows the decision making by doctors and public managers.

The number of investigations about the profile of patients with Covid-19 grows daily, with the intention of identifying characteristics that are associated with a greater risk of illness and death. Among these characteristics, occupation stands out. Identifying patients' professional profile can bring benefits for the effective control of the pandemic: i. identification of possible locations of contamination, ii. adoption of safety measures in the workplace; and iii. knowledge about the role of occupation in the transmission dynamics of the disease.

A systematic review of the literature was conducted involving scientific articles that describe the epidemiological characteristics of patients hospitalized with Covid-19 worldwide. Articles published in the PubMed, MEDLINE, and Scopus databases

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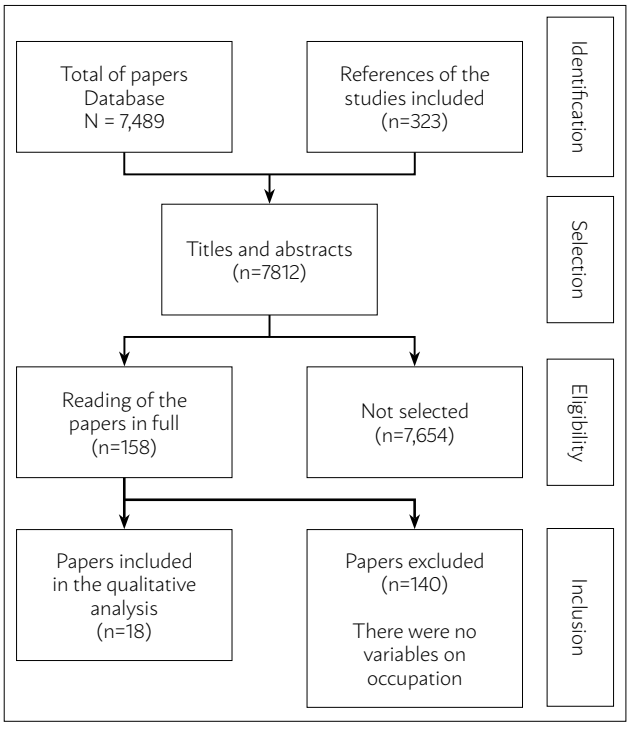
between 1 January and 24 April 2020 were selected using the following descriptors: Covid-19, Sars-CoV-2, 2019-nCoV, n-VOC, and coronavirus combined with clinical profile, epidemiology. The search was conducted on 24 April 2020.

In the study, trials, cohort studies, cross-sectional studies, clinical cases, and series of cases, both published and in pre-print, were included. The following exclusion criteria were adopted: government epidemiological bulletins, comments, literature reviews, and articles without access to their full content. After the search, three authors, independently, completed the following steps: 1- reading of the title and summary, 2- reading of the full article, 3- collection of data relating to occupation, and database assembly. The analysis was done by two other researchers independently. Then, the differences were analyzed by the investigation team.

Initially, we found 7,489 scientific papers in the databases. Of these, 158 met the inclusion criteria, totaling 100,563 patients from all continents. After reading them in full, only 18[3-20] papers had information on occupation (Figure 1): Brasil (one text; 81 patients), Thailand (one text; 11 patients), USA (one text; 48 patients), and China (15 texts; 47,870 patients), totaling 48,010 individuals, homogeneously distributed between sexes (51.62% men and 48.38% women) (Table 1).

FIGURE 1. PAPER SELECTION FLOWCHART, 2020.



In relation to professional activity, two occupations can be highlighted: 20.76% (n=9963) of patients were farmers and 19.77% (n=9,488) retired. Among the other individuals, 7.19% (n=3,453) worked in the service industry, 4.34% (n=2,085) were health professionals, 0.68% (n=327) employees, and 0.61% (n=295) self-employed. Four studies (3, 6, 9, 18) defined the other occupancies in the category '*other*', corresponding to 43.16% (n=20,719) of individuals studied. Eight papers[3,5,7,10,11,12,12,17] characterized the occupation of part of the cases, without information on the others, which were included in the field "*not informed"(n=1,680; 3.49%)* (Table 1).

The records of health professionals with the disease were observed in 12/18 articles, and four[13,14,16,19] of them were conducted exclusively on these professionals. In seven others[3,5,7,10,11,15,17], professions were not investigated, but the text highlighted the number of health professionals with Covid-19. Excluding the studies composed exclusively by health professionals, the frequency of this category varied from 3.5% to 29.0% (Table 1).

In outbreaks of infectious diseases, occupation and work environment can play an important role in the dissemination of infection due to a variety of actions that can promote this spread, such as contact with customers, food preparation, and others[21]. Studies on other diseases have already stressed the importance of professional activity in the dynamics of transmission: Danovaro-Holliday et al.[22], for example, showed that agglomerations and precarious living conditions favored outbreaks of rubella.

Approximately 10% (n=14.4 million) of workers in the United States are employed in occupations in which exposure to diseases occurs at least once a week; and 18.4% (n= 26.7 million) workers there are employed in occupations in which exposure to morbidities occurs at least once a month[21]. Given this scenario, it becomes relevant, in studies and research carried out on Covid-19, to identify the professional activities of individuals and their place of work to understand the relationship between occupation and the spread of the disease.

In this review, we observed that of 48,010 individuals, 1,680 were in the category of occupation *not informed* and 20,719 in the *other* category, which represents a shortage in specific definitions of occupation in 46,65% of the population studied. This lack of information, in general, can compromise the reliability of epidemiological information and generate false correlations in the diagnoses of health (23).

TABLE 1. CHARACTERIZATION OF THE PAPERS INCLUDED IN THE STUDY (N=18), 2020.

Paper	Country	N	Sex		Occupations reported							
			Male (%)	Female (%)	Agriculture (%)	Services (%)	Self-employed (%)	Employed (%)	Retired (%)	Health professionals (%)	Others (%)	Not informed (%)
Borba et al. (3)[a]	Brasil	81	61 (75.4%)	20 (24.7%)	-	-	-	-	-	5 (6.2%)	-	76 (93.8%)
Wang et al. (4)[b, c]	China	26	11 (42.3%)	15 (57.7%)	2 (7.7%)	-	1 (3.9%)	16 (61.5%)	4 (15.4%)	-	3 (11.5%)	-
Li et al. (5)[a]	China	548	279 (50.9%)	269 (49.1%)	-	-	-	-	-	45 (8.2%)	-	503 (91.8%)
Shi et al. (6)[c]	China	487	259 (53.2%)	228 (46.8%)	140 (28.7%)	-	219 (45%)	82 (16.8%)	38 (7.8%)	-	8 (1.6%)	-
Wang et al. (7)[a]	China	138	75 (54.3%)	63 (45.7%)	-	-	-	-	-	40 (29.0%)	-	98 (71%)
Chen et al. (8)	China	99	67 (67.7%)	32 (32.3%)	2 (2%)	-	63 (63.6%)	15 (15.1%)	19 (19.2%)	-	-	-
CCDCP (9)[d]	China	44672	22,981 (51.44%)	21,691 (48.55%)	9,811 (22%)	3,449 (7.7%)	-	-	9,193 (20.6%)	1,716 (3.8%)	20,503 (45.9%)	-
Lai et al, 2020. (10)[a]	China	278	172 (61.88%)	106 (38.12%)	-	-	-	-	-	40 (14.4%)	-	238 (85.6%)
Li et al, 2020. (11)[a]	China	425	240 (56.47%)	185 (43.53%)	-	-	-	-	-	15 (3.5%)	-	410 (96.5%)
An et al. (12)[e]	China	25	17 (68%)	8 (32%)	-	-	-	3 (12%)	-	-	-	22 (88%)
Wang et al. (13)	China	80	31 (38.75%)	49 (61.25%)	-	-	-	-	-	80 (100%)	-	-
Liu et al. (14)	China	30	10 (33.3%)	20 (66.6%)	-	-	-	-	-	30 (100%)	-	-
Cao et al. (15)[a]	China	102	53 (52%)	49 (48%)	-	-	-	-	-	24 (23.5%)	-	78 (76.5%)
Zhan et al. (16)	China	23	17 (73.9%)	6 (26.1%)	-	-	-	-	-	23 (100.0%)	-	-
Chen et al. (17)[a]	China	274	171 (62.4%)	103 (37.6%)	-	-	-	-	-	19 (6.9%)	-	255 (93.1%)
Zhang et al. (18)[d]	China	663	321 (48.4%)	342 (51.6%)	8 (1.2%)	-	12 (1.8)	211 (31.8)	227 (34.2%)	-	205 (30.9%)	-
Chow et al. (19)	USA	48	11 (22.9%)	37 (77.1%)	-	-	-	-	-	48 (100.0%)	-	-
Pongpirul et al. (20)	Thailand	11	6 (55%)	5 (45%)	-	4 (36.4%)	-	-	7 (63.6%)	-	-	-
Total	-	48,010 (100.0%)	24,782 (51.62%)	23,228 (48.38%)	9,963 (20.76%)	3,453 (7.19%)	295 (0.61%)	327 (0.68%)	9488 (19.77%)	2,085 (4.34%)	20,719 (43.16%)	1,680 (3.49%)

Legend: **a**- The study does mention the professions, but highlights the number of health professionals; **b**- The study highlights that the 'Retail Staff' occupation was the most common, with 11 individuals working in the same supermarket. This occupation was classified as "employed"; **c**- The work includes the occupation 'Student' reclassified as "other"; **d**- Occupation classified as "other" was not specified; **e**- The study shows that three patients were involved in medical waste cleaning. The 22 classified as not informed are relatives of these patients.

The correct identification of patients' occupational profiles can bring benefits for the effective control of the pandemic, guiding the adoption of effective safety measures in work environments. In the study by Wang et al.[4], of the 16 retail professionals contaminated by Covid-19, 11 and their relatives worked in the same supermarket. This scenario reinforces the need for rigorous monitoring of occupations and workplaces of patients, which is essential to prevent and/or reduce the spread of the virus in these locations and from them to their families and the community in general.

From the mapping of the professions most vulnerable to contagion, it is possible to develop actions of infection prevention and containment, as shown in the study by Wang et al.[13], in which health professionals present peculiar clinical and laboratory characteristics, which differ from those of people with other occupations and, therefore, require special attention and targeted biosafety.

According to data from the US Department of Health and Human Services/Centers for Disease Control and Prevention, 19% (n=9,282) of the confirmed Covid-19 cases in the United States were identified

in health professionals. These data may be underestimated since the health professional occupation was available only in 16% of the cases reported throughout the country[24]. In our analysis, 12 studies reported this occupation, making it necessary to ensure control in healthcare environments to reduce transmission. The contamination of these professionals has implications for the health system, both regarding the occupation of hospital beds as well as the reduction of the labor force available.

The papers used in this study present limitations. The diversity of classifications of the occupation variable hinders the identification of a risk profile. Another obstacle is the restriction of geographical area, since out of the 18 studies reviewed, 15 were conducted in the same country (China), which represents a percentage of 99.70% (n=47,870) of the entire study population, making it difficult to have comparative analysis between countries.

Based on the results presented, we advocate that studies on the profile of Covid-19 patients should include the occupation variable. In Brasil, this recommendation is of the utmost importance because it will allow us to know the risk profile and the impact of occupations in the magnitude of the pandemic. Such knowledge may subsidize the development of policies aimed at health workers and guide the process of reopening of companies/trade after this critical stage of the pandemic.

Author's Contribution

Carlos DFSouza; Aisla GG Santos; Euclides JO Cunha; Tatiana F Oliveira; Saulo HS Aquino; Rodrigo da Rosa Mesquita; Luiz CFS Junior; Fernanda MS Santana; Rafaela C Alcântara; Gabriel M Arnozo; Etvaldo RS Filho participated in the concept development, planning of the study, data collection and analysis, discussion of the results, scientific drafting, as well as in the review and approval of the final version of the paper.

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Covid-19 and Metabolic Syndrome

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Dear editors,

In the second half of 2019, a new coronavirus (Sars-Cov-2) was identified in a city of China, which soon spread to the whole world, becoming a great tragedy and reaching all continents, except for Antarctica. The numbers, widely disclosed, prove the severity of its resulting disease (Covid-19), since over 2 million cases have already been registered throughout the world, with 134,508 deaths by 16/04/2020.

After a careful analysis of 43 studies involving 3,600 patients, Fu et al.[1] pointed out the main signs and symptoms of the disease are: fever (83.3%), cough (60.3%), and fatigue (38%). On the other hand, the most common laboratory alterations were: increased C-reactive protein - PCR (68.6%), lymphopenia (57.4%), and increased lactic dehydrogenase - LDH (51.6%). Ground-glass opacities and bilateral pneumonia were the main alterations found in chest CT scans, with frequencies of 80% and 73%[1], respectively. They also found that 25.6% of patients presented severe evolution, reaching lethality in 3.6% of the cases. The authors concluded that most Covid-19 cases were symptomatic, with a moderate rate of fatality. The residents of Wuhan and those with comorbidities had more severe presentations, with higher mortality.

The severity and, consequently, the lethality and mortality present differences between regions, which is attributed to several factors, such as age and comorbidities. In Italy, 12% of the cases detected and 16% of hospitalized patients were admitted to the Intensive Care Unit, with 7.2% of lethality, according to an analysis carried out in mid-March 2020. In contrast, lethality in South Korea, during the same period, was 0.9%[2-4]. However less frequent, a severe evolution can also occur in young individuals without apparent comorbidities, but possibly with a subclinical systemic inflammatory state.

The conditions associated with greater severity and, consequently, lethality and mortality are homogeneously recognized in the literature as: obesity, chronic kidney disease, cancer, diabetes mellitus,

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hypertension, cardiovascular disease, and old age[5-8]. In other words, greater severity occurs precisely in individuals with metabolic syndrome. Based on this premise, we can better understand the reason for such varying severity in different countries and even in a single country, since the prevalence of the metabolic syndrome is known to be variable. Focusing on the Brazilian scenario, in a sample of the adult population from a city in the south of the Paraná state, a diagnosis of metabolic syndrome was found in approximately 50% of the population[9]. In another interesting study conducted in Niterói-RJ, Saad et al.[10] found a high prevalence of metabolic syndrome in the elderly, affecting 64% of them when analyzed according to the criteria defined by the IDF (International Federation of Diabetes), and 69% based on the JIS (Joint Interim Statement). That is, very likely, a possible explanation to the higher gravity also among the elderly, considering that the more time of evolution of the metabolic syndrome, the higher the probability of other associated comorbidities.

On the other hand, in an analysis we carried out on 5,000 *check-up* consultations of an adult population from São Paulo, with a mean age of 42 years, and with a predominantly male population (70%), we found that 25% of the individuals met the diagnostic criteria for metabolic syndrome (unpublished data), precisely half of the figure found in Paraná or Niterói[9,10].

All these data clearly show the possible relationship between the presence of metabolic syndrome and the severity of Covid-19. Such evidence will certainly be more abundant if we understand that the diagnosis of the metabolic syndrome often precedes the diagnosis of comorbidities. Evidently, those who already have metabolic syndrome with complications will be more susceptible to a worse evolution of Sars-Cov-2.

The variable prevalence of metabolic syndrome should contribute to the different evolution outcomes of the same disease.

To diagnose metabolic syndrome, three or more of the five criteria established by international experts and the World Health Organization need to be met. They are:

- Central obesity: waist circumference equal to or greater than 90 cm in men and 80 cm in women, although these numbers vary based on ethnicity. When the BMI is greater than or equal to 30 kg/m² there is no need to consider the abdominal circumference.
- Triglycerides: above 150 mg/dL.
- HDL cholesterol: less than 40 mg/dL in men and 50 mg/dL in women.
- Fasting glucose: over 100 mg/dL or diabetes or increased insulin resistance.
- Blood pressure: greater than or equal to 130/85 mmHg or with antihypertensive medication.

(P.S.: increased serum albumin in urine is, for some, a diagnostic criterion and, for others, a sign of kidney involvement in metabolic disease).

The main complications of metabolic syndrome are:

- Atherosclerosis - coronary, cerebral, and others.
- Diabetes type 2 or secondary to increased insulin resistance.
- Arterial hypertension.
- Chronic kidney disease.
- Several types of cancer.
- Other: polycystic ovary syndrome, urinary calculosis, acanthosis nigricans, osteoarthrosis, and hyperuricemia with or without gout, among others.

What is the link between metabolic syndrome and Covid-19? What these diseases have in common? Why is the inflammatory process of coronavirus patients accentuated in those with metabolic syndrome and the elderly?

Adipose cells, as well as the macrophages, endothelial cells, and fibroblasts, are responsible for the production of a series of substances that cause, silently, irreparable damage to our body. Among them, there are adiponectin, interleukin-6, tumor necrosis factor-alpha (TNF-alpha), resistin, leptin, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1). Adiponectin is reduced in obese patients, and its levels are inversely correlated with insulin resistance and the possible presence of antiatherogenic activity[11-14].

Interleukin-6 and TNF-alpha are pro-inflammatory cytokines that can also contribute to insulin resistance and, especially, to the subclinical systemic and continuous inflammatory process responsible for the complications found in patients with the metabolic syndrome, such as diabetes, atherosclerosis, hypertension, and chronic kidney disease. This sustained inflammatory state can be evidenced by an increase in the acute-phase proteins (CRP, fibrinogen, and ferritin).

In addition, the secretion of tissue angiotensinogen may contribute to hypertension, commonly observed in these patients, and to the secretion of PA-1 in a pro-thrombotic state, something that should be considered in patients with metabolic syndrome and Covid-19.

Therefore, in patients with metabolic syndrome, there is a constant and sustained inflammatory state that is probably exacerbated with the presence of Sars-CoV-2, worsening the clinical scenario of Covid-19.

How can the inflammatory state of patients with metabolic syndrome be reduced? This is our proposal because we believe that, if this is successful, cases will be less severe and, consequently, the lethality rate will be lower.

There are two basic ways to handle the coronavirus. One is to fight it directly with vaccines and medicines, but these possibilities are still undergoing studies[15,16]. The other, which is the reason for this analysis, although obvious, has not been highlighted in the literature. It seeks to strengthen those who are most vulnerable, i.e., patients with metabolic syndrome, and there are conditions for this. Time will be an ally, since soon we will have a specific vaccine and, possibly, effective drugs.

As we know, greater severity of the infection by the Sars-CoV-2 is due to increased systemic inflammation, particularly pulmonary, which is demonstrated by a significant elevation of cytokines ("cytokine storm"), in addition to the inflammatory markers such as ferritin, D-dimers, and PCR. In addition, it is possible to observe in these patients a prothrombotic state due to various abnormalities in the hemostatic system, such as platelet dysfunction, impairment of fibrinolysis, and endothelial dysfunction, conditions that are secondary to increased levels of plasminogen activator inhibitor-1, fibrinogen, and factor VIII activity[13,16-22]. These data suggest that patients with metabolic syndrome and Covid-19 should be anticoagulated, due to the prothrombotic state present in both conditions, at least during the period of hospitalization, in the absence of clinical contraindications and in association with all other measures.

There are some ways of reducing the inflammatory state of patients with metabolic syndrome, namely:

CLINICAL CONDUCT

Metabolic syndrome patients need to be aware of the seriousness of their illness. Perhaps this is an opportune time for changing lifestyles and eating habits. Regular physical activity that is moderate and compatible with the reality of each individual, without exaggeration, brings recognized health benefits.

It is important to emphasize that metabolic syndrome is a potentially serious disease due to all the complications that may arise and do arise from it, often, after a variable period of the syndrome. Therefore, the benefits go far beyond strengthening to handle the new coronavirus.

The improvement of the parameters of metabolic syndrome is not easy, but it starts with a change in lifestyle and with a healthy diet, considering that it is triggered by an excess of food that is harmful to health, unquestionably primarily by carbohydrates, particularly industrialized fructose.

The most recommended diets are the Mediterranean and the Dietary Approaches to Stop Hypertension - DASH, which are mainly poor in sodium and rich in fruits, vegetables, whole grains, and less fatty dairy products, which provide the improvement of several inflammatory parameters[23-25]. In other words, the increased consumption of whole grains, seafood, fish, nuts, seeds, fiber, vegetables, vegetable oils (e.g., olive oil), up to two glasses of red wine per day (with the exception of children and other health conditions), polyunsaturated fatty acids (e.g., krill oil), which are the basis of these two diets, fight the inflammation responsible for the harm caused by metabolic syndrome and reduces mortality due to cardiovascular disease.

If, on the one hand, the Mediterranean and Dash diets are important for the prevention and treatment of metabolic syndrome, on the other, the "western" diet, rich in carbohydrates, particularly fructose, contained in soft drinks, fast-food, 100% pure and sweet fruit juice, is largely responsible for the high prevalence of obesity, heart disease, and hypertension worldwide. It is important to draw attention that industrialized fructose, usually derived from corn starch, should not be mistaken with that from fruit, known to be beneficial to our health.

Considering the above, we conclude that:

The treatment of metabolic syndrome is an additional alternative for facing the novel coronavirus, but we must not forget that it is much more comprehensive, since it prevents complications that kill much more than the current pandemic.

We suggest that the Ministry of Health, especially Anvisa, classify, as is done in Australia, the quality of food to our health base on a star system visibly displayed on labels. In such a system, for example, on a scale from one to five stars, the best food items for our health would receive five stars, and the worst - which cause of obesity, diabetes mellitus, hypertension and vascular diseases, such as soft drinks, fast-food, and sugar - would receive one star. Certainly, this is more

appropriate than indicating the percentage of components on labels, since these are difficult to interpret.

A change in lifestyle is crucial. The confinement, with uncontrolled diets in homes and no adequate physical activity, will surely bring an increase of obesity with deleterious consequences for the organism.

The Mediterranean or Dash diet, rich in polyphenols, particularly resveratrol, are of unquestionable importance. We do not recommend the use of resveratrol in capsules or sachets due to the lack of relevant information, such as the risk of its use in patients with comorbidities, the still-unknown risk of drug interactions, in addition to a better definition of dose. However, the current evidence indicates that this product is highly promising in reducing inflammatory cytokines[24] and it has already been used in various studies in humans, but with small samples, usually obese patients, without concomitant use of other drugs, with positive results and good tolerance.

We recommend quarantine for protecting patients with metabolic syndrome, particularly those with four or five diagnostic criteria.

6. We suggest medication containing metformin and pioglitazone, respectively, 1,000 mg and 30 mg per day, for all of them, in the absence of contraindications, for a period determined by the assistant physician, based on the clinical and laboratory findings. The recommendation for the use of metformin and pioglitazone is due to the fact that they reduce serum levels of interleukins 6 and 8 in patients with a high insulin resistance[25]. These drugs do not have any effect against the virus, but against the existing inflammation in patients with metabolic syndrome. Therefore, its use is indicated for patients with high insulin resistance, especially before being affected by the novel coronavirus, and should not be used in patients with kidney failure.

We suggest that the isolation period should be maintained until the clinical and laboratory parameters are improved.

In addition, we also suggest prophylactic anticoagulation during the hospitalization period, especially in these patients, in view of the increased risk of thrombosis which, theoretically, they present.

We must emphasize that we had, in no way, with this text, the intention to resolve the tragedy caused by Covid-19, since this can only be accomplished through the work of scientists. Our goal, to be clear, was to warn people and the authorities that there is a widespread disease that should be widely fought and that kills more than Covid-19; it is called metabolic syndrome and, if that was not enough, it is the main responsible for the comorbidities that generate the greater vulnerability to the deleterious effects of Sars-CoV-2. Therefore, to reduce the complications that aggravate the evolution of Covid-19, we need to fight the inflammation that is at the center of metabolic syndrome.

Author's Contribution

PRC: study design, literature review, preparation of the text and revision of the final version; PDMMN: preparation of the text and revision of the final version; LVBP: preparation of the text and revision of the final version; SM: preparation of the text and revision of the final version; ESO: preparation of the text and revision of the final version; LLN: preparation of the text and revision of the final version; AMB: preparation of the text and revision of the final version; VAHS: preparation of the text and revision of the final version; BMCF: preparation of the text and revision of the final version; ALCN: study design, literature review, preparation of the text and revision of the final version.

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Primary Health Care in Brasil in the times of COVID-19: changes, challenges and perspectives

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SUMMARY

The pandemic of Coronavirus Disease 2019 (COVID-19) has put pressure on countries' health systems. Although attention is mostly directed at the hospital sector, since many critically ill people will need intensive care, Primary Health Care (PHC) has also been disrupted. In Brasil, a universal and free health system has existed since the 1988 Constitution, which re-organized the PHC to attend the population. However, like other countries, the Brazilian health system is being overloaded with the increase in the large number of COVID-19 cases. It is worth reflecting on the changes and challenges in PHC during the COVID-19 pandemic in Brasil.

KEYWORDS: *Primary Health Care. Brasil. Coronavirus Infections.*

Dear Editor,

We are going through unprecedented times. The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its spread worldwide has exposed gaps in the health systems of several countries. As the focus became hospital care, since 15% of critically ill patients will need intensive care, there has been a disruption in other sectors of the health systems[1]. Such an impact has also been observed in the Primary Health Care (PHC) systems. It is worth reflecting on the changes suffered by PHC during the 2019 Coronavirus Disease (COVID-19) pandemic in Brasil and how PHC itself can function as an important ally in combating the COVID-19 and contributing to reducing the burden on the hospital network.

In Brasil, the 1988 Constitution represented an instrument of change and a social movement that established health as a social right for the Brazilian population. The constitution mandated the state's responsibility to deliver health care to all, paving the way to the Unified Health System (Sistema Único de Saúde [SUS], in Portuguese), which is based on the pillars of university, integrality, and equity. Since then, the health systems have been systematized into levels of care, as primary, secondary and tertiary, with special importance for Primary Health Care (PHC). PHC is the essence of SUS itself, with a focus on programmatic actions, whose municipal managers along with the population (social control) become decision-makers

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for health actions implementation[2]. PHC started in Brasil in 1994, through the Family Health Program, and in 1998 became the Family Health Strategy (FHS). In 1998, there were 2,054 family health teams, and in 2018 the number of teams reached 41,619 covering approximately 75% of the country population (approximately 143 million individuals)[3].

Although each municipal manager determines which priority health actions are to be tackled, there is a national agenda with well-established guidelines that must be followed. In this context, the control of hypertension and diabetes, reproductive familiar planning, prenatal care, childcare, control of communicable diseases (most notably dengue, zika, leprosy, tuberculosis, and sexually transmitted infections) and others are among the PHC's priority actions. In addition, the PHC works as a capillary network to guide the flow of individuals who need procedures in specialized clinics and/or hospitals. However, the current crisis triggered by COVID-19 imposes changes in the PHC schedule and in its work process.

Among the main topics discussed and subsequently modified are the implementation of a care plan for suspected cases of COVID-19 and the reorganization of priority demand in primary health units. In the contingency plan for coping with the COVID-19, some primary care units located at strategic points in the territory were designated as reference units for the treatment of respiratory syndromes (flu-like syndromes), as the cases of COVID-19 show unspecified symptoms.

Health professionals were trained for the early recognition of signs and symptoms of severity initial care, transfer of cases to medium and high complexity units, as well as to proceed with the collection of material from the respiratory tract to be sent to the Central Laboratory of Public Health, where RT-PCR assays are carried out for the diagnosis of COVID-19. The respiratory samples are tested for a respiratory viral panel to identify other viruses that are concomitant, seasonal, and usually prevalent. For this purpose, the population has been extensively informed about where the reference units are located and on what occasions they should seek assistance there. Even with the widespread broadcasting of announcements, many people who are unable to access quality information still do not know how to seek help, which reveals flaws in the system.

In addition to the reference units and considering the importance of PHC in the community transmission phase, the Ministry of Health launched the Coronavirus Clinical Management Protocol for Primary Health Care with the intention of standardizing the work process at that attention level, ensuring security and resolution[4].

Because the SARS-CoV-2 is a highly infectious pathogen transmitted mainly by droplets and airborne, protocols have been instituted in primary health care, especially to people reporting respiratory symptoms[5]. There has been extensive reinforcement for the correct use of facial masks and frequent handwashing by health professionals. Patients who seek care are also instructed not to be in crowded spaces and wash hands frequently, and face masks are mandatory for those with flu-like symptoms (currently to all). Suspected cases with mild symptoms are prescribed anti-symptomatic medication and are instructed to maintain social isolation at home for a period of 14 days. They are also instructed to seek a hospital if they experience worsening of symptoms, including shortness of breath[6]. The COVID-19 pandemic also caused alterations in the flow of care in primary health care units. With the increase in suspected cases of COVID-19 and to avoid further pressure on PHC, primary health units reorganized their schedules to prioritize care for respiratory problems and urgent cases. Antenatal care schedules have been maintained, but many routine programs designed to control certain conditions, which are also important, have received less attention. For example, in many situations, actions to control hypertension and diabetes have been suspended, with only the renewal of prescriptions or emergency care being preserved. Community preventive actions, which could cause agglomerations, were temporarily canceled. It is worth mentioning that these agreements may vary from municipality to municipality, according to the local manager's understanding.

Regarding dental care, it was defined by the Federal Council of Dentistry that urgent and emergency procedures should be prioritized over elective procedures that could await care in a period of less transmissibility and risk for COVID-19[7]. Professionals started to prioritize cases in which users were experiencing pain or changes in oral tissues, taking the user to greater risk (such as abscesses and dental infections), strictly following recommendations for professional dental care safety[8].

In times of the COVID-19 pandemic, the duties for community health workers have also changed. Home visits were reduced, with priority given only

to patients with difficult mobility, serious health problems, and those who need a medical or nursing visit. Community health agents also started to deliver medicines for continuous use to people routinely assisted by a specific family health team. During the work of these workers, guidelines on social distancing and frequent hand hygiene have been reinforced as they are currently the most appropriate form of prevention[9].

To minimize the impact of the COVID-19 pandemic on health care, especially for people with chronic diseases and/or using routine medication, the Brazilian Ministry of Health (MoH), in exceptional and temporary nature, published an ordinance authorizing consultations via Telemedicine - as it is not yet regulated in the country. Telemedicine has focused on pre-clinical care, assistance support, medical consultation, treatment monitoring, and diagnosis, through information and communication technology. It can be used for SUS, as well as in supplementary and private health[10]. However, the limited access to technological resources by the poorest population and the lack of these resources in health units represent obstacles to the implementation of this measure for the public services.

Additionally, the Brazilian MoH has made digital channels and services available, including a telephone exchange and an app for people to seek health care information not only related to COVID-19. According to data from the MoH, by the first week of April 2020, more than 1 million people sought SUS call centers to receive guidance on signs and symptoms of the COVID-19. This initiative seeks to reduce the burden on the health system and provide information at a distance, reducing queues and patient crowding[11].

As the cases of COVID-19 started to appear just at the beginning of the seasonal period of flu in Brasil, the Brazilian MoH decided to anticipate the mass influenza vaccination for the older population and health professionals in order to avoid overlapping and/or coinfection cases and more pressure on health systems. To avoid agglomeration, influenza vaccination was preferably organized in public, open places, which avoided crowding and queuing with people nearby (squares, sports courts). Some municipalities in the country used the drive-thru system for the vaccination campaign and thereby reduced the possibility of crowding among people eligible for vaccination since they are also the group most at risk for adverse outcomes from COVID-19.

In view of the current epidemiological scenario, the moment seems to be one of uncertainty. The number of cases in Brasil is expected to increase in the first or second half of May. Despite PHC reorganization actions to face the COVID-19 in Brasil, the PHC in Brasil has suffered from reduced financial resources in recent years, which has hampered the work of family health teams.

Thus, it is necessary that in the period of confrontation of COVID-19 (and even afterward), PHC receives a greater contribution of investments, ranging from financial incentives for the acquisition of equipment, structuring of health units, purchase of supplies, including the training of health professionals, and psychological support to them. In addition, the number of family health teams needs to be increased to expand the care to the population. In addition, since this article reflects on the general actions implemented by PHC in Brasil, on-site studies are necessary to verify the specificities and variations that each municipality (or district) has carried out during the COVID-19 pandemic.

Author's Contribution

Gois-Santos, V.T.; Santos, V.S.; Souza, C.D.F and Tavares, C.S.S. worked on the conceptualization, discussion of the theme and writing; Gurgel, R.Q and Martins-Filho, P.R. revised and edited the text.

Conflict of interest

The authors have no conflict of interest to declare.

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PALAVRAS-CHAVE: *Atenção Primária à Saúde. Brasil. Infecções por Coronavirus.*

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11. BRASIL. Ministério da Saúde. Agência Saúde. Ministério da Saúde já atendeu 471,6 mil pessoas à distância: mais de 1 milhão de pessoas procuraram os serviços de teleatendimento do SUS para receber orientações sobre sinais e sintomas do coronavírus. [cited 2020 May 13]. Available from: https://www.saude.gov.br/noticias/agencia-saude/46675-ministerio-da-saude-ja-atendeu-471-6-mil-pessoas-a-distancia

Accuracy of the Polymerase Chain Reaction (PCR) test in the diagnosis of acute respiratory syndrome due to coronavirus: a systematic review and meta-analysis

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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

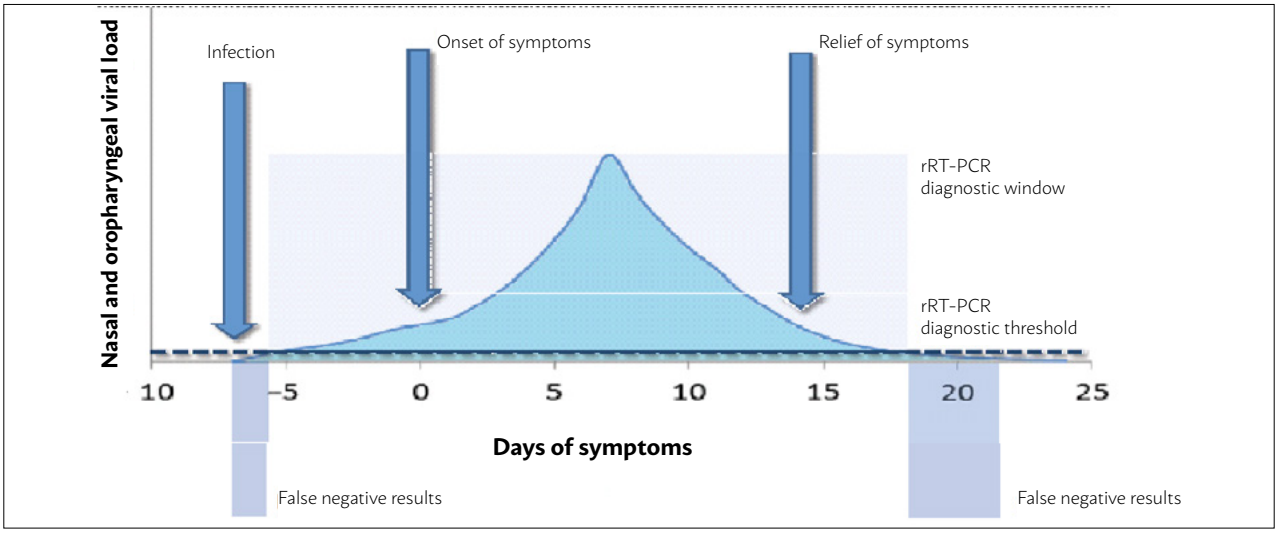
The first case of a patient with a diagnosis of respiratory syndrome due to coronavirus (SARS-COV-2), in the current pandemic, was reported in January 2020, when a patient resident of the city of Wuhan, the Hubei province, in China, was admitted to the central hospital in December 2019[1]. Patients affected by the coronavirus 2019 (COVID-19) can be asymptomatic, present mild symptoms (cough, sore throat, fever, diarrhea, myalgia, anosmia), moderate symptoms (weakness, myalgia, dyspnea), or severe symptoms with acute respiratory insufficiency, acute respiratory distress syndrome, and acute kidney failure[2]. The mortality rate can reach 0.5%[3].

The "novel coronavirus" belongs to the *Coronaviridae* family, whose genetic material is the ribonucleic acid (RNA) and which is known to cause influenza and enteric syndromes since 2003. It is associated with Severe Acute Respiratory Syndrome (SARS)[4] in Asia, with mortality rates of 8.7% (it reached 50% among people aged over 60 years), and in the Middle East Meridian East Respiratory Syndrome (MERS) in 2013, with 40% of mortality[5].

The etiological diagnosis of SARS-COV-2 he is currently carried out using the Polymerase Chain Reaction (PCR) technique to detect viral RNA in the sample; enzyme-linked immunosorbent assay (ELIZA) to detect the presence of antibodies in serum (rapid tests to detect antibodies or antigens),[6] and computed tomography[7]. The PCR technique provides better accuracy when carried out between 2 and 5 days after the onset of symptoms, with the collection of material via oral/nasal swab or sputum[8-11]; serological tests may be collected starting at the seventh day (Figure 1).

The evolution of the PCR technique resulted in a reduction in the time for executing the examination and in quantification. The real-time polymerase chain reaction (RT-PCR) uses *primers* that target the upE and ORF1a areas of the coronavirus genome[12-13]. During the PCR technique, reverse transcription can monitor the progress of the process as it takes place (in

FIGURE 1. CORRESPONDENCE BETWEEN THE VIRAL LOAD AND INFECTION BY THE CORONAVIRUS 2 (SARS-COV-2), CLINICAL SYMPTOMS, AND POSITIVE RRT-PCR.



Source: Adapted from Lippi (2020, p 4).

real-time), and the data are collected throughout the examination. The "TaqMan System®" uses a fluorescent probe for quantification and the "SYBR Green I System® uses a dye that binds specifically to DNA and accumulates during cycles for quantification. Currently, there are other enhancements to the PCR technique that aim to decrease costs and facilitate the execution of the technique.

OBJECTIVE

The objective of this review is to identify the efficacy of the PCR test in the diagnosis of patients with coronavirus.

METHODS

The clinical question is: What is the efficacy of the PCR test in the coronavirus diagnosis?

Eligibility criteria:

- Patients with a suspicion of coronavirus infection;
- Coronaviruses diagnosis by PCR;
- Collection of nasopharyngeal (NF) and/or oropharyngeal (OF) swab samples;
- Studies on the diagnosis of SARS, MERS, and SARS-COV-2;
- Clinical trials with better evidence and quality;
- No time or language restrictions;
- Full texts available for access, with results on PCR sensitivity and specificity;
- Studies with incomplete data for specificity and sensitivity and viral panel for etiologic diagnosis of respiratory tract infection will be excluded.

The search for evidence will be conducted on the following virtual scientific information databases, using the search strategies:

MEDLINE/PUBMED: ((COVID OR COV OR nCOV OR CORONAVIRUS) AND (PCR OR Polymerase Chain Reaction OR Nucleic Acid Amplification OR Nucleic Acid Amplification Techniques OR Reverse Transcriptase Polymerase Chain Reaction) AND (diagnosis/broad[filter])), date 04/2020.

CENTRAL COCHRANE: (COVID OR COV OR nCOV OR CORONAVIRUS) AND (PCR OR Polymerase Chain Reaction OR Nucleic Acid Amplification OR Nucleic Acid Amplification Techniques OR Reverse Transcriptase Polymerase Chain Reaction), date 04/2020.

The information obtained from the characteristics of the studies selected were: author's name and year of the study, study design, number of patients, population, type of test, and comparison, described in Table 1.

Data from the results will be collected in absolute numbers provided directly or by information inferred from what is reported in the text. The results from the studies will be placed in a 2x2 table, where true positive, false positive, true negative, and false negative results will be compiled. The data collection and meta-analysis process will be completed by two independent authors and revised by all authors. Disagreements will be resolved by consensus and discussion between all authors.

Bias assessment and quality of evidence

The methodology used to assess the quality of the studies was the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [14] tool, which was applied by two independent authors. Disagreements were resolved by consulting with a third independent author.

Data Analysis

The data will be extracted for the primary outcome of accuracy of the test RT-PCR for coronavirus diagnosis. The data collected will be true positive, false positive, true negative, and false negative results, sensitivity, and specificity, which will be analyzed in a 2x2 Table using the Catmaker Tables [15] software.

The results of the studies included may be aggregated and meta-analyzed using the Meta-Disc software Version 1.4 [16], through which results on the sensitivity, specificity, and positive likelihood ratio, negative likelihood ratio, and SROC curve will be obtained.

RESULTS

In the search for evidence, we recovered 1260 studies, of which 107 were selected based on their titles, 6 based on the abstract, 28 were excluded, and 22 were evaluated in full. Of the 22 studies, 9 were excluded and 13 [17-29] were selected to support this assessment; the grounds for exclusion and list of studies excluded are available in the references, Table 1, and Figure 7, in the Annexes.

The characteristics of the populations included and results extracted are summarized in Tables 2 and 3, in the Annexes.

The thirteen studies included in this review were effectively cross-sectional, with no sample size calculation, conducted in a single institution, including a total of 6295 samples taken through nasal and/or oropharynx swab.

Bias assessment and quality of evidence

We used the QUADAS-2 [14] tool to assess the quality of the thirteen studies included in this review (Figure 4). In the selection of patients, we found a low risk of bias in 12 studies (92%) and low-medium risk in one (8%). In the evaluation of the index tests, we found ten studies (77%) with low risk of bias, two studies (15%) with low-moderate risk, and one with moderate risk (8%). In comparison to the test considered the gold standard (reference), we found twelve studies (92%) with low risk of bias, and one with moderate risk. Regarding flow and time biases, eleven studies (85%) had a low risk, and two (15%) moderate risk.

Meta-analysis

Thirteen studies [17-29] presented data possible to be meta-analyzed. The sensitivity (Figure 2) of the PCR technique for coronavirus diagnosis was 86% (95% CI = 84 to 88%); I^2 = 85%.

The estimate of specificity calculated for the studies (Figure 3) was 96% (95% CI = 94 to 97%); I^2 = 0 %.

The results for a positive likelihood ratio (Figure 4) was 18.8 (95% CI = 14.5 to 24.3); I^2 = 0%.

The results for a negative likelihood ratio (Figure 5) was 0.13 (95% CI = 0.1 to 0.19); I^2 = 83.6%.

Analyzing the SROC curve (Figure 6), we estimated the value of the area under the curve (AUC) as 0.977 and Q = 0.93.

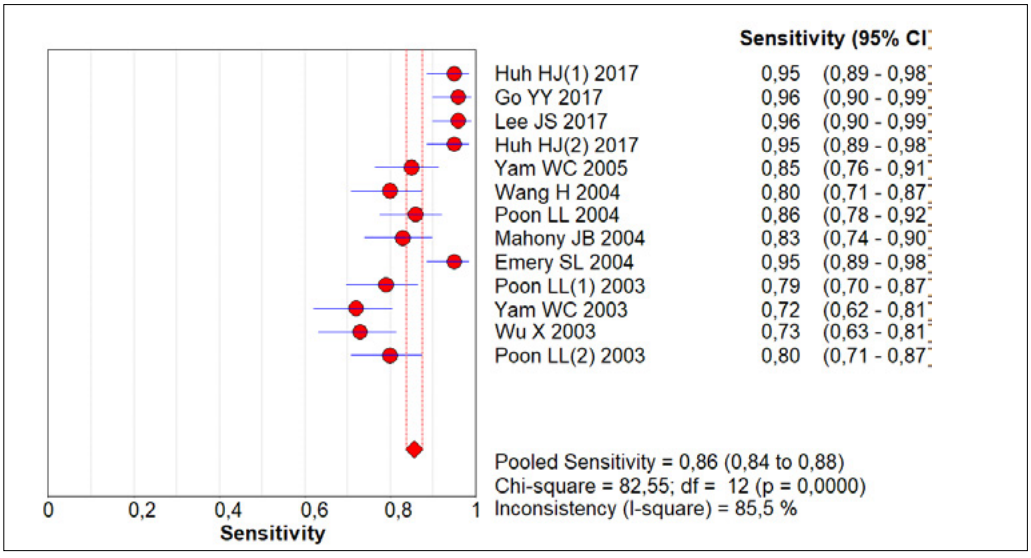


FIGURE 2. FOREST PLOT OF SENSITIVITY ESTIMATE IN THE CORONAVIRUS DIAGNOSIS BY PCR.

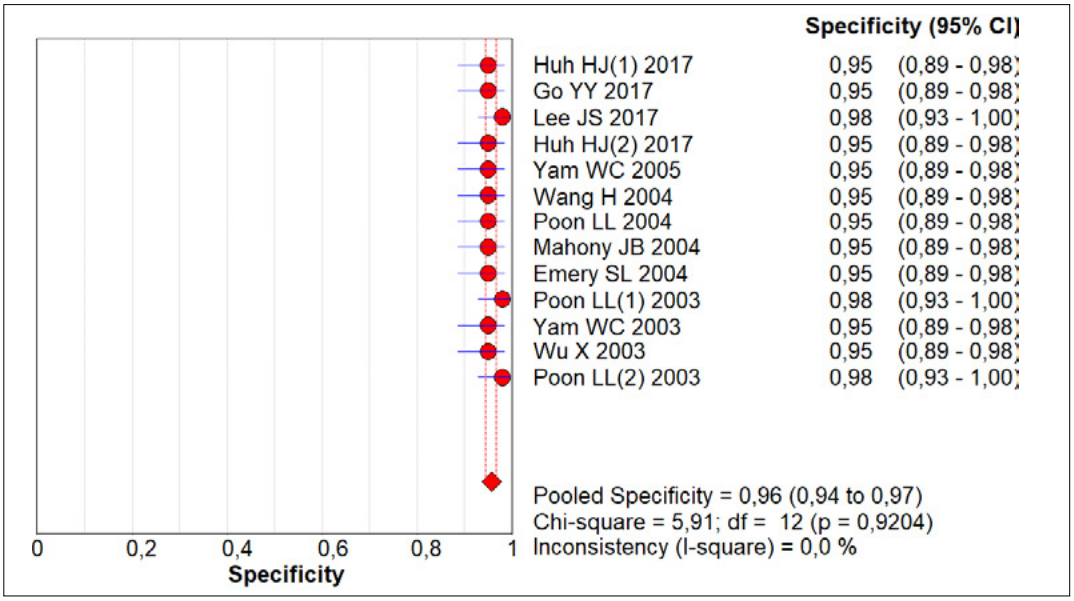


FIGURE 3.
FOREST PLOT OF SPECIFICITY ESTIMATE IN THE CORONAVIRUS DIAGNOSIS BY PCR

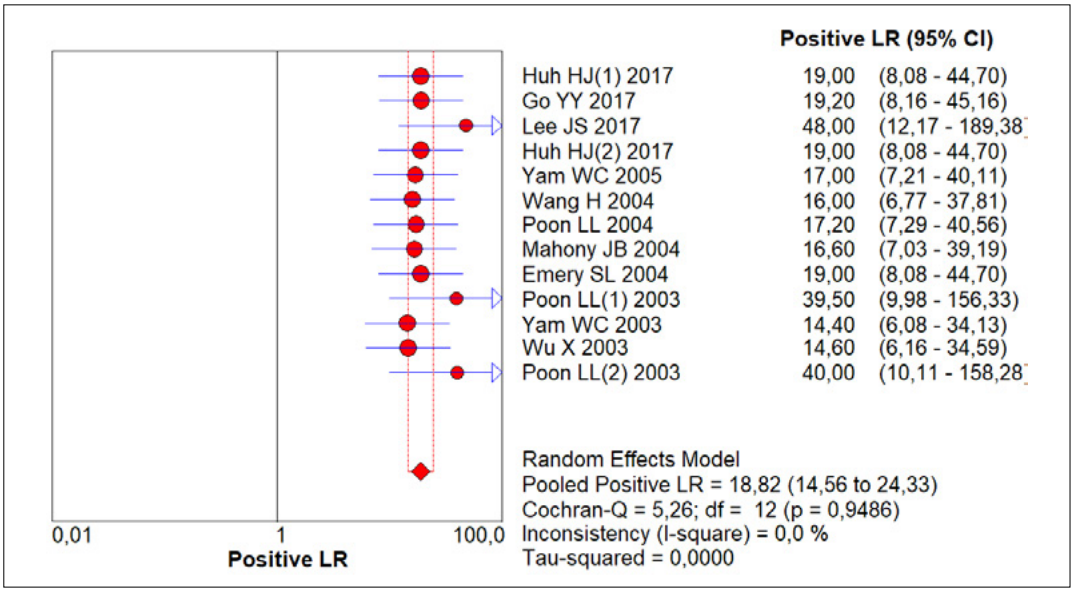


FIGURE 4.
FOREST PLOT OF THE POSITIVE LIKELIHOOD RATIO ESTIMATE IN THE CORONAVIRUS DIAGNOSIS BY PCR

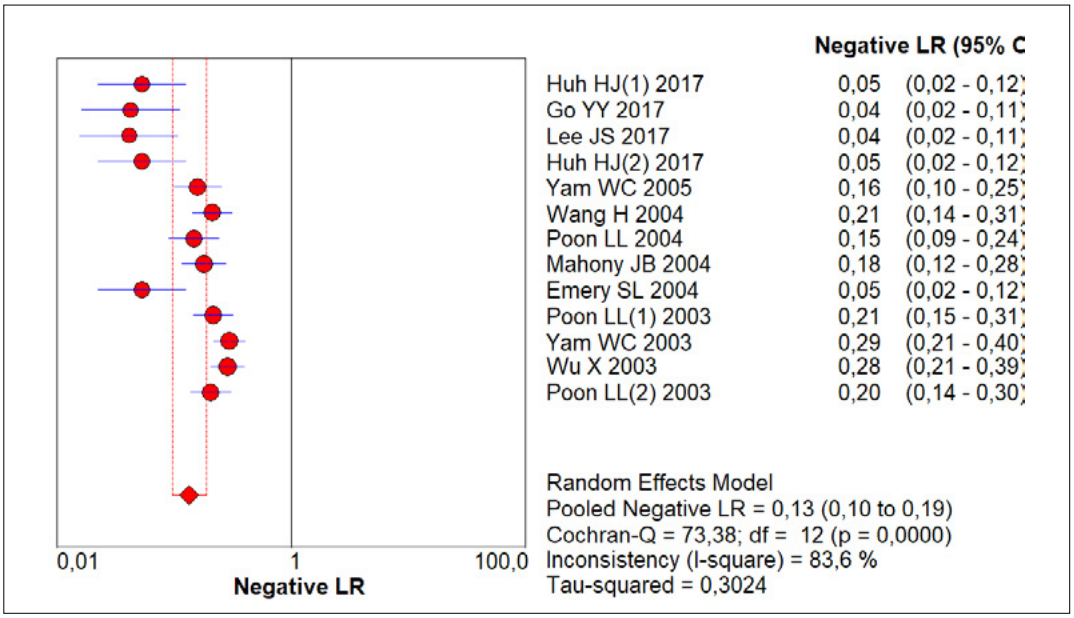


FIGURE 5.
FOREST PLOT OF THE NEGATIVE LIKELIHOOD RATIO IN THE CORONAVIRUS DIAGNOSIS BY PCR

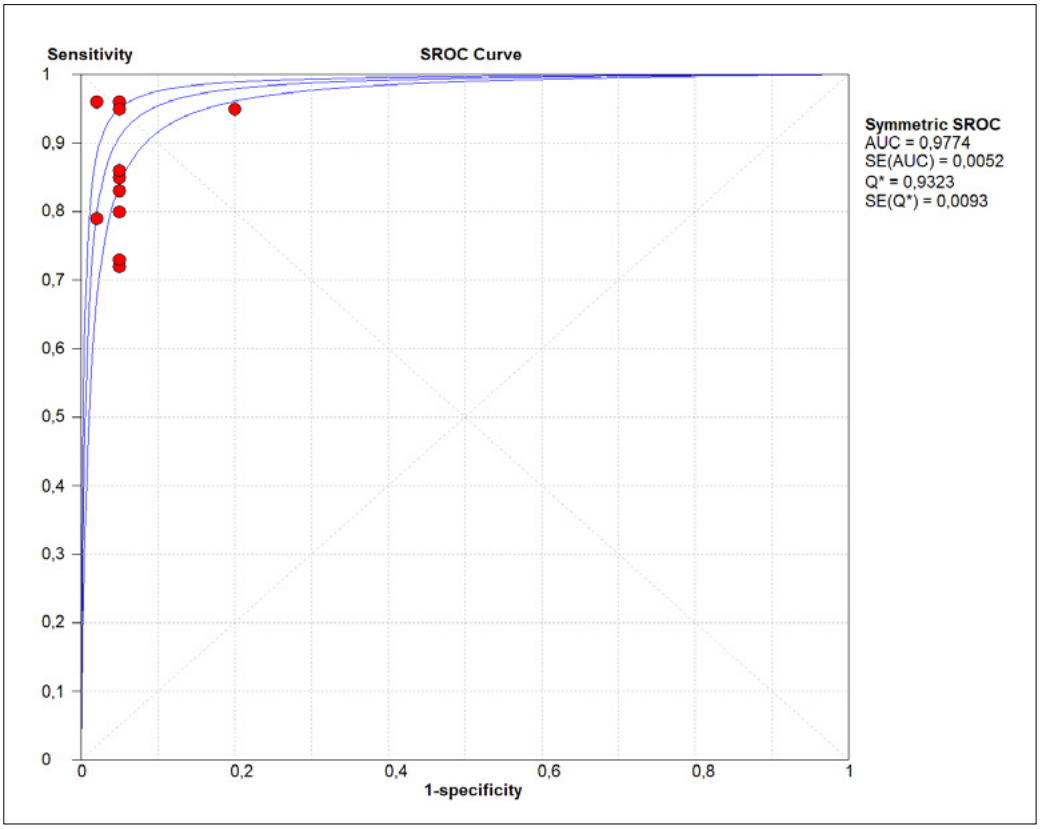


FIGURE 6. SUMMARY RECEIVER OPERATING CHARACTERISTIC CURVE (SROC) IN THE DIAGNOSIS OF CORONAVIRUS BY PCR

DISCUSSION

Since 2003, there have been cases of respiratory syndromes whose etiology is due to a coronavirus infection, with two previous epidemic outbreaks (SRAS-VOC, and MERS). In November 2019, a new outbreak began, of pandemic proportions, which has spread throughout the world at great speed, causing a large number of deaths and morbidities. At the same speed as the virus propagation, research was carried out for diagnosis and treatment of the pathology.

In this review, we looked for scientific studies of the best quality available to evaluate the accuracy of the PCR test for coronavirus diagnosis.

During our search, we retrieved only cross-sectional observational studies to support the evidence of the review, which provided us moderate quality and a low risk of bias. However, Deeks JJ, et al.[30] found a high risk of bias and low quality when they evaluated, through a systematic review, the serologic diagnosis test for COVID-19. This result was probably due to the methodological rigor applied in the assessment using the QUADAS-2 tool.

In this review, we searched for studies with suspected or diagnosed respiratory infection by the coronavirus in human patients. The PCR technique was adopted in all studies, with minor variations that do not interfere in their accuracy.

The values obtained through the meta-analysis were: sensitivity (86%), specificity (96%), positive likelihood ratio (18.82), a negative likelihood ratio (0.13), and area under the curve (AUC) (0.97).

The accuracy of the PCR test for coronavirus diagnosis can change according to the prevalence of the disease.

We can simulate 3 situations:

- With a prevalence of 50%, common among health professionals with respiratory symptoms, we found a post-test probability of 96%.
- With a prevalence of 20%, the post-test probability was 84%.
- With a prevalence of 5%, there is a 55% post-test probability.

As we can observe, even with high sensitivity and specificity of the PCR test for coronavirus diagnosis, we can obtain different results regarding its effectiveness.

We can interpret that when the test is applied in conditions of low prevalence of the disease, it allows a precise diagnosis in 55% of the cases.

Hypothetically, when carrying out a second consecutive test in the same patient, considering a prevalence of 96% (post-test probability of the first test with an

initial prevalence of 50%), there is a post-test probability of approximately 100% (diagnostic accuracy).

We should also point out the factors that can influence the results of the examination, thus producing false negative results, such as: technique and place of collection, time of onset of symptoms, storage and transportation of the sample to the location of the examination.

Synthesis of evidence

The PCR technique for coronavirus diagnosis provides a sensitivity of 86% and specificity of 96%; however, it should be applied in contexts of a high prevalence of coronavirus infection (not specific of SARS-Cov-2). When there is uncertainty regarding the diagnosis, a second sample collection can be indicated to confirm the diagnosis. Moderate quality of evidence.

ANNEXES

TABLE 1. STUDIES EXCLUDED AND REASON

Study and year	PMID	Reason for exclusion
1. Long C 2020	32229322	Comparison between CT and RT-PCR
2. Yan C 2020	32276116	Comparison between PCR techniques
3. Fang Y 2020	32073353	Comparison between CT and RT-PCR
4. Shirato k 2018	29763640	Comparison between PCR techniques
5. Pas SD 2015	26209385	Absent specificity data
6. Shirato K 2014	25103205	Absent specificity data
7. Cho CH 2014	24582583	Absent specificity data
8. Cho CH 2013	23743345	Absent specificity data
9. Corman VM 2012	23041020	Absent specificity data

TABLE 2. DESCRIPTION OF THE CLINICAL CHARACTERISTICS OF THE STUDIES INCLUDED.

Studies	PMID	DESIGN	POPULATION	TEST	COMPARISON
Huh HJ 2017	28840986	Cross-sectional	100 samples were analyzed (90 sputum, 10 NF swabs), collected from 100 different patients between June and July 2015. 50 samples were from patients with clinical suspicion of SARS and 50 asymptomatic ones.	rRT-PCR	Nested RT-PCR and sequencing of the RNA polymerase gene (RdRp) and N.
Huh HJ 2017	27834073	Cross-sectional	5,330 samples of 3,484 patients with suspected SARS-CoV were analyzed (4291 sputum, 145 AT, 732 NF, 35 OF, 62 NF and OF, and 65 others).	Real-time RT-PCR upE and ORF1a	Different locations of sample collection
Go YY 2017	28807812	Cross-sectional	Total of 55 samples collected from 20 patients positive for MERS, in 2015. Sputum collection. 48 samples of control individuals. Sensitivity analysis of the ORF1a and upE gene sequence.	RT-qPCR	RT-qPCR
Lee JS 2017	28566313	Cross-sectional	Total of 55 samples collected from 20 patients positive for MERS, in 2015. Sputum collection. 48 samples of control individuals. Sensitivity analysis of the ORF1a and upE gene sequence.	rRT-PCR	MagNA Pure 96 RNA extraction kit
Yam WC 2005	15797361	Cross-sectional	Patients with clinical suspicion of SARS. 54 NF samples collected and 10 OF by swab	rRT-PCR	Conventional PCR
Wang H 2004	15229153	Cross-sectional	44 patients with SARS admitted and diagnosed based on the WHO definition were selected	RT-PCR	Serological conversion
Poon LL 2004	15135737	Cross-sectional	Extraído 86 amostras de aspirados nasofaríngeos de pacientes que apresentaram diagnóstico clínico de SARS, com evidência sorológica de infecção por SARS-CoV	1- One step quantitative RT-PCR (monoplex)	Serological conversion

Studies	PMID	DESIGN	POPULATION	TEST	COMPARISON
Mahony JB 2004	15070991	Cross-sectional	17 NF/OF samples collected from patients with probable SARS between March and April 2003, in Toronto, Canada.	Seven types of reverse transcription-PCR (RT-PCR) tests - 3 conventional and 4 real-time	Culture of virus
Emery SL 2004	15030703	Cross-sectional	Total of 340 samples by nasal and oral swab, from 246 people with confirmed or suspected infection by SARS-CoV.	TaqMan real-time RT-PCR	Culture of virus
Poon LL 2003	12765993	Cross-sectional	29 patients selected (29 samples) with SARS and infections confirmed clinically and serologically, in Hong Kong, between February and March 2003.	Conventional RT-PCR	Patients with clinical and serological diagnosis
Yam WC 2003	14532176	Cross-sectional	124 NF and 65 OF samples collected from 163 patients hospitalized, in Hong Kong, between February and April 2003, with clinical suspicion of SARS, based on the WHO criteria.	RT-PCR - Evaluating two first-generation reverse transcription tests (WHO-HKU and WHO-Hamburg RT-PCR assays)	Serological conversion
Wu X 2003	12890368	Cross-sectional	97 samples (67 from patients with SARS e 30 from healthy individuals)	RT-PCR	Healthy vs. diseased samples
Poon LL 2003	14522060	Cross-sectional	50 patients with a clinical diagnosis of SARS were included, based on the WHO criteria, with a subsequent serological confirmation. 50 NF samples collected 1-3 days after symptom onset	Real-time RT-PCR in serum and nasopharyngeal aspirate samples	NF samples from healthy individuals and patients who presented other viruses were considered negative controls.

NF = nasopharynx, OF = oropharynx, PCR = polymerase chain reaction, RT-PCR= real-time PCR, WHO= World Health Organization.

TABLE 3. RESULTS EXTRACTED FROM THE STUDIES INCLUDED.

RT-PCR results - COVID				
Studies	PMID	DESIGN	Sensit.	Specif.
Huh HJ 2017	28840986	Cross-sectional	0.95	0.95
Go YY 2017	28807812	Cross-sectional	0.96	0.95
Lee JS 2017	28566313	Cross-sectional	0.96	0.98
Huh HJ 2017	27834073	Cross-sectional	0.95	0.95
Yam WC 2005	15797361	Cross-sectional	0.85	0.95
Wang H 2004	15229153	Cross-sectional	0.80	0.95
Poon LL 2004	15135737	Cross-sectional	0.86	0.95
Mahony JB 2004	15070991	Cross-sectional	0.83	0.94
Emery SL 2004	15030703	Cross-sectional	0.95	0.95
Poon LL 2003	12765993	Cross-sectional	0.79	0.98
Yam WC 2003	14532176	Cross-sectional	0.72	0.95
Wu X 2003	12890368	Cross-sectional	0.73	0.95
Poon LL 2003	14522060	Cross-sectional	0.80	0.98

FIGURE 7. FLOWCHART – THE SELECTION OF RETRIEVED FROM THE VIRTUAL DATABASES OF SCIENTIFIC INFORMATION IS DETAILED IN THE FLOWCHART BELOW:

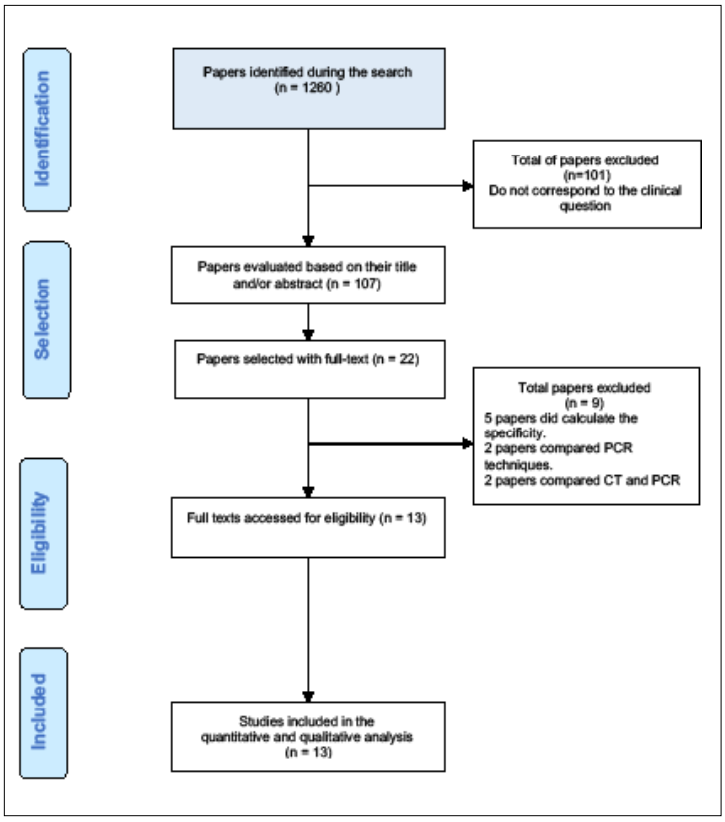


TABLE 4. RISK OF BIAS ASSESSED BY QUADAS-2

		Papers →	Go 2017	Lee 2017	Huh HJ 2017(1)	Huh HJ 2017(2)	Yam 2005	Wang 2004	Poon 2004	Mahony 2004	Emery 2004	Poon 2003(1)	Yam 2003	Wu X 2003	Poon LL 2003(2)
	Criteria of biases ↓														
Patient selection	Guiding questions	Was there consecutive or random sampling?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	uncertain	uncertain
		Was a case-control design avoided?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
		Were inappropriate exclusions avoided?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Risk of bias	Is it possible that patient selection introduced a bias?	low	low	low	low	low	low	low	low	low	low	low	low	Uncertain
		Are there concerns that the patients included do not correspond to the question of the review?	low	low	low	low	low	low	low	low	low	low	low	low	low
Test evaluated	Guiding questions	Were the index test results interpreted without knowledge of the results of the reference test?	yes	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	no
		If a threshold was used, was it predetermined?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no
	Risk of bias	Is it possible that the conduction or interpretation of the reference test introduced a bias?	low	low	low	Low	low	low	low	low	low	low	low	uncertain	High
	Concerns about the applicability	Are there concerns that the conduction or interpretation of the index test differ from the review question?	low	low	low	high	low	low	low	low	low	low	low	low	Low
Reference test	Guiding questions	Does the reference test likely correctly classifies the target clinical condition?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	uncertain
		Were the reference test results interpreted without knowledge of the results of the index test?	yes	yes	yes	no	yes	no	no	no	no	no	no	uncertain	no
	Risk of bias	Could the reference standard, its conduction or interpretation, introduce a bias?	low	low	low	Low	low	low	low	low	low	low	low	low	High
	Concerns about the applicability	Is there concern that the target condition, as defined by the reference test, does not correspond to the definition in the research question?	low	low	low	Low	low	low	low	low	low	low	low	low	uncertain
Flow and time	Guiding questions	Was there an appropriate interval between the index and the reference tests?	yes	yes	yes	I	yes	yes	yes	yes	yes	yes	yes	uncertain	uncertain
		Did all patients receive a reference standard?	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	uncertain	yes
		Did all patients receive the same reference test?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	uncertain	uncertain
		Were all patients included in the analysis?	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Risk of bias	Is it possible that patient flow introduced a bias?	low	low	low	low	low	low	low	low	low	low	low	low	uncertain

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Multiple lidocaine infusions for relief of neuropathic pain: systematic review and meta-analysis

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QUESTION: The clinical question is: What is the impact of therapy with multiple infusions of lidocaine on outcomes of pain relief for up to four weeks and adverse events in the treatment of patients with neuropathic pain, compared with a placebo?[1]

Answer: In patients with neuropathic pain, infused lidocaine once a week, for 4 weeks, compared with a placebo (saline solution 0.9%) showed no difference in pain reduction in up to 4 weeks. Moderate quality of evidence. Intravenous lidocaine increases the risk of adverse events (any) in 25% (95% CI 18 to 31%) in comparison with a placebo (saline solution 0.9%), and it is necessary to treat 4 patients for one to present an adverse event (95% CI 3 to 6). Low quality of evidence. Dizziness, drowsiness, perioral paresthesia, nausea, headache, dysarthria, dry mouth, metallic taste are some of the most common side effects.

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SPECIAL ISSUE ARTICLE

Strategic plan for the management of COVID-19 in an obstetrics department

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KEYWORDS: *Pregnant women. Coronavirus Infections. Obstetrics and Gynecology Department, Hospital.*

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has developed into a worldwide crisis for this generation[1]. In March 2020, the World Health Organization (WHO) declared the COVID-19 to be a world pandemic. Up to May 20, a total of 4,904,805 people had been confirmed to be affected by COVID-19, and 320,474 people have died from this crisis[2].

Pregnant women are vulnerable during infectious disease outbreaks due to their special physiological state[3]. Because of physiological changes in the immune and cardiopulmonary systems, pregnant women are more likely to develop severe illness after respiratory infection[4]. According to previous research, SARS-CoV and MERS-CoV (highly homologous to SARS-CoV-2) are both known to be responsible for severe complications during pregnancy, including the need for endotracheal intubation, admission to an intensive care unit (ICU), renal failure, and death[5]. Up to now, no study showed that pregnant women are more likely to be infected with COVID-19, and pregnancy outcomes are worse in diagnosed patients, and interrelated research is very inadequate[6]. Other than the maternal adverse effects of COVID-19, its potential impact on fetal and neonatal outcomes has not been ruled out either. Therefore, standard procedures are urgently needed to avoid hospital-related infection and guide the management of pregnant patients. Here, we proposed a strategic plan for the management of COVID-19 outbreaks in Obstetrics Departments, primarily focusing on the prevention and control strategies of viral infection.

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EDUCATION

Medical staff should be kept up to date with the latest information about COVID-19 on pregnant women (clinical features, complications, diagnosis, therapies, maternal and fetal outcomes, etc.). Education about COVID-19 is needed for pregnant patients and their caregivers. Patient education should include methods and timing of hand hygiene, respiratory hygiene, coughing etiquette, selection and use of mask, the transmission routes and clinical manifestations of COVID-19, and patients should be advised to stay at home and avoid densely populated areas. Besides, pregnant women should be informed to seek medical advice in case of fever, cough, weak, dyspnea. Mothers and carers should be educated in the selection and use of personal protective equipment (PPE), and how to put it on and take it off correctly.

Establishing a COVID-19 expert committee

A COVID-19 expert committee should be established in medical institutions for decision-making in multidisciplinary consultation meetings. Committee members should include: an obstetrician, respiratory physicians, infectious disease physicians, physicians from ICU, radiologists, clinical pharmacists, and medical staff from hospital infection-control departments.

Regional management strategy

To prevent cross-infection in the hospital, a regional management strategy should be used. Both employee and patient channels need to be built. Meanwhile, medical staff should wear gowns, masks, hats, and medical latex gloves when in contact with patients in the outpatient department or wards. Pre-examination and triage should be done in the entrance of the patient channel, and a special channel needs to be built for the transportation of patients with a suspicious epidemiological history or related symptoms.

Four zones should be created in the hospital to prevent cross-infection and to screen potentially infected patients. Medical staff and patients are not allowed to enter other zones without permission. Zone 1 (surveillance and screening) is for surveilling and screening subjects who are viewed by a expert as a patient potentially infected with SARS-CoV-2; each patient is isolated in a single room. Zone 2 (suspected quarantine) is for the suspected cases of COVID-19; each patient is isolated in a single room. Zone 3 (COVID-19 confirmed quarantine) is for confirmed COVID-19 cases. If the hospital does not have the necessary conditions to receive confirmed patients, then patients should be transferred immediately to specialized hospitals with the capacity for treatment. Zone 4 (obstetric ward) is for pregnant patients who do not have COVID-19. Personal protective equipment (PPE) should be provided in all zones, such as gowns, masks, eye shields, gloves, shoe covers, and hats. The printed procedures should be posted up in the workplace to remind the medical staff of when and how to use PPE.

Antenatal care management

Intrauterine pregnancy confirmation and antenatal care are essential for pregnant women. But we should reduce hospital visits and cancel part of the check-ups to avoid further spread of the epidemic. Patients need to connect with an obstetrician online first, and then determine whether it is necessary to cancel the hospital visit and routine check-up during pregnancy. Based on complications, clinical manifestation, adverse pregnancy history, and other risk factors, the obstetrician should give their expert advice on a hospital visit and routine check-up. The following check-ups are recommended: 1) in the first trimester, ultrasonographic examination to confirm pregnancy after 6 weeks of amenorrhea is advised. Ultrasonographic examination of the nuchal translucency (NT) along with blood pressure, fasting plasma glucose, ECG, ABO, and Rh blood group test, blood routine examination, routine urine test, and fetal heart rate monitoring are advised to be done in one visit between 11 to 13 weeks and 6 days of gestation; 2) in the second trimester, down's syndrome prenatal screening or non-invasive prenatal testing (NIPT) from cell-free fetal DNA are recommended to be done between 16 and 16+6 gestational weeks. Oral glucose tolerance testing (OGTT) along with fetal congenital malformations screening (by four-dimensional color Doppler ultrasound combined with system-B ultrasound) should be done in one visit between 24 to 24+6 weeks; 3) in the third trimester, a routine visit every 2 weeks should be changed to 3 weeks. Ultrasonographic examination and Group B streptococci (GBS) test are recommended to be done in one visit between 30 to 32 weeks and another visit between 35 to 37 weeks; 4) Fetal heart rate monitoring is advised, which can be done at home if rental remote monitoring device is available; 5) Certain surveillances such as measurement of uterine height, abdominal circumference, weight, fetal movement, and blood pressure can be done at home or a nearby community hospital. These measures are agreed with

recommendations given by specialists from Sichuan province[7]. Articles and courses about self-monitoring, pregnancy management, and check-up plan should be provided online. However, more frequent visits are required when there are pregnancy complications (such as gemellary pregnancy, pregnancy-induced hypertension, intrahepatic cholestasis during pregnancy, etc.).

Admission procedure for pregnant patients

Outpatient patients to the obstetrics department should make an appointment online (or by phone) and consult a obstetrician before admission, obstetricians should assess their clinical manifestations and risks by online consultation to reduce unnecessary hospital admissions. Pre-examination and triage staff are asked to screen epidemiological history, record symptoms, and test the temperature for all patients visiting hospitals. Patients with positive epidemiological history, fever, cough, or other respiratory symptoms should be directly transferred to the specific fever clinic (through special channels aforementioned) and assessed by diagnostic criteria[8]. For patients who need hospitalization, epidemiological and clinical assessments need to be repeated by obstetricians to pass the COVID-19 screening process, unless it is an emergency situation[9]. The detailed admission procedures are shown in Figure 1. After admission to hospital, only one caregiver is allowed and asked not to leave the hospital during hospitalization. Other people are not allowed to enter the obstetrics department without permission. Respiratory symptoms and body temperature need to be monitored daily. A blood routine examination is advised for all pregnant patients. Patient education about how to wash hands, wear a mask, and cough are emphasized again after admission.

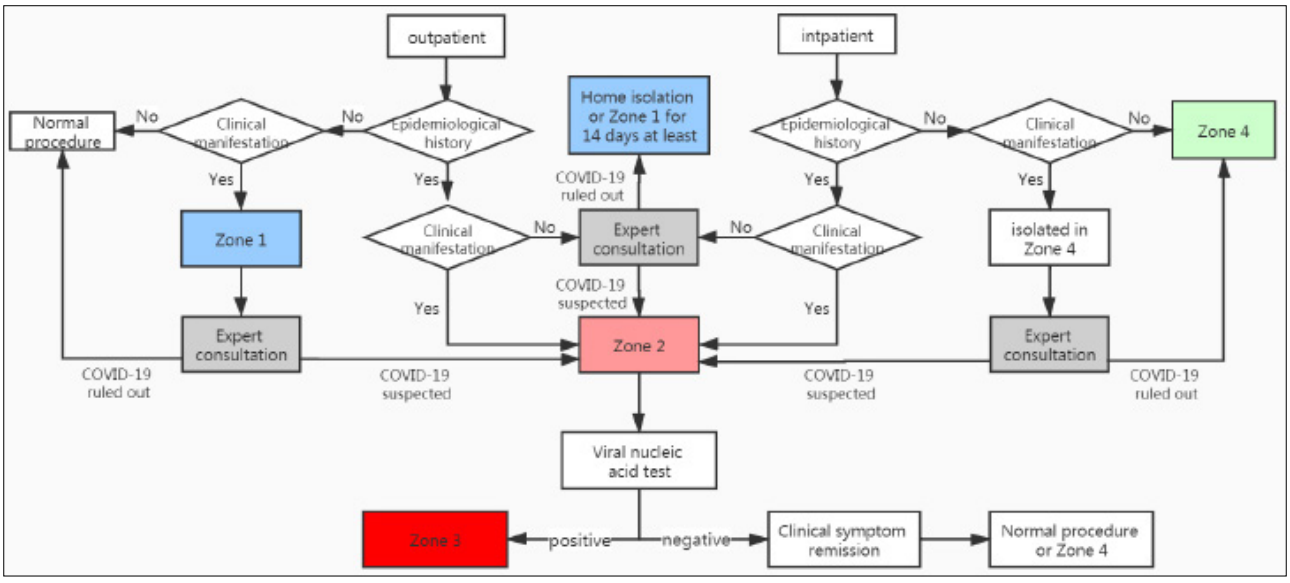
Patients who need hospitalization but whose possibility of infection is not ruled out yet should be isolated in a single bed ward (zone 1 or zone 2). Viral nucleic acid test (nasopharyngeal swab, RT-PCR) and CT scans (CT scans is just for patients from zone 2) need to be done for further confirmation.

Emergency patients (such as vaginal bleeding, premature rupture of membranes, parturition, fetal distress) could be referred directly to the obstetrics department. The COVID-19 screening process needs to be finished after admission. Before ruling out the infection, patients should be treated as a suspected case. In some cases, delivery or surgery needs to be performed immediately before ruling out the infection, then the special isolation delivery or operating rooms are needed. If possible, aerosol-generating procedures, such as general anesthesia with tracheal intubation, should be avoided during surgeries. All recyclable devices should be sterilized after contact with such cases, and standardized protection should be performed just like it is done for the confirmed patients.

Management of childbirth of suspected/confirmed patients

The special isolation delivery room (operating room) equipped with newborn rescue equipment (including neonatal incubator) is needed for suspected/confirmed patients, and the distance between

FIGURE 1



the delivery bed and newborn rescue equipment should be 2 meters at least. A plan for the intrahospital transport channel (elevator) should be made in advance. If possible consumable medical material should be used. At the time of delivery, the obstetrician should notify the newborn pediatrician to come to the operating room (delivery room) in advance to ensure that there is sufficient time for the newborn pediatrician to complete protective preparations. Medical personnel should strictly implement the hand hygiene and three-level protective measures (disposable cap, protective face shield or positive pressure headgear, goggles, medical protective mask, disposable coverall protective clothing, medical rubber gloves, and disposable shoe covers). Doctors should cut the umbilical cord as soon as possible after delivery and reduce close contact with the mother. After delivery, the puerpera should be transferred to the quarantine ward. Neonates would be quarantined in the neonatal quarantine observation ward and transported using a special neonatal incubator. Breastfeeding should be postponed until the possibility of infection is ruled out or the infection is cured. The neonatal quarantine observation period is recommended to be more than 14 days. All reusable devices, operating room (delivery room), and intrahospital transport channel should be sterilized after contact with such patients, and all medical and domestic waste should be disposed of as infectious waste.

On the basis of this management strategy, no SARS-CoV-2 infections happened in our obstetrics departments. However, the success of this strategy depends on sufficient medical resources and healthcare settings to some extent. Our recommendations should be updated continuously with accumulated clinical evidence and the increase in knowledge about COVID-19 over time.

Author's Contribution

All the authors conform with the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the paper, and gave approval for the final version. Bo Wu, Ying Pu, Han Wang contributed to the writing and editing of the paper.

Conflict of interest

The authors declare there are no conflicts of interest.

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PALAVRAS-CHAVE: *Gestantes. Infecções por Coronavirus. Unidade Hospitalar de Ginecologia e Obstetrícia.*

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Role of a Neonatal Intensive Care Unit during the COVID-19 Pandemia: recommendations from the neonatology discipline

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SUMMARY

On 11th March 2020, the World Health Organization (WHO) declared the COVID-19 a pandemic. The Obstetrics and Neonatology disciplines needed to be revised to suit the institutional need to expand intensive care beds to care for confirmed or suspected patients with COVID-19 in the state of São Paulo, following the recommendations of the Institutional Crisis Committee. Three different actions were needed: the structuring of teams and advanced medical post to attend COVID-19-free patients and those with suspect or confirmed COVID-19; elaborating the protocols from the delivery room throughout hospitalization. Some special considerations about breastfeeding and rooming-in were needed. The third action was the drafting of a protocol to admit infants from other hospitals with confirmed COVID-19 as the unit never admitted outpatients before.

KEYWORDS: *Coronavirus Infections. Intensive Care Units, Neonatal. Breastfeeding. Delivery rooms.*

INTRODUCTION

Since December 2019, cases of pneumonia have been reported in Wuhan, China caused by a new coronavirus, later called SARS-CoV-2 (Severe Acute Respiratory Syndrome by Coronavirus 2)[1]. The disease called COVID-19 (Coronavirus Infectious Disease -2019) spread in China and, a few months later, it had reached more than 23 countries worldwide. On March 11, 2020, the World Health Organization (WHO) declared a pandemic situation[2]. The Obstetrics and Neonatology disciplines needed to be revised to suit the institutional need to expand intensive care beds to care for confirmed or suspected patients with COVID-19 in the state of São Paulo, following the recommendations of the Institutional Crisis Committee.

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Structuring of teams and advanced medical post:

The first step consisted of discharging all patients eligible for discharge or transfer to other units able to attend them. Simultaneously, 14 beds at the Neonatal Intensive Care Unit (NICU) and 8 beds of intermediate care at the University Hospital were installed. The Neonatal Center sent equipment, materials, and supplies to facilitate the operation of the advanced medical post. Employees were also sent: doctors (13), nursing professionals (30), physiotherapists (6), a nutritionist (1), a social worker (1), and a psychologist (1).

Twelve doctors, thirty-two nursing professionals, six physiotherapists, a nutritionist, and a social worker remained to attend newborn (NB) babies, at the delivery room, of pregnant women with suspected or confirmed COVID and infants weighing up to 6 kg with confirmed COVID admitted at the Emergency Room (ER) or at another hospital.

The neonatology discipline revised its protocols and internal flows to adapt to the new demand.

SERVICE FLOWCHART FROM THE DELIVERY ROOM TO THE NICU

Delivery room:

Considering that the disease affects individuals of all ages but seems to be less severe in children[3] and that there has not yet been evidence of vertical transmission of the virus[4,5], the discipline suggests that:

- all NB of pregnant women with a flu-like syndrome at the time of delivery or who have confirmation of COVID-19 are considered a suspected case for 14 days before delivery up to 28 days after it[6].
- precautions should prevent the NB from becoming contaminated after birth and also prevent the contamination by health professionals, if there is manipulation of the airways[7].
- in the delivery room, the most experienced pediatrician is responsible for resuscitation, following all recommendations regarding the use of PPE (disposable long-sleeve waterproof apron, gloves, hat, N95 or FP2 mask, and face shield).
- Skin-to-skin contact and breastfeeding in the first hour are suspended for the duration of the pandemic.
- HEPA filter (High-Efficiency Particular Air) between the mask to be attached to the NB, in case it is necessary to perform positive pressure ventilation (PPV) and the device employed (self-inflating balloon or manual T-shaped mechanical ventilator)[7].

The NB will be transported in a transport incubator to the admission sector with the team in full attire.

Procedures during Hospitalization:

Since the beginning of the pandemic, the wing dedicated to rooming-in has been disabled for this purpose, making it impossible to keep the dyad together during hospitalization. *Rooming-in is not contraindicated* as long as the mother is able to remain in the infirmary and receives guidelines for cough etiquette, proper hand hygiene before handling the newborn, and wears a surgical mask that must be changed if wet or as instructed by the manufacturer. Puerperal women diagnosed with COVID-19 must stay in a private room, and the presence of a single, healthy companion without home contact with COVID-19 and under 60 years old is possible. There is no evidence of the presence of viruses in human milk to date. The benefits of breastfeeding outweigh the risks of SARS-CoV-2 transmission, and breastfeeding should be encouraged and encouraged[6,8,9].

However, just as the neonatology team was divided to meet the needs for assistance at the Clinics Hospital and at the University Hospital outpost, the obstetrics team suffered the same division. Thus, for operational reasons, rooming-in could not be maintained, and the separation of the dyad is necessary. The admission of mothers and newborns in different places is a consequence that was not foreseen at first and that may have uncalculable repercussions in breastfeeding[10].

All newborns born in the complex are therefore admitted to the Neonatal Intensive Care Center and separated according to the mother's diagnosis.

In *Room 1*, there are the newborns whose *mothers have confirmed COVID-19*, with their own air conditioning system, with double filter. The search for SARS-CoV-2 by RT-PCR (Reverse Transcription Polymerase Chain Reaction) in tracheal secretion (when intubated) or oropharyngeal swab will be performed with 48 hours of life.

In *Rooms 4 and 5*, the NB whose mothers await the results of the SARS-CoV-2 survey are admitted, with a separate air conditioning system. When the diagnosis is ruled out, if the NB is more than 48 hours

old and is healthy and all routines are complete, they will be discharged home or if there is any need for hospitalization, they will be sent to a COVID free unit. SARS-CoV-2 research will not be performed on these patients

NB should receive the care indicated for gestational age and the most prevalent diseases of this age group, and the treatment chosen must respect these characteristics. In view of the lack of knowledge of characteristic symptoms of COVID-19 in the neonatal period, newborns must be evaluated and treated as usual without running the risk of committing iatrogenesis. Respiratory insufficiencies in the neonatal period can be due to many diseases such as meconium aspiration syndrome, transient tachypnea, respiratory distress syndrome, and pneumonia for example. It is important that the neonatologist indicates the treatment that they consider most appropriate for their patient[11]. At the same time, it is equally important to be alert to unusual signs and symptoms that the NB may experience.

If there is confirmation of the presence of SARS-CoV-2 in the newborn, they will be transferred to a room with anteroom in contact isolation and aerosols or droplets depending on the severity of the condition or procedure to be performed.

The Neonatal Center is located inside a hospital dedicated to the care of patients with COVID-19 exclusively, so there is no transit of visits in the building, and the circulation of mothers with SARS-CoV-2 in the unit is not possible due to the risk contamination of newborns whose research is negative. Daily, the medical team contacts the mothers and/or another responsible person designated by the family to give news about the newborn.

Outpatients diagnosed with COVID-19

Community transmission of SARS-CoV-2 in the municipality of São Paulo has already been identified and, since March 24, 2020, quarantine has been instituted with the closure of activities not considered essential, suspension of classes, and social distancing. Despite the imposition of these measures, new cases have still emerged. The horizontal transmission maintenance reflects some social aspects not calculated. Some families, despite respecting the recommendations, live in crowded small houses with many people sharing the environment, facilitating the contamination of everyone including newborns.

External NB who have been admitted to the NICU so far had fever, tachypnea, nasal obstruction, usually with good saturation. The respiratory condition was not always the most relevant, and fever without source (FWS) was a possible diagnosis on arrival at the hospital.

Patients with flu syndrome:

- collect viral panel to search for respiratory syncytial virus, H1N1, influenza A
- RT-PCR (Reverse-transcriptase-polymerase chain reaction) for SARS-CoV-2
- X-ray (X-ray) of the chest
- Chest ultrasound (US).
- Discuss chest CT indication
- Initially, the patient should receive oseltamivir until the etiology of the viral condition is established. If the H1N1 test is negative, the medication may be stopped.

Fever without source (FWS) with identification of caregiver or resident with flu syndrome or diagnosis of COVID-19:

- collect viral panel to search for respiratory syncytial virus, H1N1, influenza A
- RT-PCR for SARS-CoV-2
- Blood count with platelets
- C-Reactive Protein (PCR)
- Blood culture (HMC)
- Urine 1
- Uroculture (URC)
- Liquor.
- Chest X-ray
- Assess need for chest US
- If there are no respiratory symptoms suggestive of flu, it is not necessary to introduce oseltamivir.
- Introduction of antibiotics to cover FWS/late neonatal sepsis according to the patient's age. Antibiotic therapy should be suspended if a bacterial infection is ruled out.

In both situations, if there is a diagnostic confirmation of COVID-19, collect creatine phosphokinase (CPK), troponin, d-dimer, and fibrinogen levels.

The chest tomography will be performed during hospitalization according to clinical evaluation, and new tests will be indicated according to the patient's clinical evolution. The NB will be hospitalized at least until the seventh day after the onset of symptoms, and that period may be extended for up to 14 days

depending on the evolution. During the stay in the hospital, visits from the asymptomatic mother will be allowed in the afternoon and the human milk collection room can perform the extraction of breast milk to offer to the child during her absence. The collection room is equipped and prepared according to the guidelines of the Ministry of Health[11,12].

Conflicts of Interest

The authors declare no conflicts of interest.

RESUMO

PALAVRAS-CHAVE: *Infecções por Coronavirus. Unidades de Terapia Intensiva Neonatal. Aleitamento Materno. Salas de Parto.*

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Expression of long noncoding RNA NBAT1 is associated with the outcome of patients with non-small cell lung cancer

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SUMMARY

OBJECTIVE: *Long noncoding RNA neuroblastoma-associated transcript 1 (NBAT1) has been reported to be involved in cancer progression. However, the clinical significance of NBAT1 in non-small cell lung cancer (NSCLC) is still unclear. Our present research aimed to explore whether NBAT1 serves as a biomarker for NSCLC prognosis.*

METHODS: *The expression of NBAT1 was examined by RT-PCR in tissue samples of 162 NSCLC patients and was compared with the adjacent non-tumor lung specimens. Then the association between NBAT1 expression and clinical-pathological parameters was further evaluated. Survival analysis was performed using the Kaplan-Meier method. The prognostic significance of NBAT1 expression in NSCLC patients was explored by the use of univariate and multivariate analyses.*

RESULTS: *NBAT1 expression was prominently decreased in NSCLC tissues compared with matched normal lung specimens ($p < 0.01$). Moreover, survival analyses indicated that patients with low expression displayed dramatically decreased 5-year overall survival ($p = 0.008$).*

CONCLUSIONS: *NBAT1 expression might contribute to tumor progression and poor prognosis of NSCLC and might be a new therapeutic target in NSCLC.*

KEYWORDS: *Prognosis. Carcinoma, non-small-cell lung. RNA long noncoding.*

INTRODUCTION

Lung cancer has been the leading cause of cancer-associated deaths both in men and women around the world for the past decades, accounting for about 13% (1.8 million) of total cancer diagnoses in 2012[1,2]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers[3]. CT perfusion can be used as an index for predicting mediastinal lymph node metastasis of lung cancer[4]. In China, the total number of deaths annually is around half a million. Therefore, NSCLC has posed a serious threat to public health[5].

Long noncoding RNAs (lncRNAs) have been identified as a subclass of ncRNAs with a length of >200 nucleotides that are unlikely to be translated into proteins due to a lack of an open-reading frame[6,7].

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Growing evidence has demonstrated that lncRNAs are involved in transcriptional, translational, and epigenetic regulation[8]. It has been identified that lncRNAs play a crucial role in several cellular processes, including cell development, growth, differentiation, invasion, and apoptosis[9,10]. The newly identified lncRNAs display specimen-specific expression patterns. Recently, growing studies report that lncRNAs play indispensable roles in several biological progressions involved in the pathogenesis of various cancers, such as proliferation and apoptosis in cervical cancer, liver cancer, NSCLC and so on, by functioning as oncogenes, tumor suppressor genes or both, depending on the conditions[11-13]. The frequent dysregulation of critical lncRNAs and their important biological function in tumors highlighted the clinical application of lncRNAs as a novel clinical tool for the diagnosis and prognosis of NSCLC patients[14,15]. Although more and more lncRNAs have been identified to have the capability to serve as a novel biomarker, due to the tremendous amount of lncRNAs, many remain to be elucidated.

LncRNA neuroblastoma associated transcript 1 (NBAT1), also known as CASC14, was located at 6p22.3 and was initially identified to be dysregulated in neuroblastoma[16]. Then, several studies reported that NBAT1 expression was down-regulated in several tumors, such as bladder cancer, glioblastoma, osteosarcoma[17-19]. In addition, both *in vitro* and *in vivo* assays confirmed the tumor-suppressive roles of NBAT1 in the above tumors. Of note, a recent study by Zheng et al.[20] firstly reported that NBAT1 may be lowly expressed in NSCLC cells, and its overexpression could inhibit tumor progress by inhibiting autophagy in NSCLC. However, the clinical significance of NBAT1 in NSCLC remained to be further demonstrated.

In this study, we provide the first clinical evidence that NBAT1 may act as a potential prognostic biomarker for NSCLC patients.

METHODS

Patients and Specimens

NSCLC tissues and normal specimens of the lung were obtained from patients who had undergone surgery at the First People's Hospital of Jinan, between 2010 and 2013. All patients included in our clinical assays were diagnosed with NSCLC by two pathologists based on histopathological evaluation. All the above specimens were flash-frozen in liquid nitrogen immediately after resection and stored at -80°C for further RT-PCR experiments. Patients who experienced any of the following conditions were excluded: recurrent NSCLC; undergoing immune inhibitive treatments; with other serious diseases. Clinical information of all NSCLC patients was available. The overall survival was defined as the time from surgery to death. The clinicopathological features of all patients are presented in Table I. Informed consent was obtained from each patient, and all of the experiments were approved by the ethics committee of the institute.

RNA preparation and quantitative RT-PCR

Total RNA was extracted from tumor specimens and matched non-neoplasm specimens using Trizol reagent (Life Technologies Corporation, Zhejiang, Hangzhou, China). First-strand cDNA was generated using the Reverse EasyScript One-Step gDNA

TABLE1. CORRELATION BETWEEN THE EXPRESSION OF NBAT1 AND CLINICOPATHOLOGICAL

Clinicopathological parameters	N of cases	NBAT1 expression		p-value
		High	Low	
Age(years)				NS
≥65	87	46	41	
<65	75	34	41	
Gender				NS
Male	104	50	54	
Female	58	30	28	
Differentiation				NS
Well, moderate	58	33	25	
Poor	104	47	57	
Tumor size				NS
≥4 cm	49	29	20	
<4 cm	113	51	62	
Primary location				NS
Left lung	76	41	35	
Right lung	86	39	47	
Histology type				NS
Adenocarcinoma	114	58	56	
Squamous carcinoma	48	22	26	
Smoking history				NS
Smokers	81	43	38	
Never smoked	81	37	44	
Lymph node metastasis				0.010
Positive	52	18	34	
Negative	110	62	58	
TMN stage				0.005
I	60	21	39	
II/III	102	59	43	

features of NSCLC patients (n=162).

Removal and cDNA Synthesis SuperMix (TaKaRa, Dalian, Liaoning, China). NBAT1 expressions were assessed applying RT-PCR with SYBR Premixe Ex Taq (TaKaRa, Dalian, Liaoning, China) and 7500 real-time PCR system (Applied Biosystems, Kunming, Yunan, China). The sequences of the primers were as follows:
NBAT1: forward ACTGAAACCCACAGAGATGAAG,
NBAT1: reverse CCCGTCATGTAGAGCAATATCC,
GAPDH: forward GGAGCGAGATCCCTCCAAAAT,
GAPDH: reverse GGCTGTTGTCATACTTCTCATGG.

Real-time RTPCR reactions were performed by the ABI7500 system (Applied Biosystems, Kunming, Yunan, China). All experiments for NBAT1 examination were performed in triplicate. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control. The relative expressing levels of NBAT1 was calculated by the use of the $2^{-\Delta\Delta Ct}$ methods.

Statistical analysis

The statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). The NBAT1 expression levels in NSCLC were compared with those in adjacent non-tumor specimens with the use of the Wilcoxon test. A χ^2 test or Fisher's exact test was applied to determine the association between NBAT1 level and clinical characteristics. Survival curves were constructed with the Kaplan-Meier method and compared by the log-rank test. For further identifying the potential independent

TABLE 2. UNIVARIATE AND MULTIVARIATE ANALYSES FOR OVERALL SURVIVAL BY COX REGRESSION MODEL.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.642	0.447-2.514	0.445	-	-	-
Gender	1.437	0.764-2.321	0.231	-	-	-
Differentiation	1.854	0.652-2.554	0.164	-	-	-
Tumor size	2.213	0.894-2.664	0.108	-	-	-
Primary location	1.885	0.752-2.441	0.113	-	-	-
Histology type	1.543	0.654-2.231	0.156	-	-	-
Smoking history	1.364	1.047-1.986	0.136	-	-	-
Lymph node metastasis	3.465	1.447-5.764	0.004	3.174	1.194-4.776	0.011
TMN stage	3.572	1.539-5.127	0.007	3.048	1.238-4.476	0.015
NBAT1 expression	3.374	1.429-4.775	0.009	2.947	1.184-4.369	0.014

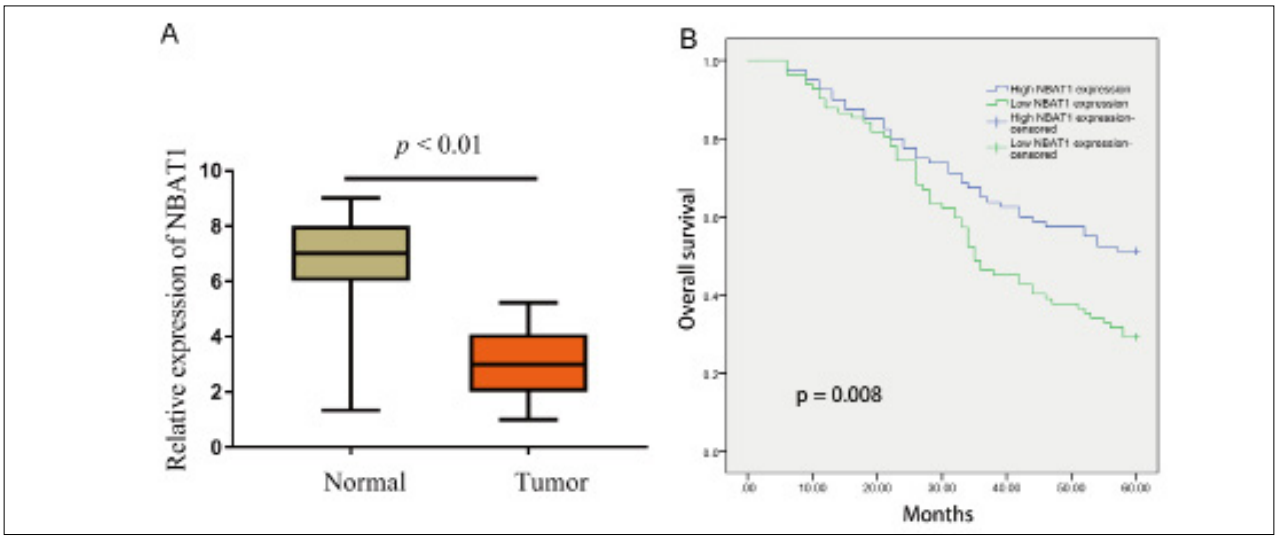

FIGURE 1. NBAT1 OVEREXPRESSION PREDICTS A POOR PROGNOSIS IN NSCLC PATIENTS.
(A) Expression levels of NBAT1 in NSCLC and adjacent non-cancerous tissues. The expression level of NBAT1 was significantly higher in NSCLC tissues than in adjacent noncancerous tissues ($p < 0.01$). (B) The association between patient survival and NBAT1 expression was estimated using the Kaplan-Meier method and the log-rank test ($p = 0.008$).

prognostic factors, the Cox proportional hazard regression model was performed. A *p*-value of less than 0.05 was considered significant.

RESULTS

Reduced expression of NBAT1 is confirmed in NSCLC

To explore whether NBAT1 could be a functional factor in NSCLC, our group secured 162 pairs of NSCLC specimens and matched non-neoplasm tissues and carried out qRT-PCR. As shown in Figure1A, quantitative data revealed that the levels of NBAT1 in NSCLC tissues were prominently lower than those in matched non-neoplasm specimens ($p < 0.01$). Our results were consistent with a previous study by Zheng et al.[20].

Association of NBAT1 expression with clinicopathological characteristics of NSCLC patients

To further understand whether the down-regulation of NBAT1 may influence the clinical progress of NSCLC patients, we divided the 162 NSCLC patients into a high expression group (n = 80) and a low expression group (n = 82) using the mean level of NBAT1 as a reference. The association between clinicopathological characteristics and NBAT1 expression is shown in Table1. The results of the chi-square test showed that a low NBAT1 level was also significantly associated with lymph node metastasis ($p = 0.010$) and advanced TMN stage ($p = 0.005$). However, no distinct difference was discovered between NBAT1 expression and patient age, gender, differentiation, tumor size, primary location, histology type, and smoking history ($p > 0.05$).

Prognostic values of NBAT1 levels in NSCLC

Then, we further explored whether NBAT1 expression was associated with the clinical outcome of NSCLC patients, and a follow-up of NSCLC patients was conducted over a 5-year period, in which the overall survival rates of patients were recorded. Furthermore, the Kaplan-Meier method and log-rank test revealed that patients with high NBAT1 expression in NSCLC had prominently longer overall survival than those with low NBAT1 expression ($p= 0.008$, Figure 1B). Then, the univariate analysis demonstrated that lymph node metastasis, TMN stage, and NBAT1 expression were statistically significant risk factors affecting the overall survival of NSCLC patients ($p<0.05$, Table 2). Of note, multivariate analysis showed that NBAT1 expression was an independent prognostic factor for NSCLC patients (HR= 2.947, 95% CI: 1.184-4.369, $p = 0.014$, Table 2). Overall, our results suggested NBAT1 is a potential prognostic regulator for NSCLC patients.

DISCUSSION

In this study, firstly, we collected tumor specimens and performed RT-PCR to further study the expression of NBAT1 in NSCLC, finding that NBAT1 expression levels were prominently lower in NSCLC tissues. Our results were consistent with previous results. Then, we further proved that low levels of NBAT1 were prominently associated with positive lymph node metastasis and advanced TMN stage, suggesting that NBAT1 may act as a positive regulator to contribute to the clinical progress of NSCLC. Subsequently, we further performed Kaplan-Meier assays to explore whether dysregulation of NBAT1 was associated with the prognosis of NSCLC patients, finding that patients with low levels of NBAT1 had poorer survival time than those with high levels of NBAT1. More importantly, based on the data of univariate and multivariate assays, low expression of NBAT1 was demonstrated to be a poor independent prognostic factor for patients with NSCLC, and the HR (95% CI) was 2.947 (1.184-4.369).

NSCLC contributes prominently to tumor-associated mortality and has become a major public health burden in China. Despite the rapid progress in NSCLC research, the survival of patients remains poor[21]. Lack of adequate cancer markers for early screening and metastasis determination further compromises the early diagnosis and treatment of this disease[22]. In addition, the precise prediction of clinical outcomes for NSCLC patients is very important for doctors to design individualized therapy[23]. Although several clinic-pathological factors have been used for the clinical application in prediction of prognosis of NSCLC patients, the specificity and sensibility of these factors remain low[24]. The clinical progress of NSCLC is involved in the dysregulation of multiple genes.

In their *in vitro* and *in vivo* assays, it was confirmed that forced expression of NBAT1 suppresses the metastasis of breast cancer cells by modulating the DKK1/PRC2 axis. Yang et al.[19] showed that NBAT1 was lowly expressed in osteosarcoma and its overexpression

growth, migration, and invasion of osteosarcoma cells via sponging miR-21. Liu et al.[17] indicated that the up-regulation of NBAT1 suppressed the migration and invasion of bladder cancer cells through the miRNA-21/SOCS6 axis. These findings suggested NBAT1 as an oncogene in the above tumors. Recently, Zheng et al.[20] firstly reported that NBAT1 expression was down-regulated in NSCLC cell lines, and its overexpression exhibited a tumor-suppressive role by suppressing autophagy by modulating ATG7. However, the expression pattern of NBAT1 needed to be further confirmed. In addition, the clinical significance of NBAT1 in NSCLC patients has not been investigated.

CONCLUSIONS

This is the first study highlighting the clinical significance of NBAT1 in NSCLC. Lower NBAT1 expression could serve as a promising target or potential prognostic indicator for NSCLC. More in-depth and larger-scale studies are required to confirm the correlation described here.

Conflict of Interest

No conflicts of interest.

Author's Contribution

All authors contributed to data analysis, drafting and revising of the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

RESUMO

OBJETIVO: *Há relatos de que o NBAT1 está associado à progressão do câncer. Contudo, o significado clínico do NBAT1 no câncer de pulmão de células não pequenas (NSCLC) ainda não está claro. O objetivo da nossa pesquisa foi explorar se NBAT1 serve como biomarcador para o prognóstico de NSCLC.*

MÉTODOS: *A expressão de NBAT1 foi examinada por RT-PCR em amostras de tecido de 162 pacientes com NSCLC e comparada a amostras adjacentes não tumorais de pulmão. Em seguida, a associação entre a expressão do NBAT1 e os parâmetros clínico-patológicos foi avaliada. A análise de sobrevivência foi realizada utilizando o método Kaplan-Meier. A significância prognóstica da expressão do NBAT1 em pacientes com NSCLC foi explorada através de análises univariadas e multivariadas.*

RESULTADOS: *A expressão do NBAT1 foi claramente diminuída nos tecidos de NSCLC em comparação aos espécimes normais dos pulmões (p<0,01). Além disso, as análises de sobrevivência indicaram que pacientes com baixa expressão apresentavam uma diminuição drástica da sobrevivência global em cinco anos (p=0,008).*

CONCLUSÃO: *A expressão do NBAT1 pode contribuir para a progressão tumoral e um prognóstico negativo do NSCLC e pode ser um novo alvo de terapia no NSCLC.*

PALAVRAS-CHAVE: *Prognóstico. Carcinoma pulmonar de células não pequenas. RNA longo não codificante.*

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Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

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SUMMARY

Churg–Strauss syndrome, Eosinophilic granulomatosis with polyangiitis (EGPA), is a systemic vasculitis that affects small– to medium-sized vessels. It is rare and part of the Anti-neutrophil cytoplasm antibody-associated vasculitis (ANCA) group.
We present a 37-year-old man, with a previous history of asthma, that was sent to the ED due to 2 weeks of productive cough, occasional dyspnea on exertion, fever (one week), asthenia, and anorexia. Upon physical examination, he was subfebrile and tachycardic. He had leukocytosis (17.00 x10^9/L) and eosinophilia of 20.0 % (3.4 X10^9/L), creatinine level of 1.5 mg/dL, subtle elevation on liver function tests and CRP of 10.82mg/dL. On Chest X-Ray, there was infiltrate on the right pulmonary base. Due to a strong suspicion of EGPA, he was started on 80mg of prednisolone from admission. ANCA MPO was positive, with the remaining auto-immune study negative. He underwent Thorax CT (under corticotherapy) without relevant changes, as well as bronchoalveolar lavage, without macroscopic signs of alveolar hemorrhage. Because of active urinary sediment, nephrotic proteinuria (6.5g/24h), and acute renal failure he underwent a renal biopsy, which revealed pauci-immune crescentic glomerulonephritis, with predominantly acute findings (in the context of ANCA-MPO Vasculitis – EGPA). After the biopsy, he received three 1g methylprednisolone pulses and was started on Cyclophosphamide. He remained asymptomatic and renal function was restored. This case highlights the importance of integrating all findings in one clinical scenario to prevent a more complex disease diagnosis, with a specific treatment, from being missed.

KEYWORDS: *Churg-Strauss syndrome. Eosinophils/pathology. Anti-neutrophil cytoplasmic antibody-associated vasculitis.*

INTRODUCTION

Churg-Strauss syndrome, currently called eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis that affects small and medium-sized vessels[1]. It is a rare disease belonging to the group of vasculitis associated with antineutrophil cytoplasmic antibody (ANCA)[2]. According to the American College of Rheumatology, the diagnosis is made when four or more of the following criteria are present: asthma, eosinophilia exceeding 10%, neuropathy, migratory or transitory pulmonary infiltrates, an anomaly of the paranasal sinuses, and biopsy with areas of accumulation of extravascular eosinophils[3]. It is a rare disease

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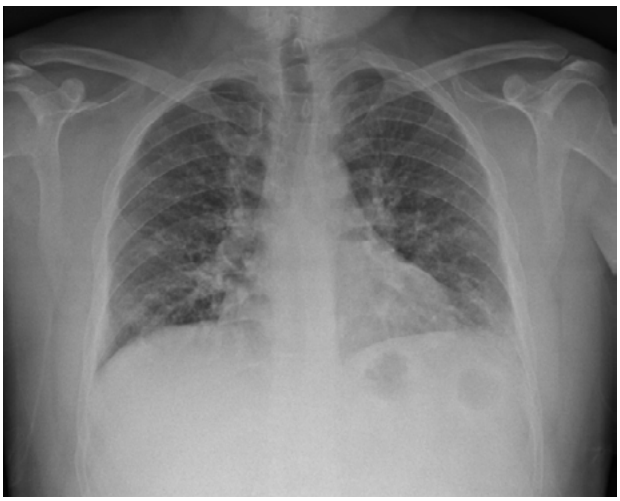
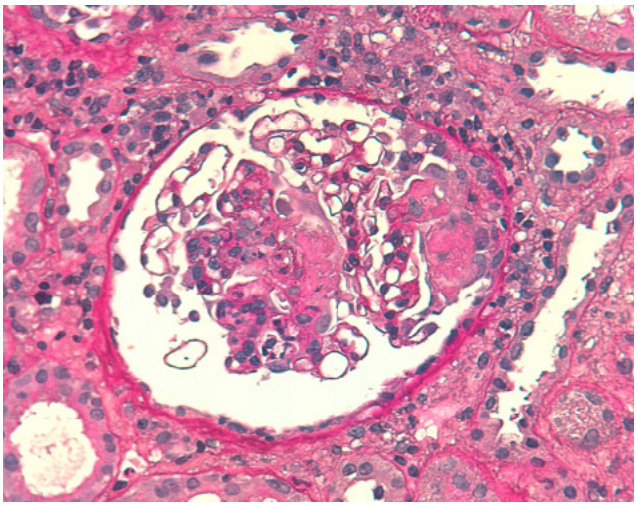
and a less common type of vasculitis[3]. We present a case of EGPA that could have gone unnoticed.

CLINICAL CASE

We present a 37-year-old man, woodworker, with a history of asthma and usually medicated with tiotropium bromide and fluticasone propionate + formoterol fumarate, who attended the ED with a productive cough that had evolved over approximately two months, occasional dyspnea on exertion, fever (with about a week of evolution), asthenia, and anorexia. There were no other symptoms associated. The patient reported a history of recurrent respiratory infections over the previous two months, having carried out several cycles of antibiotic therapy. Upon objective examination, he was subfebrile and presented tachycardia, without any other changes in the scenario. An analysis showed leukocytosis with 20.0% eosinophilia, renal dysfunction, discrete alteration of liver function, and CRP of 10.82 mg/dL (Table 1). A chest x-ray showed infiltrate in the right lung base (Figure 1). Abdominal and renal ultrasound showed kidneys of normal dimensions and increased echogenicity with reduced parenchymal-sinusal differentiation, without any other changes in the scenario. The patient was admitted to hospital for continuity of the diagnostic study. Due to a high suspicion of EGPA, prednisolone 80 mg was administered since admission. Microbiological studies, as well as serologies, came back negative

Analytical investigation at the ED			Etiologic analytical study upon admission		
Test	Results	Reference Values	Test	Results	Reference Values
Leukocytes	17.00x10^9/L	4.50-11.50	Rheumatoid Factor	17.3UI/mL	<20.0
Neutrophils	67.5%		ANA (IFI)	Negative	
Eosinophils	20.0%		Ab. Anti-DNA	Negative	
Hemoglobin	12.8g/dL	14.0-18.0	Ab. Anti dsDNA	1.0 U/mL	0.0-15.0
Platelets	336.0x10^9/L	150.0 – 450.0	ENA screen	Negative	
Creatinine clearance	1.5mg/dL	0.6 – 1.3	Anti-MPO antibodies Anti-PR3 antibodies	393.00 U/mL 0.50 U/mL	0.00-10.00 0.00-10.00
FA	116.0 UI/L	25-100	HIV 1+2 – Ag. + Total Ab.	0.15 Index	Non-Reactive
GGT	167.0UI/L	7.0-49.0	Ag. HBs Ab. HBs AB. HBc Ab. Total HCV	0.12 Index <3.1 mUI/mL 0.12 Index 0.09 Index	Non-Reactive Non-Reactive Non-Reactive Non-Reactive
ALT	110UI/L	4-43	Vit B12	497.0pg/mL	179.0-1130.0
AST	60UI/L	4-43	Tryptase	8.0µg/L	<11.4
CRP	10.82mg/dL	< 0.50	Aspergillus fumigatus (m3)	0.30 KUA/L	





(Table 1). ANCA MPO was positive, and the remainder study of autoimmunity was negative. Chest CT was performed (already under corticotherapy) without changes in the scenario, as well as bronchoalveolar lavage without macroscopic signs of alveolar hemorrhage. Due to renal involvement with active urinary sediment, proteinuria in the nephrotic range (6.56 g/24h), and acute kidney injury, a renal biopsy was performed, which showed pauci-immune crescentic glomerulonephritis, with predominantly acute findings (in the context of ANCA Vasculitis - MPO - Eosinophilic Granulomatosis with Polyangiitis) (Figure 2).

After the biopsy, three pulses of 1 g of methylprednisolone were administered. Given the severe renal involvement, cyclophosphamide was initiated with prophylaxis for associated hemorrhagic cystitis, pneumocystosis, and oral candidiasis. The patient showed improvement in the respiratory condition, becoming asymptomatic, as well as of renal function, with Cr of 1.1 mg/dL at the date of discharge. Follow-up was conducted on external consultations.

DISCUSSION

EGPA is a rare condition that mainly affects individuals aged between 7 and 74 years, with an average diagnosis age between 38 and 54 years and no gender predominance[4]. Our patient fits into the average age for diagnosis.

The etiopathology of the disease remains unknown, but some environmental factors have been mentioned as potential triggers, including allergens, infections, vaccines, and medication[2,5].

It is known that the EGPA develops in three sequential stages: the prodromal or allergic stage, the eosinophilic stage, and the vasculitis stage. The first is distinguished by the onset of asthma, allergic rhinitis, and sinusitis, and asthma is the main manifestation of this stage and present in most patients. In the second stage, patients develop the main pathological findings, with increased peripheral eosinophil count and their infiltration into various organs, particularly the lungs, heart, and gastrointestinal tract, and the pulmonary parenchyma is involved in two-thirds of patients with this diagnosis. Migratory infiltrates on chest x-ray are very characteristic of this disease. Finally, there is the vasculitis stage, in which the patient develops the consequences of necrotizing vasculitis, such as, purpura and peripheral neuropathy, which are usually accompanied by constitutional symptoms such as fever, general malaise, and weight loss[2,6]. The main histopathological findings are extravascular granulomas, vasculitis of small and medium-sized vessels, and eosinophilic infiltrates[2]. Our patient presented at the ED probably in the eosinophilic stage, progressing to the vasculitis stage, given the presence of peripheral eosinophilia, with a likely early pulmonary involvement and severe renal involvement, with acute findings of pauci-immune crescentic glomerulonephritis in renal biopsy. When a chest CT was performed, the patient was already under corticotherapy, which could justify the absence of alterations on this exam.

The differential diagnoses for EGPA are essentially eosinophilic diseases and other types of vasculitis[2,6,7].

When there is a suspicion of this disease, a biopsy is encouraged. A biopsy demonstrating vasculitis of small or medium-sized vessels, for example, fibrinoid necrosis, leukocytoclastic, or pauci-immune crescentic glomerulonephritis, along with the clinical context of asthma and eosinophilia, safely supports the diagnosis[7]. In 1990, the American College of Rheumatology defined six criteria for the diagnosis of EGPA. Since then, the most commonly used have been: asthma, eosinophilia >10%, neuropathy, migratory or transitory pulmonary infiltrates, an anomaly of the paranasal sinuses, and biopsy with areas of accumulation of extravascular eosinophils. For the diagnosis to be established, four or more of these criteria must be present[6]. In this case, there are four criteria present, one of them being the biopsy, which allowed us to confirm the diagnosis.

The treatment is based on a Five-Factor Score (FFS), with one point assigned to each one. They are gastrointestinal involvement, involvement of the central nervous system, cardiac involvement, proteinuria >1 g/24h, and serum creatinine above 1.58 mg/dL. If the patient has a FFS=0, this means a better prognosis, and therapy with glucocorticoids alone is the treatment indicated. If the patient has FFS >1, given the worst prognosis associated with this score, the indication is for treatment with glucocorticoids associated with immunosuppressive drugs, namely cyclophosphamide[2,6,7]. Our patient was under corticotherapy from admission due to the high clinical suspicion of EGPA and the observation of renal involvement; therefore, with FFS >1, cyclophosphamide pulses were started. Although Cr was 1.5 mg/dL ate admission, it was established, upon the consultation of records, that this was a chronic renal disease, so renal involvement was not assumed *ab initio*.

CONCLUSION

This case aims to draw attention to the diagnosis of a rare condition that requires attention and clinical suspicion, as well as the integration of all findings into one clinical scenario, since, in this case, right pneumonia with acute kidney injury could be easily assumed, thus ignoring a more severe diagnosis with specific treatment.

RESUMO

A vasculite de Churg–Strauss, granulomatose eosinofílica com poliangeíte (EGPA), é uma vasculite sistêmica que afeta vasos de pequeno e médio calibre. É rara e pertence ao grupo de vasculites associadas a anticorpos anticitoplasma de neutrófilos (Anca).
Apresenta-se um homem de 37 anos, com antecedentes de asma, que recorre ao SU por tosse produtiva com dois meses de evolução, dispneia ocasional em esforço, febre (uma semana de evolução), astenia e anorexia. Ao exame objetivo apresentava-se subfebril e taquicárdico. Analiticamente com leucocitose (17,00 x10^9/L) e eosinofilia de 20,0% (3,4 X10^9/L), creatinina de 1,5 mg/dL, discreta alteração das provas de função hepática e PCR de 10,82 mg/dL. Na radiografia de tórax objetivava-se infiltrado na base pulmonar direita. Por elevada suspeita de EGPA, iniciou prednisolona 80 mg desde a admissão. Anca MPO+, com restante estudo de autoimunidade negativo. Realizou TC tórax (sob corticoterapia) sem alterações de relevo, bem como lavado bronco-alveolar, sem sinais macroscópicos de hemorragia alveolar. Por sedimento urinário ativo, proteinúria na faixa nefrótica (6,56 g/24h) e lesão renal aguda, realizou biópsia renal que revelou glomerulonefrite crescêntica pauci-imune, com achados predominantemente agudos (no contexto de Vasculite Anca-MPO - EGPA). Após biópsia, realizou três pulsos de 1 g de metilprednisolona e iniciou ainda ciclofosfamida. Ficou assintomático e com recuperação da função renal.
Este caso realça a importância de integração de todos os achados num só cenário a fim de evitar que escape o diagnóstico de uma doença mais complexa e com um tratamento específico.

PALAVRAS-CHAVE: *Síndrome de Churg-Strauss. Eosinófilos/patologia. Vasculite associada a anticorpo anticitoplasma de neutrófilos.*

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The value of morphofunctional magnetic resonance imaging with hepatospecific contrast agent in the characterization of hepatocellular carcinoma in a non-cirrhotic patient with hepatitis C

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SUMMARY

Hepatocellular carcinoma in patients with hepatitis C in the absence of cirrhosis is uncommon. We demonstrate the importance of morphofunctional magnetic resonance imaging (MRI) with a hepatospecific contrast agent by describing an asymptomatic female patient with HCV, who presented with a nodule detected on ultrasound. She underwent inconclusive computed tomography, presenting no signs of chronic liver disease. MRI with hepatospecific contrast providing functional information combined with the superior tissue contrast inherent to this method stands out for its greater accuracy with the possibility of not resorting to invasive diagnostic methods. With increasing experience and the dissemination of this new diagnostic modality in the medical field, its use and other potential benefits of morphofunctional MRI with hepatospecific contrast agents may be established, benefiting patients with challenging focal liver lesions.

KEYWORDS: *Liver. Liver neoplasms. Contrast media. Diagnostic imaging. Magnetic resonance imaging.*

INTRODUCTION

Although chronic infection by the hepatitis C virus (HCV) is one of the major risk factors for the development of hepatic cirrhosis and hepatocellular carcinoma (HCC), the emergence of HCC in patients with hepatitis C in the absence of cirrhosis, particularly after treatment and achievement of sustained virologic response, is uncommon[1-3]. A proper assessment of a focal liver lesion, interpreted initially as an indeterminate nodule by ultrasound (US) and/or computed tomography (CT) scans with contrast in a patient with HCV in the absence of cirrhosis has great therapeutic and prognostic importance. Due to the

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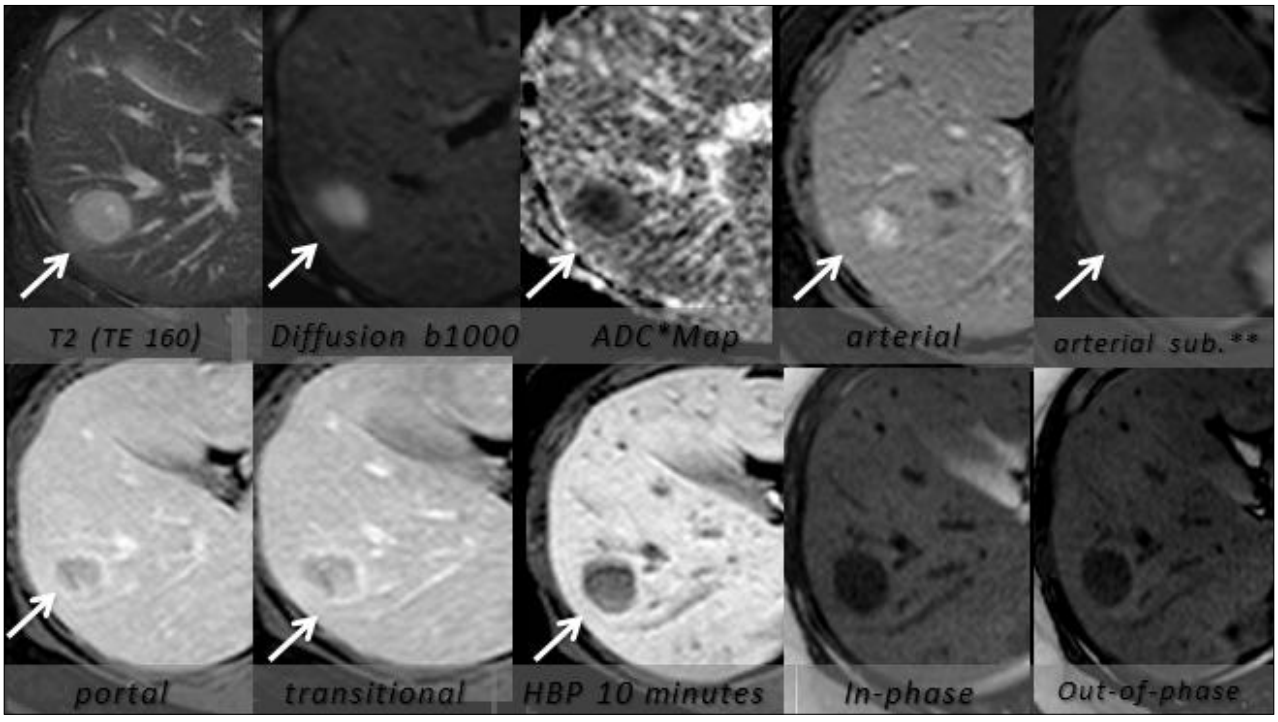
lack of descriptions with emphasis on imaging evaluation of indeterminate nodules in patients with HCV without cirrhosis, using magnetic resonance imaging (MRI) with a liver-specific contrast agent (LSCA), we are motivated to disclose the importance of this methodology in this particular scenario.

MRI is a well-established imaging method in clinical practice, producing images without ionizing radiation, with good spatial resolution and excellent tissue imaging, which allows for a very accurate assessment. The main innovations in this area are currently focused on improving anatomic resolution and, more recently, using molecular and functional methods. With the recent introduction in clinical practice, studies have demonstrated the use of the LSCA in morphofunctional imaging by MRI with a good safety profile (similar to the other conventional gadolinium contrast agents)[4,5]. The results of the use of this new contrast agent in MRI suggest a relevant impact on the definition of strategies for the approach of focal hepatic lesions, as well as in the assessment of the treatment employed[4,5]. However, due to its lower availability and higher cost in comparison with contrast CT and MRI with the conventional gadolinium contrast agent, its use is usually indicated for particular situations.

CASE

We describe a 46-year-old female patient, asymptomatic, HCV carrier, who presented with a nodule detected on the US. There were no co-infections by the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis D virus (HDV). CT was performed with inconclusive results (questionable arterial phase hyperenhancement) and no signs of chronic liver disease. MRI of the upper abdomen, before and after the administration of gadoxetic acid as a liver specific contrastagent (LSCA), detected a focal lesion of the liver in the segment VI, measuring 1.8 cm in the largest axis, with arterial phase hyperenhancement, venous washout, pseudocapsule, restriction to the diffusion of water molecules and hyposignal in the hepatobiliary phase, findings with characteristics of a small HCC (Figure 1). No other focal nodular lesions or signs of liver disease were identified. Histopathologic evaluation revealed small HCC since it measured less than 2.0 cm in diameter,

FIGURE 1. MRI USING A LIVER-SPECIFIC CONTRAST AGENT DEMONSTRATING CHARACTERISTICS OF THE HCC IN A NON-CIRRHOTIC LIVER. MILD T2 HIPERINTENSE, RESTRICTED DIFFUSION, ARTERIAL PHASE HYPERENHANCEMENT, CONTRAST AGENT WASHOUT, AND HYPOINTENSE IN HEPATOBILIARY PHASE. SIGNS OF DIFFUSE STEATOSIS (SIGNAL LOSS IN OUT-OF-PHASE SEQUENCE). *ADC - APPARENT DIFFUSION COEFFICIENT. **ARTERIAL SUB. - ARTERIAL SUBTRACTION. SOURCE: THE AUTHOR (2019).



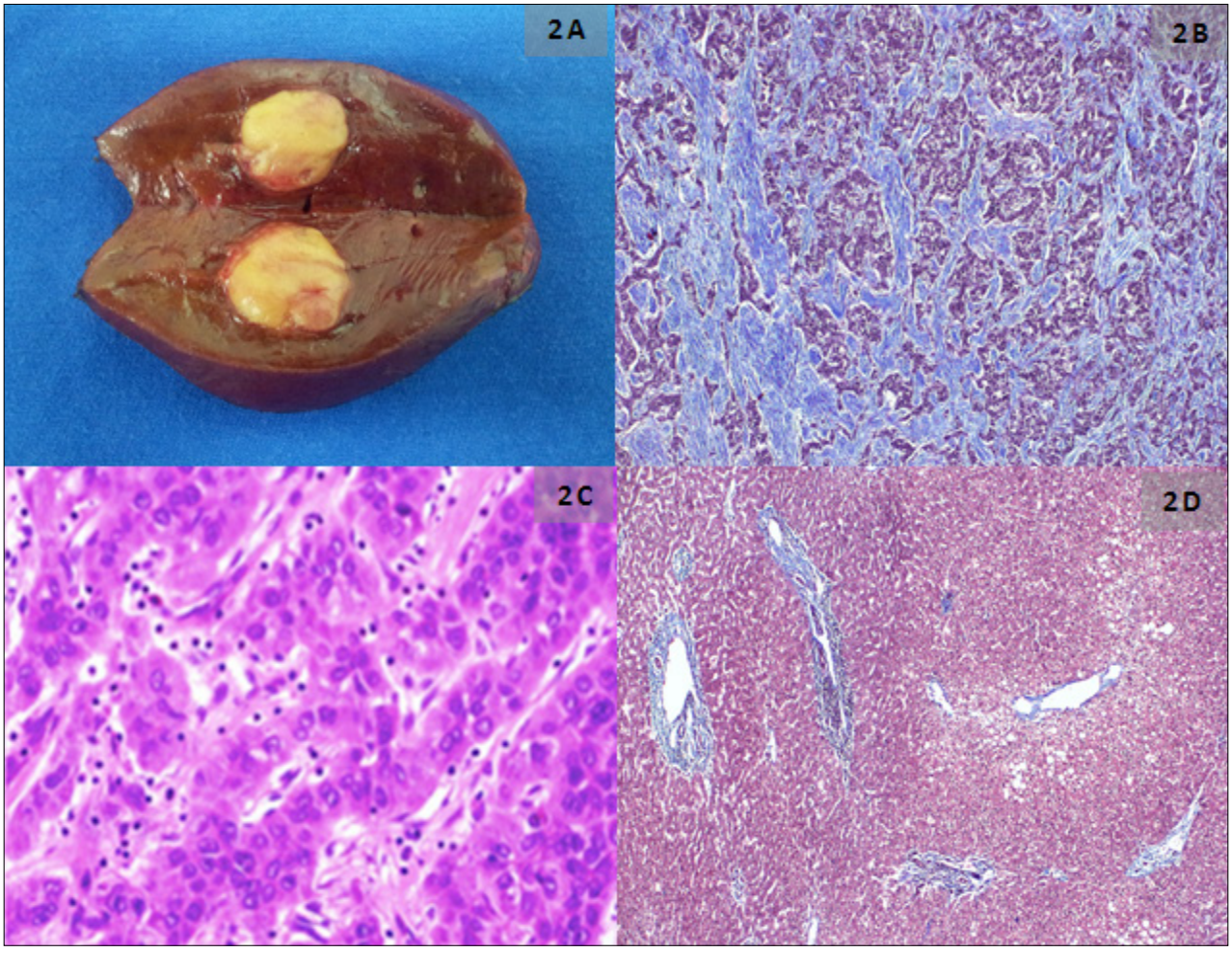
but already had well-defined peritumoral borders (Figure 2A).

The lesion showed exuberant perisinusoidal fibrous stroma, sometimes forming lamellae, with growth in irregular strings and atrophy of the neoplastic trabeculae, characterizing the cirrhosis variant of HCC, a rare presentation, occurring in less than 5% of cases, which seems to be associated with more aggressive behavior (Figure 2B). It is important to highlight that the fibrolamellar variant was excluded, since, despite the fibrous strings, the lesion was moderately differentiated (Edmondson-Steiner Grade 2) (Figure 2C) and had no neoplastic hepatocytes of an oncocytic pattern. The adjacent liver parenchyma had steatohepatitis with mild inflammatory activity, without architectural alterations of multifocal nodular transformation (non-cirrhotic liver) or other signs of chronic hepatopathy (Figure 2D). There was also no siderosis or other deposits upon the use of Perl's staining. The margin of surgical resection and Glisson capsule were free of neoplasia, and no carcinomatosis emboli, angiolymphatic or blood, were found. Currently, the patient is without complaints and in good general condition; she is undergoing outpatient follow-up for hepatitis C, without new detectable focal hepatic lesions.

DISCUSSION

The term "functional imaging" includes techniques capable of assessing *in vivo* physiological parameters of the tissues that provide additional useful clinical

FIGURE 2. FIGURE 2A. MACROSCOPY: NODULAR LESION OF WELL-DEFINED BORDERS, MEASURING 1.8 X 1.8 X 1.5 CM, WHITISH AND HOMOGENEOUS, OF FIBROELASTIC CONSISTENCY. FIGURE 2B - MICROSCOPY (MASSON'S TRICHROME, 200X): CIRRHOTIC HCC, SHOWING DENSE FIBROUS LAMELLAE PERMEATING THE NEOPLASTIC HEPATOCYTES. FIGURE 2C - MICROSCOPY (HEMATOXYLIN-EOSIN, 200X): MODERATELY DIFFERENTIATED HCC, WITH IRREGULAR TRABECULAE OF NEOPLASTIC CELLS WITHOUT ONCOCYTIC CHARACTERISTICS, EXCLUDING FIBROLAMELLAR HCC. FIGURE 2D - NON-TUMORAL, NON-CIRRHOTIC HEPATIC PARENCHYMA WITH MACROVESICULAR STEATOSIS AND HEPATOCELLULAR BALLOONING IN ACINAR ZONE 3 (STEATOHEPATITIS).



information to those obtained from imaging morphological data. It can be used in hepatology to detect and characterize tumors, in therapeutic choice, monitoring of therapeutic response, and patient follow-up[6]. There are four main functional imaging modalities used in liver assessment: 1 - Diffusion-weighted imaging (DWI), which refers to the random or "Brownian" movement of protons in water molecules through biological tissues - a marker of cellularity and microarchitecture; 2 - Contrast agents in ultrasound, computed tomography or MRI; 3 - Image of the hepatocellular function using LSCA; and 4 - Metabolic nuclear imaging using positron emission tomography (PET)/CT with radiotracers marked to assess specific metabolic pathways[6]. In this case, three of the four functional imaging modalities were used: diffusion-weighted imaging (DWI), dynamic vascular phases following contrast injection (arterial, portal and transitional phases) and hepatobiliary phase (hepatocellular function). This joint analysis provided more security in characterizing the liver injury, which was previously indefinitely as a suspected small HCC. The functional information combined with the superior tissue contrast inherent to the MRI, we have obtained greater accuracy[7], with the possibility of not resorting to invasive methods. Differential imaging diagnoses could include metastases and other atypical lesions in this case. Protocols and guidelines drawn up in a joint effort by major scientific societies have pointed to the inclusion of MRI with LSCA as an option to be inserted in the diagnostic algorithm of challenging focal liver lesions[7-11].

The LSCA approved for clinical use in Brasil in 2011 by the Brazilian Health Regulatory Agency (Anvisa) is known generically as gadoxetic acid (or gadoxetate disodium), a diagnosis medication of intravenous administration that allows for routine three-phase MRI examinations initially, followed by a hepatobiliary evaluation during the same examination[4]. Due to its hepatocellular uptake and half of its 50/50 biliary/kidney excretion in healthy individuals, this contrast agent is a marker of liver tissue normofunction. In general, if there is no gadoxetic acid uptake in the hepatobiliary phase, it is possible to infer there is an absence of viable hepatocytes (as is the case, for example, in most HCCs) or absence of biliary canaliculi (observed in hepatocellular adenomas)[4,5]. It is recommended to carry out a clinical and/or laboratory assessment of liver and renal function prior to its administration, and its use should be avoided in patients with a creatinine clearance of less than 30 ml/min. High levels of bilirubin (above 3 mg/dl) or ferritin, and the use of anionic drugs (such as rifampicin) can reduce the hepatobiliary effect of this contrast agent[5,12]. The knowledge of the biochemical properties of the LSCA has encouraged several studies based on medical genetics and protein expression, allowing for a better understanding of the *in vivo* behavior of this contrast agent and of the physiopathological basis of MRI findings in different focal liver lesions.

CONCLUSION

Morphofunctional MRI with liver-specific contrast agents can assist in the diagnosis of HCC in the absence of the typical characteristics in conventional examinations. Thus, despite its lower availability and its higher cost, the use of this methodology in well-indicated situations, as demonstrated here in the case of an indeterminate nodule found in the US upon CT with contrast in a patient with HCV without cirrhosis, is an important tool in the assessment of undetermined focal liver lesions that provides the possibility of not resorting to invasive diagnostic methods. With the accumulation of experience and dissemination of this new modality in the medical field, the use demonstrated herein and other potentials of morphofunctional MRI with liver-specific contrast as a new potential imaging tumor biomarker may be established, benefiting patients with challenging focal liver lesions.

Conflict of interest

The authors declare there are no conflicts of interest.

Ethical aspects

Project approved by the Research Ethics Committee of the institution, decision number 962.639, CAAE: 41531415.0.0000.5404

RESUMO

O surgimento de carcinoma hepatocelular em pacientes portadores de hepatite C na ausência de cirrose é de ocorrência pouco comum. Demonstramos a importância da ressonância magnética (RM) morfofuncional com contraste hepatoespecífico por meio da descrição de uma paciente do sexo feminino, assintomática, portadora do vírus da hepatite C (VHC), que se apresentou com nódulo detectado na ultrassonografia. Realizou tomografia computadorizada inconclusiva, sem sinais de hepatopatia crônica. A RM com contraste hepatoespecífico, ao proporcionar informações funcionais, somado ao superior contraste tecidual inerente ao método, destaca-se pela maior acurácia, com a possiblidade de não se recorrer a métodos diagnósticos invasivos. Com o acúmulo de experiência e divulgação dessa nova modalidade diagnóstica no meio médico, sua utilização e outros potenciais benefícios da RM morfofuncional com contraste hepatoespecífico podem vir a se estabelecer, beneficiando pacientes com lesões hepáticas focais desafiadoras.

PALAVRAS-CHAVE: *Fígado. Neoplasias hepáticas. Meios de contraste. Diagnóstico por imagem. Imagem por ressonância magnética.*

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ORIGINAL ARTICLE

Proton pump inhibitor indications in a Brazilian tertiary hospital

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SUMMARY

OBJECTIVES: *To evaluate the frequency of prescription of proton pump inhibitors (PPIs) and their indications in patients hospitalized at the Hospital de Clínicas of the Federal University of Uberlândia (HC-UFU).*

METHODS: *This is a quantitative cross-sectional observational study that analyzes data obtained from patient records on prescriptions of PPIs for patients hospitalized at the HC-UFU and from a questionnaire applied to assistant physicians on the indications of the drug in each case and evaluates the indication based on literature data.*

RESULTS: *On a pre-determined day, of a total of 462 inpatients, there was a prescription of PPI for 183 (39.3%), with a higher frequency (73.5%) in the Intensive Care Unit (ICU), followed by the infirmaries and the Emergency Room. The assistant physician was located in 116 cases, and the main motivation referred to prescription was prophylaxis of digestive hemorrhage (77%). However, after reviewing medical records, it was noticed that in 50.8% of the cases, the prescription was not supported by the literature.*

CONCLUSION: *The frequency of PPI prescriptions for inpatients in the HC-UFU is among the lowest described in the literature, but there are still unnecessary prescriptions. Instruction and awareness of the assisting team can minimize these numbers.*

KEYWORDS: *Proton pump inhibitors. Gastrointestinal hemorrhage/prevention & control. Therapeutic uses.*

INTRODUCTION

Proton pump inhibitors (PPI) are potent blockers of acid secretion by the parietal cells of the stomach. They are widely used in the treatment of peptic diseases and in the prevention of gastrointestinal bleeding (GB) in high-risk patients[1].

Among the indications for their prescription

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are the treatment and management of esophagitis, treatment of gastroesophageal reflux disease, reducing the risk of peptic ulcer associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), eradication of *Helicobacter pylori infection* in association with antibiotics, gastrinomas, treatment of gastric and duodenal ulcers, prophylaxis of lesion and GB in high-risk patients (respiratory failure, coagulopathy, etc.), as well as eosinophilic esophagitis, chemoprevention in Barrett's esophagus, and functional dyspepsia[1].

The wide prevalence of gastrointestinal diseases associated with descriptions of the effectiveness of PPIs for the gastric protection of patients who use several drugs and the belief that the use of this class of medication presents a low risk of toxicity resulted in a significant increase in its prescription[2]. These factors, along with the low dissemination of *guidelines* on its correct use, have contributed to an increase in unnecessary indications of PPIs in admissions, particularly as a prophylactic drug[2]. Studies suggest that, in many cases, prescriptions are not based on scientific evidence[3]; that improper use is still advised in some hospitalization protocols[4], and most users take high doses in the long term unnecessarily[5].

Although considered safe, PPIs have potential side effects, such as hypergastrinemia, deficient absorption of vitamin B12, iron, and magnesium, kidney failure, and gastric hyperplastic polyps. Its prolonged use is associated with a higher incidence of community-acquired pneumonia and diarrhea by *Clostridium difficile*[1,6]. Drug interactions can also occur, especially with clopidogrel and some anticonvulsant drugs. Unnecessary prescriptions also entail a significant expense in health care[3]. These conditions highlight the need for correct usage, according to specific guidelines[1,2].

Hospital admission provides an opportunity for review of therapy, with the identification of current trends in prescription. Since there are no data representing the Brazilian reality, the present study seeks to identify the frequency of the use of PPIs in patients hospitalized in the Clinical Hospital of the Federal University of Uberlândia (HC-UFU), in addition to identifying the main indications for prescription and validating them, based on the literature. Our secondary objectives were to know the reasons for prescribing PPIs in these cases, identifying the routes of administration, and evaluating the adequacy of prescription in each case.

METHODS

This is a cross-sectional observational study with a quantitative approach that analyzed data on the prescription of PPIs obtained from medical records and a simple questionnaire applied to the assistant physician of patients hospitalized in the Hospital de Clínicas of the Federal University of Uberlândia (HC-UFU). The research was approved by the Research Ethics Committee of the Federal University of Uberlândia (CAAE 96762618.4.0000.5152; Opinion 2952760).

We used the descriptor "omeprazole" (only PPI available at HC-UFU) to select the medical records from the statistics department of the hospital. Initially, we surveyed the number of prescriptions of omeprazole per day, from January to March 2018. These numbers were used to calculate the average daily prescription of the drug. In a randomly chosen day of March 2018, we identified and selected for evaluation all records of patients who were in use of the medication at the hospital.

In addition, the total number of hospitalized patients in each sector (clinical and surgical infirmaries, emergency room, intensive care unit) on the chosen date was also considered to determine the frequency of the drug in the prescriptions of each sector of the HC-UFU.

After signing the Informed Consent Form, a questionnaire was applied to the assistant physician, containing questions about the indication of the use of omeprazole in each case.

We assessed patients' data such as age and gender, in addition to the identification of the hospital sector of hospitalization, route of administration, and use indication.

When GB prophylaxis was the justification given by physicians for prescribing a PPI, a review of the records was carried out in search of the criteria of such an indication. Based on the literature, the criteria are hospitalization in Intensive Care Unit (ICU) for more than seven days; mechanical ventilation for more than 48 hours; coagulopathy; a history of gastrointestinal bleeding in the past year; hidden gastrointestinal bleeding for six days or more; burns; sepsis, shock, or organic dysfunction; organ transplantation; head trauma; multiple trauma; Glasgow coma scale score less than 10; liver failure; spinal cord trauma; and use of corticosteroids in high doses[7].

The analysis of the data was carried out based on descriptive statistics for the characterization

of indicators (frequency, percentage, and average), comparing them with similar data available in the literature.

RESULTS

From January to March 2018, omeprazole was prescribed to an average of 205 patients per day (49.49%). On the date determined for data collection, chosen at random from the month of March, there were 462 inpatients and 183 of them were using PPI, which corresponds to a prescription rate of 39.6%.

The mean age of the patients who were prescribed PPI was 50 years and 61% were male. The route of administration was intravenous in 77% of cases. Regarding the sector of hospitalization, the frequency of PPI prescriptions was 73.5%, 37.7%, and 31.8% in the ICU, infirmaries, and emergency services (ES), respectively. In surgical infirmaries, the prescription rate was 56.6%, whereas in clinical infirmaries it was 29.1%.

It was possible to reach the assistant physician and get an answer on the indication of the drug in 116 cases (88%). GB prophylaxis in high-risk patients motivated the prescription of omeprazole in 77% of the cases, followed by functional dyspepsia (9%), and other indications detailed in Graph 1.

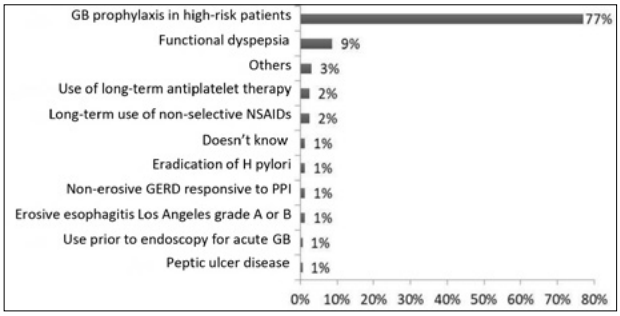
After reviewing the medical records in search of the criteria used for prescribing omeprazole as GB prophylaxis, we found that in 50.8% of cases there was no justification for such indication. When this data was stratified by sector of hospitalization, the indication was inadequate in 7%, 52%, 64%, and 76% of the prescriptions in the surgical infirmaries, clinical infirmaries, and ES, respectively, which can be observed in Graph 2.

DISCUSSION

Omeprazole was prescribed to 39.6% of patients hospitalized in the HC-UFU. When compared to similar studies conducted in tertiary hospitals, the frequency of PPI prescriptions identified in this study is low. In Ribeiro et al.[8], the use of PPI in hospitalized patients of a Portuguese hospital was present in more than half of cases (54.2%). Kelly et al.[9] found PPI prescriptions in 57.5% of the cases of hospitalized patients in Ireland. In Spain, three similar studies presented PPI prescription frequencies the prescribed PPI well above the value found in the HC-UFU. Ameijeiras et al.[10] identified a prevalence of 62.4% in the use of PPI at the university hospital of Santiago de Compostela. Ramirez et al.[2] identified omeprazole prescriptions during hospitalization in 82.62% of patients in the University Hospital of Madrid. In another tertiary Spanish hospital, Villamañán et al.[4] found a frequency of PPI prescription of 77.6% for inpatients.

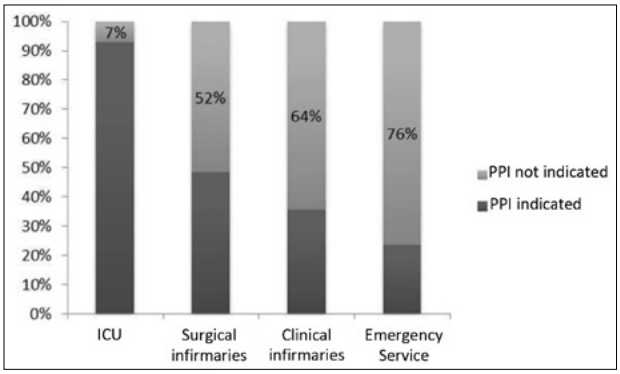
Although the PPI prescription rate in the HC-UFU is among the lowest described in the literature, there was an inadequate prescription in almost half of the cases. GB prophylaxis was the main reason for the use of omeprazole (77%), according to the assistant physicians. However, when reassessing the records in the search for criteria validated in the literature for such an indication, 50.8% of the cases presented no justification for the prescription. Similarly, Ribeiro et

GRAPH 1. INDICATION ON THE USE OF OMEPRAZOLE, DESCRIBED BY THE ASSISTANT PHYSICIAN, FOR PATIENTS HOSPITALIZED IN THE HC-UFU ON A DAY OF MARCH 2018 (MATOSO ET AL.)



Legend: HC-UFU: Hospital de Clínicas of the Federal University of Uberlândia; GB: Gastrointestinal bleeding; NSAIDs: non-steroidal anti-inflammatory drugs; H pylori: *Helicobacter pylori*; GERD: Gastroesophageal reflux disease; PPI: Proton-pump inhibitor. Data obtained through the questionnaire applied to the assistant physicians at HC-UFU.

GRAPH 2. ADEQUACY OF OMEPRAZOLE PRESCRIPTION FOR GB PROPHYLAXIS IN PATIENTS HOSPITALIZED IN THE HC-UFU (MATOSO ET AL.)



Legend: GB: gastrointestinal bleeding; HC-UFU: Hospital de Clínicas of the Federal University of Uberlândia; PPI: proton-pump inhibitor; ICU: Intensive Care Unit. Data obtained from the Medical Archive of HC-UFU.

al.[8] demonstrated an inappropriate use of PPI in 39.8% of all prescriptions for GB prophylaxis in non-critical patients. Ramirez et al.[2] did not identify an appropriate indication in 61.25% of cases, especially for GB prophylaxis (17.34%). Villamañán et al.[4] also presented similar findings: unnecessary prescription of PPI in 63.6% of cases, with an inaccurate indication for GB prophylaxis in 19.8% of prescriptions. Another study identified the inappropriate use of PPIs at even higher rates. In Ameijeiras et al.[10], the rate of incorrect prescriptions of PPI was 77.6%, despite the existence of a specific protocol drawn up by the Committee of Pharmacy and therapeutics of this center.

Regarding the different sectors of hospitalization, the prescription rate of omeprazole was higher in the ICU (73.5%) and in surgical infirmaries (56.6%). The ICU, however, was the sector with the lowest rate of inappropriate prescriptions (7%). The surgical infirmaries also had lower rates of inadequate prescription in comparison to the clinical infirmaries, i.e., 52% and 64%, respectively.

Alsultan et al.[11] found similar disparities in the inadequacy of intravenous PPI prescription for GB prophylaxis among patients hospitalized in the ICU (19.8%) and in the other hospital sectors (71.7%).

According to Heidelbaugh et al.[12], because there are well-defined guidelines for the indication of PPIs in more severe patients, prescriptions in ICUs are usually more appropriate when compared to non-ICU sectors. However, the authors alert PPIs should be discontinued after the patients are transferred from the ICU, otherwise, there may be unnecessary continuous use in other sectors after the transfer or even after hospital discharge.

A study conducted at a tertiary hospital in the United States showed that of the 248 patients in use of antisecretory therapy in the ICU, 215 continued to receive the drug after transfer to another hospital sector. Of these, 86.7% had no appropriate indication for continuing using the drug[13].

Zink et al.[14] identified that 196 of the 324 patients analyzed were unnecessarily using PPIs and that 34% of these were discharged while still using this drug. Wohlt et al.[15] got similar results from a study in a tertiary hospital of the University of Wisconsin. Of the total number of patients who were transferred from the ICU while using PPIs, there was no justification for continuing the therapy with gastric suppressors in 189 (60%) of them, and 96 (50.7%) of these patients were discharged with a prescription for the drug.

The excess of PPI prescriptions during hospitalizations and continued use of the drug after patient discharge result in increased health costs for the institution, patients themselves, and taxpayers in general[12]. In the United Kingdom, the cost of PPI prescriptions was £425 million in 2006, and its estimated cost worldwide was £7 billion[9]. Moreover, the cost with anti-secretory therapy is behind only that of statins, estimated at more than $11 billion annually in the United States, and, according to a British estimate, unnecessary expenses were around £2 billion worldwide in 2008. The substantial expenditures in PPI motivated researchers to develop strategies that are cost-effective and based on scientific evidence for anti-secretory treatments, including *step-down* and use on-demand, but few clinicians follow these recommendations[12].

The frequency of intravenous PPI prescription was high when compared to studies carried out in other tertiary hospitals. In the work of Ameijeiras et al.[10], the intravenous route was chosen in 36.2% of all prescriptions of omeprazole. In 17.7% of these prescriptions, no justification was found for the use of the drug. Ribeiro et al.[8] assessed the intravenous use from adequate prescriptions of PPI, and in approximately 13% of these, there was no contraindication for the oral use of omeprazole. This work did not aim to evaluate the adequacy of the route of PPI administration. However, the high frequency of intravenous prescription is noteworthy. It is known that this formulation also increases costs for the service and the risks to the patient.

There are no well-established protocols at the HC-UFU for prescribing and using PPIs. However, the information system provides a list of criteria for prophylactic indications of omeprazole each time the drug is prescribed. This must have contributed to the frequency of prescription at acceptable levels. Even so, the prescription could have been avoided in almost half of the cases.

CONCLUSIONS

This study alerts to the need for a more careful assessment in the prescription of PPIs for hospitalized patients. We noticed that its use, in many cases, may be unnecessary, costly, and dangerous. The definition and wide dissemination of indications, contraindications, risks, and benefits of the drug aimed at the clinical staff of the institutions are necessary for more aware and less costly prescriptions.

Author's Contribution

Abadia Gilda Buso Matoso participated in the leadership and counseling throughout the research, from the drafting and submission to the Research Ethics Committee of the organization until the submission for publication. Acted as a leader in the conceptualization, data curatorship, formal analysis, investigation, methodology, project management, supervision, validation, visualization, writing (original draft, revision, and editing).

Fernanda Arantes Mendonça Toledo Almeida, Lígia Paiva, Patrícia Munhoz Margonari and Tainá Mendes Bertolin participated as an equal, from the drafting and submission to the Research Ethics Committee of the organization until the submission for publication. Acted as an equal in the data curatorship, investigation, methodology, project management, validation, visualization, and writing (original draft, revision, and editing). Had a supportive role in the formal analysis, along with the rest of the team.

Alisson Alves Sousa, Ana Júlia Araújo de Carvalho, Ana Vera Cardoso Alves, Ébony Lima dos Santos, Lívia Lara Teodoro and Thiago Trajano da Silva contributed as an equal in the data curatorship, research, methodology, and the original draft, along with the rest of the team. Had a supportive role in the concept, formal analysis, project management, viewing, and writing (revision and editing).

RESUMO

OBJETIVOS: *Avaliar a frequência da prescrição de inibidores da bomba de prótons (IBPs) e suas indicações em pacientes internados no Hospital de Clínicas da Universidade Federal de Uberlândia (HC-UFU).*

MÉTODOS: *Estudo observacional transversal quantitativo, análise de dados obtidos em prontuários sobre prescrições de IBPs para pacientes internados no HC-UFU, aplicação de questionário aos médicos assistentes sobre as indicações do medicamento em cada caso e avaliação dessas indicações com base em dados da literatura.*

RESULTADOS: *Em um dia predeterminado, de 462 pacientes internados, houve prescrição de IBP para 183 (39,3%), com maior frequência (73,5%) em Unidade de Terapia Intensiva (UTI), seguida das enfermarias e do pronto-socorro (PS). O médico assistente foi localizado em 116 casos, a principal motivação referida para prescrição foi a profilaxia de hemorragia digestiva (77%). Entretanto, após revisão de prontuários, percebeu-se que em 50,8% a prescrição não era respaldada por literatura.*

CONCLUSÃO: *A frequência de prescrição de IBP para pacientes internados no HC-UFU está entre as menores descritas na literatura, mas ainda há prescrições desnecessárias. Orientação e conscientização da equipe assistente podem minimizar esses números.*

PALAVRAS-CHAVE: *Inibidores da bomba de prótons. Hemorragia gastrointestinal/prevenção e controle. Usos terapêuticos.*

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ORIGINAL ARTICLE

Beers AGS 2019 criteria in very old hospitalized patients

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SUMMARY

OBJECTIVE: *To define the rates and types of potentially inappropriate medications (PIMs) for older adults according to the Beers AGS 2019 criteria in oldest-old patients (aged ≥80 years) hospitalized in an Internal Medicine ward.*

METHODS: *A retrospective analysis of prescriptions from medical records of oldest-old patients hospitalized in an Internal Medicine Teaching-Hospital ward using the Beers AGS 2019 criteria was performed. Data was also collected for gender, mean age, days of hospitalization, presence of feeding tube, delirium, and polypharmacy (≥5 drugs/day). The drugs listed in Table 2 of the Beers criteria were considered PIMs.*

RESULTS: *The series comprised 39 very old patients (22 men, 17 women), with a mean age of 86.3±4.7 years and hospitalization of 22.8±21.3 days. All patients were admitted via the Emergency Room. Feeding tube placement and polypharmacy occurred in 84.6% of cases and delirium in 71.8%. The prescription of a total of 16 drugs considered PIM was detected by the Beers AGS 2019 criteria (mean 1.8 ± 1.0 PIM per patient). Main prescribed PIMs were Metoclopramide "if necessary" [IN] (41.0% of cases), Omeprazole (38.5%), Regular Insulin [IN] (23.1%), Haloperidol [IN] (18.0%), Quetiapine and Amiodarone (10% each).*

CONCLUSION: *In the present series of oldest-old hospitalized patients, significant rates of PIM were found, especially for drugs prescribed as "If Necessary", thereby increasing the risk of side-effects to that of the common polypharmacy in this age group.*

KEYWORDS: *Aged, 80 and over. Pharmaceutical preparations. Inpatients. Potentially inappropriate medication list.*

INTRODUCTION

The natural process of aging - accompanied or not by the changes resulting from diseases of higher prevalence among the elderly - represents a potential for interference on the pharmacokinetics and pharmacodynamics of the human body with a significant number of medications. This relationship is often observed in clinical practice, given the high percentage of patients in this age group who simultaneously and chronically take several medications[1,2].

Thus, it is easy to observe the medications that have a greater potential to harm than to benefit elderly patients. Defined as potentially inappropriate medications (PIM), these drugs resulted in the development of multiple lists and criteria with the purpose of guiding their use by patients of more advanced ages[3,4]. The Beers criteria - now in its sixth edition - are the most commonly used and worldwide renowned list of PIM[5]. Its previous editions served as a reference to a

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significant number of national studies, particularly for the Brazilian Consensus on Potentially Inappropriate Medications for the Elderly (2016)[6].

It is estimated that hospitalized elderly individuals take five or more medications simultaneously - defined as polypharmacy -, and one or more PIM may be present in percentages that deserve the attention of healthcare professionals[7,8]. It is estimated that the so-called "iatrogenic triad" - polypharmacy, drug interactions, and PIM - occurs in approximately one-third of elderly individuals who take medications[9].

Considering the fact that very old individuals - age greater than or equal to 80 years - are exposed to situations of fragility and reduction of functional capacity, the analysis of PIM during hospitalizations is worthy of attention and the motivation for the present study[10,11].

The goal of this study is to define the percentages and types of potentially inappropriate medications (PIM) for the elderly based on the Beers criteria AGS 2019[5] in the patients of very old age (≥80 years) hospitalized in the internal medicine ward of a tertiary hospital.

METHODS

A retrospective analysis of prescriptions from the medical records of very old patients hospitalized in the internal medicine ward of a tertiary hospital from 01/01/2018 to 27/10/2018, based on the Beers criteria AGS 2019. We considered as PIM the medications listed in Table 2 of these criteria[5]. We adapted that table for the medications approved for use in Brasil by the Brazilian Health Regulatory Agency (Anvisa), according to data on their website on 23 July 2019[12] (Table 1 of this study).

Other data collected: (1) gender, (2) mean age and standard deviation (3) days of hospitalization (mean and standard deviation), (4) presence of feeding tube (nasoenteral, nasogastric, or gastrostomy) based on the presence of medications with a contraindication for this route[13], (5) *delirium* (based on the Portuguese version of the *Confusion Assessment Method*[14]) justified due to the usual prescription of psychotropic drugs[15], (6) polypharmacy (use of five or more medications/day[7]).

Statistical analysis of the data was based on the presence or absence of a certain PIM regarding gender and age groups (80 to 89 years and equal to or greater than 90 years). We used Fisher's exact test with an alpha value of 0.05.

After being submitting the study to the Human Research Ethics Committee (CEP) of the institution to which the authors are part of and considering that the present study does not involve humans, the Committee considered there was no need to issue an opinion for it.

RESULTS

During the period of this study (300 days), 39 very old patients (22 men and 17 women) with a mean age of 86.3±4.7 years (80 to 98 years) were hospitalized in the internal medicine ward (approximate one hospitalization per week). The present sample was composed entirely of admissions from the emergency room, with an average of 22.8±21.3 days (3 to 129 days) of hospitalization. There as a need for oxygen supply and/or polypharmacy in 84.6% of cases and a diagnosis of *delirium* in 71.8%.

We detected the prescription of 16 drugs considered PIM based on the Beers criteria AGS 2019[5] (Table 2 of this study) - an average of 1.8±1.0 PIM per patient - (70 PIM/39 patients with extremes of 0 and 4 PIM). Main prescribed PIM (Figure 1): (1) metoclopramide, if necessary [IN] (41.0% of cases), (2) omeprazole (38.5%), (3) regular insulin [IN] (23.1%), (4) haloperidol [IN] (18.0%), (5 and 6) quetiapine and amiodarone (10% each). The final sum resulted in 70 PIM/39 patients.

We found statistically significant relationships between the absence or non-use of haloperidol, metoclopramide, and omeprazole in very old men grouped by age (80 to 89 years, 90 years or more). The statistical significance of haloperidol was based on the absence of use, and that of metoclopramide and omeprazole on their higher use by nonagenarians. Omeprazole was also statistically significant among elderly women, with a tendency to non-prescription for octogenarians.

DISCUSSION

The rapid process of population aging in Brasil and, consequently, the increase in hospitalizations in this age group deserves special attention from healthcare professionals[16].

Very old patients are noteworthy for the occurrence of three or more conditions - chronic-degenerative and concomitant - 66.0% more frequently than among quinquagenarians[17]. When there is an acute event and/or the decompensation of previous

TABLE 1. BEERS CRITERIA 2019 AGS® FOR POTENTIALLY INAPPROPRIATE MEDICATIONS FOR THE ELDERLY[5]. MEDICATIONS LICENSED FOR USE IN BRASIL[12].

<table>
<tr><th colspan="8">Therapeutic Class</th></tr>
<tr>
<td>Central alpha-agonists
Clonidine (for first-line treatment of hypertension)
Guanabenz
Guanfacine
Methyldopa
Reserpine (>0.1 mg/day)</td>
<td>Antidepressants
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin (>6 mg/day)
Imipramine
Nortriptyline
Paroxetine
Protriptyline
Trimipramine</td>
<td rowspan="2">First-Generation Antihistamines
Brompheniramine
Carbinoxamine
Chlorpheniramine
Clemastine
Cyproheptadine
Dexbrompheniramine
Dexchlorpheniramine
Dimenhydrinate
Diphenhydramine (oral)
Doxylamine
Hydroxyzine
Meclizine
Pyrilamine or Mepyramine
Promethazine
Triprolidine</td>
<td>Antiparkinsonian Drugs
Benzatropine (oral)
Trihexyphenidyl</td>
<td>Barbiturates
Amobarbital
Butabarbital
Butalbital
Mephobarbital
Pentobarbital
Phenobarbital
Secobarbital</td>
<td>Genitourinary drugs
Desmopressin</td>
<td>Hormones
Androgens
Methyltestosterone
Testosterone
Other hormones
Thyroid extract
Estrogen with or without progesterone
Growth hormone
Megestrol</td>
<td>Other Anxiolytics
Meprobamate</td>
</tr>
<tr>
<td>Peripheral Alpha-1 blockers for hypertension treatment
Doxazosin
Prazosin
Terazosin</td>
<td rowspan="2">Antispasmodics
Atropine (excludes ophthalmic use)
Belladonna alkaloids
Chlordiazepoxide-clidinium
Dicyclomine
Homatropine (excludes ophthalmic use)
Hyoscyamine
Methscopolamine
Propantheline
Scopolamine</td>
<td>Non-steroidal anti-inflammatory drugs
Acetylsalicylic acid (>325 mg/day)
Mefenamic acid
Ketoprofen
Ketorolac (including parenteral)
Diclofenac
Diflunisal
Etodolac
Fenoprofen
Ibuprofen
Indomethacin
Meclofenamate
Meloxicam
Nabumetone
Naproxen
Piroxicam
Sulindac
Tolmetin</td>
<td>Antipsychotics
First generation (conventional) and
Second generation (atypical)</td>
<td>Benzodiazepines
Short or intermediate action
Alprazolam
Estazolam
Lorazepam
Oxazepam
Temazepam
Triazolam
Prolonged Action
Chlordiazepoxide (alone or associated to amitriptyline or clidinium)
Clonazepam
Clorazepate
Diazepam
Flurazepam
Quazepam</td>
<td>Nonbenzodiazepine hypnotics
(Z-drugs)
Eszopiclone
Zaleplon
Zolpidem</td>
<td>Muscle Relaxants
Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Methocarbamol
Orphenadrine</td>
<td>Other cardiovascular action drugs
Amiodarone
Disopyramide
Dronedarone
Digoxin (as first-line treatment for atrial fibrillation or heart failure)
Nifedipine</td>
</tr>
<tr>
<td>Antibiotics
Nitrofurantoin</td>
<td></td>
<td>Antithrombotic drugs
Dipyridamole (oral, short-term)</td>
<td>Gastrointestinal tract
Metoclopramide
Mineral oil (oral)
Proton-pump inhibitor</td>
<td>Hypoglycemic Drugs
Sulfonylureas of prolonged action
Chlorpropamide
Glimepiride
Glyburide or
Glibenclamide
Short or fast-acting insulins
(in a scheme according to capillary glycemia)</td>
<td>Opioids
Meperidine</td>
<td>Vasodilators of dubious efficacy
Ergoloid mesylates
Isoxsuprine</td>
</tr>
</table>

diseases, the risk of hospitalization in very old patients reaches 13.6% in 12 months, in contrast to 8.9% for those aged between 50 and 59 years[18]. Both situations - multimorbidities and hospitalizations - lead to the simultaneous and progressive use of five or more medications daily in approximately 20.0% of elderly patients[19]. This therapeutic process presents a risk for adverse reactions to medications in percentages above 60.0% of hospitalized patients and to the use of PIMs[3,20].

Considering the above, it is recommended that the concept of PIM - which present a higher chance of adverse events than benefits - become part of clinical practice in the care for patients of this age group. The prescription of medications must be considered a potentially iatrogenic and lethal act, especially when there is evidence and/or alternatives of other medicines with equal or better effectiveness and that are safer for the pharmacological treatment of the patient under evaluation[3,6].

Very old patients often become prone to the so-called "iatrogenic triad" - polypharmacy, PIM, and drug interactions - a situation that can be prevented and in which criteria such as the Beers allow health professionals to take appropriate therapeutic decisions[3-5,9].

The fact that PIMs (haloperidol, insulin, and metoclopramide) are listed as "prescribed if necessary" does not minimize their potentially inappropriate indication to very old patients. It is inferred that the application of insulin with capillary blood glucose monitoring and the indication for metoclopramide for occasional vomiting incurs the false impression that episodic use does not lead to side effects and/or drug interactions. When talking about PIM, the frequency with which "if necessary" medications are used to

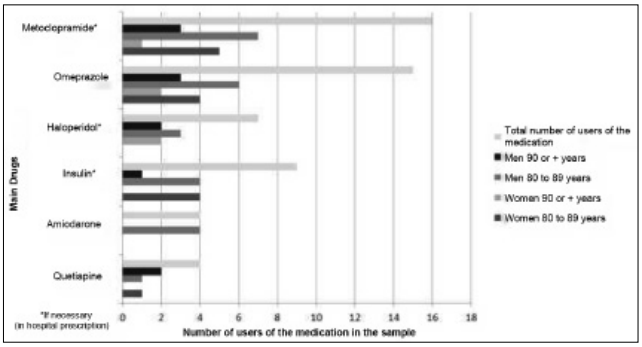
TABLE 2. MEDICATIONS CONSIDERED POTENTIALLY INAPPROPRIATE FOR THE ELDERLY BASED ON THE BEERS CRITERIA AGS 20195 AND OBSERVED IN PRESCRIPTIONS OF VERY OLD PATIENTS HOSPITALIZED IN THE INTERNAL MEDICINE WARD OF A TERTIARY HOSPITAL (70 MEDICATIONS/39 USERS).

Potentially inappropriate medications for the elderly	Women		Men		Total number of users	Percentage of users
	Age (years)		*Age (years)*			
	80 to 89	90 or +	80 to 89	90 or +		
Amiodarone	-	-	4	-	4	10.0
Atropine*	-	-	1	1	2	5.0
Clonazepam	1	-	-	-	1	2.6
Diazepam	-	-	1	-	1	2.6
Digoxin	-	-	1	-	1	2.6
Doxazosin	-	-	2	-	2	5.0
Haloperidol[IN]	-	2	3[#]	2[#]	7	18.0
Insulin[IN]	4	-	4	1	9	23.1
Methyldopa	1	-	-	-	1	2.6
Metoclopramide[IN]	5	1	7[+]	3[+]	16	41.0
Mineral oil	-	-	3	-	3	7.7
Omeprazole	4'	2'	6"	3"	15	38.5
Quetiapine	1	-	1	2	4	10.0
Risperidone	-	-	2	-	2	5.0
Tramadol	1	-	-	-	1	2.6
Zolpidem	-	-	1	-	1	2.6

* = Eye drops, [SN] = If necessary, [#]p=0.0240, p=0.0322, p=0.0251, p=0.0249

The sum of the percentages is greater than 100.0% since in this sample there are very old individuals who took more than one potentially inappropriate medication.

FIGURE 1. MAIN MEDICATIONS CONSIDERED POTENTIALLY INAPPROPRIATE FOR THE ELDERLY BASED ON THE BEERS CRITERIA AGS 20195 AND OBSERVED IN PRESCRIPTIONS OF VERY OLD PATIENTS HOSPITALIZED IN THE INTERNAL MEDICINE WARD OF A TERTIARY HOSPITAL (70 MEDICATIONS/39 USERS).



be noted, since - depending on the clinical condition - their use can become daily and not episodic[5]. The same circumstance was observed in the indication of haloperidol for very old patients with conditions of *delirium* and/or severe cognitive dysfunction since there is a risk that doses administered without a criterion of maximum value might exceed the dose of 5 mg/24 hours[15]. Thus, the standard from the place of origin of the present sample, which adds up the total doses and their milligrams, is justified to reduce the risk of adverse reactions to these medications.

Another routine in the infirmary dynamics, on which this study is based, refers to medications and feeding tubes. The indication for nutrition via alternative routes is common among the elderly - notably among very old ones - who are hospitalized. However, not all medications are able to fully accomplish their function via these routes. The Beers criteria do not comment on this aspect of the medicines analyzed in this series - digoxin, haloperidol, omeprazole, and tramadol -, which have non-crushable presentations or that precipitate with an enteral diet[5,13]. This constitutes, thus, a curious situation, in which the PIM not only is contraindicated due to a greater probability of adverse events but also for the possibility of not being absorbed in this route of administration. The association of such details is worthy of mention due to the false sense of correct prescription to very old patients with overlapping iatrogenesis, i.e., from the medication (PIM) and the procedure (feeding tubes)[21].

The prescription of omeprazole in over one-third of very old patients justifies two comments. The medication was long considered a low hazard for the elderly, and the Beers criteria included it as a PIM just in its last two updates (2015 and 2019)[5,22]. This was due to reports on adverse events during its chronic use (for more than eight weeks daily), especially among patients in this age group[23]. Omeprazole is currently

related to falls and fractures, *Clostidium difficile* infections, community-acquired pneumonia, vitamin B12 deficiency, dementia, injury, and kidney disease[23]. The second comment, which is also a relevant factor, relates to reports that approximately 63.0% of users of this proton-pump inhibitor do not exhibit gastrointestinal symptoms, diagnosis of diseases of the digestive system, and/or the simultaneous use of other medications with the potential for gastrointestinal lesions[23]. It is recommended that, prior to the prescription of a proton-pump inhibitor, a careful evaluation of medications in use be conducted to define the therapeutic purpose of each of them. By doing this, it is possible to have a simple and low-cost mechanism that can reduce the indices of polypharmacy among the elderly - notably very old ones -, creating a culture of de-prescription, something that is being developed at the hospital of origin of the present sample[24].

It is inferred that the presence of psychotropic drugs - clonazepam, diazepam, haloperidol, risperidone, quetiapine, and zolpidem - is this sample is due to the high percentage of cases of acute mental confusion, (*delirium*). It is important to note that the number of users of this pharmacological group is smaller than the percentage of patients with *delirium* in this study. This discrepancy is justified by the hospital protocol for early detection of acute confusional states on the site that originated sample, which enables the use of non-pharmacological measures and a reduction in prescriptions of psychotropic drugs[15].

The present sample - of convenience - does not allow the full generalization of the results but exposes a concrete need for the rational systematization of prescriptions for elderly patients, especially very old ones. There are tools available for that, with emphasis on PIM lists, particularly the Beers criteria[5,22].

CONCLUSION

Very old patients hospitalized and evaluated in this study based on the Beers criteria AGS 2019 showed a significant percentage of PIM, in particular, those indicated as "if necessary". This increases the risk of side effects due to the high frequency of polypharmacy in this age group and indicates the need for the systematization of therapeutic care in very old patients.

Author's Contribution

Milton Luiz Gorzoni - Data collection and analysis. Initial draft of the manuscript; Ronaldo Fernandes Rosa - Original concept, adaptation of the Beers AGS 2019 criteria to this study and revision of the manuscript.

RESUMO

OBJETIVO: *Definir percentual e tipos de medicamentos potencialmente inapropriados para idosos (MPII) pelos critérios de Beers AGS 2019 em longevos (idade ≥80 anos) hospitalizados em enfermaria de clínica médica.*

MÉTODO: *Análise retrospectiva das prescrições de prontuários de longevos internados em enfermaria de clínica médica de hospital terciário pelos critérios de Beers AGS 2019. Outros dados coletados: gênero, idade média, dias de hospitalização, presença de sonda de alimentação, delirium, polifarmácia (≥5 fármacos/dia). Consideraram-se como MPII os fármacos listados na Tabela 2 do referido critério.*

RESULTADOS: *Trinta e nove longevos (22 homens, 17 mulheres), idade média 86,3±4,7 anos e 22,8±21,3 dias de hospitalização. A presente casuística foi integralmente admitida pelo pronto-socorro, ocorrendo sonda de alimentação e polifarmácia em 84,6% dos casos e delirium em 71,8%. Detectou-se a prescrição de 16 fármacos considerados MPII pelos critérios de Beers AGS 2019 (média de 1,8±1,0 MPII por paciente). Principais MPII prescritos: metoclopramida, se necessário [SN] (41,0% dos casos), omeprazol (38,5%), insulina regular [SN] (23,1%), haloperidol [SN] (18,0%), quetiapina e amiodarona (10% cada).*

CONCLUSÃO: *Na presente casuística, longevos hospitalizados apresentaram percentuais significativos de MPII, notadamente em fármacos indicados como "se necessário", o que aumenta o risco de efeitos colaterais ao fato comum de polifarmácia nessa faixa etária.*

PALAVRAS-CHAVE: *Idoso de 80 anos ou mais. Preparações farmacêuticas. Pacientes internados. Lista de medicamentos potencialmente inapropriados.*

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ORIGINAL ARTICLE

Effect of competence health cultivation on the prevention and control of inadvertent perioperative hypothermia

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SUMMARY

OBJECTIVE: *To explore the feasibility of health competence cultivation on the prevention and control of Inadvertent Perioperative Hypothermia (IPH).*

METHODS: *Patients with expected spinal surgery were divided into group A and group B by the random number method. Group B followed routine IPH management, and health training measures for performance and ability were implemented in Group A. The scores of the health competence questionnaire, the temperature at different times, IPH complications, and hospitalization for the two groups were observed and compared.*

RESULTS: *The main evaluation indexes, such as the health competence questionnaire score, temperature fluctuations, and IPH complications, during the perioperative period in group A were significantly better than those in group B ($p < 0.05$). The indexes of anesthesia, total hospital expenses, and health service satisfaction in group A were also significantly better than those in group B, which shows the advantages of cultivating health capabilities in both doctors and patients.*

CONCLUSION: *Through health competence cultivation and feasible health management measures, the medical staff can improve the quality of IPH prevention and management.*

KEYWORDS: *Perioperative period. Hypothermia. Health management.*

INTRODUCTION

Inadvertent Perioperative Hypothermia (IPH) refers to the core body temperature of non-hypothermic patients below 36°C during the perioperative period, which is the main cause of serious complications such as perioperative cardiac accidents, increased bleeding, and post-operative infection[1].

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With the deepening of basic and clinical research, the whole process of low-body-temperature prevention and control technologies, such as pre-heat treatment during the induction period of anesthesia, body-surface hot-air insulation, whole-course heated-liquid infusion, and preoperative high-energy diet, as well as the whole process of nursing management technology are becoming more and more mature[2,3]. The direct risk factors of IPH are visceral tissue exposure, large temperature difference between the inside and outside of the body, and a high liquid-evaporation heat transfer coefficient. The adoption of preventive advanced technology and control equipment, to a certain extent, reduces the rate of occurrence of IPH[3]. For example, preheating management during the anesthesia induction period under whole-course core-body-temperature monitoring, mechanical respiratory circuit heating, whole-course intravenous infusion fluid heating or temperature-controlled pressure infusion, temperature management of non-operative parts, especially limbs in hot-air bags, hot-liquid irrigation in the operation field, etc. At the same time, we should improve doctors' standards of diagnosis and treatment and the level of medical humanistic services, enhancing the ability of doctors and patients to cooperate in the prevention and control of medical risks[4]. The expansion of IPH prevention and control technology and the promotion of medical humanities services can significantly improve the quality of perioperative management of patients undergoing surgery. Meta-literature data shows that 30% to 60% of patients had body temperature lower than 36°C one hour after anesthesia recovery, 72% of the patients with unexpected ICU monitoring and treatment after the operation had delayed anesthesia recovery or cardio-cerebrovascular complications caused by hypothermia after the operation, and 45% of the patients with delayed discharge from the daily operation were due to postoperative hypothermia[5]. IPH is a challenge for both doctors and patients, so can we: improve the health competence level of both doctors and patients through targeted health education or professional ability cultivation; guide patients to actively, scientifically, and reasonably refer to perioperative health management; strengthen doctors' professional responsibility and risk prevention and control ability; and further reduce or mitigate the health damage caused by IPH?

METHODS

IPH defect analysis

Literature studies[6] believe that the existing measures lack of patient's active participation in the guidance and assessment management of doctor's active prevention and control behavior makes IPH prevention and control management face bottlenecks; the cultivation and application of health competence in perioperative patients' health management is a new concept, whether patients can effectively adapt to the risks of surgical treatment, and whether they can cooperate with doctors to effectively improve remains unknown. Raising the level of IPH prevention and control should be an effective way to break through the bottleneck.

Doctor-patient health risk perception:

In view of IPH as a health risk factor, patient risk perception, risk prevention and control skills, cooperation efficiency, and expected evaluation are the key to active prevention and control. The assessment of overall health risk factors and targeted health education are important parts of risk reduction and the improvement of patients' health competence level[7]. Anesthesiologists in the department of anesthesia and specialized wards lack traditional medical education, practical clinical diagnosis and treatment processes and norms, and cultivation and assessment management of health education ability.

Education on prevention and evaluation of IPH

Based on the recognition of health competence theory and practical defects, the path to prevention and control and evaluation criteria based on IPH health competence were formulated after discussion (Table 1). Doctors' and patient's level of information on IPH's physical-mental-social health damages was clarified, and the corresponding countermeasures were formulated; the equipment, technology and management processes already applied were optimized, and the following aspects were strengthened: identification of the risk factors for IPH as a whole; improvement of the perioperative physiological health competence skill from spiritual-social health guidance; highlighting the overall health management service and evaluation of the benefits of IPH prevention and control from the perspective of health economy; clarification of the effect of group IPH prevention and control, highlighting effective cooperation between doctors

and patients, and emphasizing the coordination and detail management ability of head nurses in the operating room.

IPH prevention and control scheme based on health competence

The management process, core measures and indicators of doctor-patient health competence education and IPH prevention and control were formulated with the approval of the Academic Ethics Committee of the hospital (see table 2), and a questionnaire was designed based on the score of health competence for IPH prevention and control. The key points were as follows: doctors and patients discuss the standard, and the preventive and control management measures until a consensus is reached; timely coordination of medical and nursing teams could enable targeted preventive and control management measures. (3) Individualized selection and standardized implementation of overall health assessment and whole-process temperature monitoring management; (4) Harmonized and unified recognition of patients' health comfort; medical and nursing occupational comfort; and patients' participation in the management of their safety standards; (5) Knowledge and management of safety indicators of expected health maintenance quality; operating room head nurses combine a management role and ability assessment throughout the process.

Health competence training and questionnaire survey

Medical staff health competence training on IPH prevention and control adopted the random lottery method to divide the head doctors or nurses, anesthesiologists, and operating room nurses in the four orthopedic wards of our hospital into two groups, i.e., A and B. Group A was trained by health competence guidance and evaluation experts on this subject; Group B was trained by the head nurses of the operating room for routine IPH prevention and control management, before and after training and research implementation. The questionnaire for health competence in IPH prevention and control was used to evaluate the health competence scores of head doctors and nurses in the two groups. Two groups of patients were responsible for the training of ward and operating room nurses, respectively, in patients hospitalized, 48 hours before surgery, 72 hours after surgery, and 4 hours before discharge for health competence on IPH prevention and control using the questionnaire and targeted training.

TABLE 1. IPH PREVENTION AND CONTROL EDUCATION AND EVALUATION CRITERIA BASED ON COMPETENCE HEALTH

Competence Health	Risk Elements	Patient Education and Evaluation	Medical Education and Evaluation	Expected Indicators
Physiological Competence Health	Diagnosis and treatment of physiological abnormalities	Preoperative evaluation of physiological function	Omnidirectional Risk Assessment Ability	Individual physiological health indicators can be based on
	Central hypothermia	Whole-course temperature monitoring and management	Regulations and Professional Insight	Scientific and Reasonable Equipment Technical Data
	Physiological function injury	Visceral Compensation and Prevention and Control	Risk Awareness and Recognition Preventive Ability	Precise Regulation and Timely Emergency Prevention and Control
Spirit Competence Health	Health cognitive impairment	Medical risk and coping Education	Health Humanities and Medical Effectiveness Evaluation	Health Cognition and IPH Knowledge Sharing
	Psychological adaptation disorder	Early Warning Guidance and Assistant Intervention Management	Occupational Behavior Habits and Care	Understanding Care and Joint Response under Expected Goals
	Abnormal moral behavior	Risk Communication and Moral Behavior Guidance	Professional Ethics and Patient Participation in Management	Behavior Regulation and Sharing under Security Expectation
Social Competence Health	Role Recognition Adaptation	Patient Role Adaptation and Family Care	Professional Role and Professional Behavior Standards	Role Orientation and Behavior Appropriateness
	Medical Expenditure Burden	Family Economic Burden and Medicare Model	Medical Benefit Welfare and Patient Health	Optimal Medical Benefit Based on Quality and Safety
	Communication, coordination and understanding	Active and Passive Communication and Cultural Understanding Ability	Health Education and Risk Sharing Awareness	Risk Consensus Awareness and Coordination Ability

TABLE 2. IPH MANAGEMENT PROCESS, CORE MEASURES AND STANDARDS BASED ON COMPETENCE HEALTH

Number	Core Measures	Standard Achievement	Score Assignment Standard
1	Risk Cognitive Education and Competence Guidance 48 hours before Operation	Familiar with the condition, know the operation method, confirm the risk early warning	2 points per item
2	High-energy diet and physical exercise guidance to ensure sleep quality	Energy reserve > 30%, physical stability, adequate sleep > 8 hours	2 points per item
3	Adaptive Education and Participatory Skills Guidance 24 hours before Operation	Familiar with operating room environment, clear hypothermia response and understanding of treatment cooperation requirements	2 points per item
4	Preoperative IPH Cognitive Education for Relatives and Patient Care Guidance	Actively provide health information, cooperate with patients to control diet and complete physical exercise	2 points per item
5	Education and preoperative preparation of patients within 4 hours before operation	Psychological comfort and intervention of patients, preoperative preparation and evaluation, nursing handover to meet the standard	2 points per item
6	Patient guidance, anesthesia induction preheating and environmental adaptation	Timely communication and cooperation, accurate feedback, preheating body temperature feeling up to standard	3 points per item
7	Position protection and accurate temperature monitoring and control equipment connection	Room temperature standard, effective coverage, accurate monitoring data, clear physical monitoring location	3 points per item
8	The alarm response and expectation are appropriate, and the fluctuation of monitoring indicators is up to the standard	Active physical monitoring, adapting to alarm response, early warning management up to standard, data fluctuation up to standard	3 points per item
9	Awakening Preheating Management and Comfort Feedback Reaching the Standard after Awakening	Pre-heating management before operation, temperature of awake precursor reaching standard and feedback reaching standard after awakening	3 points per item
10	Transfer body temperature up to standard, key handover and monitoring clear	Transfer temperature monitoring, ward handover, patients'feelings and relatives' evaluation to reach the standard	2 points per item
11	Postoperative 24-hour temperature monitoring, doctor-patient cooperation with rehabilitation exercise	24-hour body temperature monitoring after operation, patient cooperation and rehabilitation, active prevention and control of relatives	2 points per item
12	No complications occurred 72 hours after operation, and the diet and physical fitness were up to standard.	Overall health assessment, post-operative infection, cardio-cerebral accident, and overall data evaluation	3 points per item

The overall score was 93 points, and those with 2 points for each index were scored according to whether they met the criteria or not; those with 3 points were scored according to excellent, good and scorable;

Psychological intervention is based on psychological counseling and assisted with sedative drugs when necessary;

In addition to the dietary coordination of relatives, emphasis should be placed on the rehabilitation exercise of disabled limbs and the safety protection of patients during exercise.

Prospective nursing observation method:

We determined that patients with elective spinal surgery would be selected as the target. The selection criteria were age 18-65 years old, no gender limitations, junior high school and above education level, patients with normal intelligence and mental morality were assessed on admission. We agreed to the nursing research scheme and cooperated with each other. The expected operation time was 1 hour. The expected bleeding volume was less than 10 ml/kg over an hour. Exclusion criteria: Patients who did not agree to participate in this study, significant organ dysfunction before the surgery, precursor energy index less than grade 4, etc. According to the expectation, 120 patients were divided into two groups: group A (guided by health competence) and group B (guided by routine nursing). For group B, surgeons were required to submit the elective operation plan 48 hours in advance. The trained nurses in the ward and operating room were responsible for conducting health education and ability guidance for patients based strictly on the observation process and IPH measures and standards. The focus was to enhance the ability of patients to cope with the challenges of surgical treatment and self-management, including patients' relatives. In group B, perioperative nursing management and standardized operation were carried out according to the relevant guidelines and normative requirements [2] and revised IPH prevention and control nursing standards by the expert group.

Evaluation of patients' participation in safety management and satisfaction:

All cooperation measures and supervision methods were applied by the patients. The evaluation of satisfaction with medical care was unified by the hospital health service department, and 30% of discharged patients participated in face-to-face interviews that included a unified evaluation questionnaire. A total of 20 questions were scored as excellent; good, fair, poor, and inferior scored 5-1 points.

Observation Indicators and Records:

Referring to a previous study[2], the standards for temperature monitoring and management in the perioperative period were formulated, and the methods of temperature collection, intervention red flags, abnormal analysis, and treatment measures needed for comparative analysis at key time points were determined.

Statistical analysis of data:

All 120 patients completed data acquisition by SPSS21 Chinese software, and data was counted using the chi-square test (2) and measured by students t-test; $P < 0.05$ showed significant difference.

RESULT

The nursing observation of 120 patients was completed from March 2018 to October 2018. The average age of the 120 patients was 64.82 +10.38 years, and there were 51 males and 69 females, all of whom met the criteria for nursing observation. There were 49 cases of cervical and lumbar disc herniation, 37 cases of spinal stenosis, 23 cases of vertebral fracture, and 11 cases of intraspinal tumors. The operation time ranged from 1.2 hours to 3.9 hours, with an average of 2.16 + 0.42 hours. Preoperative coexistence included 24 cases of hypertension, 17 cases of diabetes, 9 cases of coronary heart disease, and 3 cases of chronic obstructive pulmonary disease. There was no serious cardiopulmonary, liver, kidney, brain, or other important organ dysfunctions before the operations. There was no significant difference between the two groups ($p > 0.05$).

Health Competence Survey:

The statistical results of the doctor-patient health competence questionnaire are shown in Figure 1. The results show that the level of health competence in both groups is significantly higher than the basic value ($p < 0.01$) through training and effective implementation. The results from the questionnaires in all the three different observation tine points were significantly better in group A than in group B. The comparison between the two groups found differences mainly in the health competence indicators in life, psychology, and society. The scores for indicators relating to roles, thoughts, morality, and spirit, in particular, were not satisfactory in group B, which shows that both doctors' and patients' attention to social and mental health is not high in the process of traditional medical services.

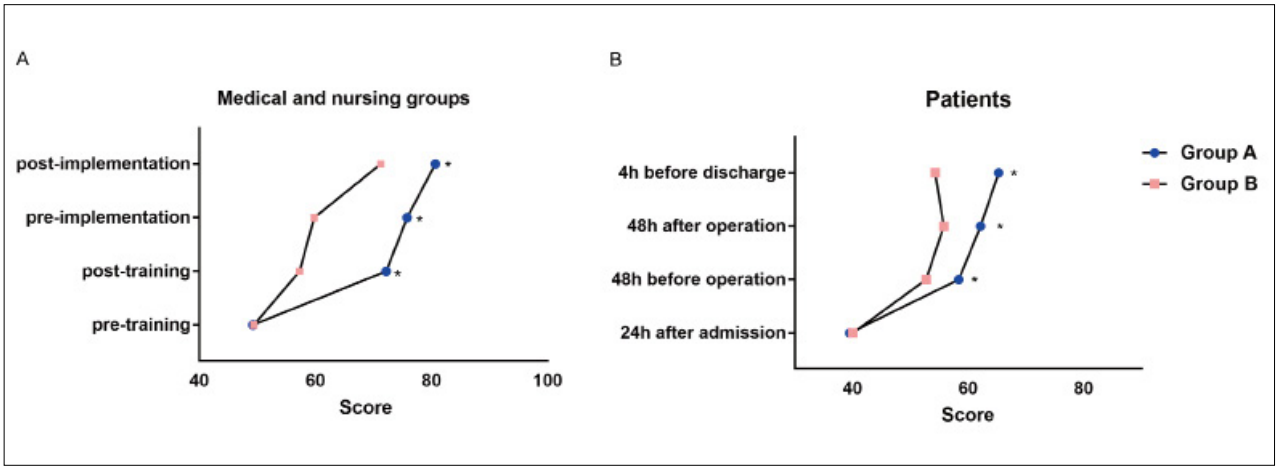
Temperature management:

The data show that the mean temperature at each time point in group A was significantly different from that in group B ($P < 0.01$). The patients' temperature stability was better, and the expected control index value more ideal.

IPH-related events:

A comparative analysis of IPH-related events between the two groups shows that the three indicators of myocardial ischemia, hypoxemia, and post-operative shivering in group B were significantly lower than those in group A ($p < 0.01$); there was a significant difference in postoperative infection ($p < 0.05$). The internal relationship analysis of the abnormal indicators shows that hypothermia affects microcirculation metabolism and impairs body immunity.

FIGURE 1



Medical expenses and satisfaction:

The hospitalization expenses, anesthesia expenses (excluding orthopedic surgery consumables) of the two groups were compared with the survey data from 72 hours after the operation or hospital discharge. The results showed that the total hospitalization expenses and ICU monitoring time of group A were significantly lower than those of group B ($p < 0.001$); the medical satisfaction and hospitalization days of group A were significantly different from those of group B ($p < 0.01$). The difference between anesthesia cost and medical satisfaction was significant (< 0.05), suggesting that IPH prevention and control based on health competence can significantly improve the quality of medical care, slow down IPH and its complications, reduce medical expenses, and improve inpatient health and medical satisfaction.

DISCUSSION

This article not only strengthens the management of the medical staff health competence health cultivation but minimizes the work flaws caused by occupational burnout. In group A, the head nurses cooperated with ward nurses, strengthening preoperative targeted active and passive physical exercise and increasing confidence in the surgical treatment for patients. Rehabilitation can also improve the tolerance of the body to changes in environmental temperature and promote the metabolism of myoblasts, improving patients' appetite and quality of dietary correction and compliance. Compared with group B, the standardized prevention and control management of IPH emphasizes holistic nursing management centered on patients' health. Medical burden is a concern of the government and family in the new era. The two groups of patients refused to use IPH prevention and control equipment when they signed the consent form based on preoperative health education, and group A was significantly higher than group B (31:18). Group A, from the perspective of health competence, further optimized the use of relevant equipment indicators, and highlighted patient autonomy. Through targeted health guidance, patients' health competence level was improved, and the medical staff was actively assisted to optimize preoperative accuracy. Preparatory measures should be taken to improve the level of physical-psychological-mental health competence, reducing the incidence of IPH and the medical burden, and improving the satisfaction of inpatient health care.

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Disclosure

The authors report no conflicts of interest in this work.

Author's Contribution

Conceptualization, Ji-Yue Shi; formal analysis, Tian-You Zhou; writing (original draft preparation), all authors; writing (review and editing), Ji-Yue Shi; supervision, Shu-Fang Du; funding acquisition, Ji-Yue Shi.

RESUMO

OBJETIVO: *Explorar a viabilidade do cultivo da competência em saúde na prevenção e controle da hipotermia perioperativa inadvertida (IPH).*

MÉTODOS: *Pacientes com cirurgia espinhal marcada foram divididos em dois grupos, A e B, pelo método de números aleatórios. O grupo B foi conduzido com base na gestão rotineira para prevenção de IPH; já no grupo A, foram implementadas medidas de treinamento em competência de saúde. As pontuações do questionário sobre competência em saúde, a temperatura aferida em diferentes momentos, complicações relacionadas à IPH e hospitalização dos dois grupos foram observadas e comparadas.*

RESULTADOS: *Os principais índices de avaliação, como a pontuação do questionário sobre competência em saúde, a variação de temperatura e as complicações relacionadas à IPH durante o período perioperatório foram significativamente melhores no grupo A do que no grupo B (p<0,05). Os índices de anestesia, despesas hospitalares totais e satisfação com o serviço de saúde também foram significativamente melhores no grupo A do que no B, o que demonstra as vantagens do cultivo da competência de saúde tanto em médicos como em pacientes.*

CONCLUSÃO: *Por meio do cultivo de competências de saúde e de medidas viáveis de gestão da saúde, a equipe médica pode melhorar a qualidade da prevenção e gestão da IPH.*

PALAVRAS-CHAVE: *Período perioperatório. Hipotermia. Gestão em saúde.*

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ORIGINAL ARTICLE

Mortality due to congenital heart disease in Pernambuco from 1996 to 2016

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SUMMARY

BACKGROUND: *To determine the magnitude and temporal trends of deaths due to congenital heart disease (CHD) in Pernambuco between 1996 and 2016.*

METHODS: *This was an ecological, time-series study, involving all cases of deaths from congenital cardiovascular malformations in the state of Pernambuco, from 1996 to 2016, using data from DATASUS, SINASC and SIM.*

RESULTS: *There were 3,584 deaths from congenital cardiovascular malformations amongst individuals aged 0 to 14 years, of which 81.94% were concentrated in children aged under one year. The infant mortality rate (IMR) presented a linear growth trend of 0.4645 per year (p <0.01). The cause-of-death code Q24 (other congenital malformations of the heart) was present in 72.54% of the death records and 48.17% of the deaths occurred in infants aged between 28 and 364 days of life. The highest occurrence of deaths was identified in children with low birth weight (500 and 1,499g), male, premature, children of mothers without schooling, in deliveries at home (p <0.05).*

CONCLUSIONS: *Congenital heart disease still represents a public health problem as a cause of death, particularly in the first year of life, with IMR in a linear growth trend. Deaths from CHD were more prevalent in male children, born prematurely, with low birth weight, born to mothers with low schooling and deliveries without medical care.*

KEYWORDS: *Infant mortality. Heart diseases. Congenital abnormalities.*

INTRODUCTION

Congenital heart diseases (CHD) are a frequent anomaly with an estimated incidence ranging from 8 to 10 per 1,000 live births and associated with a high mortality rate, significant social and health care costs[1,2]. CHD is a broad clinical spectrum, ranging from asymptomatic to complex and potentially fatal defects[1-3].

Approximately four million neonatal deaths occur each year and it is estimated that 7% are related to some type of CHD. It should be noted that without intervention, 30% of infants presenting with heart disease will not survive the first year of life[4]. CHD is the leading cause of death in neonates, the ninth cause of death in infants aged under 1 year, the eighth between

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1 and 9 years, and seventh in children aged between 10 and 14[5,6]. In the Brazilian state of Pernambuco, between 1979 and 2003, congenital malformations of the cardiovascular system accounted for 41% of the deaths among children under one year with congenital anomalies[7].

The impact of congenital anomalies on infant mortality rates is dependent on several factors, such as the quality, availability, and access to surgical treatment and primary healthcare. Thus, knowing the mortality profile of CHD is important to understand its impacts on infant health and as an indicator for primary and tertiary levels of child care. The aim of this study was to determine the magnitude and temporal trends of deaths from cardiovascular congenital malformations in Pernambuco, between 1996 and 2016.

METHODS

This was an ecological, time-series study, involving all cases of death due to congenital cardiovascular malformations in the state of Pernambuco, Brasil, between 1996 and 2016, with data collection between January and February 2019. The sample was composed of all cases of death in the population aged between 0 (zero) and 14 years, with the cause of death defined as congenital by the International Classification of Diseases (ICD 10), codes Q20 to Q28[8].

All cases of death from CHD were listed by accessing data from the Informatics Department of the Brazilian Unified Health System (DATASUS), the Live Birth Information System (SINASC), and the Mortality Information System (SIM), through the TABNET website, and data analysis was conducted in R 3.1.1®. The following variables were analyzed: deaths of infants/children aged from 0 to 14 years due to ICD-10 codes Q20 to Q28, infant death by: age group, gender, birth weight, maternal education, length of pregnancy, place of birth, and calculating the infant mortality rate (IMR).

Frequency distribution matrices were used to calculate the means and their respective standard deviations for the quantitative variables. All data presented normal distribution with the Kolmogorov-Smirnov or Shapiro tests, and the homogeneity of variances was verified with the Bartlett test. The Anova and Tukey ad hoc tests were performed to assess the differences between the mean values of three or more data sets. T-tests enabled a comparison between the mean values of two data sets. A significant difference was considered for $p \leq 0.05$. An assessment of the trends of infant mortality data was made by linear regression.

The study was approved by the Pernambuco State Secretariat for Health and by the Research Ethics Committee at the Oswaldo Cruz Complex/PROCAPE, in accordance with Report Nº 3.025.594 and CAAE: 84512018.1.0000.5192, complying with Resolution Nº 466/2012 of the National Health Council.

FIGURE 1. DEATHS DUE TO CONGENITAL CARDIOVASCULAR MALFORMATIONS X BIRTH WEIGHT. PERNAMBUCO, 1996 TO 2016

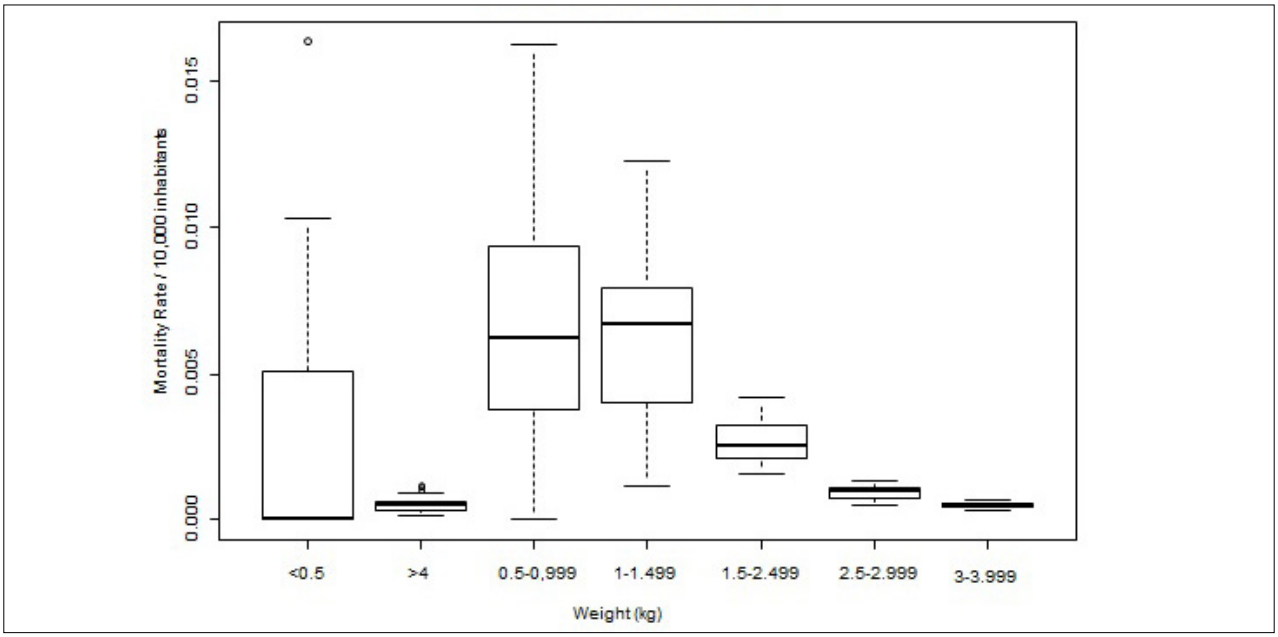

TABLE 1. OVERALL CAUSE MORTALITY Q X AGE (YEARS AND DAYS). PERNAMBUCO, 1996 TO 2016.

Code ICD-10*	Age (years)				n (%)
	< 1 year	1 a 4 years	5 a 9 years	10 a 14 years	
Q20	128	12	4	1	145 (4. 04)
Q21	278	83	23	14	398 (11.10)
Q22	48	9	5	4	66 (1.84)
Q23	51	3	8	2	64 (1.78)
Q24	2170	301	80	42	2593 (72.34)
Q25	210	10	6	4	230 (6.41)
Q26	5	0	0	0	5 (0.13)
Q27	13	1	2	6	22 (0.61)
Q28	34	11	9	7	61 (1.70)
TOTAL	2937	430	137	80	3584 (100)
Code ICD-10	Age (days)				n (%)
	0 a 6 days	7 a 27 days	28 a 364 days	Unknown	
Q20	21	42	65	0	128 (4.35)
Q21	53	43	181	1	278 (9.46)
Q22	14	9	25	0	48 (1.63)
Q23	14	14	23	0	51 (1.73)
Q24	716	439	1014	1	2170 (73.88)
Q25	58	72	80	0	210 (7.15)
Q26	2	0	3	0	5 (0.17)
Q27	4	3	6	0	13 (0.44)
Q28	10	6	18	0	34 (1.15)
n	892 (30.37)	628 (21.38)	1415 (48.17)	2 90 (0.06)	2937
(%)					(100)

* ICD-10: International Classification of Diseases and Related Health Problems, 10th Revision

TABLE 2. DEATHS DUE TO CONGENITAL CARDIOVASCULAR MALFORMATIONS VERSUS MATERNAL CHARACTERISTICS AND PLACE OF DELIVERY. PERNAMBUCO, 1996 TO 2016.

Maternal Education (in years)	n (per year)	N (per year)	MR* (mortality rate per 10 000 inhabitants) ± DP
0 (no schooling)	10.1	10226	9.9±4.7[b]
1 - 3	12.1	16136	7.5±6.1[a]
4 - 7 s	34.2	41956	8.1±1.6[a]
8 - 11	35.9	46129	7.8±2.1[a]
≥12	12.1	14486	8.4±4.3[a]
Gestational age (weeks)	**n (per year)**	**N (per year)**	**MR* (mortality rate per 10 000 inhabitants) ± DP**
< 22	3.0	109	279.5±7.3[b]
22 a 27	3.2	611	53.0±2.3[a]
28 a 31	6.0	1156	51.5±2.9[a]
32 a 36	18.7	9219	20.3±8.8[a]
37 a 41	75.2	132999	5.7±1.6[a]
42	2.1	3319	6.3±1.4[a]
Place of delivery	**n (per year)**	**N (per year)**	**MR* (mortality rate per 10 000 inhabitants) ± DP**
Health services for child birth care	131.9	146030	9.0±5.0[a]
Other health service	0.9	1350	6.7±1.1[a]
At home	5.4	1344	40.4±2.5[b]

n = mean number of deaths associated with congenital cardiovascular malformations during the study period; N = mean of live births in the study period; MR = mean mortality rate associated with congenital cardiovascular malformations. SD = standard deviation. * Means followed by the same letter do not differ statistically from each other by the Tukey test, at 5% probability..

RESULTS

The study included all cases of death from CHD amongst infants/children aged between 0 and 14 years, from 1996 to 2016, totaling 3,854 cases, of which 2,937 occurred in infants aged under one year. Thus, Table 1 presents data from the general population up to 14 years of age. In Figure 1 and Table 2, we decided to present data from the population aged one year and under, thereby representing 81.94% of all deaths.

With regard to the number of deaths of infants/children aged between 0 and 14 years of age due to CHD, there was a predominance in the group <1 year, corresponding to 2,937 of total deaths, and ICD-10 code Q24 (other congenital malformations of the heart) was the most frequent in all ages, 72.34% (n = 2,593), of all deaths (Table 1).

In infants aged under one year, the ICD-10 code Q24 represented the majority of cases of death, with 73.88% (n = 2,170). It should be noted that 48.17% (n = 1,415) of deaths occurred in infants aged older than 28 days and younger than 364 days. However, 30.37% (n = 892) occurred early in infants aged from 0 to 6 days (Table 1).

The IMR presented heterogeneous results. The lowest rate occurred in 2001 (6.64) and the highest in 2009 (11.49). However, a general increase may be observed. The IMR regression demonstrated a linear growth trend with an increase of 0.4645/year ($p<0.001$).

A significant difference (ANOVA, $F = 21.59$, $p<0.0001$) was observed in the mean values of the mortality rates of infants born weighing between 500g and 1,499g (Figure 1) and in male infants (t-test, $t=2.11$, $p<0.05$). A significant difference was observed in the occurrence of death amongst those born to mothers with no schooling (ANOVA, $F = 6.97$, $p<0.001$), whose gestation had been less than

22 weeks (ANOVA, F = 7.81, p<0.0001), and at home delivery (ANOVA, F = 12.09, p<0.0001) (Table 2).

DISCUSSION

There was a predominance of deaths from congenital malformations of the heart in the group <1 year, and the ICD-10 code Q24 was the most frequent cause of death at all ages. It should be emphasized that the data were taken from the information system and accurate diagnoses require cardiology staff, in specific services. Matos[9] reported that CHD was the leading cause of mortality amongst congenital malformations, accounting for 80% of deaths in infants aged under one year. Most CHD contributes to the occurrence of deaths since the anatomical and clinical conditions presented are often incompatible with life and are extremely dependent on advanced, appropriate medical-hospital care in order to survive[10].

Lopes et al.[11] and Brum et al.[12] highlight that CHD is associated with a higher occurrence of fetal deaths, since it is present in up to 85% of autopsy findings, and is an outstanding major factor for causing cardiac arrest during the first two years of life. It should be highlighted that the number of deaths related to CHD is officially lower than in fact it should be. Underreporting in Brasil remains a constant reality since newborns often leave hospital clinically well, and on arrival at home begin to degenerate, thereby dying without hospital records registering the true cause of death[10,12].

A study in Rio de Janeiro observed that the highest proportion of mortality was through unspecified congenital malformations of the heart[13]. These results would suggest poor access to prenatal care or to CHD diagnosis services at birth, which hinders or even prevents any timely treatment[13].

The linear regression of the evolution of the IMR demonstrated a growing trend. In Brasil, between 2003 and 2013 the IMR from congenital malformations of the heart was 1.03, and the Midwest region of the country presented the highest rate (1.25) and the Northeast the lowest (0.93)[10]. Braga et al.[14] analyzed the mortality trend from CHD in Brasil and observed that overall there was a fluctuation throughout the period with a decrease observed during the last year. Matos[9], in the state of Bahia between 2003 and 2013, reported that the IMR presented a progressive increase within the pediatric age group.

The temporal patterns of CHD present a certain degree of heterogeneity. In Canada and European countries, mortality rates due to CHD have decreased, particularly in infants aged under one year[15,16]. In contrast to previous studies, a large-sample, population-based study on CHD, using echocardiography, was conducted in China finding a CHD prevalence of 22.9%, in two years of study[17]; in Mexico, infant mortality from CHD increased 24.8% from 1998 to 2013. It should be highlighted that hypotheses have been raised to justify this increase in mortality rates, for example, the improved diagnosis of CHD and a greater number of perinatal necropsies[18].

Arruda et al.[7] assessed mortality from congenital malformations in Pernambuco from 1993 to 2003, and demonstrated that these accounted for 41% of all deaths, and that there was an increasing trend in coefficients of early neonatal (p=0.003), perinatal (p=0.005), neonatal (p=0.0007), and infants aged under one year (p=0.02) mortality.

In a study by Torres-Cosme et al.[18] conducted in Mexico, infant mortality from CHD increased by 24.8% from 1998 to 2013 (114.4 to 146.4/100,000 live births). This finding runs counter to overall global mortality, since the number of deaths in infants aged under five decreased by 47% from 1990 to 2015, from 90.6 to 42.5 deaths per 1,000 live births. Efficient strategies and actions aimed at reducing diarrhea, respiratory infections and an increase in the development and success of vaccination may also justify this fact.

It should be emphasized that mortality due to CHD varies when assessed within global rates[19]. Industrially limited countries or those classified as "developing nations", which still suffer from poor access to healthcare, present significantly higher mortality rates than those of developed countries[10]. High mortality rates due to CHD result from poor or inadequate diagnostic services during the prenatal period, thereby leading to ineffective treatments and frequent deaths. Early, accurate diagnosis is a prerequisite for a more favorable prognosis and for establishing effective healthcare.

In an analysis of the causes of death during the first 24 hours of life, Torres-Cosme et al.[18] reported that around 90% of cases did not have a specific diagnosis, which is of great concern. It is argued that newborns with a known prenatal diagnosis of CHD were significantly less likely to die before cardiac surgery when compared to those diagnosed postpartum (OR = 0.26; 95% CI: 0.08-0.84).

This result is corroborated by Matos[9], who reported that the ICD-10 code Q24 was present in 75.7% of the records, which demonstrated an inaccuracy in the

diagnosis of causa mortis pathology. This may have been due to a lack of knowledge regarding the large number of congenital heart defects by the doctors who confirmed the deaths and signed the death certificates or possibly even by the absence of an autopsy. We confirmed that a significant portion of the deaths occurred during the first days of life. Similar results were found in the state of Bahia, where 48% of deaths occurred in the post-neonatal period (28 to 364 days), followed by early neonatal, from 0 to 6 days, corresponding to 34% of total deaths[9]. The first week of life is seen as a critical period during which a significant number of CHD deaths occur. Special attention should be given to this phase, understanding that it is necessary to enable specialized health care.

Birth weight is an important factor for the occurrence of events in newborns. This study has demonstrated a statistical significance for mortality in children weighing between 500 and 1,499g. Lopes et al.[11] described that a birth weight <2,500g was a risk factor for death in newborns with CHD (RR: 2.33; 95% CI 1.26-4.29; p 0.0068), which was also reported by Brum et al.[12] (26.7% of deaths, p 0.015), Aquino et al.[20], and Carvalho et al.[21].

Araújo et al.[22] highlighted that the mortality risk for male newborns was 4.16 times higher than for girls. Furthermore, they also emphasized that early neonatal mortality was higher in males for all weight ranges.

There are very few studies that seek to associate mortality from CHD with levels of education. Araújo et al.[22] sought to describe the profile of CHD in the state of Paraiba between 2001 and 2011 and discovered that the parents of a significant proportion of CHD cases had received little education. The authors emphasized that while there was no direct biologically responsible mechanism, it is crucial to take into account that educational attainment is closely linked to obtaining information and a higher purchasing power. These factors are crucial for good prenatal care and thus for developing an effective follow-up in order to avoid a variety of risk factors detrimental to the fetus.

Aquino et al.[20] and Carvalho et al.[21] aimed to analyze the risk factors associated with perinatal mortality in Recife-PE, observed that if a mother had attended school for less than four years (OR=1.78), this was a risk factor for perinatal mortality.

Furthermore, according to Aquino et al.[20], it was observed that prematurity (OR=18.23) remained an important risk factor for perinatal mortality since this variable was most strongly associated with perinatal death. Low birth weight and length of gestation should not be studied in isolation, but as mediators through which determinants act, such as maternal education, socioeconomic conditions, biological characteristics, and life habits of the mother, as well as access to health services during pregnancy.

In Caxias do Sul (Rio Grande do Sul), it was observed that the risk of mortality in premature infants (<37 weeks) was five times higher when compared to the 39-41-week group, thereby demonstrating a marked increase in mortality as the gestational age decreases[23].

With regard to the place of delivery, Torres-Cosme et al.[18] reported that while hospital births presented the lowest CHD mortality rates, at home births presented the highest, comprising 22.3% of the total number of deaths. Homebirth is a risk factor for death with the presence of CHD (OR = 95% CI = 6.34; 5.49–7.32). This fact leads us to emphasize possible weaknesses in primary health care, particularly with regard to the conditions of delivery.

CONCLUSIONS

In the state of Pernambuco, the CCM was responsible for 3,584 deaths from 1996 to 2016, which occurred predominantly in children under one year. The IMR showed a linear growth trend. The ICD-10 Q24 cause-of-death code was present in most death certificates. The general characteristics that showed statistical significance for death were prematurity, low birth weight, male babies born to mothers with no education, with home delivery.

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Author's Contribution

João Victor Batista Cabral: participated in all stages of research, from the preparation of the project, as well as data collection and analysis, to the drafting of the paper. Aline Luzia Sampaio Guimarães: participated in data collection. Dário Celestino Sobral Filho: participated in the critical review and drafting of the work. Ana Célia Oliveira dos Santos: coordinated all stages of research, from the preparation of the project, as well as data collection and analysis, to the drafting of the paper.

RESUMO

OBJETIVO: *Determinar a magnitude e tendência temporal dos óbitos por doenças cardiovasculares congênitas (DCC) em Pernambuco entre 1996 e 2016.*

MÉTODOS: *Trata-se de um estudo ecológico, de série temporal, com todos os casos de óbitos por doenças cardiovasculares congênitas no estado de Pernambuco, entre 1996 e 2016, por meio dos dados do Datasus, Sinasc e SIM.*

RESULTADOS: *Ocorreram 3.584 óbitos por DCC entre indivíduos de 0 a 14 anos de idade, dos quais 81,94% foram concentrados em crianças menores de 1 ano de idade. A taxa de mortalidade infantil apresentou tendência linear de crescimento de 0,4645 por ano (p<0,01). A causa Q24 (outras malformações congênitas do coração) esteve presente em 72,54% dos registros de óbitos e 48,17% dos óbitos ocorreram na faixa etária de 28 a 364 dias de vida. Maior ocorrência de óbitos foi identificada entre os nascidos com peso entre 500 e 1.499 g, do sexo masculino, pré-termos, filhos de mães sem escolaridade e em partos domiciliares (p<0,05).*

CONCLUSÕES: *As cardiopatias congênitas ainda representam um problema de saúde pública como causa de mortalidade, especialmente no primeiro ano de vida. A taxa de mortalidade por DCC apresentou tendência linear de crescimento. As características gerais demonstraram significância estatística para óbitos entre crianças prematuras, com baixo peso, do sexo masculino, nascidas de mães sem escolaridade e em partos domiciliares.*

PALAVRAS-CHAVE: *Mortalidade infantil. Cardiopatias. Anormalidades congênitas.*

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ORIGINAL ARTICLE

Health production: analysis of doctors' health actions in the More Doctors program

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SUMMARY

OBJECTIVE: *Analyze the health actions carried out by the Cuban cooperated physicians and their relationship with socioeconomic characteristics of the municipalities, contained in the first supervision visit report, in 2015.*

METHODS: *This is a quantitative research that used secondary data from the reports of the 1st supervision visit of the "More Doctors Program". The dependent variables were the health actions, and the independent variables were the type of municipality, Human Development Index (HDI), Investment in Primary Health Care (PHC), health center coverage, rural population, and total population. Multiple correspondence analysis was used to identify the latent variable, related to the profile of the professional with respect to the actions/procedures carried out to which the characteristics of the municipalities were associated through frequency analysis.*

RESULTS: *Three profiles of professionals were obtained, who have their practices associated with the professional training, consolidating as a determining factor for carrying out actions compatible with the actual needs of the population. Such findings were associated with the socioeconomic variables, with emphasis on funding, health center infrastructure, and coverage.*

CONCLUSIONS: *From the observed results, we suggest strategies to expand the scope of the practices carried out in Primary Health Care, from the perspective of training and continuing education of health professionals, and the focus on the everyday life of the service being of paramount importance.*

KEYWORDS: *Primary Health Care. Family Health. Health Policy.*

INTRODUCTION

The insufficient number of workers, the demographic/epidemiological transition, and the deployment of new health care models interfere with the need for health professionals and represent the main critical issues of universal access to health actions[1,2].

The scarcity of physicians to fill job positions in the Brazilian health system is a very complex and multifactorial problem that is not restricted to overcoming a unfavorable physician-inhabitant ratio. Over time, new job openings for physicians have been offered in the country, and the number of openings is greater than the number of medical school graduates[3].

Countries such as Canada, England, Holland, and Australia depend on foreign professionals to meet the demands of their populations. Australia also faces shortages of professionals in remote areas, and the

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number of medical internships is not enough to meet their needs[4].

In Brasil, this scarcity is not evenly distributed due to geographical aspects and on account of the different health care levels of the Single Health System (SUS). Primary Health Care (PHC) is the most affected by this reality, with a great turnover of physicians and openings that are not filled in municipalities with greater social vulnerability[5].

In this context, the More Doctors Program (PMM - *Programa Mais Médicos*) was established by Law no. 12,871, on 22 October 2013, with the main purpose of solving problems relating to PHC in the scope of the SUS. The program is intended to train health professionals in the medical area of the SUS. For such, it is structured around three strategic axes: training for the Single Health System (SUS); infrastructure improvement for Basic Health Units (UBS), and emergency provision of physicians[1].

The implementation of the PMM was marked by strong resistance from the medical corporation due to the participation of foreign doctors, particularly Cubans. The resistance was based on aspects related to the shortcomings of health professionals in the labor market and to medical training, regarding the broadness and scope of foreign practices. Another aspect that was questioned was the quality of Cuban medical training to comply with the complexity of the actions required to work in primary care in the SUS[6].

After more than six years from the deployment of the PMM, with more than 18,000 doctors recruited between 2013 and 2016, it is possible to see there was a reduction in the shortage of primary care physicians, particularly in more vulnerable areas. The program was spread throughout almost the entire national territory, with greater participation of Cuban doctors, who, by 2014, accounted for 79% of the participants[6,7].

Despite the positive repercussions on the implementation and qualification of basic care, the program was unable to intervene in the structural impediments of Primary Health Care in the scope of the SUS due to its provisional character, and also on account of temporary contracts, under which the program physicians are paid through fixed grants[8,9].

In face of these aspects, this study aims to analyze the health actions carried out by the participating Cuban doctors and their relationship with socioeconomic metrics contained in the reports of the supervision first visit of the PMM, from 2015.

METHODS

This is a quantitative and observational study based on secondary data from the reports from the first supervision visit of the PMM, conducted in 2015, in the 3,816 Brazilian municipalities.

The pedagogic supervision reports were filled out by the PPM supervisors and made available *online*, hosted on the website of the Ministry of Education and in the Webportfolio System/UNA-SUS. We considered the set of actions of promotion, prevention, and health care that covers aspects of the list of doctors' activities that point to a more comprehensive and resolvent care and influential, such as the broad portfolio of services for the promotion, prevention and care, attention to spontaneous and scheduled demand, integration with other health services, interdisciplinarity, planning of interventions, and the use of clinical protocols[6].

This study focuses on health actions of the More Doctors Program, represented by a set of variables, namely: a) actions in health education; (b) actions to promote healthy eating habits and the practice of physical exercise; c) promotion and prevention actions (immunization); (d) promotion and prevention actions (cytologic collection); e) actions of child health; f) actions of women's health; (g) actions of adult health; h) actions of mental health and spontaneous demand; and (i) urgent and emergency care.

The independent variables are related to the socioeconomic conditions of the municipalities where the Cuban doctors were acting at the time of supervision, among them the type of municipality and the infrastructure of the units.

Initially, we performed a descriptive analysis of the frequency of the main actions developed by the professionals. Aiming to establish a profile of the professionals regarding these actions, we carried out a multiple correspondence analysis, which generated the variable "Health Production" and three profiles of professionals.

Correspondence analysis is the method applicable to situations in which the aim is to analyze a latent variable from the combination of different categorical variables. After including all variables related to health actions carried out (coded as "yes" and "no") in the model, a perceptual map is generated, in which the groups may be observed in dimensions and, thus, the characterization of health actions that compose a latent variable can be established.

Finally, we associated the professional profiles with the indicators in order to assess whether these different profiles could be associated with certain socioeconomic characteristics of the municipalities where these professionals acted.

It is also worth mentioning that this study involved secondary data; thus, it was not necessary to submit it to the Research Ethics Committee.

RESULTS

Figure 1 presents the results related to the health actions, divided by strata and Brazilian regions. Regarding the implementation of the actions, the most frequently carried out per region stratum were actions of spontaneous demand, carried out with greater frequency in the Central-West, Northeast, and Southeast regions.

Then, we can observe the actions of programmatic cycles, such as those of child, women, and adult health. When it comes to actions of child and women health, they are performed with greater frequency in the North, Northeast, and Central-West regions; whereas adult health actions are more often carried out in the Central-West, South, and Southeast regions, and less frequently in the North Region.

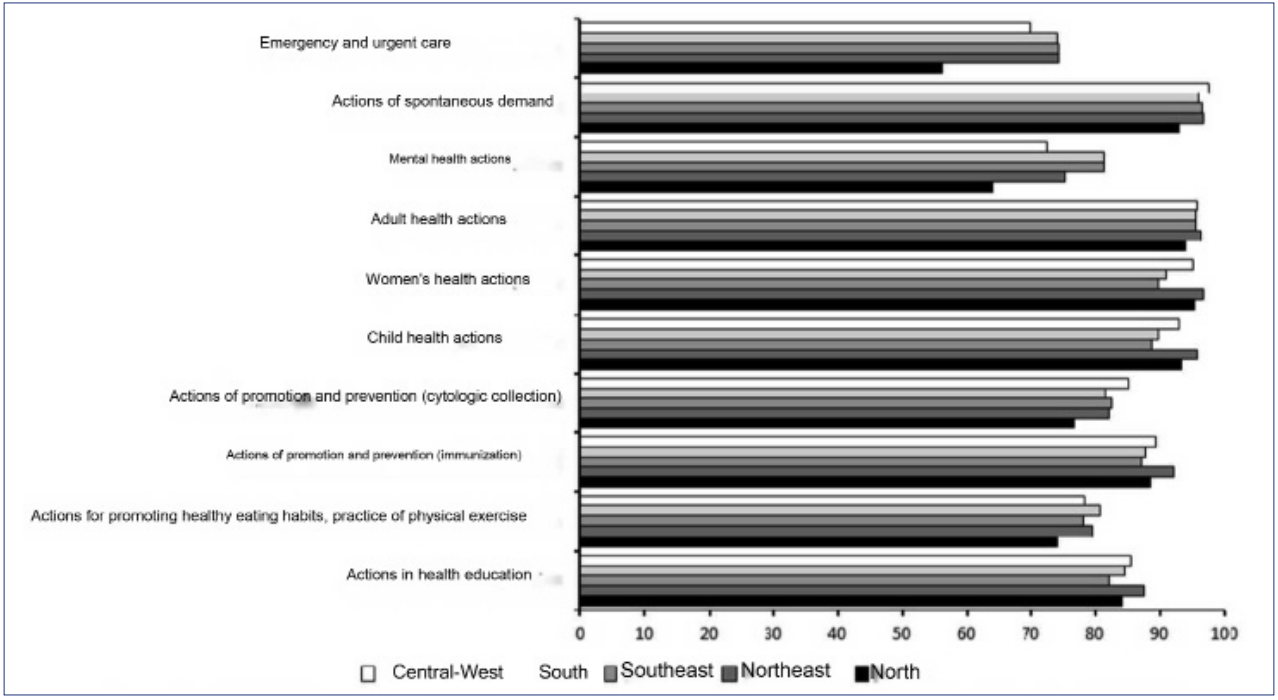
The actions less frequently carried out were those of mental health, urgent and emergency care, and the promotion and educational actions in health and prevention of diseases and injuries.

Upon an analysis per region stratum, it is possible to see that the actions of urgent and emergency care and mental health, as well as actions for the promotion of healthy eating habits and practice of physical exercise occur more frequently in the South and Southeast regions, with less prevalence in the North region of the country. Is possible to observe that promotion and prevention (cytologic collection and immunization) are less frequent in the North region of the country.

In short, from the analysis per region stratum, we observed fewer actions of urgent and emergency care, mental health, and promotion of healthy eating habits and practice of physical exercise, as well as those for promotion and prevention (cytologic and immunization). The North region stands out with fewer actions than the national average, which may be linked to a network of services with gaps and the lack of service structuring.

After analyzing the actions carried per stratum of Brazilian regions, we conducted a multiple correspondence analysis, which generated a grouping of variables into three profiles of actions, whose final result is expressed in the perceptual map (Figure 2). Once this variable was defined, we assessed its association with socioeconomic characteristics and the health services of municipalities (Table 1).

FIGURE 1. SILVEIRA NJD. PERCENTAGE DISTRIBUTION OF HEALTH ACTIONS CARRIED OUT BY DOCTORS OF THE MORE DOCTORS PROGRAM. SOURCE: FIRST PMM SUPERVISION REPORT.



The multiple correspondence analysis enabled the creation of a latent variable, which was called "production of actions in primary health care." This title emerges from the National Health Promotion Policy, which defines health promotion as an "effort to cope with the challenges of health production", considering also the production of health associated with the "production of active, critical, involved, and supportive subjectivities"[10,11].

Health´production here is understood as the production of life and health, which necessarily can only be conceived in the context of otherness. Thus, much more than a field of science, the production of health actions is the affirmation of life. The production of health is related to everyday life, styles and ways of living, which establish new ways of life[11].

Therefore, in the present study, the production of health was built from the perspective of interconnectivity, generating three profiles of professionals: profile 1 - "integral actions"; profile 2 -"actions in programmatic cycles"; profile 3 - "actions of health promotion, prevention, and education".

Profile 1 - Integral Actions

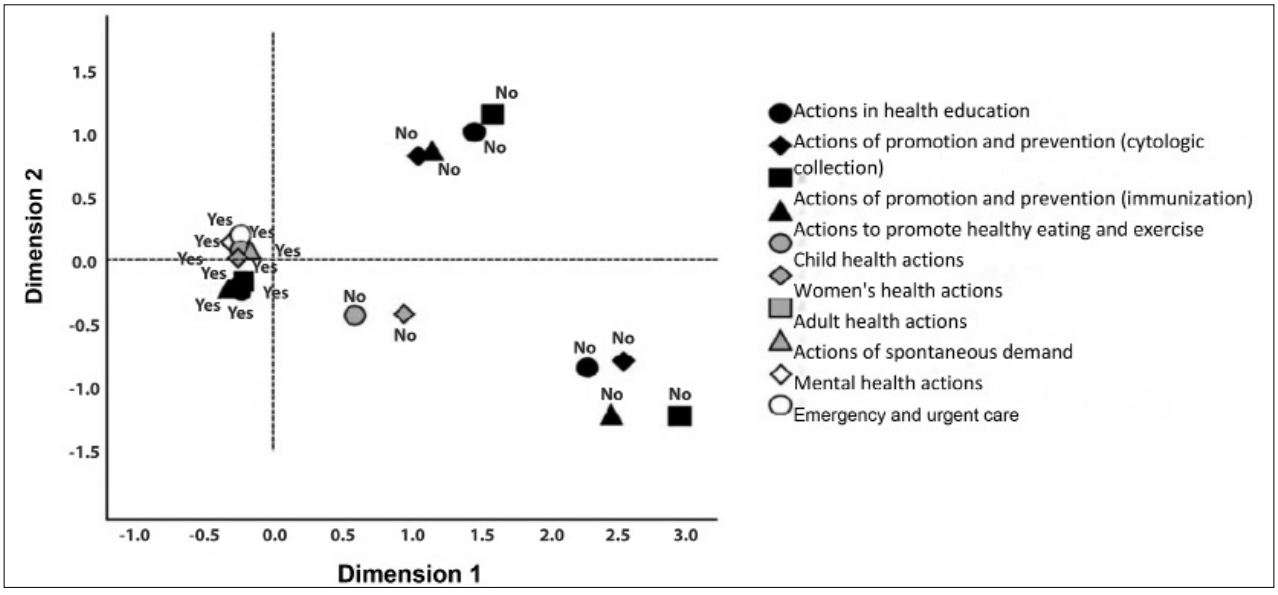
Integral actions involve the health actions that are expected to meet the real demands of Primary Health Care, but that become differentiated since they are not carried out effectively in Family Healthcare Units by the teams in general, but that became possible upon the placement of the medical professional, as illustrated in Figure 2[12].

When analyzing the correlation of this category with the Brazilian regions, we found in the South, and Southeast regions a greater number of professionals with this profile. We also found that the highest number of expected actions carried out was in the capitals and that they are associated with a better infrastructure of Family Health Units, which may corroborate a better physical structure and network of services of the municipalities studied.

TABLE 1. PERCENTAGE DISTRIBUTION OF THE PROFESSIONAL PROFILES, ACCORDING TO SOME OF THE SOCIOECONOMIC AND DEMOGRAPHIC CHARACTERISTICS OF THE MUNICIPALITIES.

	Profile 1 - Integral actions	Profile 2 - Actions of programmatic cycles	Profile 3 - Health promotion, prevention, and education actions	Total
Region				
North	30.9%	32.1%	37.0%	1,871
Northeast	44.9%	23.3%	31.8%	5,360
Southeast	47.9%	20.2%	32.0%	4,448
South	45.6%	24.1%	30.3%	2,594
Central-West	42.2%	26.5%	31.3%	1,124
Infrastructure				
Suitable	46.6%	24.6%	28.8%	11,682
Inadequate	35.6%	21.5%	42.9%	3,715
Type of Municipality				
Capital	47.4%	17.3%	35.3%	1,882
Interior	43.4%	24.8%	31.7%	13,472

FIGURE 2. SOURCE: MULTIPLE CORRESPONDENCE ANALYSIS FROM THE DATABASE OF REPORTS OF THE FIRST PMM SUPERVISION.



Profile 2 - Actions of programmatic cycles

The actions of the programmatic cycles are consistent with the teams that carry out more restricted actions, focused on programmatic life cycles, with a more "curative", "medicamental", and "hospital-centered" perspective.

We found that in the North and Central-West regions, which are more vulnerable, there is less prevalence of these actions. As to its association with socioeconomic factors, we found a greater number of actions in the countryside and in municipalities with adequate physical structure.

Profile 3 - Health promotion, prevention, and education

The third profile put together from the analysis of correspondence was associated with the actions of promotion and prevention (cytologic collection and immunization), promotion of healthy eating habits and physical exercise, and health education.

When analyzing the profile by region, we found that in the North Region there was a higher frequency of professionals with this profile, with a certain equivalence between the other regions. In fact, the physical structure became a quite explanatory variable for this profile of professionals, considering that actions of promotion, prevention, and education can occur without major losses in capitals, in regions with inadequate physical structure.

DISCUSSION

The creation of the More Doctors Program (PMM), beyond doubt, represented an important step towards meeting the demands of PHC. The presence of professionals from the PMM in 4,058 municipalities benefited approximately 63 million people, promoting the integration of teams and strengthening health actions, with a positive impact also in the reduction of some indicators, such as the hospitalizations due to sensitive conditions and child mortality[13-15].

The associations of health production with socioeconomic indicators point to inequities in health, to the extent that a scope of actions consistent with the real demands of the population is carried out in more developed regions, with a decrease in more vulnerable regions. In this process, there is a rupture of the fundamental principles of the SUS, i.e., equity in health, since these actions should be carried out in the regions of greater vulnerability, which, in general, there are those that require a greater scope of professional activities to be implemented.

The discussion about the actions that must be carried out in PHC, with a focus on medical professionals, goes beyond the training and skills required and is strongly related with the professional's desire to work on Primary Health Care through the bond established with the territory, teamwork, flexibility, and sensitivity for humanizing care[5].

In this context, a study conducted by Facchini et al.[16] concluded that the professional practice of FHS teams suffers from the incompleteness of the offer of health actions and care, despite the availability of reference standards, guidelines, goals, and work protocols. Something we observed in this study, in Profiles 2 and 3, is that the medical professionals do not carry out the full scope of actions that the practices of Primary Health Care require, which cannot be confused with the quality of the actions, considering that this research was aimed at professionals with the same training, thus the importance of socioeconomic variables are highlighted to explain the differences in the scope of actions.

Feitosa et al.[17] corroborate this discussion by observing that the inadequate infrastructure of UBSs - for example, the lack of equipment and the precariousness of labor relations - influences the quality of care provided to the population 18.

In contrast, there is evidence that, with the deployment of the PMM, the allocation of financial resources for Primary Health Care tripled. This is also attributed to the resources of the Program for the Rehabilitation of Basic Health Units, which provided an increase in the budget allocated to Primary Health Care to improve the ambiance of UBSs, the working conditions of professionals, and the funding and broadening of the scope of service practices[17,18].

CONCLUSIONS

In the face of this discussion, we propose strategies to expand and qualify the infrastructure of units, highlighting the importance of investments so that the full scope of actions required can be implemented. We add to the discussion the need for investments, from the perspective of training and continuing education of health professionals, with a fundamental emphasis in the daily aspects of service, specialization programs, residence, and professional master's in family health, access to evidence of assessments of health policies

and actions that are relevant to solving local problems and their generalization to the basic health network. Educational activities allow for the development of professional skills, improving the scope and breadth of the provision of care[19-21].

Author's Contribution

Natércia Janine Dantas da Silveira: was responsible for writing the manuscript, tabulating the data, and helped compile the theoretical references; Lyane Ramalho Cortez: contributed with the correction/revision of the final version of the manuscript and helped compile the theoretical references; Yan Nogueira Leite de Freitas: contributed with the revision of the manuscript, statistical analysis and database research in order to enrich the theoretical framework of the study; Angelo Giuseppe Roncalli: was responsible for counseling throughout the entire process, from the conception of the study to its final adjustments.

RESUMO

OBJETIVO: *Analisar as ações em saúde realizadas pelos médicos cooperados cubanos e sua relação com características socioeconômicas dos municípios, contidas no primeiro relatório de visita de supervisão, em 2015.*

MÉTODOS: *Pesquisa quantitativa que utilizou dados secundários dos relatórios da primeira visita de supervisão do Programa Mais Médicos. A variável dependente foram as ações em saúde e as variáveis independentes foram o tipo de município e infraestrutura. Utilizou-se a análise de correspondência múltipla para a identificação da variável latente, relativa ao perfil do profissional com relação às ações realizadas, a qual foi associada às características dos municípios por intermédio de análise de frequência.*

RESULTADOS: *Foram obtidos três perfis de profissionais, que possuem suas práticas associadas à formação profissional, consolidando-se como um fator determinante para efetivação de ações condizentes com as reais necessidades da população. Tais achados estiveram associados às variáveis socioeconômicas, tendo como destaques a infraestrutura das unidades e o tipo de município.*

CONCLUSÕES: *A partir dos resultados observados, sugerem-se estratégias para ampliar o escopo das práticas desenvolvidas na APS, na perspectiva de formação e educação permanente de profissionais de saúde, sendo fundamental a ênfase no cotidiano do serviço.*

PALAVRAS-CHAVE: *Atenção Primária à Saúde. Saúde da Família. Política de Saúde.*

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ORIGINAL ARTICLE

Alcohol consumption by medical students

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SUMMARY

OBJECTIVE: *Excessive alcohol consumption is a global health issue. This article aims to evaluate the consumption of alcohol by medical students in relation to their personal and social aspects.*

METHODS: *This study was conducted with students in the first, third, and sixth year of medical school at the Federal University of Minas Gerais in 2019. Students were invited to participate anonymously by responding to a questionnaire with 15 questions regarding student characteristics (gender, age, family income, physical activity, origin, housing condition, and academic performance) and alcohol consumption (onset, reason, occasions of use, type of drink, amount consumed). Data were compared with significance corresponding to p<0.05.*

RESULTS: *A sample of 382 students of both sexes responded to the questionnaire. Alcohol consumption was reported by 85% of students. About 70% of first and third-year students and 47% of those of the sixth year were motivated by socializing with peers. Alcohol consumption was prevalent among those who practice physical activities (93%) and live with their families (89%). Around 80% had consumed alcohol before starting medical school, and consumption was more frequent in males.*

CONCLUSIONS: *Alcohol consumption begins during high school, stimulated by socialization. Men who practice physical activities and live with their families are the largest consumers.*

KEYWORDS: *Alcoholism. Students, medical. Family. Socialization. Academic performance. Physical activity.*

INTRODUCTION

The growing use of psychotropic substances is a serious public health problem[1]. These substances that are present in the life of most social groups include natural or synthetic products, which act on the central nervous system and alter its function, causing variations in consciousness and behavior[2]. Among them, alcoholic beverages are noteworthy, since due to being licit and socially accepted drugs, they are widespread. In Brasil, alcohol is the drug most consumed by young people, followed by tobacco, marijuana, and mental stimulants[3].

With respect to students of medicine, despite their extensive knowledge about the harmful effects of alcohol[4], there is high consumption of alcoholic beverages among them, with a likely negative impact on their intellectual performance and, possibly, future professional practice[4-6]. Such consumption may have negative social, economic, and cognitive impacts, leading to the use of other drugs and hindering educational activities[7]. Evaluating alcoholism among medical students is essential to analyze the quality of student's life based on their physical

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health, emotional state, personal conduct, and social relationships[8].

The goal of this study was to evaluate the consumption of alcoholic beverages by medical students and assess its associated factors.

METHODS

This study was approved by the Human Research Ethics Committee of the Federal University of Minas Gerais (UFMG), under case CAAE - 01912118.3.0000.5149; Opinion No. 3,113,455 and carried out at the Faculty of Medicine of UFMG in 2019.

Medical students of 1st, 3rd, and 6th years were informed publicly about the purpose of the study and invited to voluntarily participate, anonymously and with secrecy concerning the identification of those who accepted to be part of it. After signing the informed consent, 400 students of the 1st, 3rd, and 6th years received a self-administered questionnaire consisting of 15 questions relating to their personal characteristics (gender, age, family income, practice of physical activities, origin, housing conditions, and student performance) and consumption of alcoholic beverages (beginning, motivation, occasions in which it is consumed and quantity consumed).

Statistical analysis was performed using the Epi Info *software* version 7.2.2.6 and PASW Statistics 18. The comparison of the means was done by Student's t-test, and the proportions were evaluated using the chi-square test. Differences were considered significant for values of $p<0.05$.

RESULTS

Of the 400 questionnaires distributed to the medical students of the UFMG, 382 (96%) were considered valid, and the respondents were 51% female and 49% male (Table 1). The most frequent age was in the range between 21 and 24 years (51%), followed by 17 to 20 years (31%), and 25 to 30 years (17%). At the time of the survey, 167 (44%) were in the 1st year, 109 (29%) in the 3rd year, and 106 (28%) in the 6th year (Table 1).

The motivation for alcoholism for 70% of the students of the 1st and 3rd years was socializing with friends and colleagues, while only 47% of the 6th year students had the same motivation. The consumption of alcoholic beverages prior to admission in college was reported by 80% of the students of both sexes, of which 46% were influenced by friends outside of college (Table 2).

The practice of physical activity was reported by 87% of the students, of which 27% exercised at least three times a week, which showed a significant association with alcohol consumption (OR=4.33; CI=1.58-11.83; p=0.024). Alcohol consumption was declared by 76% of the students who reported not practicing regular physical activity, by 81.9% of those who reported practicing it only once a week, by 83.1% of those who practiced it two or three times per week, and by 93.2% of those who reported practicing it more than three times a week.

TABLE 1. CHARACTERIZATION OF THE SAMPLE ACCORDING TO THE CHARACTERISTICS ADDRESSED BY THE QUESTIONNAIRE (N=382).

Characteristics	Sample	
	n	%
Sex		
Male	188	49.2
Female	194	50.8
Total	382	
Age (years)		
17-20	117	30.6
21-24	196	51.3
Over 25	69	18.1
Study Cycle		
Basic	167	43.7
Clinical	109	28.5
Practical	106	27.7
Income		
Up to 3 minimum wages	46	12.0
Between 3 and 10 minimum wages	167	43.7
Over 10 minimum wages	168	44.0
Practice of physical activities		
Never	50	13.1
Rarely (once a week)	105	27.5
Frequently (2-3 times/week)	124	32.5
Always (over 3 times/week)	103	27.0
Housing		
With family	197	51.6
Without family	185	48.4
Origin		
Belo Horizonte	176	46.1
Interior of the state of Minas Gerais	129	33.8
Other states	77	20.2
Academic performance		
Between 40% and 60%	4	1.0
Between 60% and 80%	171	44.8
Above 80%	207	54.2

With regard to sex, 86.2% of men and 83% of women reported consuming alcohol (p=0.39). Alcoholism was more present among men, with 68% consuming more than 700 ml of beer (Figure 1), compared with 49% of women (OR=2.26; CI=1.38-3.69; p=0.001). The weekly consumption for 34% of men was over two times, compared with 24% of women (OR=1.62; CI=1.03-2.53; p=0.044).

Regarding the presence of family members in the daily life of students, 80.2% of those who claimed to live with family members and 89.2% of those who do not live with them consume alcohol (OR=0.49; CI=0.28-0.88; p=0.022).

There was no significant association between the origin (p=0.064), income (p=0.13), and students' performance (p=0.13) with the consumption of alcoholic beverages.

TABLE 2. CHARACTERIZATION OF THE SAMPLE ACCORDING TO THE CONSUMPTION OF ALCOHOL (N=382).

Characteristics	Sample	
	n	%
Alcohol consumption		
No consumption	59	15.4
Up to once a week	214	56.0
Between 1 and 3 times/week	98	25.7
Over 3 times/week	11	2.9
Beginning of consumption		
Before the start of the program	261	80.3
During the first year of the program	53	16.3
On the other years of the program	11	3.4
Reason for consumption		
Fun	221	68.0
Socialization	205	63.1
Relax	155	47.7
Taste	126	38.8
Escape	40	12.3
Occasions in which consumption occurs		
Social events	285	87.7
Meals	79	24.3
At home with relatives	108	33.2
At home alone	54	16.6
Amount consumed per occasion		
1 can of beer (350mL) or equivalent	33	10.2
2 cans of beer (700mL) or equivalent	68	21.0
Over 2 cans of beer (700mL)[a]	222	68.7
Who stimulated consumption initially		
Friends	147	45.5
Program peers	66	20.4
Family	41	12.7
Partner	11	3.4
Idol	5	1.5

[a] or equivalent

DISCUSSION

College students are a particular group in terms of the consumption of alcoholic beverages. Factors such as increased independence, reduction of parental supervision, greater social contact with people of the same age, and social acceptance of alcoholism contributed to its increased consumption in this study, with a tendency of abuse[9,10]. Is possible to observe that, unlike one would imagine, the independence of students while away from family life brings greater responsibility, thus reducing the consumption of alcoholic beverages in comparison with students who live with their families.

According to the First National Survey on the Patterns of Alcohol Consumption in the Brazilian Population, published by the National Anti-Drug Secretariat in 2007, men consume alcoholic beverages in greater volume and with more frequency, as was observed in this study[11]. However, it is worth noting that, even though their consumption is lower, women are more vulnerable to diseases caused or triggered by alcoholism, particularly since the consumption of alcoholic beverages is increasing among females[12,13].

Surprisingly, most alcoholics practiced routine physical activities (Figure 2), in contrast with what is found in the literature, which associates alcoholism with other behaviors that are harmful to health and multiple diseases[14-16]. It is also considered that the practice of sports prevents alcoholism[17]. However, there are studies that indicate greater alcohol consumption among athlete students, due to the pressure

FIGURE 1. AMOUNT OF ALCOHOLIC BEVERAGES (ML) CONSUMED ON EACH OCCASION BY 382 STUDENTS OF THE FACULTY OF MEDICINE OF UFMG, ACCORDING TO GENDER, MALE (M) AND FEMALES (F). (N = 382).

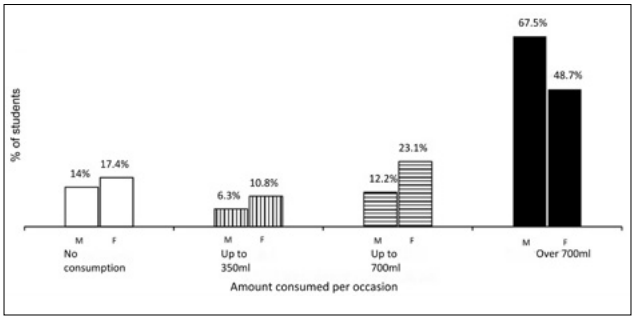


FIGURE 2. CONSUMPTION OF ALCOHOLIC BEVERAGES, BASED ON THE FREQUENCY OF SPORTS PRACTICE, BY 382 STUDENTS OF THE FACULTY OF MEDICINE OF UFMG, MALE (M), FEMALE (F).

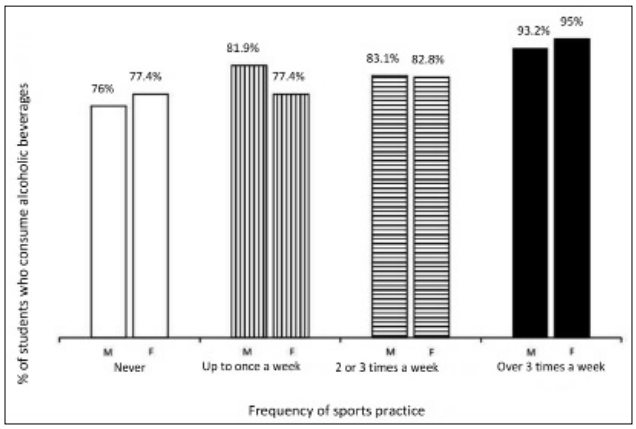
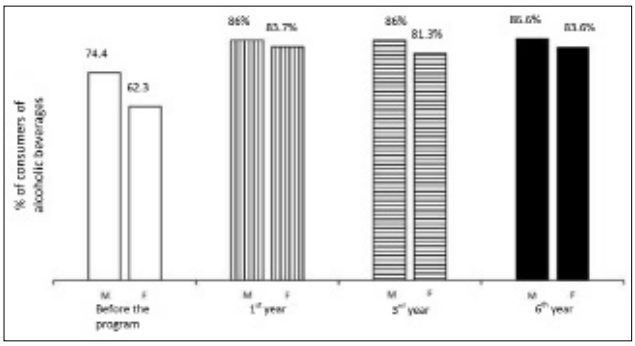


FIGURE 3. PERCENTAGE OF 382 STUDENTS FROM THE FACULTY OF MEDICINE OF UFMG, MALE (M) AND FEMALES (F) WHO CONSUMED ALCOHOLIC BEVERAGES BEFORE AND DURING THE PROGRAM.



suffered regarding their academic and sports performance[18]. There is still the false belief that alcohol relieves stress. In university parties, with emphasis on those that are sports-related, there is, in general, wide availability of free alcoholic beverages, facilitating the onset or maintenance of this addiction[19].

Alcohol is the most consumed drug worldwide among the adult population, who, for considering it of low risk, do not abstain from consuming it, which makes its use excessive in countries where alcoholism is cultural[20,21]. In our environment, the beginning of alcoholic drink consumption has been observed in increasingly younger ages, which was confirmed in this study, and a large proportion of students started alcoholism before entering university[22].

In this study, no variation in alcohol consumption was found between students' years (Figure 3), in contrast with other studies from the health area, in which the consumption decreased near graduation[23]. In addition, there was no significant variation in alcohol consumption regarding the origin, family income, and the academic performance of students, differing from the results of other studies involving students[24,25].

CONCLUSIONS

The consumption of alcoholic beverages by medical students is motivated by the need to socialize, especially in the first years of study. Men who practice physical activities routinely and live with their families are the most alcoholic.

Acknowledgments

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RESUMO

OBJETIVO: *O consumo excessivo de álcool é um problema de saúde presente no mundo inteiro. Este artigo avalia o consumo de bebidas alcoólicas por estudantes de Medicina e sua relação com características pessoais e aspectos sociais.*

MÉTODOS: *Estudo realizado com estudantes dos 1º, 3º e 6º anos do curso de medicina da Universidade Federal de Minas Gerais no ano de 2019. Os alunos foram convidados a participar anonimamente, respondendo a um questionário com 15 perguntas relativas a características do estudante (sexo, idade, renda familiar, prática de atividades físicas, origem, condição de moradia e desempenho discente) e ao consumo de bebidas alcoólicas (início, motivo, ocasiões de uso, tipo de bebida, quantidade consumida). Os dados foram comparados com significância correspondente a p<0,05.*

RESULTADOS: *Um total de 382 estudantes de ambos os sexos respondeu ao questionário. O consumo de bebidas alcoólicas foi relatado por 85% dos entrevistados. Cerca de 70% dos alunos de 1º e 3º anos e 47% dos alunos do 6º ano foram motivados pela socialização com colegas. O consumo de bebida alcoólica foi prevalente entre os que praticavam atividades físicas (93%) e moravam com a família (89%). Ao redor de 80% consumiram bebidas alcoólicas antes do ingresso na faculdade, com maior frequência no sexo masculino.*

CONCLUSÕES: *O consumo de álcool começa durante o ensino médio, estimulado pela socialização. Os homens que praticam atividades físicas e moram com a família são os maiores consumidores.*

PALAVRAS-CHAVE: *Alcoolismo. Estudantes de medicina. Família. Socialização. Desempenho acadêmico. Atividade física.*

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ORIGINAL ARTICLE

Overexpression of long noncoding RNA PTPRG-AS1 is associated with poor prognosis in epithelial ovarian cancer

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SUMMARY

OBJECTIVE: *Long noncoding RNAs (lncRNAs) have been shown to play a critical role in tumor progression. Abnormal expression of LncRNA PTPRG antisense RNA 1 (PTPRG-AS1) has been reported in several tumors. Hence, we aimed to determine the expression and clinical significance of PTPRG-AS1 in epithelial ovarian cancer (EOC) patients.*

METHODS: *The expressions of PTPRG-AS1 were assessed in 184 pairs of EOC tumor specimens and adjacent normal tissues. The levels of target lncRNAs and GAPDH were examined using standard SYBR-Green methods. The relationships between the expressions of PTPRG-AS1 and the clinicopathological features were analyzed using the chi-square test. Multivariate analysis using the Cox proportional hazards model was performed to assess the prognostic value of PTPRG-AS1 in EOC patients.*

RESULTS: *We confirmed that the expressions of PTPRG-AS1 were distinctly higher in the EOC tissue compared with the adjacent non-tumor specimens ($p < 0.01$). Higher levels of PTPRG-AS1 in EOC patients were associated with advanced FIGO stage ($p = 0.005$), grade ($p = 0.006$), and distant metastasis ($p = 0.005$). Survival analyses revealed that patients with high expressions of PTPRG-AS1 had a distinctly decreased overall survival ($p = 0.0029$) and disease-free survival ($p = 0.0009$) compared with those with low expressions of PTPRG-AS1. Multivariate assays indicated that PTPRG-AS1 expression was an independent prognostic factor for both overall survival and disease-free survival in EOC (Both $p < 0.05$).*

CONCLUSIONS: *Our study suggests that PTPRG-AS1 may serve as a novel prognostic biomarker for EOC patients.*

KEYWORDS: *RNA, long noncoding. Carcinoma, ovarian epithelial. Prognosis.*

INTRODUCTION

Ovarian cancer is a leading cause of death among gynecological tumors worldwide[1]. Epithelial ovarian cancer (EOC) is a major subtype of ovarian cancer, accounting for ~85% cases[2]. Although the quality of life of many EOC patients has been distinctly improved with the advancement of treatment strategies in recent years, the five-year survival rate of advanced-stage EOC is unsatisfactory (below 25 %)[3,4]. The poor prognosis of EOC patients is mainly due to the frequent recurrence and metastasis and various drug-resistance[5]. Thus, the identification of reliable biomarkers for EOC is urgently required for the improvement of EOC treatments.

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Long noncoding RNAs (lncRNAs), > 200 nucleotides in length, are a newly identified type of by-products of genetic transcription with limited protein-coding function due to the lack of open reading frame[6]. Growing studies have demonstrated the potential regulators of lncRNAs in the modulation of genes by several mechanisms, such as transcriptional and post-transcriptional levels[7]. Given the positive influence of lncRNAs on tumor-related genes, it is no surprise that lncRNAs may be involved in the progression of cancers[8,9]. In recent years, more and more dysregulated lncRNAs in various tumors have been identified using high throughput sequencing, followed by further demonstration using RT-PCR experiments[10,11]. Then, many functional experiments revealed that lncRNAs can modulate tumor cellular behaviors by acting as tumor promoters or anti-oncogenes[12,13]. The frequent dysregulation of lncRNAs and their important function in tumor progression highlighted the great potential of lncRNAs as novel biomarkers[14,15].

LncRNA PTPRG antisense RNA 1 (PTPRG-AS1), a newly identified lncRNA, was firstly functionally elucidated in nasopharyngeal carcinoma by Yi et al.[16]. Previously, the expression of PTPRG-AS1 was also reported in lung and breast cancer[17,18]. However, their function in the above two tumors remained to be explored. Up to date, whether PTPRG-AS1 was abnormally expressed in EOC has not been confirmed. In this study, for the first time, we provided evidence that PTPRG-AS1 was highly expressed in EOC tissues and has the potential to act as a novel prognostic biomarker for EOC patients.

METHODS

Patients and Specimens

EOC tissues (184 cases) and matched non-tumor specimens from patients who underwent operations between July 2011 and June 2014 were obtained from Changzhi Medical College. Post-operative EOC samples were verified via pathological diagnosis by three experienced pathologists. None of the patients had received chemotherapy and radiotherapy prior to the collection of specimens. All specimens were frozen immediately in liquid nitrogen and stored at -80 °C for the application of RT-PCR. The clinical data of 184 patients are presented in Table I. Clinical specimens were applied for experiments after obtaining informed consent from all patients. Our research protocols were approved by the Ethics Committee of our hospital.

TABLE 1. RELATIONSHIP BETWEEN PTPRG-AS1 EXPRESSION AND CLINICOPATHOLOGICAL VARIABLES IN EOC PATIENTS.

Variable	Number	PTPRG-AS1 expression		p value
		High	Low	
Age (y)				NS
<50	94	41	53	
≥50	90	50	40	
Tumor size (cm)				NS
≤ 8	109	49	60	
> 8	75	42	33	
Ascites				NS
<100	104	47	57	
≥100	80	44	36	
FIGO stage				0.005
I + II	112	46	66	
III + IV	72	45	27	
Grade				0.006
G1	119	50	69	
G2 + G3	65	41	24	
Distant metastasis				0.005
Yes	127	54	73	
No	57	37	20	

RNA isolation and real-time RT-PCR

Total RNA was extracted from EOC tissues and matched normal specimens by Trizol reagent (Invitrogen, Carlsbad, CA, USA). 400 ng RNAs were collected and then converted into cDNA using the PrimeScript™ RT reagent Kit (Takara, Dalian, Niaoning, China). The levels of target lncRNAs and GAPDH were examined using standard SYBR-Green methods on ABI-7300Plus PCR System (Applied Biosystems, Foster City, CA, USA). The Opticon Monitor 2 software was used for the assays of the PCR data. Human GAPDH was used as an endogenous control. All primers were purchased from Gema (Pudong, Shanghai, China) and the sequences are were as follows: PTPRG-AS1 sense 5'-AAGCCAAGCAGTCAGAAGC-3'; PTPRG-AS1 antisense 5'-CAATGACCCCTTCATTGAC-3'; GAPDH sense 5'-GACAAGCTTCCCGTTCTCA-3'. The levels of PTPRG-AS1 were quantified by examining Ct values and normalized by the use of the $2^{-\Delta\Delta ct}$ methods.

Statistical analysis

All statistical analyses were performed using the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA). The differences in PTPRG-AS1 expressions between the two groups were examined by applying the two-sided Student's t-tests. Chi-square tests were

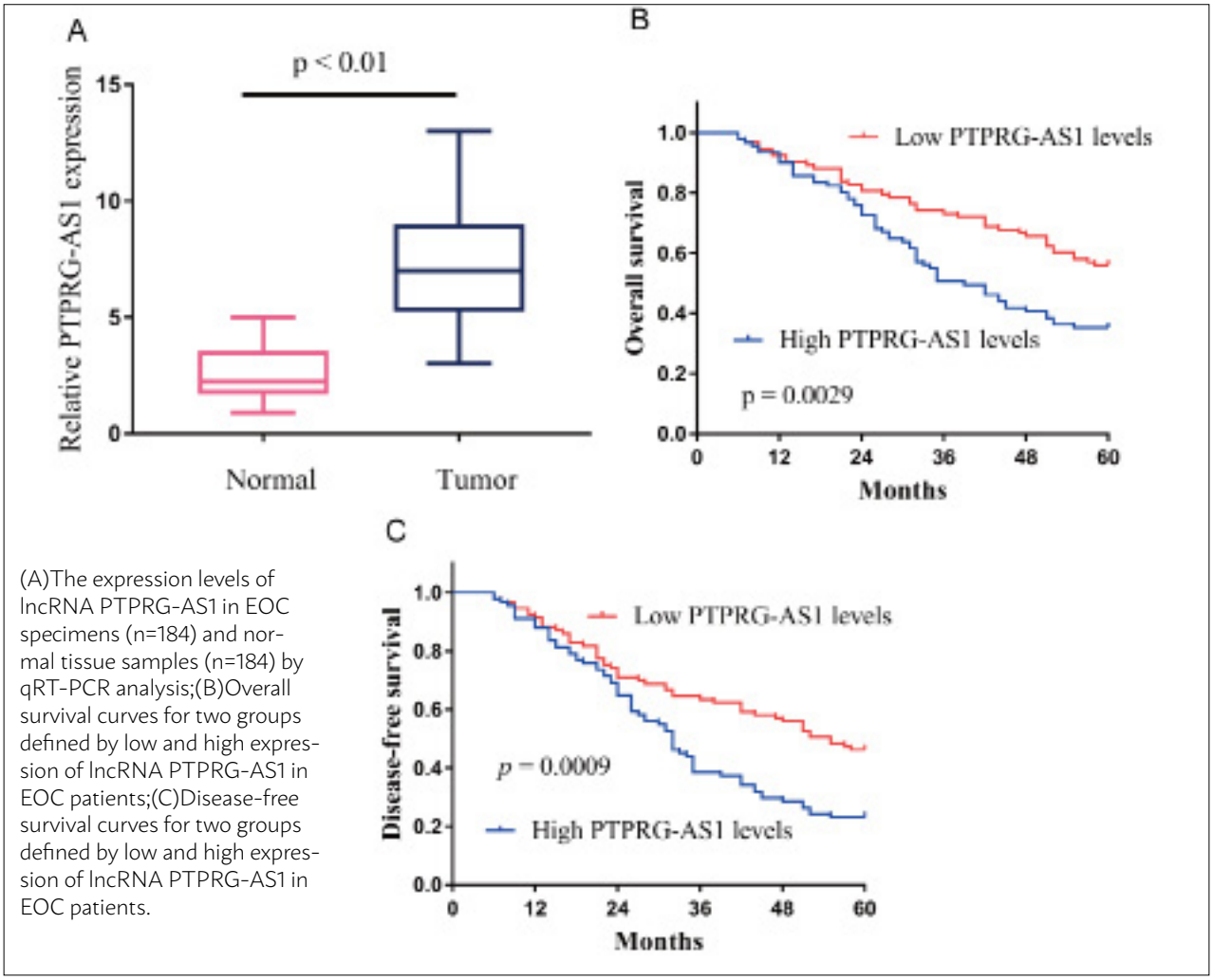
performed to determine the clinical significance of PTPRG-AS1 on clinical characteristics. The survival curve was calculated using Kaplan-Meier methods. The univariate and multivariate assays were performed in a Cox's regression model. Differences were considered statistically significant when $p < 0.05$.

RESULTS

Upregulated PTPRG-AS1 was observed in EOC tissues

Previously, PTPRG-AS1 levels had been confirmed to be overexpressed in breast cancer and nasopharyngeal carcinoma. Hence, we also performed RRT-PCR to

FIGURE 1. CORRELATIONS BETWEEN PTPRG-AS1 EXPRESSIONS AND CLINICAL OUTCOME OF EOC PATIENTS



(A)The expression levels of lncRNA PTPRG-AS1 in EOC specimens (n=184) and normal tissue samples (n=184) by qRT-PCR analysis;(B)Overall survival curves for two groups defined by low and high expression of lncRNA PTPRG-AS1 in EOC patients;(C)Disease-free survival curves for two groups defined by low and high expression of lncRNA PTPRG-AS1 in EOC patients.

TABLE 2. MULTIVARIATE ANALYSES FOR OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL BY COX REGRESSION MODEL.

Variable	Overall survival			Disease-free survival		
	HR	95% CI	p	HR	95% CI	p
Age	0.724	0.436-1.885	0.273	0.982	0.587-1.992	0.318
Tumor size	0.562	0.328-1.852	0.437	0.882	0.572-2.127	0.114
Ascites	0.852	0.562-1.775	0.218	0.774	0.627-2.014	0.128
FIGO stage	3.276	1.237-4.886	0.012	3.352	1.375-5.012	0.015
Grade	3.015	1.382-4.662	0.018	3.229	1.429-5.212	0.013
Distant metastasis	3.427	1.428-5.337	0.003	3.672	1.528-5.663	0.001
PTPRG-AS1 expression	2.896	1.283-4.952	0.009	3.018	1.365-5.328	0.005

examine whether the expression levels of PTPRG-AS1 were abnormal in EOC tissues. As presented in Figure 1A, the higher levels of PTPRG-AS1 were observed in EOC specimens compared to matched normal specimens ($p < 0.01$). Thus, the expression trend of PTPRG-AS1 in EOC tissues was in line with that in the two tumors above, suggesting its possible functional effects in EOC patients.

Association between clinicopathological characteristics and PTPRG-AS1 expressions in EOC patients

Having shown the distinct up-regulation of PTPRG-AS1 in EOC, we further explored its possible influence in the clinical progress of EOC. Using the median PTPRG-AS1 levels of all EOC samples, all 184 samples were classified into a low-expressing PTPRG-AS1 group and a high-expressing PTPRG-AS1 group. Then, the chi-square test was performed, and the results revealed that high levels of PTPRG-AS1 in EOC patients displayed advanced FIGO stage ($p = 0.005$), grade ($p = 0.006$) and distant metastasis ($p = 0.005$). However, no distinct differences were observed between PTPRG-AS1 levels and other factors ($p > 0.05$).

Correlations between PTPRG-AS1 expressions and clinical outcome of EOC patients

Then, we further examined whether PTPRG-AS1 had prognostic value for the prediction of overall survival and disease-free survival of EOC patients. Our group collected five-year survival data from 184 EOC patients and then performed statistical assays using Kaplan-Meier methods. As shown in Figure 1B, patients with high levels of PTPRG-AS1 had shorter overall survival than low-level groups ($p = 0.0029$). In addition, a similar influence of high PTPRG-AS1 on disease-free survival was also observed ($p = 0.0009$, Figure1C). Then, we performed multivariate assays for the prognostic determination of several clinical factors, finding that PTPRG-AS1 levels, FIGO stage, grade, and distant metastasis were independent prognostic indicators for both overall survival and disease-free survival ($p < 0.05$, Table II).

DISCUSSION

EOC, a major concern for women's health worldwide, is correlated with a high mortality rate[19]. The lack of satisfactory therapeutic outcomes encouraged a big scientific effort for the discovery of new approaches for early screening, prediction of clinical outcome, and cancer monitoring[20,21]. In recent years, many possible biomarkers were identified. However, low sensitivity and specificity of these markers limited their clinical application[22]. Recently, as novel gene modulators, lncRNAs may be used as novel biomarkers due to their involvement in tumor progression and the development of chip sequencing[23,24].

Aberrant expressions of several lncRNAs have been demonstrated to be involved in the modulation of the recurrence, invasion, and clinical outcome of EOC[25]. For instance, Liu et al.[26] reported that lncRNA NEAT1, a positive regulator involved in many tumors, was overexpressed in ovarian cancer and promoted the metastasis of tumor cells via the modulation of miRNA-382-3p/ROCK1 axis. Li et al.[27] showed that lncRNA H19 whose upregulation was a common event in various tumors was a distinct upregulated lncRNA in EOC. Further assays revealed that lncRNA H19 served as a tumor promoter in EOC progression due to its knockdown suppressing TGF-β-induced EMT pathway by regulating miRNA-370-3p. These findings supported the fact that lncRNAs acted as important regulators in the development of EOC. Thus, the possibilities of lncRNAs used as novel biomarkers encouraged us to further identify novel functional lncRNAs in EOC.

Recently, a newly identified lncRNA, PTPRG-AS1, was reported to be highly expressed in several tumors. Besides, its oncogenic roles in nasopharyngeal carcinoma were also confirmed using loss-of-function assays. In this study, we firstly provided clinical evidence that PTPRG-AS1 was distinctly overexpressed in human EOC tissues. The expression trend of PTPRG-AS1 in EOC tissues was consistent with that in lung cancer and breast cancer. Then, we analyzed the clinical value of PTPRG-AS1 in EOC patients and found that PTPRG-AS1 expression predicted distant metastasis, suggesting that the levels of PTPRG-AS1 may influence the tumor progression of EOC. Furthermore, Kaplan-Meier analysis suggested that the patients with high PTPRG-AS1 expression had a poor clinical outcome. Finally, the multivariate analysis suggested that PTPRG-AS1 expression provided an independent prognostic biomarker for the prediction of both overall survival and disease-free survival. However, the precise roles of

PTPRG-AS1 on the progression of EOC remain to be elucidated, and further studies using cell and animal models are necessary.

CONCLUSION

Our results showed that PTPRG-AS1 may be useful for evaluating the clinical outcome and may provide a new treatment target for patients with EOC.

Conflict of Interest

The authors declare that they have no conflict of interests.

Author's Contribution

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

RESUMO

OBJETIVO: *Sabe-se que RNAs longos não codificantes (lncRNAs) desempenham um papel crítico na progressão tumoral. A expressão anormal do RNA 1 anti-senso LncRNA PTPRG (PTPRG-AS1) já foi relatada em diversos tumores. Assim, buscamos determinar a expressão e significância clínica do PTPRG-AS1 em pacientes com câncer de ovário epitelial (COE).*

METODOLOGIA: *As expressões do PTPRG-AS1 foram avaliadas em 184 pares de amostras tumorais de COE e tecidos normais adjacentes. Os níveis de lncRNAs e GAPDH alvo foram examinados usando o método padrão de SYBR Green. As relações entre as expressões do PTPRG-AS1 e as características clínico-patológicas foram analisadas através do teste qui-quadrado. Uma análise multivariada utilizando o modelo de riscos proporcionais de Cox foi realizada para avaliar o valor prognóstico do PTPRG-AS1 em pacientes com COE.*

RESULTADOS: *Constatou-se que as expressões do PTPRG-AS1 foram nitidamente maiores nos tecidos de COE em relação aos espécimes adjacentes não tumorosos (p<0,01). Níveis mais elevados do PTPRG-AS1 em pacientes com COE foram associados a um estágio avançado de FIGO (p = 0,005), grau (p = 0,006) e metástases à distância (p = 0,005). As análises de sobrevida revelaram que pacientes com expressões elevadas do PTPRG-AS1 tiveram uma diminuição significativa da sobrevida global (p = 0,0029) e da sobrevida livre de doença (p = 0,0009) em relação àqueles com baixas expressões do PTPRG-AS1. As análises multivariadas indicaram que a expressão do PTPRG-AS1 foi um fator de prognóstico independente tanto para a sobrevida global quanto para a sobrevida livre de doença em pacientes com EOC (p < 0,05).*

CONCLUSÃO: *Nosso estudo sugere que o PTPRG-AS1 pode ser um novo biomarcador prognóstico para pacientes com COE.*

PALAVRAS-CHAVE: *RNA longo não codificante. Carcinoma epitelial do ovário. Prognóstico.*

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ORIGINAL ARTICLE

Assessment of neutrophil and neutrophil/lymphocyte ratio in coronary collateral developed patients with acute coronary syndrome

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SUMMARY

OBJECTIVE: *Inflammation-related markers provide diagnostic and prognostic information for coronary artery disease and acute coronary syndrome. We aimed to compare neutrophil count and neutrophil/lymphocyte ratio (NLR) in acute coronary syndrome patients with coronary collateral development in our study.*

METHODS: *A total of 426 patients (102 unstable angina pectoris (USAP), 223 non-ST-elevation myocardial infarction (non-STEMI), 103 ST-elevation myocardial infarction (STEMI) were compared regarding hemoglobin, platelet, lymphocyte, neutrophil count, and NLR.*

RESULTS: *Neutrophil count and NLR were significantly lower in USAP patients and higher in STEMI patients; 5.14± 1.79 vs. 7.21± 3.05 vs. 9.93±4.67 and 2.92±2.39 vs. 5.19±4.80 vs. 7.93±6.38, p <0.001. Other parameters, i.e., hemoglobin, platelet, and lymphocyte count, were not significantly different between the groups.*

CONCLUSIONS: *In our study, it was concluded that there may be a statistically significant difference in the number of neutrophil counts and NLR among the types of acute coronary syndromes with coronary collateral development.*

KEYWORDS: *Acute coronary syndrome. Collateral circulation. Neutrophils. Lymphocytes.*

INTRODUCTION

The mechanism responsible for coronary artery disease and acute coronary syndrome is inflammation[1]. The relationship between the degree of inflammation and the level of hematological markers has been studied in many diseases in the literature[1-3]. In the process of inflammation, blood cells continue to be the subject of studies because they involve the process of and also are affected by inflammation.

Coronary collateral circulation becomes visible after the presence of at least 90% stenosis in the main coronary artery. In a study conducted in patients with myocardial infarction, almost all patients showed the development of collateral flow in the first 24 hours[4]. There are many benefits of coronary collateral circulation, such as prevention of ischemia, reduction of infarction area, prevention of development of left ventricular aneurysm, improvement of left ventricular functions after infarction, reduction of coronary mortality and prolongation of survival[5]. Coronary angiography is the method used to determine collateral

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circulation, although it does not become visible before reaching 100 microns in size[6]. Coronary artery stenosis or occlusion has been shown to induce collateral circulation by affecting the balance between oxygen supply and demand[7]. Also, in cases with increased inflammation, it has been shown that coronary collateral circulation is less developed[8].

In coronary artery disease, acute coronary syndromes are characterized by exacerbation periods with a wide range of unstable angina pectoris, non-ST elevation myocardial infarction, and ST-elevation myocardial infarction. The relationship between the prognosis of the three groups and hematological markers is still the subject of research; their use in prognostic classification has the advantage of being widely available and cost-effective.

The level of NLR, which is associated with mortality in acute coronary syndromes, is the strongest prognostic predictor in hematological markers as a result of comprising two parameters used to assess the degree of inflammation[9-11]. NLR has also been studied in many clinical scenarios and it was used as a marker of chronic systemic inflammation. For example, in the literature, it may be used as an activity parameter in ulcerative colitis or as an indicator of the presence of Hashimoto's thyroiditis[12,13].

Our study aimed to compare neutrophil and neutrophil/lymphocyte ratio between the types of coronary collateral developed acute coronary syndromes.

METHODS

In our single-centered study, 426 patients who were admitted to Bolu Abant Izzet Baysal University Hospital and underwent coronary angiography with acute coronary syndrome between March 2015 and November 2018 were included.

The patients were divided into three groups: 102 patients with diagnosed USAP, 223 with diagnosed non-STEMI, and 103 with STEMI; all patients' emergency laboratory parameters were taken. Demographic data and laboratory parameters of the patients were recorded. Serum glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using an automatic biochemical analyzer (Architect C8000, USA). Complete blood count (CBC) was determined using simultaneous optical and impedance measurements (Cell Dyn 3700; Abbott Diagnostics, Lake Forest, Illinois, USA). NLR was calculated by dividing the neutrophil count by the lymphocyte count.

The presence of hypertension was defined as systolic blood pressure > 140 mmHg, and/or diastolic blood pressure > 90 mmHg, or already receiving antihypertensive treatment. Diabetes was defined as fasting blood glucose > 126 mg/dl or related drug intake. Hyperlipidemia was defined as total cholesterol > 200 mg/dl or triglyceride > 150 mg/dl.

While USAP, non-STEMI, and STEMI were diagnosed according to the recommendations of the current guidelines; patients with acute chest pain and persistent (>20 minutes) ST-segment elevation were defined as STEMI. The patients with acute chest pain but no persistent ST-segment elevation (transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo-normalization of T waves or normal ECG) and a hint for myocardial necrosis were defined as non-STEMI. USAP was defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis.

The criteria for ST-segment elevation were as follows: 1) At least 1 mm ST-segment elevation in at least two successive leads, 2) 2.5 mm in men under 40 years of age, 2 mm in men over 40 years, and 1.5 mm ST-segment elevation in women in V2 and V3, 3) 0.5 mm ST-segment elevation in V7-V9 (at least 2 consecutive lines), 4) 0.5 mm ST-segment elevation in V3R and V4R (1 mm in men under 40).

Coronary angiography was performed by the femoral or radial route using the Seldinger technique and coronary angiography results were evaluated independently by at least two cardiologists. In our study, we included patients with acute coronary syndrome who had at least 95% stenosis in the coronary artery. Although different methods are used for angiographically identifying and classifying coronary collateral circulation, Rentrop classification is the most accepted classification and was used in our study[14]. According to this classification: Rentrop 0 shows the absence of collateral current; Rentrop 1 is the presence of weak collateral flow; Rentrop 2 is the presence of partial collateral; while Rentrop 3 shows the presence of complete collateral.

The exclusion criteria of the study were history of coronary bypass graft operation, presence of decompensated heart failure, severe valve disease, atrial fibrillation, cardiomyopathy or congenital heart disease, inflammatory disease, renal or hepatic failure, malignancy, active infection, and pregnancy.

The study was approved by the Local Ethics Committee of the Bolu Abant Izzet Baysal University Hospital, Turkey.

Statistical analyses

SPSS 18.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) was used for analysis. Quantitative variables are expressed as mean ± standard deviation (SD) and qualitative variables as numbers and percentages. The One-way ANOVA Test (with Post-Hoc Tukey HSD) was used for comparing variables in study groups. Post-Hoc Tukey Test was applied in group differences. The neutrophil to lymphocyte ratio (NLR) value was determined by the division of neutrophils by lymphocytes. Receiver operating curve (ROC) analysis was used to find the difference in neutrophil and NLR in the two groups of acute coronary syndrome (STEMI and without –STEMI). A two-tailed P value of <0.05 was considered significant.

RESULTS

A total of 426 patients (301 male, 125 female) were included in the study. There was no significant difference between the three groups regarding the demographic data (Table 1). Laboratory parameters were compared and no significant difference was found between creatinine, glucose, and lipid panels. Neutrophil count and NLR were significantly different; 5.14± 1.79 vs. 7.21± 3.05 vs. 9.93±4.67 and 2.92±2.39 vs. 5.19±4.80 vs. 7.93±6.38, p <0.001) (Table 2). No significant difference was found between the groups regarding the site of coronary lesions (Table 3).

In order to understand which group has mainly caused a significant difference between the study groups, the One-way ANOVA Test with Post-Hoc Tukey Test was applied. The differences in NLR and neutrophil count were caused by the differences between the USAP and non-STEMI (p<0.001), USAP and STEMI (p<0.001), and non –STEMI and STEMI (p<0.001) groups by Tukey Test.

A receiver operating curve (ROC) analysis was used to find the difference in neutrophil and NLR in the two groups of acute coronary syndrome (STEMI and without –STEMI). At the cut-off value of >7.22 u/mm^3, sensitivity and specificity of neutrophil were 71 % and 69 %, respectively (AUC = 0.738, 95% CI, 0.683-0.793). At the cut-off value of >3.87, sensitivity and specificity of NLR were 71% and 62%, respectively (AUC = 0.712, 95% CI, 0.655-0.770) (Figure 1).

DISCUSSION

In our study, we compared neutrophil count and NLR in patients with coronary collateral developed acute coronary syndromes and found that neutrophil and NLR were higher in STEMI patients than in non-STEMI and USAP patients.

Coronary artery disease and acute coronary syndromes are inflammatory diseases caused by atherosclerosis[15]. Therefore, inflammation-related

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY GROUPS

Baseline characteristics	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
	MEAN			
Age (mean ±SD) (years)	64 ±12	67±12	67±13	0.11
Body mass index (kg/m^2)	25±4	26 ± 4	25±3	0.43
Male/female	79/23	146/75	76/27	0.08
Hypertension (%)	67(65%)	139(63%)	53(51%)	0.07
Smoking(%)	42(41%)	81(37%)	35(34%)	0.56
Family history(%)	16(16%)	26(12%)	(88%)	0.21
Diabetes mellitus(%)	39(38%)	83(37%)	27(26%)	0.10
Acetylsalicylate (%)	35(34%)	70(32%)	29(28%)	0.63
Clopidogrel(%)	17(17%)	25(11%)	13(12%)	0.41
Statin(%)	25(24%)	46(21%)	13(13%)	0.08
Calcium channel blocker(%)	15(14%)	44(20%)	12(12%)	0.15
ACE inhibitor(%)	27(26%)	41(19%)	14(14%)	0.06
ARB (%)	21(21%)	36(16%)	18(17%)	0.64
Beta-blocker(%)	38(37%)	63(28%)	30(29%)	0.26

ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, SD: standard deviation.

TABLE 2. LABORATORY DATA OF THE STUDY COHORT

	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
	MEAN			
Creatinine (mg/dl)	1.0±0.3	1.0 ± 0.8	1.0± 0.3	0.50
Fasting plasma glucose (mg/dl)	130±42	138 ± 50	139±50	0.32
LDL-cholesterol (mg/dl)	113±44	115±41	118± 44	0.68
HDL-cholesterol (mg/dl)	42±9	45±11	43± 10	0.12
Triglyceride (mg/dl)	159±91	151± 92	157±102	0.76
Total cholesterol (mg/dl)	185±49	189±49	191± 51	0.74
Hemoglobin	13.6±1.6	13.5± 2.0	13.6± 1.9	0.84
Platelet counts (k/mm^3)	224±71	235±67	237±72	0.29
Lymphocyte (u/mm^3)	2.18±0.90	1.92±1.09	1.76±1.05	0.013*
Neutropil(u/mm^3)	5.14± 1.79	7.21± 3.05	9.93±4.67	<0.001*
NLR	2.92±2.39	5.19±4.80	7.93±6.38	<0.001*

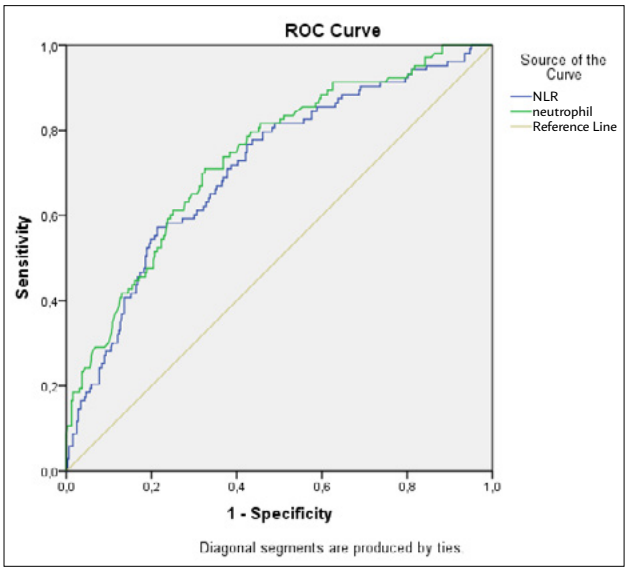
NLR: Neutropil to lymphocyte ratio; *One-way ANOVA test with Post HocTukey HSD; *Difference is statistically significant P < 0.05 levels

TABLE 3. CORONARY ANGIOGRAPHIC LABORATORY FINDINGS OF THE STUDY WORKING

Coronary artery	USAP (n=102)	Non-STEMI (n=221)	STEMI (n=103)	p
LMCA	12(12%)	18(8%)	8(8%)	0.098
LAD	86(84%)	193(87%)	90(87%)	0.281
CX	62(60%)	158(71%)	77(75%)	0.305
RCA	91(91%)	195(88%)	96(93%)	0.015

LMCA: left main coronary artery, LAD: left anterior descending, CX: circumflex, RCA: right coronary artery.

FIGURE 1. ROC CURVE ANALYSIS OF NEUTROPIL AND NLR FOR PREDICTION OF STEMI.



At the cut-off value of >7.22 u/mm3, sensitivity and specificity of Neutropil were 71 % and 69 %, respectively (AUC = 0.738, 95% CI, 0.683-0.793). At the cut-off value of >3.87, sensitivity and specificity of NLR were 71% and 62%, respectively (AUC = 0.712, 95% CI, 0.655-0.770). AUC: Area under the curve, CI: Confidence interval.

markers provide diagnostic and prognostic information for both coronary artery disease and acute coronary syndrome[16].

NLR is an inexpensive marker that can be easily calculated from peripheral blood tests and gives diagnostic and prognostic information in many diseases.

Lymphocytes have inflammation-suppressing properties and low levels of lymphocytes in cardiac diseases have been associated with poor prognosis[17-19]. As an example of this, Blum et al. found that it is possible to associate lymphopenia with low ejection fraction and high myocardial loss. In another study, low lymphocyte count in USAP patients was reported as an independent risk factor for major adverse coronary events[19].

On the contrary, high levels of pro-inflammatory and pro-atherogenic substances secreted by activated neutrophils are associated with a poor prognosis of cardiovascular disease[20,21]. Examples of this condition include restenosis associated with the infiltration of neutrophils in balloon-injured arteries[22]. Sezer et al.[21] showed a direct correlation between reperfusion injury and neutrophil count in patients with acute coronary syndrome. In parallel with our study, Biasucci et al.[23] found that the neutrophil count was higher in acute MI patients than in USAP and stable coronary artery disease patients.

NLR can be easily calculated by peripheral blood test and is a parameter that includes both neutrophil and lymphocyte count. In many studies comparing white blood cell count and all subtypes in acute coronary syndrome, NLR has been shown to be the most potent predictive value for both death and MACE (Major Adverse Cardiac Event)[9-11]. For example, Núñez et al.[24] showed that the NLR-maximum level calculated in the first 96 hours of STEMI patients was a marker for mortality.

In the study of Erturk et al.[1], the NLR among the types of acute coronary syndromes was the highest in STEMI and the lowest in USAP, similar to what we found in our study. Our study was the first to show the presence of the highest-burden of inflammation in STEMI with NLR elevation among the types of acute coronary syndromes with coronary collateral development.

It was concluded that NLR is correlated with the degree of coronary artery calcification in males, not only in acute coronary syndromes, and also in asymptomatic healthy group[25]. The NLR in patients with stable coronary artery disease is a parameter that predicts the functional severity of coronary artery stenosis evaluated by Fractional Flow Reserve (FFR)[2].

In contrast to previous studies, Kurtul and Ozturk[26] showed the presence of good coronary collateral circulation was independently associated with increased in-hospital mortality. In their study, which emphasized the benefits of good collateral development, they presented several possible mechanisms to interpret these results. The most likely mechanism is that these patients have high-risk factors and more severe clinical features affecting mortality.

In another study, patients were classified according to coronary angiography results as acute coronary syndrome, stable angina pectoris, and normal coronary arteries groups. The NLR value between the groups was found to be related to both the severity and progression of coronary artery disease; for the patients with high NLR, in-hospital and long-term adverse cardiac events were found[3].

CONCLUSION

In our study, we compared the neutrophil counts and NLR by classifying acute coronary syndrome with coronary collateral development patients as USAP, non-STEMI, and STEMI. Even in patients with acute coronary syndrome who developed collaterals, we found that NLR and neutrophil values were significantly higher in the STEMI group, which was known to have the highest inflammation burden in comparison with non-STEMI and USAP groups. Despite the disadvantage of having ambiguous cut-off values, NLR and neutrophil counts are important biomarkers that can be used in diagnosis and prognosis in acute coronary syndromes with cheap, fast, and easy application. Being single centered is the limitation of our study.

Conflict of interest

None

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None

Author's Contribution

Conception and design of the research: Mansiroglu AK, Sincer I, Gunes Y; Acquisition of data: Mansiroglu AK, Sincer I; Analysis and interpretation of the data: Sincer I, Gunes Y; Statistical analysis: Sincer I; Writing of the manuscript: Mansiroglu AK; Critical revision of the manuscript for intellectual content: Gunes Y;

All authors checked the final version of the manuscript.

RESUMO

OBJETIVO: *Marcadores relacionados a inflamação fornecem informações de diagnóstico e prognóstico para doença arterial coronariana e síndrome coronariana aguda. Nosso objetivo foi comparar o número de neutrófilos e razão neutrófilos/linfócitos (RNL) em pacientes com síndrome coronariana aguda com desenvolvimento de circulação colateral.*

MÉTODOS: *Um total de 426 pacientes [102 com angina de peito instável (APIN), 223 com infarto do miocárdio sem supradesnível de ST (IMSS), 103 com infarto do miocárdio com supradesnível de ST (IMCS)] foram comparados em relação a hemoglobina, plaquetas, linfócitos, neutrófilos e RNL.*

RESULTADOS: *O número de neutrófilos e RNL estavam significativamente mais baixos em pacientes com APIN e mais altos nos pacientes com IMCS; 5,14± 1,79 vs. 7,21± 3,05 vs. 9,93±4,67 and 2,92±2,39 vs. 5,19±4,80 vs. 7,93±6,38, p <0,001. Os outros parâmetros (hemoglobina, contagem de linfócitos e plaquetas) não foram significativamente diferentes entre os grupos.*

CONCLUSÃO: *No nosso estudo, concluiu-se que pode haver uma diferença significativa no número de neutrófilos e RNL entre os tipos de síndromes coronarianas agudas com desenvolvimento de circulação colateral.*

PALAVRAS-CHAVE: *Síndrome coronariana aguda. Circulação colateral. Neutrófilos. Linfócitos.*

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ORIGINAL ARTICLE

Depression, anxiety and spirituality in oncology patients

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SUMMARY

OBJECTIVE: *To relate anxiety and depression levels to the spirituality levels of oncology patients in the ABC region.*

METHODS: *Cross-sectional study performed at the ABC University Center oncology outpatient clinics. For the evaluation of spirituality, the Religiosity, Spirituality, and Personal Beliefs instrument of the World Health Organization (SRPB-WHO) was applied. To evaluate the levels of depression and anxiety, the Hospital Anxiety and Depression Scale (HADS) was applied. Qualitative variables were described by frequency and percentage, and quantitative variables by mean and standard deviation or median and range. Relationships were established using either the T-test or Wilcoxon-Mann-Whitney test and correlations with Pearson or Spearman tests, depending on the normality assessed by the Shapiro-Wilk test.*

RESULTS: *We included 99 patients, 68% female, with a median age of 60 years (19 to 81). A total of 24% had high or borderline levels of anxiety and 21% of depression. There was a negative correlation between levels of depression and spirituality (rho = -0.44, p <0.001), and anxiety and spirituality (rho=-0.232, p=0.02). We found no significant difference between levels of anxiety, depression, or spirituality when stratified by schooling, income, ethnicity, or marital status. There was a positive correlation between levels of anxiety and depression (cor = 0.477, p <0.001).*

CONCLUSION: *Spirituality can be a complementary tool in the treatment of patients with cancer.*

KEYWORDS: *Neoplasms. Spirituality. Depression. Anxiety.*

INTRODUCTION

Neoplasms, based on estimates from the World Health Organization (WHO), will be the leading cause of death, surpassing coronary heart disease[1]. Demographic and epidemiological transitions caused an increase in the number of cases of cancer, in particular in developing or underdeveloped countries[2].

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Regarding Brasil, an increase in mortality is expected due to cancer, particularly in the North and Northeast regions of the country, by 2030[3]. Cancer patients, in comparison with patients without the disease, exhibit more symptoms such as fear, despair, emotional and physical exhaustion, and, as a consequence, higher rates of depression and anxiety[4].

As to psychiatric disorders, anxiety disorders and depression are the most incident worldwide[5]. The World Health Organization, in its Dalys Brasil instrument, makes it clear that neuropsychiatric disorders occupy the second position, after cardiovascular disorders and diabetes. The clinical scenario is often similar and may become chronic or recurrent, affecting the individual's performance and abilities[6]. Thus, these diseases are directly related to a reduction in quality of life and increased mortality and morbidity[7].

It is estimated that 3.6% of the world population suffers from anxiety disorders, and females are the most affected. The prevalence of anxiety in the Brazilian population reaches 9.3%[5]. The WHO estimates that approximately 300 million people worldwide are affected by depression disorders (4.4% of the population), which are the main cause of disability[5].

However, the rates of depression vary between different countries, which shows that cultural differences and different risk factors affect the expression of the disease[8].

In Brasil, it is estimated that the prevalence of depressive disorders in the general population is around 5.8%, and it is more often found in female patients[5]. A meta-analysis identified that approximately 27% of outpatients have depression or depressive symptoms, varying according to the specialty[8].

Thus, the data show that Brasil is the country with the highest prevalence of anxiety disorders and the fifth in the ranking of depression[5].

spirituality has been increasingly used and recognized as a tool for overcoming this issue and as a complementary treatment for cancer patients[9.10].

Recently, themes such as spiritual well-being and spirituality have been increasingly studied in patients in general, especially in those with cancer[11.12].

Thus, considering the connections between neoplasms and psychiatric diseases, it makes sense to evaluate the prevalence of the two most common psychiatric disorders (GAD and MDD) in patients undergoing cancer treatment, as well as analyze the relationships between these diseases and spirituality in these patients.

OBJECTIVES

- Assess the level of spirituality of a population of cancer patients treated in outpatient clinics of the Faculty of Medicine of ABC (FMABC).
- Assess possible correlations between the level of spirituality, demographic variables, and presence of anxiety or depression by the Hospital Anxiety and Depression Scale (HADS).

METHODS

A descriptive, cross-sectional, and observational study, in which we evaluated the prevalence of major depressive disorder (MDD) and generalized anxiety disorder (GAD) in a group of consecutive patients aged over 18 years and treated in outpatient clinics of the Faculty of Medicine of ABC.

The assessment was carried out through the application of a questionnaire for the patients.

The questionnaire used the Hads[13] scale for anxiety and depression. In addition, patients' epidemiological and demographic factors were discussed, such as age, sex, race, and marital status. Patients' habits were also assessed, such as the use of alcohol, tobacco, and illicit drugs and the practice of physical activity.

Finally, we analyzed the socioeconomic data, such as average family income (in minimum wages) and formal education. To assess their spirituality, we used the World Health Organization Quality of Life instrument - Spirituality, Religiousness, and Personal Beliefs module (WHOQOL-SRPB)[14].

The inclusion criteria were patients treated in the oncology clinics of the Faculty of Medicine of ABC and their corresponding hospitals and the completion of the ICF.

The exclusion criterion: incorrect or incomplete filling of the questionnaire.

STATISTICAL ANALYSIS

The data collected were tabulated and subsequently submitted to statistical analysis. The categorical variables were analyzed for frequency and percentages.

For the continuous variables, was used averages or medians, based on the distribution of the data. We used the Shapiro-Wilk test to determine whether the distribution of the data was parametric or not.

In the continuous data with normal distribution, we used the Pearson's correlation test. For continuous

data with non-parametric distribution, we used the Spearman correlation test.

For qualitative data, we used the Fisher test or the chi-square test, depending on the size of the sample. Continuous data with qualitative outcomes and normal distribution were evaluated by t-test; and data with non-normal distribution were evaluated by the Mann-Whitney test.

TABLE 1. PATIENTS' DEMOGRAPHIC AND SOCIOECONOMIC DATA AND HABITS

Variable	N	%
Sex	99	
Male	31	31.31
Female	68	68.68
Marital Status	95	
Married	53	55.78
Single	17	17.89
Divorced	9	9.47
Widow(er)	16	16.84
Color	90	
White	58	64.44
Black	8	8.88
Brown	22	24.44
Yellow	2	2.22
Formal education	97	
Illiterate	2	2.06
IEE	32	32.98
CEE	20	20.61
IUSE	4	4.12
CUSE	28	28.86
IHE	3	3.09
CHE	8	8.24
Alcohol use	99	
Yes	86	86.86
No	13	13.13
Smoking	99	
Yes	16	16.16
No	81	81.81
Former smoker	2	2.02
Illicit drug use	99	
Yes	2	2.02
No	97	97.97
Physical activity	99	
Yes	30	30.30
No	69	69.69
Variable	Median	Range
Age	60	19-81
Income (R$)	2000	0-15000

Legend: IEE = Incomplete Elementary Education; CEE = Complete Elementary Education; IUSE = Incomplete Upper Secondary Education; CUSE = Complete Upper Secondary Education; IHE = Incomplete Higher Education; CHE = Complete Higher Education

Finally, the Anova and Kruskal-Wallis tests were applied to analyze the different demographic subgroups, based on the distribution of the data.

P values lower than 0.05 and a confidence interval of 95% were considered significant.

RESULTS

We included a total of 99 patients. Demographic data are described in Table 1. Most patients were female (68.6%), married (55.7%), white (64.4%) and with incomplete elementary education (32.9%)

Regarding the patients' habits, most drank at least socially (86.8%), 16.6% were smokers, and 2% former smokers; 69.6% were sedentary.

Upon completion of the Hads questionnaire for depression and anxiety, we observed that 24.24% of the patients had borderline or high levels of anxiety and 21.21 of depression.

The results on the relationships between the levels of anxiety, depression, and spirituality between themselves and between the demographic and socioeconomic data analyzed are presented in Table 2.

We observed a negative correlation between the levels of depression and spirituality (rho = -0.44, p<0.001) (Figure 1A) and the levels of anxiety and spirituality (rho = -0.232, p=0.02) (Figure 1B). No significant

TABLE 2. RELATIONSHIP BETWEEN THE LEVELS OF ANXIETY, DEPRESSION, AND SPIRITUALITY AND THE DEMOGRAPHIC AND SOCIOECONOMIC DATA.

	SRBP		HADS anxiety		HADS Depression	
Variable	rho	p	rho	p	rho	p
Age	-0,042	0,676	-0,070	0.49	0,047	0,641
Income	-0,101	0,365	-0,141	0,206	0,123	0,912
Variable	Median	p	Median	p	Median	p
Formal education						
Higher	128	0,442	6	0,498	2	0,426
Non-higher	132		4		4.5	
Marital status						
Married	133	0,562	4	0,693	4	0,579
Single	129		5		5	
Ethnicity						
White	129	0,226	4.5	0,792	4	0,878
Non-white	136		5		5	
Gender						
Male	127	0,295	3	0,050	2	0,214
Female	132		6		5	

difference was observed between the levels of anxiety, depression, or spirituality upon stratification by formal education, income, ethnicity, or marital status.

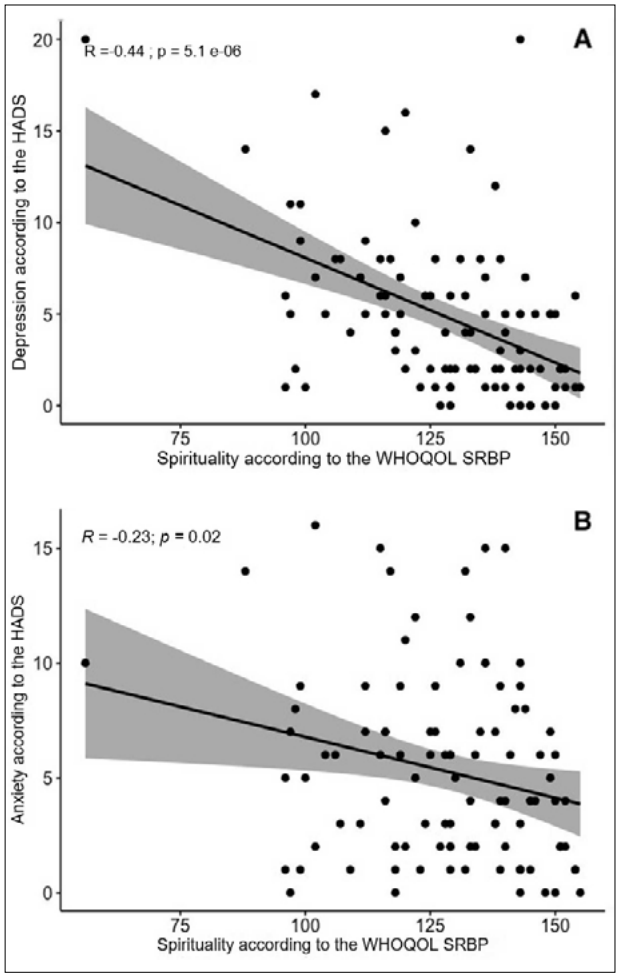
Finally, there was a positive correlation between the levels of anxiety and depression (cor=0.477, p<0.001).

DISCUSSION

Spirituality appears as an important ally for people who find themselves in adverse situations, particularly patients with psychiatric disorders and cancer patients[9].

Increasingly, spirituality presents itself as an alternative and coping strategy in the face of situations considered difficult and impactful, as is the case of the diagnosis and treatment of cancer, which produces several stressful events. Some of the positive strategies associated with spirituality are: improvement of mental health, reduction of stress, spiritual growth, and colaboration[15]. The purpose of this study was to evaluate if correlations between the level of spirituality, demographic variables, and the presence of anxiety or depression are reproduced in our population.

FIGURE 1. CORRELATION BETWEEN THE LEVELS OF SPIRITUALITY ACCORDING TO THE WHOQOL-SRBP AND DEPRESSION (1A) AND ANXIETY (1B) BASED ON THE HADS



According to the data studied, 21% of the patients had borderline or high levels of depression, and there was a negative correlation between depression and spirituality. The findings of our study corroborate data from the literature, which found a negative correlation between depression and spirituality[16,17]. These findings suggest that the spiritual well-being, obtained from giving meaning to life or through religious practice, combined with physical well-being, is useful for handling depression.

The fact that spirituality is negatively correlated with depression and anxiety stressed the significant role of the spiritual state in the daily clinical practice of palliative care and for the preservation or improvement of emotional suffering, as well as in the control of symptoms[18]. It is worth noting that often there are factors that can influence patients' stage of depression, such as the time of diagnosis of neoplasia, age, among others, and these affect the positive understanding of spirituality.

We found that the higher the level of spirituality, the lower the level of anxiety. Although this finding is observed in other studies in the literature, the causal relationship and attempts at an explanation for this phenomenon vary and are still a topic for speculation[19]. The findings suggest that the search for a meaning to life, peace and understanding of the universe through faith make the individual more aware of the process of becoming ill and the natural course of the disease itself, making the experience of the diagnosis, treatment, and follow-up more optimistic and positive. Prayer, through spirituality, also reliefs tension and increases hope, reducing the levels of anxiety[20].

We observed a positive mean correlation between anxiety and depression evaluated by the Hads in our patients. Both depressive and anxiety disorders can lead to significant losses in the functioning of individuals, such as decreasing their self-esteem and increasing hopelessness in the case of depression, and feelings of fear and behavioral disturbance in anxiety. Although they are different disorders, symptoms may appear together[21]. Beck et al.[22] reported that anxiety is a disorder often presented by depressive patients, particularly when they experience a worsening of depression.

In our study, we observed women tend to have more anxiety (p=0.05) in comparison with men.

Women have higher rates of prevalence of anxiety and mood disorders than men, who tend to have more problems related to the use of psychoactive substances and antisocial and schizotypal personality disorder. Female sex steroids, particularly estrogen, act in the modulation of mood, which explains the higher prevalence of mood and anxiety disorders in women[23].

For Barlow[24], women are more susceptible to stressful events in childhood and adolescence, which is associated with the perception that their behaviors cause little impact in the environment and may lead to a feeling of lack of control and the consequent development of pessimistic patterns of assessment of reality.

Limitations

This is a cross-sectional and observational study, therefore, relations of cause and effect cannot be established.

CONCLUSION

We found high levels of depression and anxiety among cancer patients. There was a negative correlation between the presence of depression and spirituality in these patients, which leads us to conclude that spirituality can be a complementary tool in the treatment of patients with cancer.

RESUMO

OBJETIVO: *Relacionar os níveis de ansiedade e depressão com os de espiritualidade dos pacientes oncológicos da região do ABC.*

MÉTODO: *Estudo transversal realizado nos ambulatórios de oncologia do Centro Universitário ABC. Para avaliação da espiritualidade, foi aplicado o questionário Religiosidade, espiritualidade e crenças pessoais da Organização Mundial da Saúde (SRPB-WHO). Para avaliar os níveis de depressão e ansiedade foi aplicado a Hospital Anxiety and Depression Scale (Hads). Variáveis qualitativas foram descritas por frequência e porcentagem, as quantitativas por média e desvio padrão ou mediana e intervalo. Relações foram feitas por meio do teste de t ou Wilcoxon-Mann-Whitney e correlações pelo teste de Pearson ou Spearman, a depender da normalidade avaliada pelo teste de Shapiro-Wilk.*

RESULTADO: *Foram incluídos 99 pacientes; 68% do sexo feminino, mediana de idade 60 (19 a 81); 24% tiveram níveis altos ou limítrofes para ansiedade e 21% para depressão. Foi observada correlação negativa entre os níveis de depressão e espiritualidade (rho=–0,44, p<0,001) e ansiedade e espiritualidade (rho=–0,232, p=0,02). Não foi observada diferença entre os níveis de ansiedade, depressão ou espiritualidade ao estratificar por escolaridade, renda, etnia ou estado civil. Houve correlação positiva entre os níveis de ansiedade e depressão (cor=0,477, p<0,001).*

CONCLUSÃO: *A espiritualidade pode ser uma ferramenta complementar a ser utilizada no tratamento do paciente com câncer.*

PALAVRAS-CHAVE: *Neoplasias. Espiritualidade. Depressão. Ansiedade.*

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ORIGINAL ARTICLE

Serum sclerostın levels ın chronıc otıtıs medıa wıth and wıthout cholesteatoma

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SUMMARY

OBJECTIVE: *Sclerostin is a glycoprotein that plays a catabolic role in bone and is involved in the regulation of bone metabolism by increasing the osteoclastic bone resorption. In this study, serum sclerostin levels were measured in chronic otitis media (COM) with and without cholesteatoma, assuming that it might have a role in the aetiopathogenesis of bone resorption.*

METHODS: *A total of 44 patients with cholesteatomatous COM (cCOM) (n = 22) and non-cholesteatomatous COM (ncCOM) (n = 22) were included in this study, and 26 healthy volunteers without any chronic ear disease problem(s) constituted the control group (n = 26).*

RESULTS: *No significant difference was not found in terms of serum iPTH, ALP, and vitamin D levels between ncCOM, cCOM, and the control groups. A significant difference was found in terms of serum sclerostin, Ca, and P levels between ncCOM, cCOM, and the control groups ($p<0.05$). Serum sclerostin levels in the study groups were significantly higher but their serum Ca and P levels were significantly lower compared to the control group.*

CONCLUSION: *We think that serum sclerostin concentrations, which were significantly higher in patients with cCOM and ncCOM compared to healthy controls are associated with bone erosion. There is a need for further studies with larger samples in order to determine the relationship between sclerostin and bone erosion in cholesteatoma to help in establishing preventive measures against cholesteatoma and set new targets for the development of non-surgical treatments.*

KEYWORDS: *Otitis media. Cholesteatoma. Ear, middle. Bone morphogenetic proteins.*

INTRODUCTION

Chronic otitis media (COM) is a chronic infection and inflammation of the middle ear. Although COM has been defined as a multifactorial disease, it's etiopathogenesis has not been fully enlightened.[1] Many factors, such as genetics, Eustachian tube disorder, autoimmunity, infection, osteoclastic activity, cytokines, endotoxins, and lipid peroxidation products due to oxidative stress, have been held responsible for the chronicity of inflammation in otitis media. Cholesteatoma is a destructive squamous epithelial lesion of the temporal bone disrupting the balance between bone formation and resorption that gradually expands and leads to severe complications due to the destruction of nearby bony structures, ossicular chain, and otic capsule. Erosion in the ossicular chain and bony labyrinth may lead to hearing loss, vestibular dysfunction, facial paralysis, labyrinthine fistula, and intracranial complications. Although bone erosion can

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be observed in COM with and without cholesteatoma, it is more common in the cholesteatomatous type. Some studies that were carried out to investigate the aetiopathogenesis of bone resorption in cholesteatoma showed that cholesteatoma was associated with bone formation and absorption.[1,2] There are also studies indicating that cholesteatoma is associated with other bone diseases such as osteoporosis.[3] According to the majority of recent studies, osteoclasts act as "terminal function cells" in the bone resorption process. It has been demonstrated that osteoclasts exist in the ossicles eroded with cholesteatoma in the middle ear. The activation and maturation of osteoclasts play an essential role in bone resorption and remodeling of middle ear cholesteatoma. Nevertheless, the exact mechanism of bone resorption in cholesteatoma has not yet been explained.[4,5]

Bone formation and resorption mechanisms are related to balanced functions of osteoblasts, and osteoclasts.6 Sclerostin is a glycoprotein that plays a catabolic role in the bone, increasing osteoclastic bone resorption by modulating the nuclear factor κB ligand: osteoprotegerin (rankl: opg) ratio in osteocytes, and it is involved in the regulation of bone metabolism.7 Sclerostin affects the activity of bone morphogenetic proteins (BMPS) and is an inhibitor of the metabolic pathway of wnt/β-catenin in bone cells. Osteocytes suppress the release of sclerostin in response to mechanical stimuli affecting the bone; thus, the osteogenic pathway promotes wnt/y-catenin activation in osteoblasts. This signaling pathway plays an important role in osteogenesis and bone turnover. The antibodies directed against sclerostin are considered a new therapeutic option by increasing osteoblast-mediated bone formation while reducing osteoclast-dependent bone resorption in the treatment of osteoporosis with increased bone resorption and chronic inflammatory diseases, such as rheumatoid arthritis and ankylosing spondylitis.[8]

The treatment of cholesteatoma is currently surgical; however, surgical treatment cannot compensate bone loss or prevent recurrence.[9] There are a limited number of studies on the non-surgical treatment of cholesteatoma, and sclerostin antibodies may be considered a new therapeutic option in cCOM associated with bone erosion as well as in chronic inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis. There is no previous study on this subject in the literature.

The aim of this study was to investigate the aetiopathogenesis of bone resorption in COM by measuring serum sclerostin levels in patients with cCOM and ncCOM, help take preventive measures against the development of cholesteatoma, and set new targets for the development of non-surgical treatment strategies.

METHODS

A total of 70 participants consisting of 44 patients with cCOM (n=22) or ncCOM (n=22)were included in this prospective study, and 26 healthy volunteers without chronic disease with ear problems constituted the control group. The diagnosis of COM was made by anamnesis and otomicroscopic examination. All patients were examined by pure-tone audiometry and computed tomography (CT) of the temporal bone. The patients with soft tissue density in mastoid cells and the middle ear in CT were selected for the study. All patients underwent tympanomastoidectomy. The individuals aged below 15 years and those over 50 years, with diabetes mellitus, chronic kidney, and/or chronic liver diseases were excluded from the study. All individuals in the experimental and control groups were selected from the same geographical region, and blood samples were studied simultaneously. Blood samples were drawn in the morning after 12 hours of fasting before surgery. Blood samples were aliquoted by centrifugation at 1250 g for 10 minutes, and 1 mL aliquots of serum were collected and kept in the freezer (HERA Freeze, Thermo Fisher Scientific, Waltham, Massachusetts, USA) at -80°C until the analysis. The samples were gradually brought to room temperature just before the analysis on the day of the study.

Serum Ca (Cat. No. 7D74-20), and P (Cat. No. 7D74-20) concentrations were measured with the Abbott kit and Architect c8000 instrument (Abbott, Chicago, IL, USA) by using standard procedures of the central laboratory of our hospital, serum iPTH (Cat. No. 8K25), and 1.25OH Vitamin D (Cat. No. 3L52) concentrations were measured with the Abbott kit and Architect i2000SR instrument (Abbott, Chicago, IL, USA).

Serum sclerostin concentrations were measured with an ELISA kit (Cloud-Clone Corp., Katy, TX 77494, USA). The intra-assay and inter-assay coefficients of variances (CVs) for sclerostin were less than 10% and <12%, respectively, with a measuring range of 0.312-20 ng/mL, and limit of detection of 0.118 ng/mL.

The participants who met the inclusion criteria were informed about the study and their approval

was received. Subsequently, they were included in the study. This study was carried out in adherence to the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects after and ethical approval was obtained from the clinical research ethics committee of our institution under decision number of 2018/227.

Statistical analysis

For descriptive statistics, mean and standard deviation or median and minimum-maximum values were given in numerical variables, while the number was given as categorical variables. The normality hypothesis was tested by the Shapiro-Wilks test. In the comparison of groups, one-way analysis of variance (ANOVA) was used when assumptions for normality hypothesis were met, and the Kruskal-Wallis test was used when they were not met. In cases where there was a difference between the groups, paired comparison analyses were used to determine the group/groups that caused a difference. The results of analyses were evaluated using IBM SPSS v.21. The level of significance was set at $p<0.05$.

RESULTS

Demographic and clinical data of the ncCOM, cCOM, and control groups are presented in Table 1. No significant difference was found between the ncCOM, cCOM, and control groups in terms of female/male ratios (p=0.805) and mean age of the patients (p=0.970). No significant difference was found in terms of serum iPTH, ALP, and vitamin D levels between the patient and control groups. A significant difference was found in serum Ca levels between the patient and control groups ($p<0.001$). Serum Ca levels were significantly lower in the cCOM group compared to the control group ($p<0.001$) (Figure 1). A significant difference was found in serum P levels between the patient and the control groups (p=0.013). Serum P levels were significantly lower in the cCOM group compared to the control and ncCOM groups (p=0.026 and p=0.035, respectively) (Figure 2).

A significant difference was found in terms of serum sclerostin levels between the patient and control groups ($p<0.001$) (Table 2). Serum sclerostin concentrations were significantly higher in the cCOM and ncCOM groups compared to those in the control group ($p<0.001$ and p=0.001). The mean sclerostin plasma concentration was higher in the cCOM group in relation to the ncCOM patient group. However, this difference between the groups was not statistically significant (Figure 3).

DISCUSSION

This study demonstrated the relationship between the serum sclerostin levels of patients with ncCOM, cCOM, and healthy controls. How serum sclerostin levels were affected in patients with COM was investigated. The mean sclerostin plasma concentration in patients with COM was found to be significantly higher compared to age-, and sex-matched healthy controls ($p<0.001$). When ncCOM and cCOM groups were compared, the mean plasma sclerostin concentration

TABLE 1. DEMOGRAPHIC AND CLINICAL DATA OF THE PATIENT AND CONTROL GROUPS

	ncCOM	cCOM	Control	P value
Gender, F/M	11/11	9/13	11/15	0.805
Age, year	36.23 11.75	37.05 11.0	36.69 10.20	0.970
ALP, U/L	68.41 14.28	62.73 16.29	67.92 18.01	0.440
Calcium, mg/dL	8.78 0.41	8.48 0.41[a]	9.04 0.48	<0.001
Phosphorus, mg/dL	3.61 0.68[b]	3.19 0.48[a]	3.61 0.47	0.013
iPTH, pg/mL	53.35 [23 - 139]	49.35 [20.4 – 154.2]	40.85 [6.7 – 69.5]	0.091
Vitamin D, ng/mL	8.65 [4.3 – 17.8]	9.1 [2.5 – 23.8]	11.65 [2 – 33.4]	0.299

a: Significantly differs from control. b: Significantly differs from cCOM. The results are expressed as mean ± SD for the data with normal distribution, and median [min-max] for the data with non-parametric distribution

TABLE 2. COMPARISON OF SERUM SCLEROSTIN LEVELS OF THE PATIENT AND CONTROL GROUPS

	ncCOM	cCOM	Control	P value
Sclerostin, ng/mL	3.77 1.31[a]	3.89 1.27[a]	2.55 0.61	<0.001

a: Significantly differs from control

FIGURE 1. COMPARISON OF SERUM CA LEVELS OF THE PATIENT AND CONTROL GROUPS (*:P<0.05)

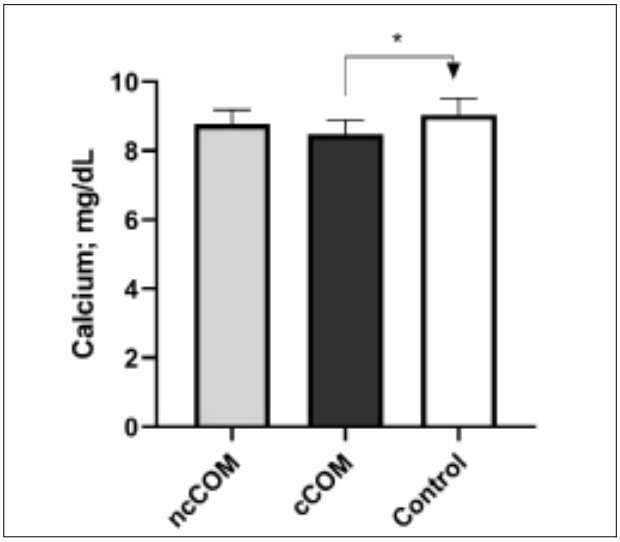


FIGURE 2. COMPARISON OF SERUM P LEVELS OF THE PATIENT AND CONTROL GROUPS (*:P<0.05)

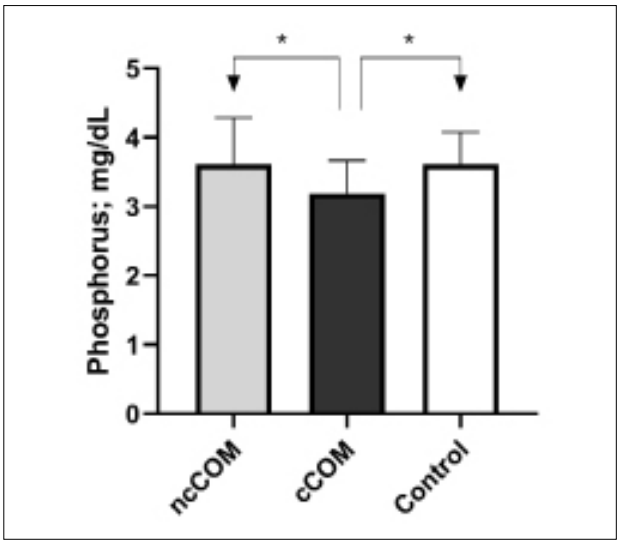
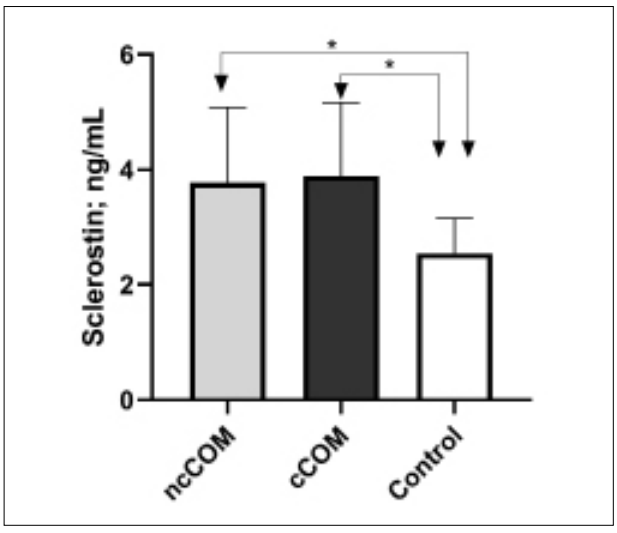


FIGURE 3. COMPARISON OF SERUM SCLEROSTIN LEVELS OF THE PATIENT AND CONTROL GROUPS (*:P<0.05)



was higher in the group of patients with cCOM, without any statistically significant intergroup difference.

In a study carried out by Elemraid et al.[10], it was demonstrated that serum Ca values were lower in children with COM compared to healthy controls. Similarly, in a study carried out with adults in China, it was reported that people with normal serum Ca concentrations were less prone to COM.[11] In our study, similar to the literature, while Ca was found to be significantly lower in the patients with cCOM and ncCOM compared to healthy controls, serum P levels were found to be lower in the cCOM group. Nevertheless, there was no significant intergroup difference for serum vitamin D, ALP, and iPTH values, which we interpreted as an indication of a lack of additional bone metabolic disease in our patients that could affect serum sclerostin levels in both groups.

The underlying mechanism of bone erosion in cCOM, which is a chronic inflammatory disease of the temporal bone, is still unclear. In the studies in the literature, the role of osteoclastic activity in bone resorption in cholesteatoma was emphasized. Firstly, in the ultrastructural study carried out by Chole et al.[12], evidence indicating that bone erosion was associated with osteoclastic activity in human and experimental cholesteatoma was found. Hamzei et al.[13] reported that there were osteoclast precursor cells in all cholesteatoma tissue samples. Si et al.[5] demonstrated the presence of osteoclasts in the bones eroded by middle ear cholesteatoma. Furthermore, Sudhoff et al.[14] compared the cholesteatoma model in the temporal bone of mice with control samples, and they demonstrated significantly increased osteoclast density in affected mice. In a study carried out by Imai et al.[15] in 2019, it was reported that there were more osteoclasts in the eroded bone adjacent to cholesteatomas than in unaffected areas. In our study, we found that sclerostin blood levels increased in cases with osteoclastic bone resorption in the cCOM group, which may lead us to infer that the increase in osteoclastic activity may be the result of the increased blood level of sclerostin. Contrary to the studies supporting the presence of osteoclastic activity in cholesteatoma, in some studies in the literature, it was reported that osteoclasts were not detected in the cholesteatomatous bones.[16]

The studies indicating that cholesteatoma is associated with other bone diseases such as osteoporosis suggest that the osteoclastic activity in cholesteatoma may also lead to local bone erosion along with systemic bone erosion. In their cohort study, Wang et al.[3]

found that the incidence of cholesteatoma increased in patients with osteoporosis. Individuals diagnosed with osteoporosis were excluded from the study so that our study results would not be affected. Thus, we aimed to investigate the effect of sclerostin on osteoclastic activity rather than osteoporosis.

Bone remodeling is a process involving bone resorption with osteoclasts and bone formation with osteoblasts.[17] The studies on sclerostin, which affects bone remodeling and increases osteoclastic bone resorption by inhibiting the metabolic pathway of wnt/β-catenin, have gained increasing interest in recent years.[18] The fact that serum sclerostin levels in the cCOM group were found to be higher in our study supports the literature findings.

The formation of ncCOM and cCOM and the presence of inflammation coexistent with bone erosion are already known.[19,20] It was demonstrated that osteoclastogenesis was activated by increased RANKL production due to inflammation in degenerative bone diseases, such as rheumatoid arthritis and periodontitis.[17,21] Similarly, it was reported that osteoclastogenesis was induced by cholesterol-RANKL found in cholesteatomas.[15] Sclerostin induces osteoclastogenesis through a pathway linked to RANKL.[7] The detection of higher serum sclerostin levels in the ncCOM and cCOM groups in our study supports the assumption that sclerostin may affect the development of cholesteatoma through inflammatory pathways.

The role of sclerostin in bone erosion observed in chronic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis has been revealed in various studies. The level of sclerostin was found to be lower in patients with ankylosing spondylitis compared to healthy controls, suggesting the role of sclerostin in suppressing bone formation. Higher levels of sclerostin in patients with rheumatoid arthritis that may cause both local and systemic bone erosion compared to healthy controls have been associated with bone erosion. In our study, serum sclerostin levels were significantly higher in patients with ncCOM and cCOM compared to healthy controls. High levels of sclerostin indicate that bone erosion in ncCOM and cCOM may be associated with sclerostin. We haven't encountered any study in the literature examining the relationship between cholesteatoma that can cause serious complications with bone erosion and serum sclerostin levels.

The established relationship revealed between sclerostin and bone resorption, as a potentially novel option in the treatment of diseases associated with bone erosion antibodies directed at sclerostin, has been investigated. As demonstrated in experimental animal models, the use of sclerostin antibodies in multiple bone diseases, such as myeloma and osteoporosis, decrease bone resorption.[22] In the clinical studies carried out, it was demonstrated that the use of a sclerostin antibody in women with postmenopausal osteoporosis decreased bone resorption.[23] Sclerostin antibodies, which are in the clinical development stage, can also be considered a promising option for the non-surgical treatment of cholesteatoma.

As a limitation of our study, we think that our detection of statistically insignificant levels of serum sclerostin in cCOM patients with higher bone erosion, in contrast to its higher levels in patients with ncCOM, was due to our small number of cases. There is a need for further studies with larger samples in order to determine the interaction between cholesteatoma and sclerostin. Furthermore, when the literature is reviewed, cases with hearing loss were observed in various disease groups, which may also be encountered in patients with cholesteatoma.[24-26] The relationship between sclerostin level and hearing loss can also be evaluated in future studies.

CONCLUSION

We believe that serum sclerostin concentrations, which were significantly higher in patients with cCOM and ncCOM compared to healthy controls, are associated with bone erosion. The sclerostin levels that are increased both in inflammatory disorders and in osteoclastic hyperactivity may have a role in the progression of COM to cholesteatoma. There is a need for further studies with larger samples in order to determine the relationship between sclerostin and bone erosion in cholesteatoma since these studies may help to establish preventive measures against cholesteatoma and set new targets for the development of non-surgical treatment strategies.

This study was carried out in adherence to the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, after ethical approval was obtained from the clinical research ethics committee of our institution under decision number of 2018/227 at 29/11/2018. There are 272 words for the abstract and

2301 words for the full text, 25 references, 2 tables, and 3 figures in this manuscript.

We have no conflicts of interest.

Author's Contribution

Concept – Elif Karali, Ozgur Mehmet Yis ; Design – Elif Karali, Ozgur Mehmet Yis; Supervision – Elif Karali, Ozgur Mehmet Yis; Resources – Elif Karali, Ozgur Mehmet Yis ; Materials – Elif Karali, Ozgur Mehmet Yis; Data Collection and/or Processing- Elif Karali, Ozgur Mehmet Yis; Analysis and/or Interpretation – Elif Karali, Ozgur Mehmet Yis; Literature Search – Elif Karali, Ozgur Mehmet Yis; Writing Manuscript – Elif Karali, Ozgur Mehmet Yis;

RESUMO

OBJETIVO: *A esclerostina é uma glicoproteína que desempenha um papel catabólico no osso e também envolve a regulação do metabolismo ósseo, aumentando a reabsorção óssea osteoclástica. Neste estudo, os níveis séricos de esclerostina foram medidos em otite média crônica (OMC) com e sem colesteatoma, e presumiu-se se que ela poderia ter um papel na etiopatogênese da reabsorção óssea.*

MÉTODOS: *Um total de 44 pacientes com otite média crônica colesteatomatosa (OMCc) (n=22), não colesteatomatosa (OMCnc)(n=22) foram incluídos neste estudo, e 26 voluntários saudáveis e sem doenças crônicas do ouvido constituíram o grupo de controle (n=26).*

RESULTADOS: *Não foi encontrada diferença significativa em termos de níveis séricos de iPTH, ALP e vitamina D entre OMCnc, OMCc e o grupo de controle. Foi encontrada uma diferença significativa em termos de níveis séricos de esclerostina, Ca e P entre OMCnc, OMCc e o grupo de controle (p<0,05). Os níveis séricos de esclerostina nos grupos de estudo foram significativamente mais altos, mas os níveis séricos de Ca e P foram significativamente mais baixos em comparação com o grupo de controle.*

CONCLUSÃO: *Acreditamos que as concentrações séricas de esclerostina, significativamente maiores em pacientes com OMCc e OMCnc em relação aos controles saudáveis, estão associadas à erosão óssea. Há necessidade de mais estudos com amostras maiores para determinar a relação entre esclerostina e erosão óssea no colesteatoma, já que essas pesquisas podem ajudar a estabelecer medidas preventivas contra o colesteatoma e novas metas para o desenvolvimento de tratamentos não cirúrgicos.*

PALAVRAS-CHAVE: *Otite media, Esclerostina, Colesteatoma, Orelha Média.*

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ORIGINAL ARTICLE

Do medical interns feel prepared to work in the COVID-19 pandemic?

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SUMMARY

OBJECTIVE: *To learn about the perceptions of medical internship students about the early conclusion of the course and their preparation to act in the fight against COVID-19.*

METHODS: *An online questionnaire was applied with questions about the socioeconomic profile and the object of investigation. The data were analyzed using the Bioestat 5.0 software.*

RESULTS: *111 students participated, most of whom (61.3%) were male, aged 20 to 25 years (80.2%), of Catholic religion (57.5%), and attending the 2nd year of internship (50.5%). A small portion (22.5%) reported being in total social isolation. The majority (57.5%) considered themselves unprepared to act in the fight against the pandemic, and 86.8% of the students believe that the early conclusion of the course will contribute to the fight against COVID-19 in the country.*

CONCLUSION: *This scenario points to the urgency of measures that provide, to recent graduates, timely technical preparation, safe work conditions, and emotional support even at the beginning of their professional career, leading them to competent, dignified and healthy work, during and after the pandemic.*

KEYWORDS: *Pandemics. Coronavirus. Public Health. Internship and Residency.*

INTRODUCTION

The novel coronavirus pandemic that started in December 2019 in Wuhan, China, due to the potential of lethality related to the massive alveolar damage and progressive pulmonary failure caused by the Sars-COV-2 virus, has consolidated itself as a matter of global concern[1].

Initially classified as an epidemic, Covid-19 spread among the Chinese and foreigners who were in that province at the end of that year and, due to its rapid spread across several countries and continents, on 30 January 2020, it was promoted to a Public Health Emergency of International Importance[2,3].

In Brasil, the first confirmed case of Covid-19 was recorded on 26 February 2020, imported from Italy, and by 23 May over 310,000 confirmed cases and 20,000 deaths had already been recorded in the

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country, triggering the need for intensification of specific strategic actions to control the spread of the disease and the number of severe hospitalizations[4,5].

Among the combat possibilities announced by the Brazilian Federal Government, the Ministry of Education (MEC) took the exceptional measure, through the publication of Decree 374, on 3 April 2020, and subsequently repealed by Decree 383, on 9 April 2020, of allowing the early graduation of health students to fight the Covid-19 pandemic[6,7].

Under the allegation that health professionals, particularly doctors and nurses, would be taken away from their positions due to the virus and in face of the substantial increase of patients in need of hospital care, the MEC considered that the measure would make more professionals available to work in the context of the pandemic and thus meet shortages of workers like the ones that were already taking place in states where the incidence of the disease is high[8].

One Brazilian states that experienced the early graduation of medical students and other health programs was Ceará. With eight medical programs offered in the state, the press reported, on the day following the publication of Decree 383 by the MEC, the early graduation of the first 82 students of the medicine, physiotherapy, and nursing programs, who are now authorized to act in health services of the entire country[9,10].

On the other hand, on 15 April 2020, the press reported that 28 health professionals in Ceará had been removed from their positions due to confirmed contamination by Covid-19, among them: eight nursing technicians/assistants, five doctors, and three nurses. Other 109 workers were suspected of having contracted the disease and were awaiting the results of serology[11].

In this scenario, and considering that the early graduation had the purpose of expanding the labor force available to the care of hospitalized patients, we present the following question: do students consider themselves prepared for the management of infected patients and other actions to fight Covid-19? What do they think about the early graduation to act in the context of the pandemic?

Understanding the perspective of students who are enrolled in the last periods of programs on such issues can assist in the elucidation of the challenges and possible fears related to this atypical moment experienced by all, which would allow us to have targeted and safe strategies for the work of these young professionals. Thus, the goal of this study was to investigate the perceptions of medical interns about early graduation and preparation to work in the combat against the Covid-19 pandemic.

METHODS

This is a cross-sectional study, of the opinion poll type, with no identification of its participants, based on the provisions of the Resolution 510/2016 of the National Health Council, conducted through online questionnaires on the Google Forms Platform sent to all students duly enrolled in the last two years of the medical program of a public university in the state of Ceará, totaling a pool of 166 students. Data collection began on 3 April, when the first ordinance by the MEC on the matter was issued, and ended on 22 April, when the necessary sample size was achieved, considering a confidence interval of 95% and error of 5%.

The questionnaire was prepared with sociodemographic variables and the questions: Do you believe you are prepared to handle the Covid-19 in your professional practice? What your behavior regarding social isolation? Did you request early graduation? Are you familiar with the protocols and guidelines by the Ministry of Health for the management of Covid-19? Do you believe that early graduation will contribute to the fight against the pandemic?

The data were exported from the Google Forms platform in the format of an electronic spreadsheet and analyzed using Bioestat 5.0. The absolute and relative frequencies of all variables of the study were calculated, and the association between them was verified by the G test (Wiliams). Statistical significance was considered when $p<0.05$.

RESULTS

The study sample consisted of 111 students, most of which (50.5%) enrolled in the 2nd year of internship. Regarding sex, 61.3% of the population was male and 38.7% female. The ages were mostly in the age group of 20 to 25 years (80.2%). As to family income, we found that 55% were in the range of up to four minimum wages, 40.5% in the range of over four minimum wages, and 4.5% reported a family income of less than one minimum wage. Most declared to be Catholic (57.7%), and 26.1% stated they have no religion.

When asked about the practice of social isolation, only 22.5% said they were practicing the "total" type,

i.e., are not leaving their homes or receiving visits; of those who reported being in partial isolation, 72.1% justified it by claiming they needed to leave the house to go to the pharmacy and/or supermarket, 4.5% reported leaving a few times to visit family and/or friends, and one person claimed not to leave the house but receive the visit from someone hired to perform domestic services daily.

Regarding their preparation to act as doctors in the fight against Covid-19, 57.7% said they did not consider themselves prepared, while 42.3% responded affirmatively. The feeling of preparation was more prevalent among: males (35.1%), age 20-25 years (30.7%), with an income between one and four minimum wages (20.8%), enrolled in the 2nd year of internship (27.1%), Catholics (29.7%), with knowledge of the Covid-19 protocols (47.7%), and who were in partial isolation (28.9%). Except for the gender variable, all other variables significantly influenced the perception expressed by students (Table 1).

In a complementary manner, 95.5% of the students reported being aware of one or more ministerial protocols for the management of Covid-19, while 4.5% reported not knowing any of the official documents; one student remarked that he did not know the existence of specific documents on the various clinical contexts involved in the pandemic. The ministerial protocols on Covid-19 known by the students are listed in Table 1.

DISCUSSION

The pandemic caused by Covid-19 has changed the daily lives of everyone significantly. It affected various aspects of people's behavior, which include work, study, family life, and even spiritual life; the topic has influenced these scenarios mediated by strategies for coping with the crisis which is still present in many places.

In Brasil, the fight against the pandemic has been made possible by the existence of a universal health care system, which features a hierarchical and regionalized network of services, and by its body of workers, which together constitute the patrimony of the country[12]. However, the increase in contamination among these professionals, as a result of an unhealthy working environment, exhaustive work hours, and problems regarding the supply of inputs for individual protection, results in the removal of professionals from their functions, generating the need for other professionals to join in on the frontline of health services.

Faced with this context, the Ministry of Health authorized the early graduation of health students in the last year of university so that they can help overcome shortcomings identified in places with a greater number of people affected. However, the government measure generated disagreements among professional bodies, society in general, and students themselves, bringing to the heart of the discussion aspects that involve the preparation to act and appropriate and safe work conditions for young professionals, since these students, although graduated and trained to provide care in all contexts, are not trained to handle crisis situations such as the presents one[13].

TABLE 1. ASSOCIATION BETWEEN THE PREPARATION TO ACT IN THE FIGHT AGAINST COVID-19 AND THE SOCIODEMOGRAPHIC VARIABLES OF THE INTERVIEWEES.

Variables	Preparation to act in the fight against Covid-19				p-value*
	Yes		No		
	f	%	f	%	
Gender					0.0974
Female	14	12.6	32	28.9	
Male	39	35.1	36	32.4	
Age range					0.0183*
20-25	34	30.7	55	49.5	
26-30	7	6.3	8	7.2	
31-40	6	5.4	0	0	
>40	0	0	1	0.9	
Income (minimum wages)					0.4893
<1 wage	3	2.7	2	1.8	
1 to 4 wages	23	20.8	38	34.2	
> 4 wages	21	18.9	24	21.6	
Internship year					0.0159*
1st year	17	15.3	38	34.2	
2nd year	30	27.1	26	23.4	
Religion					0.0020*
Catholic	33	29.7	31	27.9	
Christian	0	0	1	0.9	
Spiritualist	1	0.9	6	5.4	
Evangelical	0	0	10	9.0	
No religion	13	11.8	16	14.4	
Is familiar with Covid-19 protocols					0.0233*
Yes	53	47.7	63	56.8	
No	0	0	5	4.5	
Social isolation behavior					0.0456*
Partial	32	28.9	54	48.6	
Total	15	13.5	10	9.0	

* Williams G-test of 0.05.

In the present study, medical interns gave their opinion on early graduation and preparation to act professionally in the context of a pandemic. The findings revealed that the younger ones and those in the 1st year of internship are more insecure. We suppose that experiences acquired with age and during the internship, in addition to prior work in the health workforce, contribute so that older individuals feel more confident to act.

Religion was another significant variable in this study. Most students who declared having some kind of religious belief feel prepared to act in the fighting against the virus. It is understood that religion can positively influence students' health practices since spirituality is a human dimension that can put health and disease experiences in a meaningful context, and when medical students understand its importance, they are able to reflect on this in relation to their professional activity and themselves, which is reflected in things such as self-care and self-protection[14].

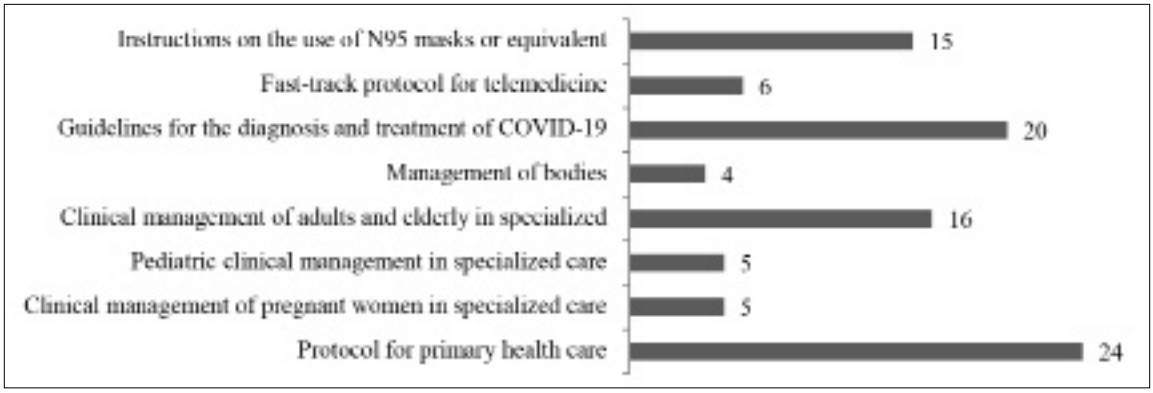
Considered by the World Health Organization as a measure of self-protection, social isolation has been adopted as a way of hindering the transmission of the virus and was an aspect investigated among students, most of whom declared risk behaviors for contagion. Although all interviewees are practicing some form of isolation, most of them informed partial isolation, a similar result found by a study conducted in Ceará in the general population[15]. We suppose that this behavior by the students is due to the fact that part of this group lives far from their families and are the only ones responsible for acquiring basic supplies and performing essential services.

In the context of public health, the impacts caused by a virus of fast and easy propagation are severe, resulting in abrupt changes in health services due to the increased number of hospitalizations and the collapse of the health care system. Although one of the currently most widespread guidelines is social distancing, this does not include activities that are essential to society, such as those performed by health professionals[16]. The presence of these workers in their work environments is necessary to ensure essential care related to various health aggravations, such as Covid-19, but it may also lead to an increasingly unhealthy work environment due to the high probability of contamination related to work in this new condition of risk.

In this sense, the preparation of the students to act in health care services in the context of a pandemic was investigated in this study. Although most declared knowing at least one of the protocols by the Ministry of Health about Covid-19, a portion of the students does not feel prepared for professional practice. It should be emphasized that these young professionals, in the absence of safe work conditions, will be exposed to contamination in similarly to other workers, since, even to those who are directly involved with patients, little has been discussed about work conditions and organization, up until now, there have been protocols with recommendations of individual measures, which are important but insufficient for the general control of the spread of the disease and exposure to the virus[17].

The students demonstrated knowing the ministerial protocols that involve the management of the disease at the primary or tertiary level of care, which may be due to intrinsic motivation since curriculum classes at the institution investigated have been suspended[18]. However, the protocol on the use of N95 masks or equivalent was not often mentioned by the participants, which may suggest little importance attributed to the subject or ignorance about the existence of this particular document, which emphasizes

FIGURE 1. MINISTERIAL PROTOCOLS ON COVID-19 KNOWN BY THE STUDENTS



Source: Prepared by the authors.

the need for raising awareness among students about the importance of personal protection, on the sufficient and safe use of PPE, and technical preparation for work, all important measures to reduce the risk of infection for health workers[19].

The early graduation was also the object of this study. With the onset of the Sars-Cov-2 pandemic, several countries presented alternative tracks for the graduation of students, and the Brazilian Ministry of Education softened the requirements for regular medical internship duration, allowing also the abbreviation of programs, provided that 75% of the hourly load planned for the medical internship is completed[20].

Most students in this study believe that early graduation will contribute to solving the health system crisis; however, the Federal Council of Medicine (CFM) clarifies that the early graduation of medical students is harmful to the training of future physicians, in addition to not bringing obvious benefits for the care of the population[21].

It should be emphasized that the interruption of activities in medical schools, which will have an impact on the time necessary for new professionals to graduate, was another factor for consideration in the context of Brazilian universities which was taken into account in the discussions on the early graduation. In a virtual survey conducted by the Brazilian Association of Medical Education (Abem) in March and April 2020, when questioned about the interruption of activities, teachers, students, and administrators revealed a trend of slow and gradual return, without concrete prospects[22].

There are still questions about the characteristics of this new and young labor force of physicians in the country after the scenario of the pandemic. With the early graduation of medical students with a course load that exceeds 75% of the total requirements, it is not possible to ensure that everyone has experienced all practical scenarios necessary for adequate training. Therefore, students who do not have sufficient practical experience in urgent and emergency or primary health care may graduate early, since the areas in question add up to 30% of the load of medical internships, which may interfere with the quality of the services provided by these professionals[23].

Another issue to be considered in this context is the growing circulation of fake news about Covid-19 in social media[24]. Information on effective pharmacological treatments is disclosed based on inconclusive studies, leading specialized medical and scientific groups to various reflections and encouraging professional debate, which requires these newly graduated physicians to have knowledge about and discernment regarding the best practices for the clinical scenarios related to Covid-19[25].

Despite the different contexts and scenarios, in face of an unprecedented pandemic and located in a state where there is a low density of professionals, the alternative of early graduation for medical interns of the last years is a strong alternative that has been put into practice in several Brazilian medical schools.

CONCLUSION

The results of this study indicate that the debates on early medical graduation require greater depth so that the integration of recent graduates into the workforce can effectively constitute a strategy of expansion in the context of the pandemic. In addition, these findings indicate the need for improved training of these young professionals on Covid-19 and how to combat it, in addition to adequate work conditions and emotional support that lead them to a responsible, safe, and healthy practice in the context of the pandemic and after it.

Author's Contribution

Moreira MRC, Parente NC, Aquino RF, and Barros LL contributed to the concept and design of the study, data collection, analysis and interpretation of the results, preparation and critical review of the manuscript. Cândido EL, Oliveira AMF, and Machado MFAS contributed to the analysis and interpretation of the results, preparation and critical review of the manuscript. All authors approved the final version of the manuscript and declare themselves to be responsible for all aspects of the work, ensuring its accuracy and integrity.

RESUMO

OBJETIVO: *Conhecer as percepções de estudantes do internato médico sobre formatura antecipada e preparo para trabalhar no combate à pandemia da Covid-19.*

MÉTODOS: *Aplicou-se questionário on-line com questões sobre o perfil socioeconômico e o objeto de investigação. Os dados foram analisados pelo software Bioestat 5.0.*

RESULTADOS: *Participaram 111 estudantes, a maioria (61,3%) do sexo masculino, na faixa etária de 20 a 25 anos (80,2%), de religião católica (57,5%) e cursando o 2º ano do internato (50,5%). Pequena parcela (22,5%) informou estar em isolamento social total. A maioria (57,5%) se sente despreparada para atuar no combate à pandemia, e 86,8% consideram que a formatura antecipada contribuirá para o enfrentamento da Covid-19 no País.*

CONCLUSÃO: *Este panorama remete à urgência de medidas que propiciem, aos recém-graduados, preparo técnico oportuno, condições de trabalho seguras e suporte emocional já neste início de carreira profissional, conduzindo-os ao trabalho competente, digno e saudável, durante e após a pandemia.*

PALAVRAS-CHAVE: *Pandemias. Coronavírus. Saúde pública. Internato e residência.*

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ORIGINAL ARTICLE

Evaluation of anxiety and depression in patients with thyroid function disorder

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SUMMARY

OBJECTIVES: *We aim to determine the anxiety and depression levels of patients treated for hypothyroidism who assumed euthyroid status. These patients also frequently attend family medicine outpatient clinics.*

METHODS: *This study was conducted on 76 euthyroid volunteer participants (patient groups) who were treated for hypothyroidism and followed-up and 22 healthy volunteers (control group). Questionnaires were administered to all participants to assess anxiety and depression levels. The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were applied to all the groups. In addition, BAI sub-parameters were evaluated in detail.*

RESULTS: *At least mild depression was detected in 54.5% of the first group, 41.7% of the second group, and 33.3% of the third group. When the BDI and BAI total scores of the participants in different groups were compared, statistically significant differences were determined. Statistically significant results were detected related to different BAI sub-parameters between the patient groups and in comparison to the fourth group.*

CONCLUSIONS: *We found that patients were predisposed to anxiety and depression even if they were euthyroid. When the sub-parameters of BAI were evaluated in detail, we observed that the duration of the disease significantly affected some anxiety-related symptoms.*

KEYWORDS: *Anxiety. Depression. Thyroid diseases.*

INTRODUCTION

It is known there is a relationship between brain functions and thyroid hormone levels. Intracranial receptors and intracerebral biochemical reactions are closely related to thyroid hormones. There is also a common relationship between thyroid hormone levels and anxiety-depression in hypothyroid patients[1]. It is known that anxiety disorder, major depression, and psychosis are seen in an average of 30%, 40%, and 5% of the patients with hypothyroidism[2]. It has been also reported that thyroid dysfunction may affect mood and the progression of mood disorders.

Initially, nonspecific symptoms are seen. However, depression, forgetfulness, deceleration in thought, and concentration problems may be seen in later stages in hypothyroidism. In severe clinical conditions, psychotic symptoms may appear[3]. A depressive mood is the most common psychiatric symptom in patients with thyroid dysfunction. In addition, anxiety and sleep disorders are common in these patients. Some of these signs and disorders persist after thyroid functions have improved. Most of the symptoms disappear after treatment[4].

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Chronic hypothyroidism may cause permanent cognitive changes[5]. In patients with thyroid dysfunction, many symptoms, such as dyspnoea, sweating, and palpitations may be observed in patients with panic attacks. Nevertheless, anxiety disorders associated with thyroid dysfunction still remain unclear[6].

Patients with thyroid dysfunction frequently attend family medicine outpatient clinics. Therefore, we aimed to determine the anxiety and depression levels of the patients who were treated due to hypothyroidism and became euthyroid in terms of family medicine. In addition, we aimed to raise awareness among family physicians about mood disorders that may develop due to thyroid dysfunctions. Also, we aimed to evaluate the sub-parameters of the Beck Anxiety Scale (BAI) in detail. When the literature was evaluated, we did not find any studies in which the sub-parameters of the BAI were evaluated in detail in patients with thyroid disorders.

METHODS

Study population

Necessary permissions were obtained (2018-320-14). This study was conducted as a prospective and randomized controlled study. The study was performed to determine the anxiety and depression levels of patients who were followed up due to thyroid dysfunction in our family medicine outpatient clinic.

All patients who were followed-up and treated for hypothyroidism between November 1, 2018, and May 1, 2019, were evaluated. 76 patients were included in the study.

The 76 volunteered participants who were treated and followed-up for hypothyroidism were included in the study. In addition, 22 healthy volunteers between the ages of 25-45 years were included as a control group. Participants in the control group were randomly selected.

Patients who were followed-up for hypothyroidism, received thyroid hormone replacement therapy, and had euthyroidism based on thyroid function test results were included in our study. Complete blood counts and the biochemical test results of the participants were evaluated. Participants with additional hematological disorders were excluded from the study. In addition, participants who were diagnosed with systemic diseases such as hypertension (HT) or diabetes mellitus (DM) during the study and who had a history of using anti-depressants or a different psychiatric drug within the previous year were excluded. The control group consisted of healthy participants who had no health problems.

Patient evaluation scales used in the study

The participants in the patient group were evaluated for age, gender, duration of thyroid disease in years, and whether they were attending regular follow-ups. Then, the BAI and Beck Depression Inventory (BDI) were applied to the volunteers in the patient and control groups.

The patient group was divided into three subgroups. Group 1 consisted of euthyroid patients who were followed-up for 1 year due to thyroid dysfunction. Patients with euthyroid status followed-up for at least 5 years due to thyroid dysfunction who become euthyroid constituted Group 2. Patients with euthyroid status followed-up for at least 10 years due to thyroid dysfunction were included in Group 3. The healthy volunteers constituted Group 4.

The BAI and BDI total scores were compared between the groups. The differences in the BAI sub-parameters between groups were also analyzed in detail. The sub-parameters of the BAI included in the evaluation are presented in Table 1.

TABLE 1. THE SUB-PARAMETERS OF THE BECK ANXIETY SCALE (BAI) USED AND EVALUATED IN THE STUDY

Sub-parameters of the BAI
Tingling or numbness in any of your body parts?
Feeling hot?
Wobbliness of legs
Unable to relax
Fear of the worst happening
Feeling dizzy or lightheaded
Heart pounding/racing
Feeling unsteady
Feeling terrified or afraid
Nervousness
Feeling of choking
Hands trembling
Feeling shaky/unsteady
Fear of losing control
Difficulty in breathing
Fear of dying
Being scared
Indigestion
Fainting/lightheaded
Facial flushing
Sweating (unrelated to environment temperature)

Statistical Analysis

Numerical data were calculated as arithmetic mean ± standard deviation and percentage (%). The Chi-square test and T-test were used to compare the data between the groups. In addition, Cronbach's alpha value was calculated in a reliability analysis because our study was a survey. $p < 0.05$ was considered statistically significant. Data were analyzed using the SPSS v21.

RESULTS

The mean age of the patient groups was 39.05 ± 5.9 (min: 23, max: 45) and the control group was 38.73 ± 5.71 (min: 25, max: 45) years. Sixty-four (84.2%) female and 12 (15.8%) male participants were included in the patient group. Sixteen (72.7%) female and 6 (27.3%) male participants were in the control group. There was no statistically significant difference between the groups in terms of age, education level, and gender. The Cronbach's alpha value found was 0.876 (> 0.7).

BDI scores of ≥ 14 points were detected in the respective number of patients in groups, and at least mild depression was detected in these patients. The total scores of BAI and BDI in the patient groups were evaluated; the mean BAI and BDI scores of the groups were estimated. The mean BAI score of the 76 participants was determined as 14.53 ± 9.39. The mean BAI score of the 22 participants in the control group was found to be 4.36 ± 3.34. The mean BDI score of the 76 participants was 13.66 ± 8.09. The mean BDI score of the 22 participants in the control group was 6.68 ± 2.93 (Table 2).

When evaluating the effectiveness of rates of patients' regular attendance to the physicians' to control anxiety and depression in the patient groups, the mean BAI score of 50 (65.8%) participants who regularly attended their check-up visits was 13.36 ± 8.19, while the 26 (34.2%) participants who did not regularly attend to their check-up had a BAI score of 16.77 ± 11.39. In addition, the mean BDI score of 50 (65.8%) participants who had attended their regular follow-up visits was 13.24 ± 7.34, and the BDI score of 26 (34.2%) participants who did not regularly attend their control visits was 14.46 ± 9.64. When evaluated statistically, it was concluded that attending regular control visits had no effect on the severity of anxiety and depression (p=0.11, p=0.390).

Statistical evaluation data of the Beck Anxiety Inventory (BAI) sub-parameters between the groups are presented in Table3. The mean BDI and BAI scores of each group are also presented in Figures 1 and 2.

DISCUSSION

In the clinical practice of family medicine, there are many patients with thyroid dysfunction who become euthyroid and are followed-up with drug therapy. Therefore, we think that family physicians should also evaluate whether these patients are affected psychologically.

Thyroid hormones have an important role in many organ functions and their deficiencies cause diseases of a wide clinical spectrum[7]. The rate of psychiatric symptoms is between 2-12% in these patients[8]. In cases of acute hypothyroidism, anxiety rates are in the range of 30-40%[9]. In this study, we mainly evaluated the relationship between anxiety and depression in patients with euthyroid status following thyroid hormone replacement therapy. Also, in the literature, BAI sub-parameters in different disease states have been evaluated in detail[10]. However, there are no studies evaluating the sub-parameters of BAI in individuals with thyroid dysfunction who achieved euthyroid status with treatment. In a

TABLE 2. BECK DEPRESSION SCALE (BDI) AND BECK ANXIETY SCALE (BAI) MEAN SCORES AND STANDARD DEVIATION (SD) IN EACH GROUP, AND NUMBER OF PATIENTS WITH BDI SCORES OF ≥ 14 POINTS IN GROUPS

BAI			N	Mean ± SD	
	Patient Group	Group 1a	22	16.27±11.01	
		Group 2b	24	12±6.71	
		Group 3c	30	15.27±10.13	
		Total	76	14.53±9.39	
	Control Group	Group 4d	22	4.36±3.34	
BDI			N		N (BDI scores of ≥ 14)
	Patient Group	Group 1	22	15±7.23	12 (54.5%)
		Group 2	24	13.33±8.16	10 (41.7%)
		Group 3	30	14.75±9.19	10 (33.3%)
		Total	76	13.66±8.09	
	Control Group	Group 4	22	6.68±2.93	

a- Euthyroid patients who were followed-up for 1 year due to thyroid dysfunction (Group 1); b- Patients with euthyroid status followed-up for at least 5 years due to thyroid dysfunction and who became euthyroid constituted Group2; c- Patients with euthyroid status followed-up for at least 10 years due to thyroid dysfunction were included in Group 3; d- The healthy volunteers constituted the control group (Group 4)

TABLE 3. STATISTICAL EVALUATION DATAS OF THE BECK ANXIETY INVENTORY (BAI) SUB-PARAMETERS BETWEEN GROUPS

	P1	P2	P3	P4	P5	P6
Tingling or numbness in any of your body parts?	0,722	0,422	0,013	0,404	0,022	0,330
Feeling hot?	0,022	0,000	0,000	0,152	0,318	0,740
Wobbliness of legs	0,000	0,000	0,001	0,769	0,292	0,360
Unable to relax	0,000	0,000	0,000	0,000	0,366	0,014
Fear of worst happening	0,019	0,069	0,008	0,408	0,845	0,299
Feeling Dizzy or lightheaded	0,023	0,016	0,001	0,614	0,558	0,195
Heart pounding / racing	0,000	0,000	0,000	0,296	0,455	0,820
Feeling unsteady	0,000	0,000	0,000	0,838	0,386	0,381
Feeling terrified or afraid	0,000	0,000	0,000	0,440	0,081	0,431
Nervousness	0,194	0,007	0,067	0,481	0,898	0,453
Feeling of choking	0,000	0,000	0,000	0,026	0,613	0,057
Hands trembling	0,000	0,004	0,000	0,701	0,764	0,423
Feeling shaky/unsteady	0,000	0,000	0,000	0,736	0,804	0,844
Fear of losing control	0,056	0,073	0,420	0,008	0,018	0,264
Difficulty in breathing	0,000	0,000	0,000	0,039	0,603	0,037
Fear of dying	0,000	0,390	0,000	0,000	0,516	0,000
Being scared	0,000	0,021	0,000	0,002	0,269	0,002
Indigestion	0,550	0,027	0,277	0,051	0,238	0,409
Faint/lightheaded	0,051	0,005	0,013	0,058	0,079	0,754
Facial flushing	0,000	0,000	0,003	0,975	0,178	0,145
Sweating (unrelated to ambient temperature)	0,378	0,021	0,097	0,424	0,775	0,456

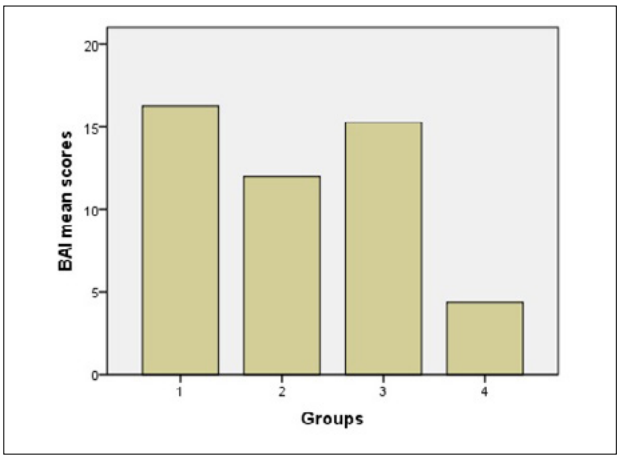
*P1; Group 1 vs Group 4, P2; Group 2 vs group 4, P3; Group 3 vs group 4, P4; Group 1 vs group 2, P5; Group 1 vs group 3, P6; Group 2 vs group 3.

study, the average of 94 patients followed-up with a diagnosis of subclinical hypothyroidism was found to be 49.1. In these studies, anxiety and depression levels were found to be higher compared to the control group[11]. In another study, the age range of 51 patients was determined as 26-35 years. The authors argued that this age range was selected in order to avoid endogenous depression and to exclude the psychiatric symptoms of patients with menopause[8]. In this study, the average age found was 39.05 years. In addition, in this study, we determined the age range of our patient group to be between 23 and 45 years in order to exclude the effects of menopause and endogenous depression.

In a different study, 32 patients with subclinical hypothyroidism and 29 euthyroid cases were evaluated, and significant increases in the anxiety levels of patients with subclinical hypothyroidism were found compared to euthyroid patients[12]. There are many studies in the literature showing that anxiety levels are higher in patients with thyroid disorders. In addition to this high frequency of anxiety, symptoms of depression in patients with hypothyroidism have been encountered in these studies[13]. In a review, it was shown that hypothyroidism had a significant effect on depression and anxiety, and it was emphasized that it is absolutely necessary to evaluate psychiatric disorders in these patients[13]. Hypothyroidism, subclinical hypothyroidism, and a control group were evaluated in a different study examining the relationship between anxiety and depression with thyroid dysfunction. BAI and BDI scores were found to be significantly higher in both hypothyroid and subclinical hypothyroid patients[14].

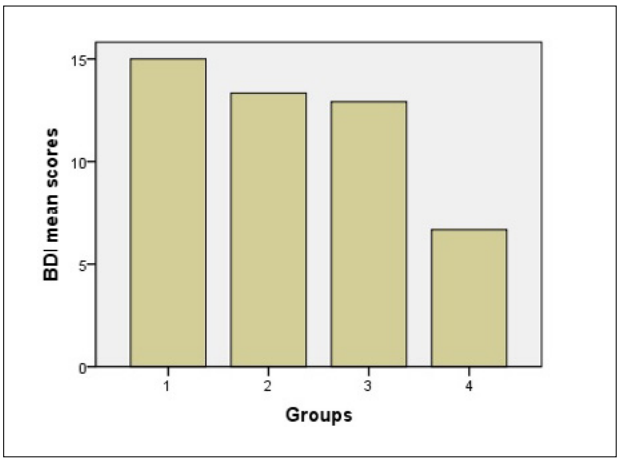
In the literature, there are studies conducted in patients undergoing thyroid hormone replacement therapy for hypothyroidism in whom euthyroidism has been achieved. In a similarly performed study, significant decreases in anxiety and depression scores were demonstrated after treatment in 43 subclinical hypothyroid patients evaluated before and after treatment[15]. However, in a different study, no significant differences in depression scores were found in the evaluation of 89 patients before and after treatment[16]. Again, in a different study, there were no significant differences in the anxiety and depression scores of 38 patients who were evaluated before and after treatment[17].

FIGURE 1. BECK ANXIETY SCALE (BAI) MEAN SCORES IN EACH GROUP



1- Euthyroid patients who were followed-up for 1 year due to thyroid dysfunction (Group 1); 2- Patients with euthyroid status followed-up for at least 5 years due to thyroid dysfunction and who became euthyroid constituted Group
2; 3- Patients with euthyroid status followed-up for at least 10 years due to thyroid dysfunction were included in Group 3 ; 4- The healthy volunteers constituted the control group (Group 4).

FIGURE 2. BECK DEPRESSION SCALE (BDI) MEAN SCORES IN EACH GROUP



1- Euthyroid patients who were followed-up for 1 year due to thyroid dysfunction (Group 1); 2- Patients with euthyroid status followed-up for at least 5 years due to thyroid dysfunction and who became euthyroid constituted Group2
; 3- Patients with euthyroid status followed-up for at least 10 years due to thyroid dysfunction were included in Group 3 ; 4- The healthy volunteers constituted the control group (Group 4).

In this study, we determined that anxiety and depression scores were higher in patients compared to the control group. However, when the literature is evaluated, the studies are generally based on the comparison of patients with abnormal thyroid function values and euthyroid patients both among themselves and with control groups[18]. In this study, we evaluated patients with hypothyroidism who achieved a euthyroid state with thyroid hormone replacement therapy in consideration of the duration of preexisting diseases. Although several studies in the literature evaluated BAI sub-parameters, we have not found any detailed analysis of these sub-parameters in any study. In this study, we evaluated sub-parameters of the BAI, and in comparison with the control group, we found statistically significant differences in all sub-parameters of the BAI in all patient groups, including hot flushes, weakness, and tremors in the legs, dizziness or drowsiness, palpitations, a feeling of loss of balance, becoming terrified, tremors in the hands, tremor and flushing of the face. However, we have determined that the duration of the disease has no effect on these parameters.

In our evaluation, we found significant statistical differences in all patient groups compared to the control group in terms of the BAI sub-parameter of feeling like choking. In addition, there were significant differences during the early stages of the disease process compared to the advanced stages of the disease; however, this significant difference disappeared as the years progressed. In addition, when the data of our study is evaluated, significant increases in the frequency of the BAI sub-parameters such as fear of dying and fear of the worst happening in the first year of the disease, compared to the control group.

In the sub-parameters of the BAI such as difficulty in breathing, being terrified, and inability to relax, significant statistical differences were found in all patient groups in relation to the control group. In addition, in the early stages of the disease, increases in the frequency of these three sub-parameters were observed, while these complaints decreased in the following years.

In this study, we could not evaluate the anxiety and depression levels of the patients in the patient groups before and after the treatment or carry out a detailed analysis of the sub-parameters of the BAI. This constituted the limitation of our study. In addition, we suggest that studies should be planned by conducting a detailed analysis of the sub-parameters of the BAI before and after the treatment, which will represent significant ad\ances in the approach to the patients. In addition, in studies performed considering the thyroid

autoantibody positivity in patients, the BAI sub-parameters can be evaluated in detail and awareness may be created in the approach to patients. In this study, we evaluated patients who had thyroid dysfunction and became euthyroid with treatment. Patients were predisposed to anxiety and depression even if they were euthyroid. In addition, when the BAI sub-parameters were evaluated in detail, we found that the duration of the significantly affected some anxiety-related symptoms.This suggests that close follow-up of anxiety and depression is necessary even if the patients are euthyroid.

Acknowledgment

We would like to thank the Scientific Research Support Unit in our faculty for the statistical analysis of the study.

Conflicts of interest

None

Financial disclosures

None

RESUMO

OBJETIVOS: *Nosso objetivo é determinar os níveis de ansiedade e depressão de pacientes tratados por hipotireoidismo que passaram a um estado eutireoideo. Esses pacientes frequentemente se consultam em clínicas de medicina da família.*

METODOLOGIA: *Este estudo foi realizado em 76 voluntários em estado eutireoideo (grupos de pacientes) que foram tratados por hipotireoidismo e passaram por acompanhamento e 22 voluntários saudáveis (grupo de controle). Foram aplicados questionários a todos os participantes para avaliar os níveis de ansiedade e depressão. O Beck Depression Inventory (BDI) e o Beck Anxiety Inventory (BAI) foram aplicados a todos os grupos. Além disso, os subparâmetros do BAI foram avaliados em detalhe.*

RESULTADOS: *Pelo menos depressão leve foi detectada em 54,5% do primeiro grupo, 41,7% do segundo grupo, e 33,3% do terceiro grupo. Quando comparadas as pontuações totais do BDI e do BAI dos participantes de diferentes grupos, diferenças estatisticamente significativas foram encontradas. Resultados estatisticamente significantes foram observados em relação a diferentes subparâmetros do BAI entre os grupos de pacientes e em comparação ao quarto grupo.*

CONCLUSÃO: *Observamos que os pacientes estavam predispostos a ansiedade e depressão, mesmo em estado eutireoideo. Quando os subparâmetros do BAI foram avaliados em detalhe, observou-se que a duração da doença afetou significativamente alguns sintomas relacionados à ansiedade.*

PALAVRAS-CHAVES: *Ansiedade. Depressão. Doenças da glândula tireoide.*

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ORIGINAL ARTICLE

Nuclear factor erythroid-2 related factor 2 inhibits human disc nucleus pulpous cells apoptosis induced by excessive hydrogen peroxide

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SUMMARY

OBJECTIVE: *Nuclear factor erythroid-2 related factor 2 (Nrf2)/ antioxidant response element (ARE) is a novel defensive pathway involved in the oxidative and chemical stress of cells. The aim of the study was to explore the role of Nrf2 on the apoptosis of human disc nucleus pulpous cells induced by hydrogen peroxide (H_2O_2).*

METHODS: *The degeneration model of human intervertebral disc nucleus pulpous cells was established. The expression of Nrf2 was interfered with using sulforaphane (SFN); for that end, three groups were established: a blank group (H_2O_2-/SFN-), control group (H_2O_2+/SFN-), and an experimental group (H_2O_2+/SFN+). CCK8, Hoechst 33258 living cell staining was used to detect reactive oxygen species (ROS) content.*

RESULTS: *The apoptotic rates of the three groups were [(0.40±0.46)%], [(25.98±11.28)%], and [(3.83±2.06)%, respectively. The difference was statistically significant ($p<0.05$). The relative content of ROS in the three groups was [(100±7)%], [(1538±91)%], and [(818±63)%]; the difference was statistically significant ($p<0.05$). In Western blotting, Nrf2 content in the experimental group was higher than that in the control group.*

CONCLUSION: *Nrf2 exists in the nucleus pulpous cells of human intervertebral discs, which is related to the degeneration of the intervertebral disc. It has negative feedback regulation and can prevent the degeneration of the intervertebral disc by inhibiting the apoptosis of nucleus pulpous cells of human intervertebral discs caused by excessive ROS, which provides a new intervention strategy for the prevention and treatment of the degeneration of intervertebral discs.*

KEYWORDS: *NF-E2-related factor 2. Intervertebral disc degeneration. Spinal diseases. Nucleus pulposus.*

INTRODUCTION

Degeneration is a chronic disease with high incidence[1] and is considered to be one of the main causes of chronic back pain[2,3]. Due to the change of the material and structure inside the intervertebral disc, the disc becomes unstable and its function is changed. Under the action of a slight external force, the fibrous

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ring of the disc is broken, the nucleus pulpous protrudes the fibrous ring, and the nerve root of the spinal cord is compressed, causing severe pain[4]. About 20% of patients in the world suffer from chronic lower back pain[5], 17% of them have obvious activity limitations due to severe pain[6], which brings huge social and economic burden[7]. Degeneration is mainly treated by surgery[8]. However, due to the complexity of patients with disc degeneration, there are often various complications and surgical failures after the operation, and the reoperation rate is about 13%[9]. Therefore, understanding the molecular mechanism of the onset and development of degeneration and the key factors of regulation in its related pathways will provide a new strategy to prevent this condition.

It has been confirmed that oxidative stress is an important cause of disc degeneration. Excessive reactive oxygen species (ROS) can promote the apoptosis of functional cells of the intervertebral disc, accelerating the progression of degeneration10. The nuclear factor erythroid-2 related factor 2(Nrf2)/antioxidant response element (ARE) signaling pathway is an important way to avoid excessive ROS damage to cells[11]. Nrf2, as a key factor of the ARE signaling pathway, plays an important role in oxidative stress[12]. Some studies have reported that Nrf2 plays an important role in the antioxidant damage of the liver, kidney, nerves, and other organs and tissues, inhibiting ROS-induced apoptosis[13-15]. However, most of the current studies on the relationship between Nrf2 and the intervertebral disc mainly focus on rat derived nucleus pulpous cells[16-18]. The effect of Nrf2 on human intervertebral disc nucleus pulpous cells is still unclear.

Therefore, the purpose of this study is to explore the relationship and significance of Nrf2 on the hydrogen peroxide(H_2O_2)-induced apoptosis of human disc nucleus pulpous cells and provide a new intervention strategy for the prevention and treatment of disc degeneration.

METHODS

Reagent

Sulforaphane (SFN, Meilun biology, China), 3% hydrogen peroxide (H_2O_2, Sigma Aldrich, USA), Hoechst 33258 (solar bio, China), active oxygen detection kit (solar bio, China), cell counting kit 8 (CCK8, Japanese colleague), double antibody (GIBCO, USA), fetal bovine serum (GIBCO, USA).

Cell culture

The human intervertebral disc nucleus pulpous cells were purchased from Wuhan prosaic Life Technology Co., Ltd. with the immunofluorescence identification report attached to them. Nucleus pulpous cells were cultured in DMEM/F12 medium mixed with 10% fetal bovine serum and 1% double-antibody in a wet incubator at 37°C and 5% CO_2.

Establishment of the cell model

Nucleus pulpous cells were seeded in 96 well plates at a density of 5×10^3 per well and cultured for 48 hours. 3% H_2O_2 was diluted with DMEM/F12 medium gradient into 6 concentration groups of 0um, 100um, 150um, 200um, 250um, and 300um, which stimulated nucleus pulpous cells for 6 hours; the cell activity was detected by CCK8. The appropriate concentration was taken as the model to establish the concentration.

Drug interventions

The medullar cells were inoculated at a density of 5×10^3 per hole on a 96 well plate for 48 hours. The medullar cells established the degradation models, and different concentrations of SFN (0uM, 0.5 uM, 5UM, 10UM, 15UM, 20UM) were added for 6 hours. CCK8 detected cell activity in each concentration group and screened the best concentration of cell activity as an experimental group. At the same time, a blank group (H_2O_2-/ SFN-) and a control group (H_2O_2+/ SFN-) were set up.

Hoechst 3258 living cell staining

The density of nucleus pulpous cells was 1.5×10^5 cells per pore in the 6-well plate, cultured for 48 hours. After H_2O_2 and SFN treatment, the original solution was removed, PBS was washed twice, Hoechst 33258 diluted at 1:1000 was added and placed in a wet incubator at 37°C for 20 minutes. The staining solution was removed, PBS was washed twice, and the fluorescence of cells in each group was observed by a fluorescence microscope.

ROS content detection

After the cells were attached to the wall, they were stimulated with 200 um H_2O_2 for 2 hours and then treated with SFN for 2 hours. The original solution was removed, PBS was washed once, 1:3000 diluted DCFH-DA 1ml was added, the dye was placed in a 37°C incubator for 20 minutes. The dye solution was removed, and the PBS washed three times. The

expression of ROS was detected by fluorescence microscopy, and the fluorescence intensity was measured by enzyme labeling.

Western blotting

The cells were collected, scraped off with Ripa lysate (Biyuntian, China), split on ice for 30 minutes, vibrated once every 10 minutes, split by ultrasound twice, and then centrifuged. BCA protein quantitative Kit (Solar Bio, China) was used to detect the protein concentration and then balanced. 20ug protein per pore was separated by 10% gel, transferred to a PVDF membrane, sealed with 5% milk for 1 hour, then the membrane was cut according to the target protein quality (Nrf2, GAPDH), 1:1000 diluted GAPDH (cell signaling technology, CST, d16h11), Nrf2 (Abcam, ep1808y) were incubated overnight at 4°C, TBST washed membrane three times, a second antibody (Biyuntian, China) was applied for one hour, TBST washed membrane three times, ECL substrate, chemical exposure.

Statistical analysis

All statistical analyses were carried out using the GraphPad Prism 6.0 Software (Analytic Technologies, Louisville, KY, USA). One way ANOVA was performed for comparisons between more than two groups. All the tests were two-sided and the value of p< 0.05 (two-sided) was considered to be statistically significant.

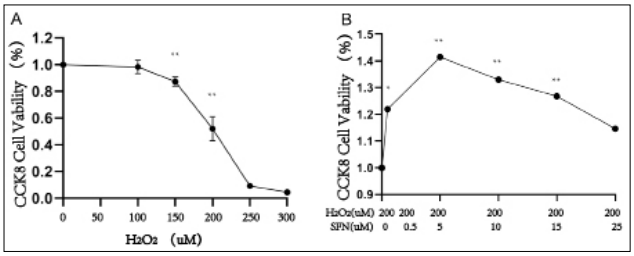
RESULTS

Establishment of the degenerated cell model

CCK8 detection shows that H_2O_2 in the range of 100-300um can inhibit the activity of nucleus pulpous cells [(98.3 ± 4.84)%, (87.36 ± 3.41)%, (52.02 ± 9.15)%, (9.19 ± 1.37)%, (4.45 ± 1.07)%] in a concentration-dependent manner after 6 hours of use (Figure 1A). With the increase of H_2O_2 concentration, the apoptosis of nucleus pulpous cells is more obvious. The activity of nucleus pulpous cells in the 200 uM group was (52.02 ± 9.15)%, which was used to model nucleus pulpous cells.

After modeling, SFN (Nrf2 activator) with a concentration of 0.5-20um was added. The results showed that the relative activity of nucleus pulpous cells [(121.94 ± 3.1)%, (141.43 ± 11.54)%, (132.99 ± 10.42)%, (126.75 ± 4.86)%, (114.6 ± 5.19)%] was higher than that of the 0uM Group [(100 ± 13.23)%], and the apoptosis of cells was significantly inhibited. 5uM was admitted as the drug intervention concentration (Figure 1B).

FIGURE 1



Cell viability detection by CCK8.(A) CCK8 was added to the nucleus pulposus cells treated with different concentrations of H_2O_2 for 6 hours. (B) The nucleus pulposus cells were treated with H_2O_2 at 200 um for 6 hours, then the SFN of different concentrations of the Nrf2 activator was replaced for 6 hours, and CCK8 was added to analyze the cell activity.

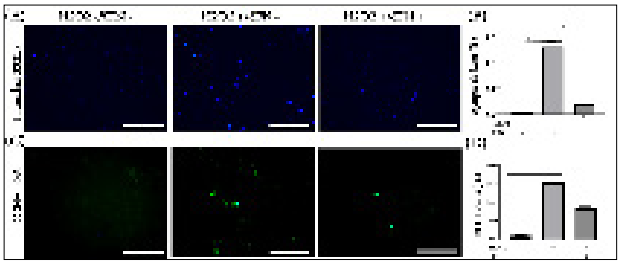
*P<0.05,**P<0.001.

Nrf2 activator can inhibit apoptosis of nucleus pulpous cells caused by ROS excess.

In order to better understand the inhibitory effect of Nrf2 on the apoptosis of nucleus pulposus cells, Hoechst 33258 was used for living cell staining (Figures 2A and 2B). The results showed that the apoptosis rates of the blank group, control group, and experimental group were [(0.40±0.46)%], [(25.98±11.28)%], [(3.83±2.06)%], respectively. Compared with the control group, the nucleus pulposus cells in the blank group basically did not show the concentrated apoptosis cells. After H_2O_2 peroxide stimulation, the apoptosis rate in the control group was up-regulated, and the concentrated apoptosis cells were increased under the microscope. Compared with the control group, the apoptosis of the experimental group was significantly inhibited after NRf2 activator treatment, and the concentrated apoptosis cells were reduced under the microscope, with significant statistical differences. (Figures 2C and 2D) The content of ROS was detected by a DCFH-DA probe, and the fluorescence intensity was measured by an enzyme labeling instrument. The relative content of ROS in the three groups (in relation to the blank group) was [(100 ±7)%], [(1538±91)%], and [(818±63)%]. Compared with the blank group, the ROS content increased, and green fluorescence increased after H_2O_2 peroxide stimulation in the control group; compared with the control group, ROS content decreased and green fluorescence decreased after Nrf2 activator intervention in the experimental

and control groups. All of the above differences were statistically significant. H_2O_2 can up-regulate ROS content and induce apoptosis. In contrast, the Nrf2 activator can inhibit the progress of apoptosis by down-regulating ROS content.

FIGURE 2

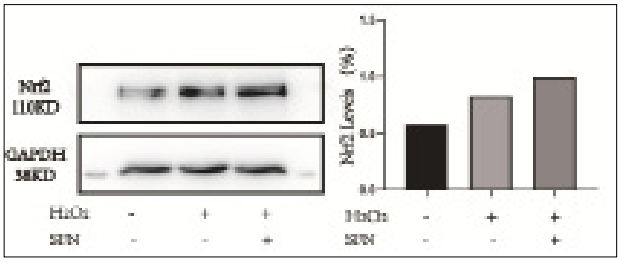


Hoechst 33258 staining. (A)The dark blue in the picture is an apoptotic cell. (B) The apoptotic rate of the blank group is significantly higher than that of the control group, and the apoptotic rate of the experimental group is significantly lower than that of the control group, with statistical significance (P < 0.001). (C) The content of ROS was measured by DCFH-DA. Under a fluorescence microscope, (D) fluorescence intensity was detected by the fluorescence enzyme. The content of ROS in the experimental group was lower than that in the control group (P < 0.001). Note: Apoptosis rate = number of apoptotic cells/total number of visual field cells; ROS content% = absorbance value of each sample/average absorbance value of the blank group. Note: apoptosis rate = number of apoptotic cells/total cells.

Nrf2 activator SFN up-regulates Nrf2 expression in nucleus pulposus cells

Western blotting (Figure 3) showed that Nrf2 was present in normal nucleus pulposus cells, and Nrf2 activator could up-regulate the expression of Nrf2 protein in the nucleus pulposus cells. A grayscale analysis showed that Nrf2 in the experimental group increased from 57% to 82%.

FIGURE 3



Effect of H_2O_2 and SFN on Nrf2 and GAPDH protein expression. The expression of Nrf2 and GAPDH protein was analyzed by Western blot after 6 hours of treatment with 200um H_2O_2 and 5um SFN.

DISCUSSION

In this experiment, H_2O_2 was used to stimulate the cells of the nucleus pulposus of human intervertebral discs to create an imbalance of the redox environment. The activity of CCK8 decreased by about 50% at the concentration of 200um. Compared with previous studies, the concentration of the model is consistent, and the model is effective[19,20]. CCK8 screened the appropriate concentration of Nrf2 activator intervention. In the experiment, it can be seen that Nrf2 activator can significantly inhibit the decline of cell viability caused by H_2O_2, of which the effect is most obvious when the concentration is 5um. This was admitted as the appropriate concentration for the next experiment.

Degeneration is one of the main causes of chronic low back pain. Haefeli et al.[21] found in 41 routine autopsies (7 months to 88 years old) in 2006 that extensive macroscopic changes in the disc had occurred in the second decade of life. Healthy people also have low-grade disc degeneration, which seriously affects human health. Oxidative stress inhibited the proliferation of human nucleus pulpous cells and induced premature senescence[22]. Suzuki et al.[23] believe that excessive ROS is the treatment target of disc degeneration. When the redox balance is destroyed, the anti-oxidation system of cells will take effect, and the cells will return to redox homeostasis. The mechanism of cytoprotection is controlled by the transcription of the Nrf2-ARE pathway[24].

The results show that excessive ROS can induce apoptosis of human disc nucleus pulposus cells and promote the degeneration of the human disc. In order to explore the role of Nrf2 and ROS in the apoptosis of human disc nucleus pulpous cells. In this study, compared with the control group, the blank group showed a significant increase in the concentration of blue fluorescent cells in the Hoechst 33258 staining control group, which were apoptotic human disc nucleus pulpous cells. The green fluorescence intensity of the DCFH-DA staining group was also up-regulated, and the green fluorescence was ROS content.

There are some strengths and limitations to this study. The strength was that the results suggested that Nrf2 can inhibit apoptosis of nucleus pulpous cells induced by ROS. The alternative signaling pathways which may be involved in the apoptosis of human disc nucleus pulpous cells induced by H_2O_2 include p38, STAT3, and interferon regulatory factor. Therefore, we can't exclude the possibility that another signaling pathway was also involved in the H_2O_2-induced apoptosis of human disc nucleus pulpous cells.

CONCLUSION

Nrf2 can regulate the antioxidant system in the human disc nucleus pulpous cells.

Acknowledgments

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Competing interests

The authors declare that they have no competing interests.

Author's Contribution

Conceptualization, Hao Lin; formal analysis, Yingxin Wang; writing of the original draft, Hao Lin; review and editing, Kaipeng Jing and Tingrui Wu; supervision, Yanru Niu; funding acquisition, Jinsong Wei.

RESUMO

OBJETIVO: *O fator 2 relacionado a NF-E2 (Nrf2)/elemento de resposta antioxidante (ARE) é uma nova via defensiva envolvida no estresse oxidativo e químico das células. O objetivo deste estudo foi explorar o papel do Nrf2 na apoptose das células do núcleo pulposo do disco humano induzida pelo peróxido de hidrogênio (H_2O_2).*

MÉTODOS: *O modelo de degeneração das células do núcleo pulposo do disco intervertebral humano foi estabelecido. A expressão do Nrf2 foi interferida utilizando-se sulforafano (SFN). Para isso foram estabelecidos três grupos: um grupo vazio (H_2O_2-/SFN-), um grupo de controle (H_2O_2+/SFN-), e um grupo experimental (H_2O_2+/SFN+). Utilizando CCK8 e Hoechst 33258, o conteúdo de espécies reativas de oxigênio (ERO) foi detectado.*

RESULTADOS: *As taxas de apoptose dos três grupos foram [(0,40 ± 0,46)%], [(25,98 ± 11,28%)] e [(3,83 ± 2,06)%], respectivamente. A diferença apresentou significância estatística (p < 0,05). O conteúdo relativo de ERO nos três grupos foi [(100±7)%], [(1538±91%)], e [(818±63%); a diferença foi estatisticamente significativa (p < 0,05). O método de Western blotting indicou um maior conteúdo de Nrf2 no grupo experimental do que no grupo de controle.*

CONCLUSÃO: *O Nrf2 existe em células do núcleo pulposo do disco intervertebral humano, que estão relacionadas à degeneração do disco intervertebral. Ele apresenta regulação por feedback negativo e pode evitar a degeneração do disco intervertebral inibindo a apoptose de células do núcleo pulposo do disco causada por excesso de ERO. Essa informação proporciona uma nova estratégia de intervenção para a prevenção e o tratamento da degeneração do disco intervertebral.*

PALAVRAS-CHAVE: *Fator 2 relacionado a NF-E2. Degeneração do disco intervertebral. Doenças da coluna vertebral. Núcleo pulposo.*

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ORIGINAL ARTICLE

Effect of radiation on endothelial functions in workers exposed to radiation

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SUMMARY

OBJECTIVE: *Our aim is to determine whether radiation affects the endothelial function of hospital staff working in the radiation unit for diagnostic and therapeutic purposes. We have evaluated endothelial function with vascular imaging parameters such as flow-mediated dilatation (FMD) and aortic stiffness index (ASI).*

METHODS: *A total of 75 employees, 35 of whom are exposed to radiation due to their profession and 40 as the control group, were included in our single-centered study. Demographic data, FMD, aortic stiffness, and echocardiographic findings of the two groups were compared.*

RESULTS: *There were no significant differences in demographic data. Median FMD values tended to be lower in the radiation exposure group [7.89 (2.17-21.88) vs. 11.69 (5.13-27.27) p=0.09]. The FMD value was significantly lower in the catheter laboratory group than in the radiation-exposed (p=0.034) and control (p=0.012) groups. However, there was no statistically significant difference between the non-catheter lab radiation exposed group and the control group (p=0.804). In addition, there was no statistically significant difference in the ASI value between the groups (p=0.201).*

CONCLUSION: *We have found that FMD is decreased among hospital staff working in radiation-associated areas. This may be an early marker for radiation-induced endothelial dysfunction.*

KEYWORDS: *Aortic Stiffness. Flow-Mediated Dilatation. Radiation. Endothelium, vascular. Occupational exposure. Radiation exposure.*

INTRODUCTION

Radiation is an important part of both diagnostic tests and treatment management of many diseases. When the literature was reviewed, increased cardiovascular events were noted in the follow-up of radiotherapy patients[1-3]. While many studies about radiotherapy patients have attracted attention, cardiovascular events in the employees who are exposed to ionizing radiation at work were not well defined.

It has been shown that thoracic radiotherapy in particular has accelerated the atherosclerotic process, increased frequencies of left-sided valve deterioration (most frequently aortic regurgitation), acute or chronic pericardial diseases and effusions, cardiomyopathies and conduction diseases even in patients with no cardiac risk factor[4].

There are several methods for evaluating

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endothelial dysfunction. Nowadays, ultrasonographic evaluation from the forearm of the flow-dependent vasodilatation is commonly used due to its simplicity, low cost, and lack of intervention. This method has proven to be quite reliable when compared to invasive methods[5]. Many blood vessels respond to shear stress by vasodilatation. This event is called flow-mediated dilatation. Radiotherapy has been shown to generate reactive oxygen species and activate the inflammatory process. Moreover, this event resulted in endothelial dysfunction in patients with Hodgkin lymphoma who received radiotherapy[4]. In addition, endothelial dysfunction is believed to be the earliest factor of many diseases[6].

Aortic elasticity is closely related to cardiovascular mortality[7]. Aortic distensibility (AD) and aortic strain (AS) are the elasticity indices of the aorta and reflect aortic stiffness[7]. It has been shown that non-invasive methods such as echocardiography and magnetic resonance were found to be as reliable as the invasive measurement with the use of a catheter with a micro manometer for the demonstration of the elastic properties of the aorta[8]. Many studies have shown that inflammation has a role in arterial stiffness probably due to endothelial dysfunction[9].

Here, we aimed to study FMD and aortic elasticity indices among radiation-exposed and unexposed hospital staff.

METHODS

This is a single-centered cross-sectional study conducted between August and November 2018 at the Bolu University Hospital. The study included 35 employees who have occupational radiation exposure (20 of them are interventional cardiologists and catheterization lab staff, 4 of them are orthopedists, 5 are interventional radiologists, and 6 urologists) and 40 employees who are away from radiation areas. The cath. lab. interventional cardiologist and lab. staff use Siemens Axiom Artis Cath/Anjio System and Siemens Axiom Artis Zee Floor Cath/Anjio System; interventional radiologists use Siemens Axiom Artis Cath/Anjio System and Siemens Artis Q Floor Cath/Anjio System; urologists and orthopedists use Siemens PowerMobile C-arms and GE OEC Brivo Prime C-arm 785 in the operating room.

All participants were informed about the study and were older than 18 years old. In the radiation-exposed group, the total working time with radiation ranged between 6 months and 26 years (6.3 ± 5.9 years). Demographic data and laboratory parameters of all employees were recorded. Presence of coronary artery disease, left ventricular heart failure (EF <50%), moderate and severe mitral and/or aortic valve disease, congenital heart disease, atrioventricular conduction abnormality, presence of pericardial effusion, moderate and severe kidney or liver disease, thyroid diseases, anemia, diabetes mellitus, dyslipidemia, hypertension, electrolyte imbalance, systemic inflammatory or infectious diseases or poor transthoracic echocardiography window were determined as the exclusion criteria. We received informed consent from each participant after approval of the study protocol by the Local Ethics Committee.

Echocardiographic evaluation

Echocardiographic procedures were performed with the 4-Mhz transducer of Vivid S6 (GE Vingmed, N-3191 Horten-Norway). All echocardiographic images were taken by a single-blind cardiologist within the left lateral position in the presence of continuous electrocardiography. And the mean of three consecutive cardiac cycles was used.

Left ventricular end-diastolic and end-systolic diameter, left ventricular septum thickness, left ventricular posterior wall thickness, and left atrium diameter were measured. Left ventricular ejection fraction was measured by modified Simpson's rule[10]. Two-dimensional and pulsed doppler measurements were taken according to the Criteria of the American Society of Echocardiography[10].

Aortic stiffness evaluation

Internal dimensions of the ascending aorta were measured in at least three consecutive cardiac cycles, at 3 cm from the origin of the aorta. The aortic systolic diameters (AoSD) and the diastolic diameters (AoDD) were taken, and then aortic strain, aortic distensibility, and aortic stiffness index were calculated according to the formulas[11]. While the systolic diameter was measured from the peak of the aorta, the diastolic diameter was measured from the R peak of the ECG.

1. Aortic diameter change (ADC): AoSD – AoDD
2. Aortic strain (AS) (%): ADC/AoDD
3. Aortic distensibility: 2x AS/PP
4. Aortic stiffness index: (SBP/DBP)/ [(ADC)/AoDD].

(SBP: systolic blood pressure, DBP: diastolic blood pressure, PP, pulse pressure: systolic blood pressure–diastolic blood pressure)

Ultrasonographic evaluation

After resting for at least 15 minutes in a quiet, dark, air-conditioned room (22–25 °C), the parameters were measured. Also, subjects were advised about going fasting for at least 8 hours and exercising, smoking, consuming alcohol or caffeine before taking the FMD measurements. The brachial artery diameter was measured in the antecubital fossa with a 7.5 MHz linear array transducer (GE Healthcare, M4S-RS, Tokyo, Hino-Shi, Japan).

The skin was marked with a pencil, so all evaluations were obtained from the same line.

TABLE 1. GENERAL CHARACTERISTICS OF THE STUDY GROUPS

Baseline characteristics	Radiation exposed group (n=35)	Control group (n=40)	P
	MEDIAN (Min-Max.)		
Age (years)	32 (22-51)	29 (20-52)	0.12
	MEAN		
Body mass index (kg/m2)	26 ±4	25± 5	0.33
Male/female	20/15	16/24	0.14
Hypertension (%)	3 (8%)	2 (5%)	0.54
Smoking (%)	12 (34%)	10 (25%)	0.38
Family history (%)	2 (6%)	7 (17%)	0.12

TABLE 2. ECHOCARDIOGRAPHIC DATA OF WORKING GROUPS

	Radiation exposed group (n=35)	Control group (n=40)	P
	MEDIAN (Min-Max.)		
EF (%)	62±5	63±4	0.23
LVDD	4.49±0.30	4.36±0.39	0.108
LVSD	2.68±0.27	2.75±0.29	0.361
LA	3.14±0.32	3.04±0.37	0.199
FMD	7.89 (2.17-21.88)	11.69 (5.13-27.27)	0.09
ASI	11.64 (3.70-76.57)	10.25 (5.63-54.06)	0.81
PW	0.92 (0.72-1.29)	0.90 (0.70-1.30)	0.11
IVS	0.89 (0.72-1.30)	0.90 (0.70-1.30)	0.17

EF: ejection fraction, LVDD: left ventricular end diastolic diameter, LVSD: left ventricular end systolic diameter, LA: left atrium, FMD: flow mediated dilatation, ASI: aortic stiffness index, PW: posterior wall, IVS: interventricular septum

TABLE 3. FMD VALUE OF WORKING GROUPS

	Radiation exposed-catheter lab group (n=22)	Non-catheter lab radiation exposed group(n=13)	Control group (n=40)	P
FMD %	5.96 (2.17-20.51)	11.90 (5.77-21.88)	11.69 (5.13-27.27)	0.025
ASI	13.9 (6.0-75.1)	9.8 (3.7-76.5)	10.2 (5.6-54.0)	0.201

FMD: flow mediated dilatation, ASI: aortic stiffness index

First, the basal diameter and flow rate of the brachial artery were taken. Then, the pressure was inflated up to 50 mmHg above the systolic blood pressure and waited for 5 minutes so the arm remained ischemic. The diameter and flow rate of the brachial artery were measured again 1 minute after the cuff pressure was lowered. FMD was calculated with the formula: FMD=100 x (maximum diameter after hyperemia-baseline diameter/baseline diameter)[11].

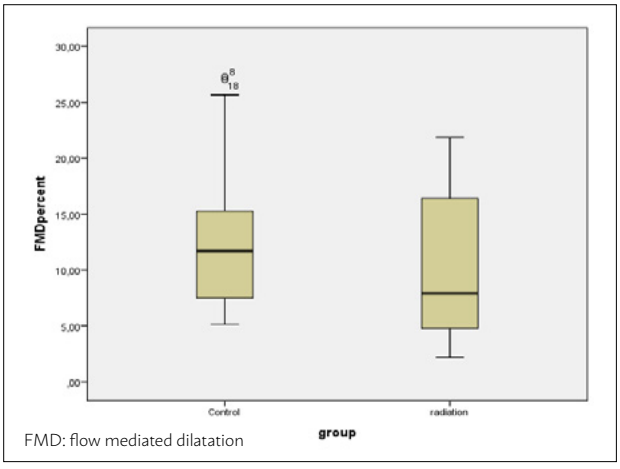
Statistical analysis

Quantitative variables were stated as mean± standard deviation (SD) and qualitative variables were expressed in numbers and percentages. The differences among independent groups were analyzed by the Student t-test in the case of normal distribution. The Mann-Whitney U test was used to compare variables without normal distribution. The Chi-Square test was used for the qualitative variables. To compare high-radiation exposed catheter lab medical staff with other medical staff and the control group, the Kruskal-Wallis test was used. A p-value < 0.05 was considered significant. Statistical analysis was carried out using SPSS v.18.0 software (IBM).

RESULTS

No significant difference was observed between the two groups in terms of demographic data (Table 1). Transthoracic echocardiography, FMD, and ASI parameters of the participants are shown in Table 2. Albeit not significant, the FMD of the radiation-exposed group tended to be lower than that of the control group [7.89 (2.17-21.88) vs. 11.69 (5.13-27.27], p=0.09 (Figure 1).

FIGURE 1. FMD COMPARISON OF CONTROL AND RADIATION GROUPS



FMD: flow mediated dilatation

The Kruskal-Wallis test revealed that the FMD value was significantly lower in the catheter laboratory group than in other radiation-exposed (p=0.034) and control (p=0.012) groups. However, there was no statistically significant difference between the non-catheter lab radiation exposed group and the control group (p=0.804). Also, there was no statistically significant difference in the ASI value between the three groups (p=0.201) (Table 3).

In Pearson's Correlation Test, the FMD value (-r=0.36, p=0.015) was significantly and negatively correlated with the presence of mean exposure time.

DISCUSSION

In our study, we found that the median FMD value tended to be lower in radiation-exposed workers.

The acute effects of radiation on the cardiovascular system may be undetected since this phase is usually asymptomatic. Therefore the rate of involvement is not clear. Endothelial damage, lipid, and inflammatory cell infiltration and lysosomal activation have been defined in this silent acute phase[12]. The use of FMD as an indirect marker of inflammation to determine this asymptomatic period is therefore important and constitutes the main purpose of our study. Reactive oxygen radicals and pro-inflammatory cytokines have been accused of radiation-mediated endothelial dysfunction. This is demonstrated by the rise of IL-6, CRP, TNF-α, and INF-ϒ-like pro-inflammatory cytokine in survivors of atomic bombs. It was also shown that the dose-dependent increase of markers that reflect systematic inflammation such as erythrocyte sedimentation rate (ESR) and IgG, IgA, and total immunoglobulins were increased[13]. Leukocyte aggregation is observed as a result of ICAM-1 and PECAM-1 activation in radiation-exposed endothelial cells[13]. With the release of thrombomodulin and PAI-1-like cytokines, endothelial cells become pre-thrombotic and atherogenic, and the pro-fibrotic process begins[14]. Increased levels of TGF-β through radiation result in collagen synthesis and fibrosis, leading to changes in the extracellular matrix[15].

In a study performed in patients with breast cancer, the endothelium-dependent vasodilatation of the axillary artery on the irradiated side was significantly reduced compared to the opposite side[16]. In another study, impaired NO-mediated relaxation in irradiated cervical arteries was related to a lack of expression of endothelial NO synthetase[17]. While carotid intima-media thickness of Hodgkin lymphoma patients increased compared with the control group in a 3-year follow-up, flow-mediated dilatation decreased in a persistent manner[18].

The known long latent period of radiation requires the follow-up of the patients after radiation exposure in a wide period of 10-15 years[19]. Radiation has effects on the pericardium, myocardium, valves, coronary arteries, and conduction system in the heart; pathology in the epicardial and endocardial coronary arteries may result from coronary obstruction; semilunar and atrioventricular valve pathology, stenosis or regurgitation are caused by valvular fibrosis; and pathology in the myocardium may result in cardiomyopathy[19]. Pericardial construction and inflammation, as well as pathologies in the transmission system and pericardium, may occur[19]. The most common cardiac effects are pericardial, while the lesser effects are in the conduction system[2]. The long latent period and the absence of specific symptoms in patients suggest that the number of patients known to be affected is very low. However, in these patient groups, the primary mechanism for death, 10 years after radiation exposure, was cardiac mortality[1]. Myocardial infarction was the most common cause of cardiac mortality[3]. Compared to the general population, 2.2-2.7 times more cardiac disease was observed in these patients[2].

Since patients with breast cancer and Hodgkin lymphoma have a relatively long cancer-specific survival and can be followed up for 10-15 years after receiving radiotherapy at a young age, cardiac effects of radiation have been examined in this patient group treated with thoracic radiotherapy (RT)[11]. Cardiac damage has been less reported in lung cancer patients treated with radiotherapy; the late-term effects of radiation could not be detected in these patients due to insufficient survival of this patient group[20]. In our study, the mean radiation exposure time is 6,3 years, and the amount of irradiation is quite lower than in patients treated by radiotherapy. Total radiation dose can reach >30-35 Gy in radiotherapy and this dose is a risk factor for radiation-induced cardio toxicity[4]. However, interventional cardiologists in high-volume centers have a radiation exposure of about 5 mSv/per year[21]. This exposure dose is higher than that of the medical staff that works at the catheter laboratory. Although we couldn't observe chronic effects that may be associated with radiation exposure, it is noteworthy that FMD value began to deteriorate even in the short term and with the low exposure dose among catheter laboratory medical staff that are relatively exposed to

higher radiation dose than other radiation-exposed medical staff and control group.

It has been shown that there is a correlation between the presence of coronary artery disease (CAD) and the elastic parameters of the aorta[22]. In this hypothesis, it is suggested that vasa vasorum originating from the coronary arteries and feeding abnormalities in the arterial wall disrupt the elastic properties of the aorta in the presence of CAD[22]. It is also known that radiation-induced fibrosis may result in increased arterial stiffness and, consequently, may be a potential biomarker of radiation-induced atherosclerosis[23]. In our study, ASI parameters were not significant between the two groups. This may be explained by the process that requires 10-15 years for CAD in radiation exposure, and our study is insufficient to assess the process currently.

The most obvious effects of ionizing radiation among medical staff are on the skin and eye, especially due to direct unprotected exposure[24]. While erythema in the skin can be observed within a few hours, cataract may occur about 6 months after exposure[24]. In a meta-analysis in which cardiologists performing cardiac catheterization were compared with the control group, cataract cases were found to be significantly higher among cardiologists; the underlying biological mechanism has been interpreted as the accelerated proliferation of the endothelium and blood cells by radiation[25].

Our study is single-centered. Because there is a small number of employees in the catheter laboratory, in order to obtain the sufficient number of employees, those who received radiation as per their occupation such as orthopedy, interventional radiology, and urology, but whose exposure dose is not as high as those working in the catheter laboratory were also included. The statistical insignificance of FMD and ASI values may be due to that. Because of this, we compared three groups and showed that the FMD value was significantly lower in the catheter laboratory group. We aimed to overcome this limitation by planning a future multi-center study, with only catheter laboratory staff. In addition, the inclusion of employees from the different departments brought about the use of different brands and models of devices. Due to the irregular use of dosimeters, the exposed dose values were not included in our study. We designed our study with employees in units exposed to radiation for at least 6 months. This is one of the limitations of our study.

CONCLUSIONS

We have found that FMD may decrease among hospital staff that are exposed to radiation due to their profession. This may be an early marker for radiation-induced endothelial dysfunction and routine cardiovascular monitoring of radiation workers may prevent future cardiovascular events. Long-term follow-up and larger-scale studies should be considered for a better definition of possible cardiovascular effects among radiation-exposed medical staff.

Competing interests

The authors declare that they have no competing interests

RESUMO

OBJETIVO: *O nosso objetivo é determinar se a radiação afeta a função endotelial de funcionários do hospital que trabalham em unidades com exposição à radiação para fins diagnósticos e terapêuticos. Avaliamos a função endotelial com parâmetros de imagens vasculares, tais como dilatação fluxo-mediada (FMD) e o índice de rigidez aórtica (ASI).*

METODOLOGIA: *Um total de 75 funcionários, 35 expostos à radiação devido à sua ocupação e 40 como grupo de controle, foram incluídos em nosso estudo monocêntrico. Os dados demográficos, de FMD, rigidez aórtica e ecocardiográficos dos dois grupos foram comparados.*

RESULTADOS: *Não houve diferenças significativas nos dados demográficos. Os valores médios de FMD, em geral, foram mais baixos no grupo de exposição à radiação [7,89 (2,17-21,88) e 11,69 (5,13-27,27) p=0,09]. O valor de FMD foi significativamente menor no grupo laboratorial com cateter do que no exposto à radiação (p=0,034) e no de controle (p=0,012). No entanto, não houve diferença estatisticamente significativa entre o grupo laboratorial sem cateter e exposto à radiação e o grupo de controle (p=0,804). Além disso, não houve diferença estatisticamente significativa quanto ao valor de ASI entre os grupos (p=0,201).*

CONCLUSÃO: *Observamos que a FMD é menor entre funcionários que trabalham em setores hospitalares associados à radiação. Isso pode ser um marcador inicial de disfunção endotelial induzida por radiação.*

PALAVRAS CHAVE: *Radiação. Endotélio vascular. Exposição ocupacional. Exposição à radiação.*

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REVIEW ARTICLE

Benzodiazepinics and the treatment of delirium: a literature review

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SUMMARY

OBJECTIVE: *To discuss the role of the benzodiazepine class in delirium patient management.*

METHODS: *Using the PubMed database, articles were reviewed after the year 2000 containing in their title the words 'delirium' and 'benzodiazepines'.*

DISCUSSION: *Delirium is an acute confusional state that leads to altered attention, awareness, and cognition. It presents with some well-established risk factors, especially older individuals with cognitive decline. There is currently no definite consensus regarding its pathophysiology, nor regarding pharmacological measures, especially concerning the benzodiazepine class.*

CONCLUSION: *Evidence suggests that there may be a role for the use of pharmacological class in the treatment of this condition, indicating a change in the previously paradigmatic pattern of treatment.*

KEYWORDS: *Delirium. Benzodiazepines. Review.*

INTRODUCTION

Delirium is an acute confusional state observed mainly in patients with specific characteristics and in contexts of greater vulnerability, such as lower cognitive reserve and prolonged hospital admissions, that evolves with a significant increase in morbidity and mortality of patients affected[1,2]. In studies conducted in the general population, the prevalence of the condition was 1% in individuals from the age of 55 years, demonstrating, also, to be the cause of 5% to 10% of elderly care in the emergency services[3]. According to the DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, the criteria of delirium focus on symptoms developed over a short period, such as change of attention, consciousness, and cognition. It can present in three forms: hyperactive, hypoactive, and mixed level of activity; its physiopathology

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remains not entirely understood and involves a complex interaction between precipitating and predisposing factors[4]. The risk factors include individuals above 65 years of age, cognitive decline, infection, iatrogenic factors - such as immobilization and sleep deprivation[5] - in addition to its association with the use of medications, particularly those that act in the dopaminergic, cholinergic, or gamma-aminobutyric receptors. Pharmacological treatments that involve the class of benzodiazepines are commonly remembered as a potential risk for the development of delirium; however, recent trials and meta-analyzes have had results that question such a risk, which motivated this article.

Currently, the focus of the treatment is on the cause of the delirium; drugs are resources for situations in which patients present psychomotor agitation, psychotic symptoms, or insomnia, and in scenarios that are refractory to the initial non-pharmacological approaches. Benzodiazepines, well-established drugs for the treatment of delirium associated with alcohol abstinence are also often used as sedatives in other presentations of the condition, despite its association, by several studies, with the onset or perpetuation of the condition.

METHODS

We used the PubMed database as a source for this study; we accessed it in August 2019. The articles were screened based on their titles, abstracts, and year of publication. We retrieved a total of 19 publications with the keywords "delirium and benzodiazepines", used as inclusion criterion the English or Portuguese language; the exclusion criteria included date prior to 2000 (two papers excluded), articles specifically on delirium tremens (two papers excluded), and republished articles (two papers excluded). In total, 14 articles were selected and reviewed, including a meta-analysis published in 2019[6] to discuss the pharmacological approach of delirium.

RESULTS AND DISCUSSION

Randomized clinical trials that establishing a causal relationship between drugs, particularly benzodiazepines, and delirium, are old. Many of them are based on inconclusive findings[7] or were interrupted due to severe adverse effects, such as severe sedation. Other studies have shown evidence that suggests an increased risk of developing a confusional state associated with the use of benzodiazepines[1,2,4,5,8].

Lonergan et al.[2] published a literature review on the use of benzodiazepines and delirium, selecting only randomized, double-blind clinical trials. A single study conducted by Pandharipande in 2007 demonstrated the superiority of dexmedetomidine in minimizing delirium, when used sedating patients under mechanical ventilation, in comparison with lorazepam. Patients treated with the first drug had more days without coma or delirium; however, its use in a highly select group - those in mechanical ventilation - prevents the extrapolation of the results to the population with delirium as a whole. In addition, the absence of control groups makes it impossible to compare the effects of lorazepam on the scenario in question[2]. We found no controlled studies to support the use of benzodiazepines in the treatment of delirium unrelated to alcohol abstinence, denoting the need for new research with this purpose[2].

A review aiming to relate drugs potentially associated with delirium found a nested case-control study that associates benzodiazepines to an increased risk of delirium (RR 3.0; CI 95% 1.3-6.8)[8].

A prospective cohort study conducted by Smith et al.[5] in 300 pediatric patients from 6 months to 5 years of age, from March 2013 to October 2014, with the goal of determining risk factors associated with delirium, found that exposure to benzodiazepines was the only independent predictor for the development of delirium on the day following the exposure in comparison with the normal mental state (RR 2.47; 95% CI 1.36 to 4.49; p=0.005).

In 2015, in another retrospective observational study conducted in a pediatric population that had been screened prospectively for delirium, with six-month duration, also found that benzodiazepines were strongly and independently associated with the transition from a normal mental state to delirium, more than quadrupling the rates (OR, 4.4; 95% CI, 1.7-11.1; p=0.002), when compared to children with a normal cognitive state who did not receive sedatives. A univariate model also evaluated the dose-response relationship, showing that, for each logarithmic increase in the dose of benzodiazepines, there was an increase of 43% in the risk of transition to delirium in the following day[4]. Regarding the different types of delirium, the most common was hypoactive, found in 52% of cases, followed by the mixed and hyperactive presentations[4].

The iatrogenic damage from the use of benzodiazepines in adults has been consistently shown to include greater development and duration of delirium, greater duration of mechanical ventilation, and a longer stay in the ICU and hospital[5]. In addition, patients with high exposure to benzodiazepines were significantly more likely to develop delirium on the day following the exposure, when compared to those with minimal or no exposure[5]. A set of evidence focused on modifiable risk factors showed clear associations between exposure to benzodiazepines and the development of delirium in surgical and ICU patients (Pandharipande, 2006).

In 2018, a review by Hui[9] was published aiming to evaluate the role of benzodiazepines in the management of hyperactive delirium in palliative care; it included three randomized controlled trials and concluded that the literature based its application on terminal delirium and delirium tremens. Midazolam and lorazepam are among the drugs of choice, depending on the time of short half-life and parenteral availability. The association between lorazepam and haloperidol was also assessed and proved to be superior to haloperidol alone to manage the resistance of hyperactive delirium and promote more comfort for terminally ill patients[9].

A meta-analysis conducted by Wu et al.[6] and published in February 2019 confronted the use of benzodiazepines in the management of delirium. It assessed 58 articles: 20 related drug therapy with delirium, both in an interventional and preventive way, with the participation of 1,435 patients, and 38 articles focused on the prevention of the condition, with the participation of 8,168 individuals. Interventional therapeutic actions demonstrated the statistical superiority of the association of haloperidol and lorazepam (OR 28.13; CI 95% 2.38-333.08) or haloperidol alone (OR 2.37; 95% CI 1.04-5.43) in comparison to a placebo/control. However, it is important to emphasize that none of the other drugs studied obtained results lower than the placebo/control (rivastigmine tartrate, chlorpromazine hydrochloride, lorazepam, quetiapine, amisulpride, ziprasidone hydrochloride, haloperidol, and rivastigmine tartrate, risperidone, ondansetron)[6].

Currently, the management of delirium is mostly focused on treating the underlying cause while providing physical, sensory, and environmental support. Drug therapy is usually used in patients who manifest psychosis or insomnia. The drug of choice is haloperidol, orally, twice a day (⅔ administered before sleep). However, due to its effects on the heart, such as the prolongation of the QT interval, an electrocardiogram should be performed initially and then monitored. The use of benzodiazepines is more indicated for the management of insomnia, and those with a short or intermediary half-life are the most widely used. In addition, it is recommended to avoid its use alone in the treatment of delirium unrelated to alcohol abstinence[3].

CONCLUSION

With this review, we noticed that currently there is no consensus regarding drug therapy. Health services usually try to identify the underlying causes, establish a non-pharmacological treatment and, as a last resort, if necessary, make use of drugs, particularly antipsychotics, to try to stabilize patients in the best possible way. Many variables limit the creation of a guideline on the management of these patients, including the patient's age, presence of comorbidities, type, and duration of delirium. With this review, it is possible to observe that the articles that focused on the deleterious association between the use of benzodiazepines and delirium failed to reach a consensus on that association[7,8]. The meta-analysis published in 2019 by Wu et al.[6] demonstrated benefits from the association between lorazepam and haloperidol, which may suggest a change in the previously paradigmatic pattern of treatment for acute confusional state[6,9].

RESUMO

OBJETIVO: *Discutir o papel da classe de benzodiazepínicos no manejo do paciente em delirium.*

MÉTODOS: *Utilizando base de dados PubMed, foram revisados artigos posteriores ao ano 2000 contendo em seu título as palavras "delirium" e "benzodiazepines".*

DISCUSSÃO: *O delirium é um estado confusional agudo, que cursa com alteração da atenção, consciência e cognição. Apresenta-se com alguns fatores de risco bem estabelecidos, sobretudo em indivíduos de maior idade e com declínio cognitivo. Não há, atualmente, um consenso definido quanto a sua fisiopatologia, tampouco referente às medidas farmacológicas, principalmente acerca da classe dos benzodiazepínicos.*

CONCLUSÃO: *Evidências sugerem que pode haver um papel do uso da classe farmacológica no tratamento do quadro em questão, indicando uma mudança no padrão anteriormente paradigmático do tratamento.*

PALAVRAS-CHAVE: *Delírio. Benzodiazepinas. Revisão.*

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REVIEW ARTICLE

Hyperbilirubinemia impact on newborn hearing: a literature review

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SUMMARY

The increase in bilirubin levels in newborns can cause toxic effects on the auditory system, which can lead to hearing loss. This review aimed to verify the impact of hyperbilirubinemia in the hearing of newborns, relating audiological findings to serum levels of bilirubin. A literature review was conducted during October 2017, using the terms "hyperbilirubinemia", "jaundice", "infant", "newborn" and "hearing loss", on databases CAPES journals, MEDLINE and BIREME (SciELO, BBO). 827 studies were identified and 59 were selected for full-text reading, resulting in the selection of seven articles that met the inclusion criteria and were considered relevant to the sample of this study. All the reviewed studies performed brainstem auditory evoked potential as the main test for audiological evaluation. Changes in the audiological findings of neonates with hyperbilirubinemia were observed in all studies. There was no consensus on the serum bilirubin levels that may cause auditory changes; however, the relationship between hearing disorders and blood levels of bilirubin was positive. We identify the need to establish reference values for bilirubin levels considered critical for the occurrence of hearing disorders as well as the audiological follow-up of neonates with hyperbilirubinemia.

KEYWORDS: *Hyperbilirubinemia. Infant, newborn. Jaundice. Hearing loss.*

INTRODUCTION

Neonatal hyperbilirubinemia affects approximately half of all newborns (NB) born at full term and 80% of pre-term infants during the first week of life[1,2]. The increase in the levels of bilirubin is usually mild, transient, and not harmful to the neonates[1]. However, since it is liposoluble, high levels of bilirubin can cross the blood-brain barrier and cause damage to the central nervous system (CNS)[3,4]. High serum bilirubin levels also have a toxic effect on the auditory system, although many of these damages are reversible[5]. Studies indicate that the auditory nuclei in the brainstem, the inferior colliculus, and the superior olivary complex are particularly more susceptible to the effects of bilirubin, and lesions in these structures may lead to sensorineural hearing loss[4,6].

The Auditory Brainstem Response (ABR) is the most sensitive measurement to assess retrocochlear lesions, as well as the integrity of the auditory pathway. However, the use of this measurement in cases of neonatal hyperbilirubinemia is quite controversial, since the relationship between the serum levels of bilirubin and auditory alterations is not well defined[4,6,7]. Some studies suggest abnormalities in the ABR when there is an increase of bilirubin levels, while others

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do not report the same findings[7]. In the same way, the thresholds of blood bilirubin considered critical to the development of auditory changes have not been determined. Some authors suggest that levels above 20 mg/dL may cause sensorineural hearing loss[1,5,7,8], while others consider severe hyperbilirubinemia when the levels of serum bilirubin reach 17 mg/dL[4]. Auditory alterations have also been described in preterm newborns with levels of serum bilirubin levels below the thresholds set for exchange transfusion[9].

Thus, the objective of this systematic literature review was to evaluate the impacts of hyperbilirubinemia in newborn hearing, correlating the audiological findings to serum bilirubin levels.

METHODS

Bibliographical research was carried out in October 2017 on the Latin American and Caribbean Health Sciences Literature (Lilacs), Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Coordination for the Improvement of Higher Education Personnel Journal Portal (Capes) electronic databases. We searched for papers published by September 2015, without limitation of the initial date. The search strategy applied followed recommendations of the Cochrane Handbook for Systematic Reviews of interventions[10]. All terms used in the search are terms indexed in the Health Sciences Descriptors (DeCS) vocabulary, and the search for the review was conducted in the databases using all possible combinations between the terms *hyperbilirubinemia*, *jaundice*, *infant*, *newly-birth* and *hearing loss*, using the AND operator.

For the selection and evaluation of the studies retrieved, the following inclusion criteria were established: original studies involving full-term and preterm newborns with hyperbilirubinemia confirmed by laboratory exams, submitted to at least one clinical Auditory Brainstem Response evaluation (ABR) and/or evoked otoacoustic emissions (OAE), published in Portuguese, English, and Spanish. We excluded from the analysis studies performed on animals, studies in which hyperbilirubinemia was not the only one risk factor for hearing loss, studies that used other audiological examinations, literature reviews, letters to the editor, and case studies. The methodology followed the recommendations of the Oxford Center for Evidence-Based Medicine[11], using studies up to level 3 due to their scientific impact.

After analyzing the abstracts and titles of the studies found in the initial search, 59 were selected for the reading of the full texts. Of these, we excluded those that did not meet the inclusion criteria, after which nine studies remained.

The nine studies selected were analyzed using the Critical Appraisal Skills Programme (CASP)[12] instrument, after which two were excluded, one for not presenting a statistical analysis of the data and the other due to inconsistencies in the sample selection.

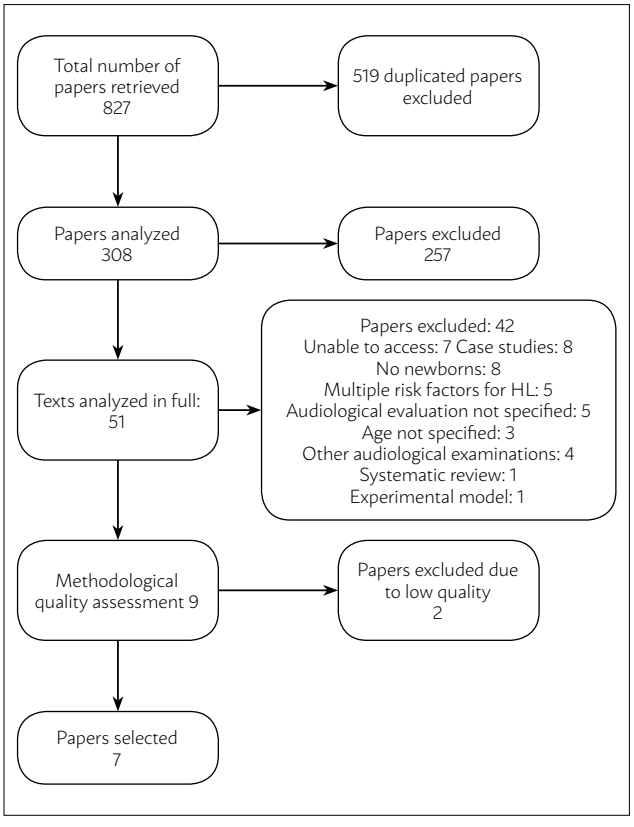
The process of selection of articles is described in Figure 1.

The analysis of the studies selected considered the author and year of publication, type and design of the study, sample characterization (number, gender, and mean age), audiological procedures used, the period of auditory assessment, bilirubin levels, in addition to the results and conclusions obtained.

RESULTS

The seven papers selected were published between 1990 and 2017. As for the country of origin, three were from India[13-15], one from Mexico[16], one from Iran[3], one from Singapore[17] and one from Brasil[18]. Of these, only

FIGURE 1



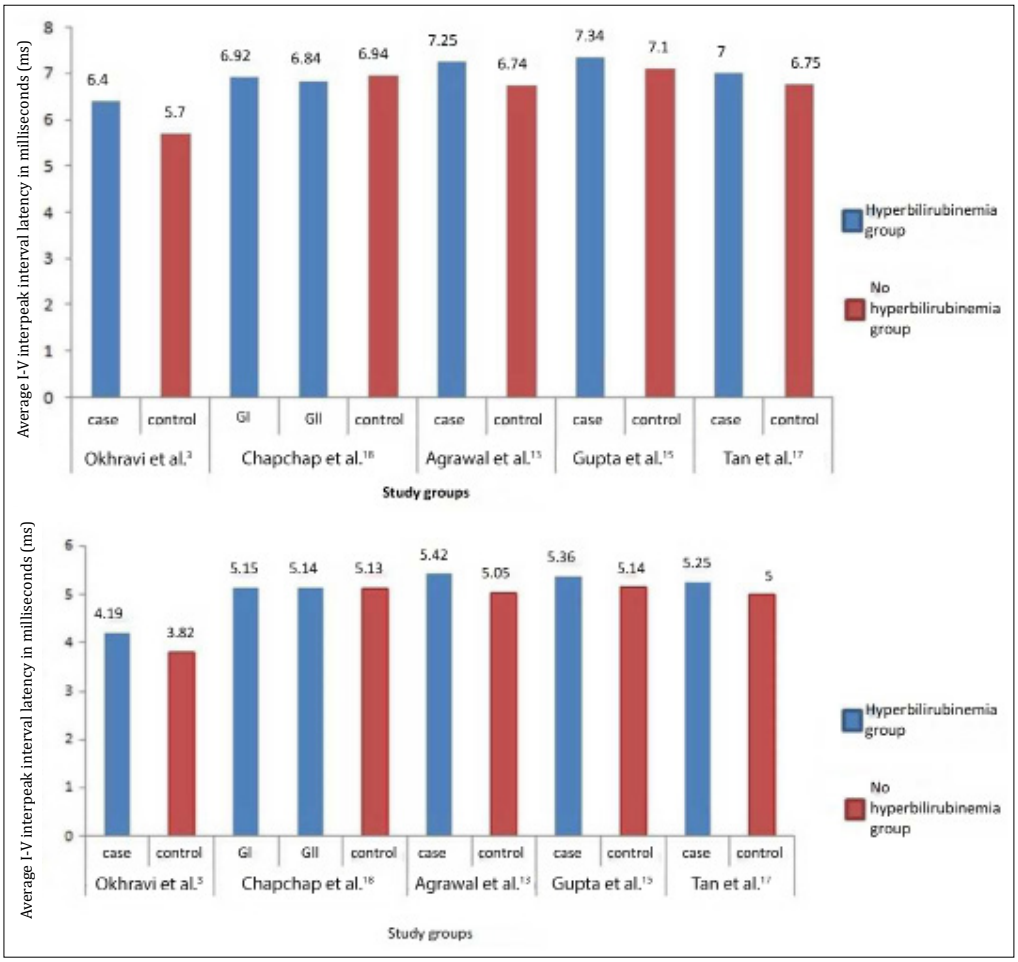
one[16] was published in Spanish, while the others were published in English.

The sample sizes varied from 25 to 71 neonates (average of 39.7 subjects per study), with a predominance of male infants in 80% of the studies in which this data was specified[3,13,15,16].

In all the studies analyzed, the ABR was the main audiological examination performed, and only one study the Otoacoustic Emissions (OAE) were also used[16]. As for the period in which the audiological examination was performed, the data found were quite distinct. In two studies, the assessment was carried out at the time of hospital discharge, when the bilirubin levels were already normalized[3.15], but in only one of them, there was an indication to retest at three and six months if the outcome of the first evaluation was abnormal[15]. One study carried out an audiological follow-up along with the phototherapy treatment[17]. Another study performed the audiological evaluation on the day of the highest peak of serum bilirubin[18]. In both surveys, the ABR was performed before and after the treatment of hyperbilirubinemia[13.14], and in one of these there was also a follow-up, with auditory evaluations of the infants at 14 weeks and again at 1 year of age[13]. Only one study did not explicitly mention when the audiological evaluation was performed, stating that it was not possible to test all neonates before the treatment, which allowed us to infer that the tests were performed after the treatment[16].

Alterations were observed in the ABR evaluation of newborns with hyperbilirubinemia in all studies reviewed. With regard to their absolute latencies and interpeak intervals, 71% of the studies reported increased wave V latency and increased interpeak I-V interval in the groups of children with hyperbilirubinemia in comparison to the groups without hyperbilirubinemia[3,13,15,17,18]. These data are detailed in Figure 2. Only one study reported a reduction of wave III absolute latency and amplitude which were justified as an isolated event due to a reduction in the auditory propagation[16]. In this study, abnormalities in the ABR were observed only in cases in which the bilirubin levels were above 28 mg/dL.

FIGURE 2



In total, four studies conducted auditory evaluations pre- and post-treatment[13-15,17]. In only one the reduction of absolute latencies and interpeak intervals after the treatment was not statistically significant[14]. In three, it was possible to observe reductions in the absolute latencies and interpeak intervals after the reduction of the bilirubin levels[13,15,17], and in one[13], the authors reported that of the 15 neonates with ABR abnormalities before the treatment, in only three the abnormalities remained when retested at 14 weeks.

The relationship between the audiological alterations and bilirubin levels was statistically significant in five of the studies reviewed[3,13,15,17]. In cases in which the auditory evaluation was performed before and after the treatment, the reduction or absence of abnormalities in the ABR followed the decline of the bilirubin levels[13,15,17]. In one study, a weak positive association was observed between the levels of indirect bilirubin and the ABR[18]. This association was found only when the two groups of neonates with jaundice were analyzed as a whole, in comparison to the control group. In two other studies, no correlation between the levels of bilirubin and abnormalities in the ABR was found[14.16].

In this review, two studies reported the use of serum bilirubin as a marker[3.15]: one used total bilirubin[13] and two indirect bilirubin[16.18]. Only one study used direct bilirubin[17], while one did not mention the method used for bilirubin measurement[14].

In most studies (n=4), the cause for hyperbilirubinemia was idiopathic, i.e., physiological changes in the bilirubin levels became pathological due to unknown causes[3,14,16,18]. These same studies reported the percentage of cases due to incompatibilities of the ABO system (blood types A, B, AB, and O) or of Rh (*Rhesus*) factor. The other studies did not report the causes[13,15,17].

In Table 1, we present the seven studies selected and their main characteristics.

DISCUSSION

In all studies, the ABR was used in the assessment of newborns. Considering that the toxicity of bilirubin affects the auditory nuclei in the brainstem, the use of evoked potentials seems to be more effective in detecting retrocochlear alterations[1,4,7]. In addition, other studies have demonstrated that the OAE alone is not adequate for auditory evaluation in cases of hyperbilirubinemia[5.19]. Still, according to other studies, auditory neuropathy, often caused by hyperbilirubinemia, is defined by alterations or the absence of waves on the ABR, while OAE remains present[1]. These data indicate the need to associate both examinations for a more comprehensive audiological evaluation[5.19].

The studies presented differences regarding the time chosen for evaluation. In general, we observe that there is no standardization for the auditory evaluation of newborns with hyperbilirubinemia, and it is more common to carry out examinations when the bilirubin levels are within the normal range, at the time of hospital discharge. In Brasil, the Ministry of Health drew up the Attention Guidelines for Neonatal Hearing Screening to guide children's hearing health care, determining that hyperbilirubinemia is a risk factor for hearing loss and, therefore, requires following a specific flow for hearing monitoring. In relation to these guidelines, newborns with risk indicators for hearing loss should undergo screening within the first 30 days of life, preferably using the ABR and, even when the results are satisfactory, babies need undergo audiological follow-up at 7 and 12 months[20].

In addition, it is important to highlight that in all studies alterations were observed in the ABR evaluation in this population, and most of the studies reported increased wave V latency and increased interpeak I-V interval[3,13-15,17], which is similar to findings of other studies with a comparable population[5,7,19]. These changes suggest that the neural conduction in the brainstem is changed by the neurotoxic effects of bilirubin[1]. The audiological findings of each study are shown in Table 1.

Some researchers argue that the auditory changes resulting from the toxicity of bilirubin in the CNS are reversible before the first two years of life[5]. In another study, it was observed that abnormalities in the ABR may remain even after the treatment with phototherapy/exchange transfusion, indicating the need for audiological follow-up to identify whether these changes are really transient or if it is a case of auditory neuropathy induced by the bilirubin levels[3].

There was a statistically significant correlation between the audiological changes and the bilirubin levels in most of the studies included in the review[3,13,15,17]. However, the literature has been quite controversial as to this direct relationship between changes in the ABR and the bilirubin levels. Some studies have shown that this relationship between audiological changes and hyperbilirubinemia exists[1,5,8], contradicting the results of other studies that report that this correlation could

TABLE 1. DATA EXTRACTED FROM THE STUDIES SELECTED.

Author and year	Study design	Population studied and bilirubin levels	Exams Carried out	Time of the auditory evaluation	Objective of the study	Audiological results
Okhravi et al.[3] (2015)	Case-control	Full term and pre-term NB with serum bilirubin ≥18 mg/dL.	ABR	At hospital discharge.	Compare the ABR results of NB with and without hyperbilirubinemia.	Increase of absolute waves I, III, and V latencies and of interpeak intervals (I-V, I-III and III-V) at hospital discharge.
Chapchap et al.[18] (2006)	Case-control	Full-term NB with hyperbilirubinemia GI: severe physiological jaundice. GII: hemolytic jaundice.	ABR	On the day of the highest peak of serum bilirubin.	Evaluate the conduction of stimulus in the auditory pathway, comparing the responses between the two groups evaluated.	Increase of the absolute latency of wave I and of interpeak III-V interval
Martiñón et al.[16] (2000)	Case-control	Full-term NB with different levels of bilirubin GI: 12 -20.9 mg/dL GII: 21 -24.9 mg/dL GIII: 25 -27.9 mg/dL GIV: ≥28 g/dL	EOA and ABR	After the treatment (phototherapy and/or exchange transfusion)	Evaluate and compare the responses obtained from the four groups studied.	Adequate absolute latency of waves I and V, and reduction of the absolute latency and amplitude of wave III.
Agrawal et al.[13] (1998)	Case-control	Full-term NB with different levels of bilirubin GA: 15 -20 mg/dL GB: 21 -25 mg/dL GC: >25 mg/dL	ABR	Before the treatment (phototherapy/exchange transfusion); when bilirubin levels <12 mg/dL; 14 weeks; 1 year.	Compare the findings obtained on the ABR between the groups, as well as before and after the treatment.	Increase of absolute latency of waves I, III, and V and of interpeak intervals (I-III and III-V). Reduction of these after the treatment.
Bhandari et al.[14] (1993)	Longitudinal	Full-term NB with plasma bilirubin ≥15mg/dL	ABR	24h after the hyperbilirubinemia diagnosis and after the treatment, when bilirubin ≤10 mg/dL	Study the effect of hyperbilirubinemia in ABR and analyze the responses obtained on the ABR after the treatment.	Increase of absolute latencies of waves I, III, and V and of interpeak intervals (I-V, I-III, and III-V) before the treatment and their reduction after the treatment.
Tan et al.[17] (1992)	Case-control	Full-term NB with a diagnosis of hyperbilirubinemia.	ABR	Before phototherapy; 24h after phototherapy; after phototherapy; one day after the end of phototherapy.	Evaluate how the reduction of bilirubin levels from phototherapy affects the ABR.	Increase of the absolute latency of wave V and of interpeak I-V and III-V. After phototherapy, the values were close to normal.
Gupta et al.[15] (1990)	Case-control	Full-term NB with serum bilirubin ≥20mg/dL.	ABR	At hospital discharge. RN who failed this test were reassessed at 3 and 6m.	Evaluate abnormalities in the ABR in newborns with hyperbilirubinemia who underwent exchange transfusion compared to NB without jaundice.	Increase of the absolute latency of waves III and V and of the interpeak intervals I-V. The latencies decreased at the retest after 3 months.

NB: newborn; G: group, ABR: Evoked auditory brainstem response; OAE: distortion-product otoacoustic emissions; mg/dL: milligrams per deciliter

not be established[4,9,21]. In many cases, the absence of correlation is justified by differences in the bilirubin levels defined as critical to the start of treatment, as well as the type of bilirubin used in the examinations.

The studies presented differences regarding the type of bilirubin used as a marker of the levels of the substance in the blood. In addition, there is no standard value defined as critical for hyperbilirubinemia. In the studies reviewed, the values ranged from 12 to 35 mg/dL. The Joint Committee on Infant Hearing (JCIH)[22] has also not defined values, just refers as risk factors for hearing loss the hyperbilirubinemia cases in which in the serum levels of total bilirubin require exchange transfusion[2,21,22]. The most widely used value as an indicator of the need for treatment is total bilirubin >20 mg/dL[1]. However, other studies have reported changes in the ABR results of preterm neonates who have not reached the thresholds of bilirubin considered critical for exchange transfusion[2,9]. These data indicate the need for standardization of the values and type of bilirubin used as a reference for risk of hearing loss induced by bilirubin, differentiating them especially according to the presence of prematurity, in addition to using them as reference for treatment referral.

Another point to be discussed is the etiology of hyperbilirubinemia which, according to the studies analyzed, is multifactorial. The matter is that in cases in which hyperbilirubinemia is caused due to incompatibilities of the ABO or Rh systems, there is an increase in the rate of hemolysis; therefore, the bilirubin levels may be higher than in other pathological conditions[21]. One study made a distinction between these two groups, showing that the bilirubin levels were lower in the group with aggravated physiological jaundice, although there was no distinction in the ABR results between the groups, only when they were

compared together against the control group[18]. These data confirm the need for standardization of bilirubin values in different situations, so as to achieve an early diagnosis of hearing loss, as well as for audiological follow-up in cases of remission.

In addition, it was possible to note the need to establish reference values for the bilirubin levels considered critical for audiological abnormalities, as well as to carry out audiological follow-up of newborns with hyperbilirubinemia, particularly of preterm infants.

CONCLUSION

The relationship between audiological changes and blood levels of bilirubin, though sometimes controversial, proved to be positive. Using the ABR as the clinical examination of choice for assessing the newborns, we found that in hyperbilirubinemia cases, changes occur in the absolute latencies and interpeak intervals, suggesting a loss of neural conduction in the brainstem, possibly caused by the toxicity of bilirubin, which can be the cause of sensorineural hearing loss.

Author's Contribution

MHT chose the descriptors, analyzed the studies included and excluded, was responsible for the scientific writing of the study; VMSB aided in the scientific writing of the study and provided intellectual contribution; RSR offered guiding and intellectual contributions; PS offered guiding, chose the descriptors, analyzed the studies included and excluded, was responsible for the scientific writing of the study and provided intellectual contributions.

RESUMO

O aumento nos níveis de bilirrubina no neonato pode provocar efeitos tóxicos no sistema auditivo, podendo levar à perda auditiva. O objetivo desta revisão foi verificar o impacto da hiperbilirrubinemia na audição de recém-nascidos, relacionando os achados audiológicos aos níveis séricos de bilirrubina. Realizou-se uma revisão sistemática de literatura durante o mês de outubro de 2017, utilizando-se os termos hyperbilirubinemia, jaundice, infant, newborn e hearing loss, nas bases de dados periódicos Capes, Medline e Bireme (SciELO, BBO). Foram identificados 827 estudos, dentre os quais 59 foram selecionados para leitura do texto na íntegra, resultando na seleção de sete artigos que atendiam aos critérios de inclusão e foram considerados relevantes para a amostra deste trabalho. Em todas as pesquisas revisadas, o potencial evocado auditivo de tronco encefálico foi o principal exame audiológico realizado. Em todos os estudos foram observadas alterações nos resultados audiológicos de neonatos com hiperbilirrubinemia. Não houve consenso quanto aos níveis séricos de bilirrubina que podem causar alterações auditivas, porém, a relação entre as alterações audiológicas e os níveis sanguíneos de bilirrubina foi positiva. Percebeu-se a necessidade de estabelecer valores de referência para os níveis de bilirrubina considerados críticos para a ocorrência de alterações audiológicas, assim como de acompanhamento audiológico dos neonatos com hiperbilirrubinemia.

PALAVRAS-CHAVE: *Hiperbilirrubinemia. Recém-nascido. Icterícia. Perda auditiva.*

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COMMENTARY

Comment on "Comparison of the effect of ultrasound-guided thoracic paravertebral nerve block and intercostal nerve block for video-assisted thoracic surgery under spontaneous-ventilating anesthesia"

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Dear Editor,

We read with great interest the study by Zheng et al.[1] in which they demonstrated that ultrasound-guided thoracic paravertebral nerve block was superior to ultrasound-guided intercostal nerve block during video-assisted thoracic surgery for pulmonary lobectomy under spontaneous-ventilating anesthesia. In our opinion, there are some issues that should be addressed.

To begin with, this study was prospective. The authors enrolled 50 patients for investigating the methods; however, 100 patients were included in the results section. Thus, the sample size should be confirmed. Additionally, how many patients were lost during follow-up in this prospective study?

Many factors may influence the results, for example, the type of surgery. It is difficult to reach the conclusion that the frequency of vascular puncture was different between the two groups. Vascular puncture was noted in four patients in the intercostal nerve block group and in one patient in the thoracic paravertebral nerve block group for chronic pain. Thus, a study involving a larger sample should be conducted to confirm the merit of thoracic paravertebral nerve block.

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COMMENTARY

Comment on "Musculoskeletal computational analysis on muscle mechanical characteristics of drivers' lumbar vertebras and legs in different sitting postures"

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Dear Editor,

We read with great interest the study by Gao et al.[1] in which they demonstrated that a much larger back-rest inclination angle, approximately 15°, and a slight backward seat-pan, about 7°, may relieve the muscle fatigue and make driving more comfortable. In our opinion, there are some issues that should be addressed.

Firstly, it is novel to use AnyBody to evaluate drivers' sitting postures. Even though this article is not an application case but a scientific study, it is still worth to explore this attempt. The effect of this model should be confirmed in practice.

Secondly, the authors present an interesting study to find the most comfortable driving posture. However, I am concerned there are basic methodological limitations that make it fail to answer the study question. For example, seat conditions such as cushion, material, shape, and boundary conditions related to car driving phenomena were not shown in the study. Thus, some factors that may influence driving posture should be considered in a future study. Also, it is necessary to show the criteria to determine a comfortable driving posture.

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COMMENTARY

Comment on "Is Uric Acid elevation a random finding or a causative agent of diabetic nephropathy?"

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Dear Editor,

We read with great interest the study by Kocak et al.[1] in which they demonstrated that UA levels may be an important predictor of nephropathy in diabetic patients. Although this article is interesting, in our opinion, there are also some concerns that should be addressed.

To begin with, the authors should give the definition of diabetic nephropathy. Additionally, the diagnosis criteria for diabetic nephropathy should be referenced. In table 1, we believe the mean with the corresponding statistics deviation may be more adequate for systolic blood pressure, diastolic blood pressure, body mass index, and so on. In general, the above variables should have a normal distribution. If the variables fail to show normal distribution, more samples should be included in the study.

Secondly, when you study the relationship between uric acid and diabetic nephropathy, the subjects included should be subjects with diabetic nephropathy and normal controls. The changes in uric acid may change with the process of diabetic nephropathy development.

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COMMENTARY

Comment on "Positive outcomes of phosphodiesterase type 5 inhibitor on histopathologic and biochemical changes induced by ureteral obstruction"

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Dear Editor,

We read with great interest the study by Köktürk et al.[1] in which they demonstrated that tadalafil prevents or slows down the onset of ureter inflammation and urothelial degeneration in rats with unilateral ureteral obstruction. In my opinion, there are some issues that should be addressed.

This was a experiment study and an interesting topic. To begin with, the age of the experimental rats is not provided, which is very important for the author. The authors divided the rats into five groups. Additionally, phosphodiesterase type 5 level or activity was not determined in the unilateral ureteral obstruction mice model. I believe that phosphodiesterase type 5 level or activity should be tested in a future study. The level or activity of phosphodiesterase 5 may change with the change of expressions of alpha-smooth muscle actin and transforming growth factor-beta. The underlying relationship between phosphodiesterase type 5 and transforming growth factor-beta should be explored.

It is difficult to reach the conclusion that tadalafil prevents or slows down the onset of ureter inflammation and urothelial degeneration in rats with unilateral ureteral obstruction. If we want to draw a reliable conclusion, more group experiments should be done, such as by giving inhibitors first and then performing surgery for unilateral ureteral obstruction and, at the same time and in another group, performing surgery first and then giving inhibitors.

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COMMENTARY

Comment on "Assessment of Neutrophil and Neutrophil/lymphocyte ratio in coronary collateral developed patients with acute coronary syndrome"

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Coronary collateral circulation (CCC) development is an adaptive response to acute or chronic myocardial ischemia and serves as a conduit bridging the significantly narrowed epicardial coronary artery.[1] Theoretically, well-developed CCC is expected to protect the myocardium from ischemia, improve residual myocardial contractility, and thus reduce anginal symptoms and adverse events. Indeed, many studies have shown that good collaterals improve prognosis in patients with chronic coronary syndrome.[2-4] However, in the setting of acute coronary syndrome (ACS), the impact of CCC on mortality is still not fully clarified. On the one hand, there are published studies showing that a well-developed CCC is beneficial on mortality in ACS[5-7], on the other hand, some publications present that the presence of CCC is not beneficial even related to increased mortality in these patients.[8-9]

The role of inflammation in critical myocardial ischemia, which is the primary stimulus for CCC development, has been previously shown.[10,11] In the settings of ACS, there are conflicting results in publications on this subject as well. For example, while İleri and his colleagues[12] found that neutrophil-to-lymphocyte ratio (NLR), together with the presence of diabetes mellitus, total white blood cell and neutrophil counts, was an independent positive predictor of poor CCC; on the contrary, Tenekecioglu et al.[13] concluded that higher NLR was significantly associated with good CCC development in patients with ACS.

In their original article, Mansiroglu et al.[14] compared the neutrophil count and NLR in patients with coronary collateral developed ACS. They reported a significant difference in the number of neutrophil counts and NLR among the types of ACS, namely, NLR and neutrophil counts were significantly higher in the ST-elevation myocardial infarction (STEMI) group in comparison with non-STEMI and unstable angina pectoris groups. The results of this study suggest that the development of CCC is positively affected in the case of STEMI, in which there is the highest inflammatory burden. It would be better if the information about the short and long term clinical results of the study patients were also known.

Despite the advances regarding the knowledge about CCC development, which is mostly from inflammatory marker-based retrospective studies, I think that there are still gaps in respect to the clinical importance of coronary collaterals in the settings of ACS. Further large prospective studies are needed to investigate the association of CCC with inflammation and the prognostic significance of coronary collaterals in ACS patients.

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Erratum

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Regarding the article "Prevalence and associated factors in community-dwelling subjects - a population-based study" with DOI number: https://doi.org/10.1590/1806-9282.66.6.830 , published in Journal of the Brazilian Medical Association, 2020;66(06), page 830, title in the article changed from: Prevalence and associated factors in community-dwelling subjects - a population-based study
To: **Nocturia: Prevalence and associated factors in community-dwelling subjects - a population-based study**