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ASSOCIATION OF COVID-19 SYMPTOMS WITH SEX AND CHRONIC NON-COMMUNICABLE DISEASES

ASSOCIAÇÃO DOS SINTOMAS DA COVID-19 COM O SEXO E DOENÇAS CRÔNICAS NÃO-TRANSMISSÍVEIS

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ABSTRACT: This study aimed to analyze the association of chronic noncommunicable diseases (NCDs), sex, and age with prevalent symptoms of COVID-19. Data was collected from the records of participants in an extension program with molecular tests for COVID-19 detection services from 2020 to 2023. The chi-square test and relative risk were used to assess the association of individual characteristics with symptom severity (mild, moderate, and severe), considering $p<0.05$. Of the 9,371 participants, most were adults and females. Mild symptoms of COVID-19 were reported by more than 50% of them, while moderate/severe symptoms were reported by 45.4%. Most positive cases with NCDs were female, but symptom severity was associated with male sex and hypertension ($p<0.05$). Males and individuals with hypertension showed a higher risk of developing moderate/severe symptoms of COVID-19.

KEYWORDS: Communicable diseases. COVID-19. Pandemics. Public health.

RESUMO: O objetivo deste estudo foi analisar a relação de doenças crônicas não-transmissíveis (DCNT's), sexo, e idade com sintomas prevalentes em indivíduos com COVID-19. Coletaram-se dados dos registros de participantes de um programa de extensão com testes de detecção molecular da COVID-19 de 2020 a 2023. O teste de chi-quadrado e o risco relativo foram utilizados para avaliar a associação das características individuais com a severidade dos sintomas (leves, moderados e graves), considerando p<0,05. Dos 9.371 participantes, a maioria era adulta e do sexo feminino. Sintomas leves da COVID-19 foram relatados por mais de 50% destes, enquanto sintomas moderados/graves por 45,4%. A maioria dos casos positivos com DCNT's eram do sexo feminino, mas a gravidade dos sintomas mostrou associação com sexo masculino e hipertensão (p<0,05). O sexo masculino e hipertensão arterial foram características que representaram maior risco para desenvolver sintomas moderados/graves da COVID-19.

PALAVRAS-CHAVE: Doença por Coronavírus-19. Doenças transmissíveis. Pandemias. Saúde Pública.

INTRODUCTION

COVID-19 is a systemic, infectious-contagious disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2)[1]. At the end of 2019, an outbreak occurred in Wuhan (China). After a few months, the COVID-19 pandemic was declared, affecting many individuals and significantly increasing the number of deaths caused by this infectious disease[2,3].

Initially, the rapid spread of COVID-19 led to an overload of hospital systems, particularly in the United States (USA), the United Kingdom, and Italy, due to the high demand from individuals with moderate and severe symptoms of the disease[4]. However, implementing containment measures for the SARS-CoV-2 virus, such as lockdowns, mass testing, improvements in the healthcare infrastructure, and later, the vaccination, helped improve the epidemiological situation in developed countries[5]. Countries unable to implement these measures effectively, such as Brazil, suffered from a lack of access to medical resources and resistance to sanitary measures[6].

According to the World Health Organization (WHO), the severity of COVID-19 symptoms can be categorized into mild cases, such as cough, sore throat, or runny nose, with or without anosmia, ageusia, diarrhea, abdominal pain, chills, myalgia, fatigue, and/or headache; moderate cases, characterized by persistent cough and fever; and severe cases, including severe acute respiratory syndrome (SARS) and dyspnea[7].

The disease caused by SARS-CoV-2 can be divided into three phases. In the 1st phase, the virus invades cells by interacting with its viral spike glycoprotein (S) and the host cell's ACE-2 receptor, changing the alveolar and vascular epithelium. The initial symptoms are mild and generally nonspecific, such as malaise, fever, and cough, but in some cases, it can be asymptomatic. The innate immune system is highly stimulated due to cellular invasion, triggering the 2nd phase. In this stage, a primary immune response occurs with the secretion of important pro-inflammatory cytokines, which can progress to more severe conditions such as viral pneumonia and SARS. Initially, patients do not present hypoxia despite pulmonary inflammation. The 3rd phase is characterized by systemic hyperinflammation, with massive release of cytokines and pro-inflammatory mediators. Due to this exacerbated inflammatory response, systemic symptoms emerge, leading the patient to the most severe stage, which manifests as an extrapulmonary systemic hyperinflammatory syndrome[1,8-9].

Factors associated with non-communicable chronic diseases (NCDs) in infected individuals, such as hypertension, obesity, cardiovascular problems, and diabetes, increase the incidence of severe cases of the disease[1,8-9]. Independently of COVID-19, NCDs are the leading causes of illness and death worldwide, with poor diet being one of the main contributors to this scenario[10]. The prevalence of hypertension, obesity, and diabetes is gradually increasing among the adult population in Brazil[11], playing a significant role in the global burden of morbidity and mortality, leading to loss of quality of life, functional limitations, and disabilities[12].

A study conducted in a town in the state of Rio Grande do Sul (RS) showed that cardiovascular diseases, including hypertension, were the most prevalent comorbidities among individuals tested for COVID-19, being present in 15.4% of positive cases. Additionally, diabetes was also positively associated with a positive COVID-19 test[13].

A meta-analysis involving 10,014 patients infected with SARS-CoV-2 in the USA, China, and Italy (55 studies) showed that males and those over 50 years old had a higher risk of developing severe symptoms. The same study revealed that comorbidities and clinical manifestations such as fever, cough, fatigue, anorexia, dyspnea, chest tightness, hemoptysis, diarrhea, and abdominal pain could significantly affect the prognosis and severity of COVID-19[14].

In Brazil, the profile of cases was similar to the international scenario but with the additional aggravating factor of social inequality. A study conducted with 104,384 COVID-19 cases reported in 2020 found that, besides male sex and old age, people of yellow or black race/skin color, with no formal education, and with multimorbidity were associated with a higher risk of unfavorable infection outcomes[15]. Besides age, sex, and chronic diseases, socioeconomic factors and disparities in healthcare access may also pose risks for COVID-19 outcomes, as seen in higher transmissibility rates among vulnerable populations such as active workers, Indigenous people, institutionalized individuals, and prisoners[13].

Despite the evidence mentioned above, studies addressing the relationship between these risk factors and the severity of COVID-19 symptoms among Brazilians are limited, especially outside the states' capitals. This study is justified by the need to analyze and understand the profile of risk groups with the primary intention of supporting strategies to prevent the worsening of COVID-19 symptoms, as well as assisting in the decision-making and implementation process of health promotion measures in the face of infectious diseases. Thus, this study aimed to analyze the relationship between the severity of COVID-19 symptoms and sex, age, and certain NCDs among individuals treated in healthcare units in the northern region of Rio Grande do Sul.

METHODOLOGY

This study was designed as quantitative, documentary, observational, and retrospective, evaluating symptoms of respiratory infections in adult individuals with COVID-19 at the time of diagnosis. The analyses were conducted using data from the UFSM-Detecta extension program of the Universidade Federal de Santa Maria, which performed RT-qPCR tests for COVID-19 diagnosis during the pandemic (2020 to 2023) for 50 municipalities in the northern and northwestern regions of Rio Grande do Sul, described previously[16].

During the data collection period, from 2020 to 2023, UFSM-Detecta conducted 49,741 COVID-19 tests in the northern region of Rio Grande do Sul, which has an estimated population of approximately 10.9 million[16-17]. Municipal healthcare services sent the data recorded in patient care forms to the program, which subsequently analyzed them.

The study included individuals tested through the UFSM-Detecta extension program between July 29, 2020, and January 27, 2023. The exclusion criteria were individuals under 18 years old, those who tested negative for COVID-19, asymptomatic individuals, or those with missing relevant data.

The study assessed sex, age group, reported comorbidities (hypertension, diabetes, and obesity), and days from the first symptoms until the data collection (1-10 days of symptoms). The prevalent symptoms were categorized as follows:

- Mild symptoms: runny nose, and/or fatigue, and/or sore throat, and/or myalgia, and/or diarrhea, and/or headache, and/or cough.
- Moderate and severe symptoms: fever, and/or dyspnea, and/or severe acute respiratory syndrome (SARS).

Regarding ethical considerations, this study followed Resolution No. 466/2012 of the National Health Council and received approval (number 5041431) from the Human Research Ethics Committee of the Universidade Federal de Santa Maria.

The Chi-square test and Fisher's exact test were used, as appropriate, to assess the association between sex, age, non-communicable chronic diseases (NCDs) (obesity, diabetes, and hypertension), and

the number of symptomatic days with the severity of symptoms, grouped into mild and moderate + severe symptoms. A significant association was considered when $p<0.05$.

The relative risk (RR) was calculated to evaluate the strength of the observed association, where: RR between 1 and 2 indicated a low-strength association; RR higher than 2 indicated a stronger association. Additionally, it was considered that: RR = 1 represented "No difference in risk", RR > 1 "Higher risk of developing moderate and severe symptoms"; and RR < 1 "Lower risk of developing moderate and severe symptoms". A 95% confidence interval (CI) was also used to measure the effect size.

The GraphPad Prism version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for data analysis.

RESULTS

The SARS-CoV-2 test was positive for 13,233 individuals. After applying the remaining exclusion criteria, 9,371 individuals participated in this study.

Table 1 outlines the traits of sex, age, and non-communicable chronic diseases (NCDs) among study participants. On average, participants were 46.7 years old, and most were younger than 60. Female patients averaged 45 years of age, while male patients had an average age of 46.2 years.

Table 1. Characteristics of the participants in the study (N=9,371). Palmeira das Missões (RS), Brazil, 2023.

Characteristic	N	Percentage
Male	4167	44.5%
Female	5204	55.5%
Adult	7660	81.7%
-18 to 39 years old	*-4334*	*-46.25%*
-40 to 59 years old	*-3326*	*-35.49%*
Elderly	1711	18.3%
-60 to 79 years old	*-1467*	*-15.65%*
-80 to 105 years old	*-244*	*-2.60%*
Obesity	62	0.7%
Hypertension	358	3.8%
Diabetes	167	1.8%

The most frequently reported symptoms, affecting more than 50% of patients, were headache, cough, and sore throat. Other reported symptoms included fever, fatigue, myalgia, runny nose, dyspnea, diarrhea, and severe acute respiratory syndrome (SARS), as shown in Figure 1.

Female patients had a higher prevalence of NCDs, as illustrated in Figure 2a. Among patients with hypertension, 69.55% were women over 50 years old, with the 50-69 age group being the most affected (53.9%). Similarly, for diabetes, most patients were female and between 50 and 69 years old (55.7%).

Obesity was also more frequent among women, although in a slightly younger population: 45% of obese individuals were between 30 and 49 years old, while 16.13% of women over 60 years old had obesity. Among men, the most common NCDs were hypertension, diabetes, and obesity, in descending order.

When analyzing the prevalence of NCDs by sex in proportion to the studied population (Figure 2b), no significant differences were observed ($p>0.05$ according to the chi-square test).

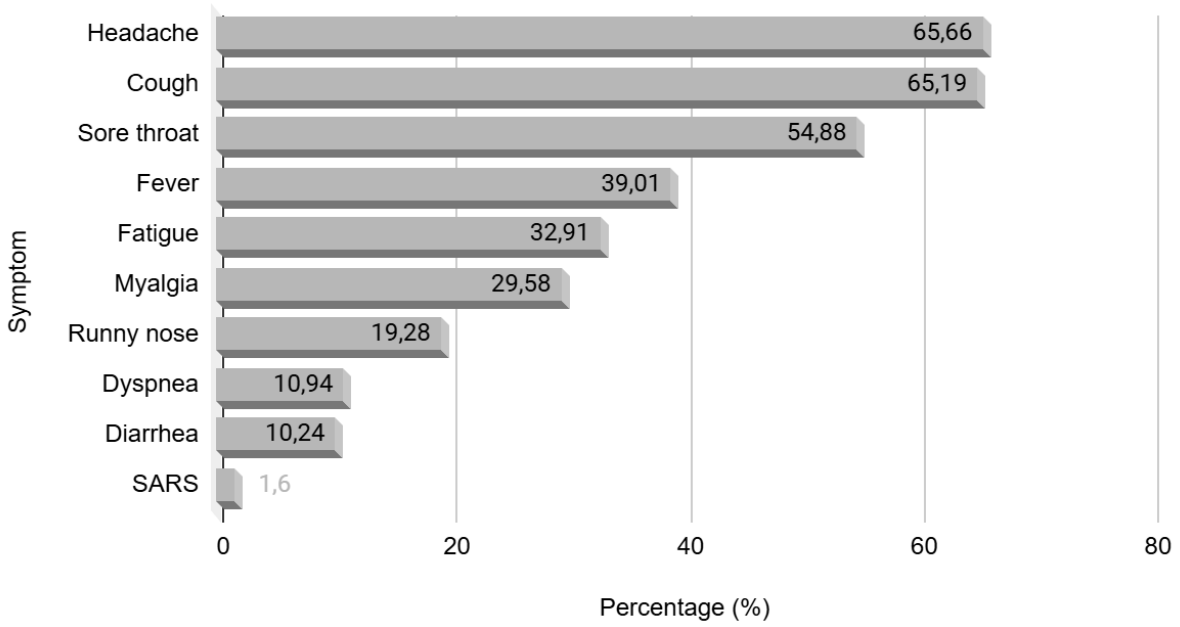

Figure 1. Prevalence of symptoms in COVID-19 patients (*N*=9,371). Palmeira das Missões (RS), Brazil, 2023. Source: The authors.

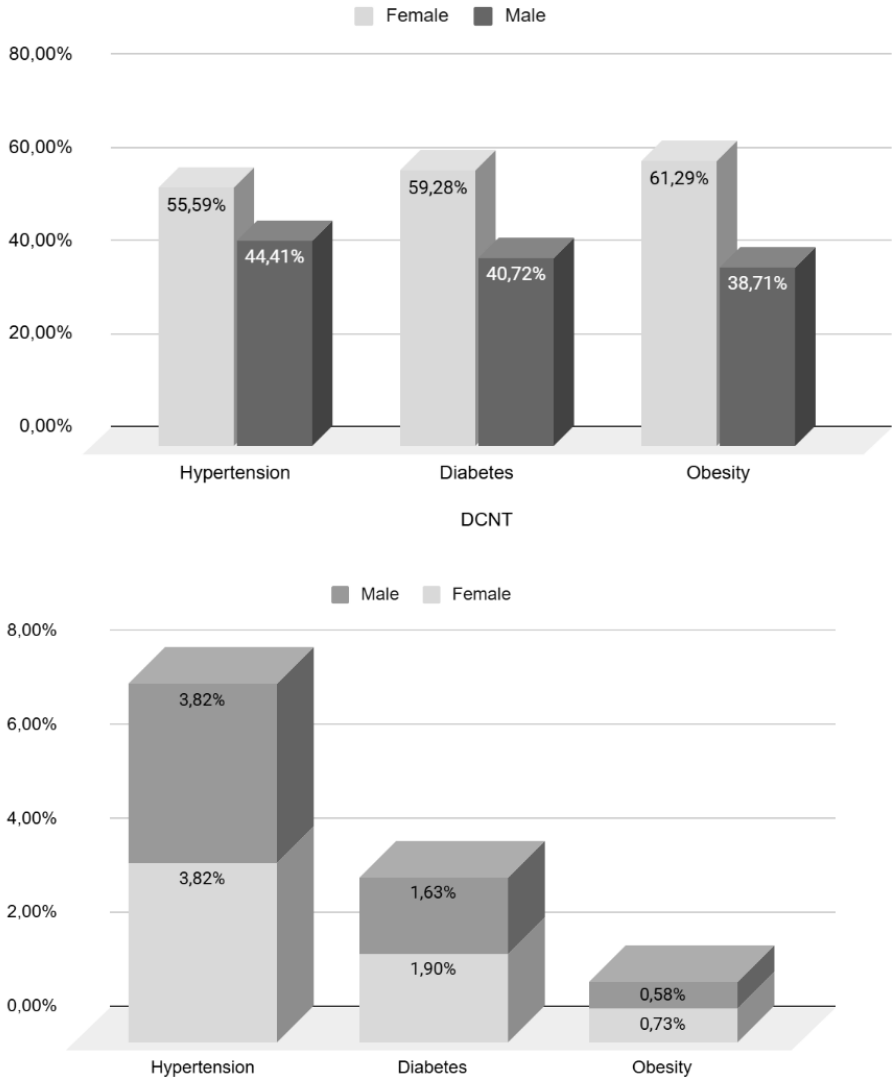

Figure 2. Prevalence of comorbidities according to the sex of COVID-19 patients *(N*=9,371). Palmeira das Missões, RS, Brazil, 2023. b) There was no significant association between the prevalence of NCDs and gender according to the chi-square test, considering $p<0.05$. Source: The authors.

Moderate + severe symptoms were reported by 45.4% of patients, while 54.6% reported mild symptoms. A low-strength significant association was found between symptom severity and the male sex, despite the higher number of diagnosed women. Male patients had a 25% higher relative risk of developing moderate/severe symptoms compared to female patients (Table 2).

Symptom severity was also significantly associated with hypertension. The association between hypertension and the development of moderate to severe symptoms was low in strength, with a 12% higher risk compared to the non-hypertensive group. No significant association was found when analyzing the variables adults, elderly individuals, obesity, diabetes, and symptom duration (Table 2).

Table 2. Association between symptom severity and participants' characteristics (N=9371). Palmeira das Missões (RS) Brazil, 2023.

	Moderate + Severe	**Mild**	P	**RR**	**CI 95%**
Male	2128 (22.7%)	2039 (21.8%)	<0.001	1.25	1.20 to 1.31
Female	2128 (22.7%)	3076 (32.8%)			
Adult	3497 (37.3%)	4163 (44.4%)	0.332	1.03	0.97 to 1.09
Elderly	759 (8.1%)	952 (10.2%)			
Obese	32 (0.3%)	30 (0.3%)	0.325	1.14	0.89 to 1.45
Non-obese	4224 (45.1%)	5085 (54.3%)			
Hipertense	181 (1.9%)	177 (1.9%)	0.046*	1.12	1.01 to 1.24
Non hipertense	4075 (43.5%)	4938 (52.7%)			
Diabetic	83 (0.9%)	84 (0.9%)	0.262	1.10	0.94 to 1.28
Non-diabetic	4173(44.5%)	5031 (53.7%)			
≥ 7 days#	533 (5.7%)	594 (6.3%)	0.172	1.05	0.98 to 1.12
≤ 6 days#	3723 (39.7%)	4521 (48.2%)			

#Days since the first symptoms. *Significant association according to chi-squared test considering (p<0.05).

DISCUSSION

The results of this study showed that COVID-19 affected more female individuals, but with milder symptoms, whereas male individuals and those with hypertension were more frequently associated with moderate/severe symptoms.

This study found a predominance of SARS-CoV-2 carriers in adults (81%), with the 18-29 age group accounting for 24.31% of the confirmed cases. In Rio Grande do Sul, most confirmed cases occurred in individuals aged 30 to 39 years, corresponding to the productive sector of society, which was more exposed to contamination[18]. There are several reasons why this age group accounts for a significant number of infected individuals, including mobility, social interaction, occupational exposure, risk behaviors, and a lower likelihood of experiencing severe symptoms[19].

Headache, cough, and sore throat were the most prevalent symptoms among individuals with COVID-19 in this study. The clinical manifestation of COVID-19 is related to the ability of SARS-CoV-2 to infect cells by binding to the angiotensin-converting enzyme-2 (ACE-2) receptor, triggering an inflammatory response that affects multiple body systems[20]. SARS-CoV-2 primarily affects the respiratory tract, leading to cough, which can progress to shortness of breath when airway inflammation worsens, resulting in mucus production and tissue damage[21]. Headaches may develop when the virus initiates inflammation in nerve tissue, causes vascular dysfunction, or leads to tissue hypoxia[21].

Fever, fatigue, and muscle pain were also reported, as these symptoms result from the systemic inflammation caused by the virus[22]. Diarrhea and other gastrointestinal symptoms were also observed, likely because ACE-2 receptors are also present in the intestines. Loss of smell and taste, which have been reported in other studies, is linked to viral invasion of the olfactory system[23]. Severe symptoms occur due to excessive immune activation and blood clot formation, which can lead to multisystem complications[24].

Women were more affected by COVID-19 but developed fewer moderate+ severe symptoms. They tend to have stronger immune responses than men, which may help fight SARS-CoV-2 infection. The X chromosome contains several genes related to immune function and inflammatory response, and women have two copies of these genes, leading to enhanced antibody production and a more balanced immune response[25-26]. A low-strength significant association was observed between symptom severity and male sex, as men have more ACE-2 receptors than women[27-28]. Additionally, men are less likely to seek healthcare services, adhere to treatments, or engage in preventive care[29].

In this study, symptom severity was also significantly associated with hypertension, albeit with low strength. The high prevalence of hypertension in the general population may explain this finding. Consequently, many COVID-19 patients also had hypertension simply due to its prevalence in the studied population[30]. Another possible explanation is the initial concerns regarding certain hypertension medications, such as ACE inhibitors and angiotensin receptor blockers, which were initially suspected of influencing COVID-19 severity and were temporarily discontinued[31]. However, later studies showed that these drugs do not increase risk and may have protective effects[32].

Although obesity and diabetes were not significantly associated with symptom severity in this study, it is important to monitor disease progression in individuals with these NCDs[33]. Due to reduced lung capacity and increased vulnerability to respiratory infections, obese individuals are at a higher risk of developing severe symptoms of COVID-19[34] and requiring hospitalization[35]. These chronic diseases are linked to low-grade chronic inflammation, which could impair immune function and increase susceptibility to COVID-19 complications, making treatment more challenging[33-34].

The interpretation of results in this study should consider methodological limitations. The analysis was based on secondary data recorded by health professionals based on patient reports, which may introduce bias due to the subjective nature of the data[13]. Another limitation is the sampling, as the study only included individuals who sought healthcare services in the region. This may not represent the broader population, including infected individuals who did not undergo molecular testing or any other diagnostic test.

Despite these limitations, this study included 9,371 tested individuals from 50 municipalities, providing a regional overview of COVID-19 trends in northern Rio Grande do Sul. Analyzing COVID-19 symptoms and other aspects of the pandemic is essential for understanding clinical manifestations of SARS-CoV-2 infection and its variants, allowing for the early implementation of public health interventions[36].

Even though the COVID-19 pandemic has officially ended, this study contributes to understanding new epidemiological challenges. Just as early pandemic research on similar pathogens helped identify COVID-19 cases, assisted in diagnosis and screening, and identified risk groups, this study provides insights into future preventive actions[16].

International research highlights that comorbidities and advanced age are risk factors for poor COVID-19 outcomes[14,33]. Therefore, epidemiological studies using Brazilian data, particularly from areas away from the states' capitals, are valuable for epidemiological surveillance, guiding public policies, monitoring disease progression, and tracking viral variant spread in these regions.

CONCLUSION

This study found that COVID-19 affected more females, but they experienced milder symptoms than males. Hypertension was identified as the most frequently associated comorbidity with moderate/severe symptoms.

This study has relevant implications for health and education, emphasizing the need for public policies that prioritize prevention as the primary governmental strategy. Despite its limitations, generating data on COVID-19's public health impact opens doors for post-pandemic research, allowing the identification of better preventive strategies for respiratory infections and health promotion.

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