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Multimorbidity, Morbidities and Long COVID-Findings of the Sulcovid Longitudinal Study

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Abstract

Background: The aim of this study was to evaluate the association between long COVID, morbidities and multimorbidity in adults and older adults six to nine months after infection with the SARS-CoV-2 virus in Southern Brazil.

Methods: Baseline data were obtained from the longitudinal study, Sulcovid, conducted on individuals diagnosed with COVID-19 through RT-PCR testing from December 2020 to March 2021, who were symptomatic and living in a city in Southern Brazil. Long COVID was assessed based on the affirmative response to at least one of the 18 symptoms investigated and categorized as musculoskeletal, neurological, respiratory, sensory or digestive. Morbidities were assessed based on the presence of at least one of nine self-reported diseases. Data were analyzed using the Stata 15.0 statistical package. Crude and adjusted analyses were performed using Poisson regression to assess the relationships between morbidity, multimorbidity and long COVID.

Results: In total, 2,919 people were interviewed. The most prevalent morbidities were anxiety (26.3%), hypertension (25.3%) and depression (19.4%). In addition, 17.8% reported two previous morbidities and 22.6% had three or more comorbidities. Individuals with depression (PR=1.17 95% CI 1.05-1.30), anxiety (PR=1.33 95% CI 1.21-1.47), two or more morbidities (PR=1.22 95% CI 1.07-1.39) and three or more morbidities (PR=1.40; 95% CI 1.24-1.57) were more likely to have long COVID. A linear trend was observed, where individuals with two and three or more morbidities were 1.22 (95% CI 1.07-1.39) and 1.40 (95% CI 1.24-1.57) times more likely to develop long COVID than those with no or one morbidity.

Conclusion: The findings of this study reinforce that individuals with morbidities and multimorbidities prior to infection had greater vulnerability to long COVID.

Keywords: Multimorbidity; RT-PCR; SARS-CoV-2; Hypertension; Overweight

Introduction

Long COVID is defined as a multisystem condition of persistent symptoms that occurs in individuals with a history of SARS-CoV-2 infection [1,2]. The estimated global prevalence of long COVID lasting 28 days or more after acute infection is approximately 43.0% [3]. A meta-analysis that evaluated the long-term effects of COVID-19 over 12 months or more found a 57.0% prevalence of at least one symptom of long COVID, with the most common symptoms being dyspnea on exertion (34.0%), difficulty concentrating (32.0%) and fatigue (31.0%) [4].

Currently, the literature presents several mechanisms to explain the pathophysiology of long COVID, including mitochondrial dysfunction, persistence of SARS-CoV-2 viral RNA and proteins in various tissues, immune dysregulation, microbiota disruption, autoimmunity, coagulation and endothelial abnormality, dysfunctional neurological signaling, Epstein-Barr virus, human herpesvirus 6 and severe acute respiratory syndrome related to SARS-CoV-2 [5-7].

Multimorbidity or the coexistence of two or more chronic Non-communicable Diseases (NCDs) in an individual, has a prevalence of 29.4% to 58.6% in Brazil and is related to the occurrence of long COVID, corroborating it as a risk factor for the development of the disease [8,9]. The prevalence of pre-COVID-19 morbidities was 62.1% in adults and older adults. Particularly, hypertension (34.5%), diabetes mellitus (17.6%), chronic kidney disease (14.2%) and cancer (12.8%) were most prevalent.

Although multimorbidity has been shown to increase the probability of complications, hospitalizations and deaths from COVID-19, it is still necessary to understand the mechanisms of the relationship between morbidities and multimorbidity in long COVID, since morbidities and multimorbidity should be included in the strategic plan for decision-making in the management of patients with long COVID.

Due to the high prevalence of morbidities and multimorbidity in Brazil, a country with a continental dimension, and because its population has a higher risk of developing long COVID, the present

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study aimed to evaluate the association between long COVID, morbidities and multimorbidity in individuals following SARS-CoV-2 infection in Southern Brazil.

Materials and Methods

This cross-sectional study used baseline data from the Sulcovid-19 longitudinal study, with the objective of monitoring individuals infected with SARS-CoV-2 in the port city of Rio Grande in the extreme south of Brazil. The municipality has a land area of 2,682.867 km² and a population of 191,900. This study was approved by the Health Research Ethics Committee (CEPAS) of the Federal University of Rio Grande (FURG) (CAAE:39081120.0.0000.5324) and more details about the design and methods of the study can be found in the literature.

To delimit the sample, the epidemiological health surveillance department of the municipality was contacted to identify adults and older adults with COVID-19 during the study period and to create a list of 4,014 individuals with positive RT-PCR results and their respective data (name, address, telephone number and presence of symptoms). After excluding individuals without telephone contact or addresses, 3,822 individuals were selected for the study.

Trained interviewers collected data via telephone. To reduce losses and refusals from individuals who were fearful or had discomfort in answering the survey *via* telephone contact, a home visit was offered for the application of the face-to-face instrument. In cases where an individual could not be found after five attempts to contact them by phone, a standard message briefly explaining the study and requesting for the best time to contact them was sent to those who had Whatsapp. For those who could not be contacted *via* Whatsapp, received home visits. Individuals who could not be located after five attempts at telephone contact and three home visits were considered lost.

Data were collected from July to October 2021, six to nine months after infection with SARS-CoV-2. Questionnaires were electronically collected (tablet) using the REDCap program and smartphones were used for telephone calls. To ensure the safety of the researcher and interviewees, calls were recorded through a free mobile application (Callmarter) and stored in a specific e-mail account. The time taken to answer the questionnaire was approximately 20 min.

The questionnaire used in the study was developed for this study and is available in supplementary material. The outcome of long COVID was investigated based on the answer to the following question: "Which of these symptoms did you have after COVID-19?" and "If yes" > "At this moment, do you still have this symptom?". A total of 18 symptoms of long COVID were investigated, namely headache, shortness of breath, dry cough, cough with phlegm, pain during breathing, loss of taste, loss of smell, change in sensitivity, tiredness or fatigue, sore throat, runny nose, nasal obstruction, diarrhea, nausea, joint pain, muscle pain, memory loss and loss of attention. Each symptom was questioned individually and operationalized in a dichotomous way (yes/no). The presence of long COVID was considered an affirmative response to at least one of the symptoms investigated.

The symptoms were also grouped under one of the following categories: Musculoskeletal (muscle pain, joint pain and fatigue), neurological (headache, memory loss, and loss of attention), respiratory (shortness of breath, dry cough, cough with phlegm, pain to breathe, sore throat, runny nose and nasal obstruction), sensory (changes in sensitivity, loss of smell and loss of taste) and digestive (nausea and diarrhea). The presence of at least one symptom in a category (yes/no) was considered positive.

Exposure to morbidities was collected from the following question: "At some point in your life, has any physician ever said that you have XX morbidity?", with a dichotomous answer option (yes or no). Nine self-reported morbidities were assessed: Depression, anxiety, respiratory diseases (asthma/bronchitis/emphysema/chronic obstructive pulmonary disease), osteoporosis (or weak bones), rheumatic diseases (arthritis/arthrosis/rheumatism), Systemic Arterial Hypertension (SAH), diabetes mellitus, heart disease (heart failure, weak heart and large heart) and cancer. Mental health morbidities (depression and anxiety) require diagnosis by a physician or health professional (psychiatrist or psychologist).

Multimorbidity was assessed considering the morbidities mentioned above and was operationalized in the ordinal form of "0 or 1" "2" and "≥ 3" and the presence of two or more diseases was considered a multimorbidity. Sex (female or male), age (18-59 years or 60 years or older), skin color (white, yellow, black, brown and indigenous), marital status (married, living with a partner/single, separated and widowed), education (first grade, high school or higher education), economic class (A, B1, B2, C1, C2, D, E), health insurance (yes/no), body mass index-BMI, physical activity-150 min per week or more (no/yes) and hospitalization due to COVID-19 (no/yes) were used to adjust variables.

Descriptive data were presented as proportions and 95% Confidence Intervals (95% CI). Crude and adjusted analyses were performed using Poisson regression with robust variance adjustment. All associations with a 95% Confidence Interval (CI) with no overlap between categories were considered statistically significant. Data were analyzed using the Stata 15.0 statistical package.

Results

Among the 3,822 individuals eligible for the study, 2,919 adults and older adults were interviewed after 631 were lost and 272 refused to participate. The sample consisted mostly of females (58.6%) with white skin (77.9%), aged between 18 and 59 years (59.6%) and were married or living with a partner (60.6%). Approximately 40.0% had an income between R$ 1,001.00 and R$ 2,000. Regarding BMI, most were overweight or obese (73.3%), approximately 25.0% were smokers and among those investigated, only 3.7% required hospitalization.

Approximately 45.0% of the interviewees had at least one preexisting morbidity, the most prevalent being anxiety (26.3%; 95% CI 24.7-27.9), SAH (25.3%; 95% CI 23.8-27.0), and depression (19.4%; 95% CI 18.0-20.9), whereas 17.8% (95% CI 16.5-19.3) had two diseases and 22.6% (95% CI 21.1-24.2) had three or more previous morbidities.

The prevalence of long COVID in the sample without any previous illness was 48.3% (95% CI 46.5-50.1). In those who reported having previous illness to infection, symptoms of long COVID were present with a higher prevalence in participants with osteoporosis (68.0%; 95% CI: 59.2-75.7), followed by rheumatic diseases (63.7%; 95% CI 58.4-68.6), anxiety (62.9%; 95% CI 59.3-66.3) and depression (62.3%; 95% CI 58.2-66.2) (Table 1).

Previous illnesses	Musculoskeletal[a] % (IC 95%)	Neurological[b] % (IC 95%)	Respiratory[c] % (IC 95%)	Sensory[d] % (IC 95%)	Digestives[e] % (IC 95%)	Long COVID % (IC 95%)
No previous illness	25.5 (23.9-27.1)	26.8 (25.2-28.5)	15.7 (14.4-17.1)	17.4 (16.0-18.8)	2.1 (1.7-2.8)	48.3 (46.5-50.1)
Depression	35.9 (32.1-40.0)	40.8 (36.8-44.9)	21.5 (18.3-25.1)	23.7 (20.3-27.4)	4.2 (2.9-6.3)	62.3 (58.2-66.2)
Anxiety	34.7 (31.3-38.1)	39.0 (35.5-42.5)	21.1 (18.3-24.1)	24.1 (21.2-27.2)	3.7 (2.5-5.3)	62.9 (59.3-66.3)
Respiratory diseases	35.5 (31.4-39.9)	36.6 (32.4-41.0)	27.3 (23.5-31.5)	20.9 (17.5-24.8)	4.7 (3.1-7.0)	59.9 (55.5-64.2)
Osteoporosis	45.6 (37.0-54.5)	41.6 (33.2-50.5)	33.6 (25.8-42.4)	21.6 (15.2-29.8)	6.4 (3.2-12.4)	68.0 (59.2-75.7)
Rheumatic diseases	40.9 (35.8-46.2)	37.8 (32.8-43.0)	26.7 (22.2-31.6)	23.8 (19.6-28.6)	4.6 (2.8-7.4)	63.7 (58.4-68.6)
HAS	32.7 (29.4-36.2)	31.7 (28.4-35.2)	20.3 (17.6-23.4)	20.0 (17.3-23.1)	3.1 (2.1-4.7)	55.8 (52.1-59.3)
Diabetes	31.5 (26.4-37.1)	28.6 (23.7-34.1)	22.6 (18.1-27.8)	18.8 (14.7-23.8)	3.8 (2.1-6.7)	53.8 (48.0-59.5)
Cardiopathy	33.1 (27.6-39.1)	34.4 (28.8-40.4)	24.3 (19.5-30.0)	20.8 (16.2-26.2)	3.8 (2.1-7.0)	54.7 (48.5-60.7)
Cancer	23.5 (14.8 -35.3)	20.9 (12.6-32.6)	20.6 (12.4-32.2)	16.2 (9.0-27.2)	2.9 (0.7-11.4)	49.3 (37.3-61.3)
Morbidity						
0-1	18.4 (16.6-20.3)	20.5 (18.7-22.5)	10.6 (9.2-12.1)	14.2 (12.6-16.0)	1.7 (0.7-1.7)	39.7 (37.4-42.1)
2	30.3 (26.4-34.5)	29.1 (25.2-33.3)	15.3 (12.4-18.7)	17.7 (14.6-21.3)	2.0 (1.1-3.4)	54.2 (49.7-58.5)
3 or more	38.5 (34.7-42.3)	39.6 (39.5-43.5)	27.1 (23.8-30.7)	23.4 (20.3-26.8)	4.2 (2.9-6.1)	63.4 (59.6-67.1)

Note: [a]muscle pain, joint pain, fatigue, [b]headache, memory loss, loss of attention, [c]shortness of breath, dry cough, cough with phlegm, pain in breathing, sore throat, runny nose, nasal obstruction, [d]changes in sensation, loss of smell and loss of taste, [e]nausea and diarrhoea. Respiratory diseases: Asthma/bronchitis/emphysema/COPD; Rheumatic diseases: Arthritis/arthrosis/rheumatism; Cardiopathy: Heart failure, weak heart, large heart

Table 1: Long COVID and symptoms according to the presence of previous morbidities and multimorbidity (n=2.919).

When assessing the presence of at least one symptom of long COVID, regardless of the symptom, it was found that the occurrence can be up to 20 percentage points (p.p.) higher among those with previous morbidities compared to those without previous diseases. Individuals with multimorbidity also had a higher prevalence of long COVID symptoms, with a dose-response effect, leading to a higher prevalence among those with three or more previous morbidities (Table 1).

Table 2 presents the crude analysis of long COVID, previous morbidities and multimorbidities. It was observed that all previous diseases that were evaluated, except for cancer, increased the probability of presenting with at least one symptom of long COVID, with emphasis on anxiety, osteoporosis, rheumatic diseases and depression. The presence of two or more previous illnesses increased the probability of long COVID symptoms by 36.0% (95% CI 1.23-1.51) and 60.0% (95% CI 1.47-1.73), respectively (Table 2).

Previous morbidities	Musculoskeletal[a] % (IC 95%)	Neurological[b] % (IC 95%)	Respiratory[c] % (IC 95%)	Sensory[d] % (IC 95%)	Digestives[e] % (IC 95%)	Long COVID % (IC 95%)
Depression	1.56 (1.37-1.78)	1.73 (1.53-1.98)	1.50 (1.24-1.80)	1.49 (1.25-1.77)	2.49 (1.51-4.10)	1.39 (1.28-1.50)
Anxiety	1.56 (1.37-1.76)	1.73 (1.54-1.95)	1.54 (1.29-1.83)	1.60 (1.36-1.88)	2.38 (1.45-3.91)	1.46 (1.35-1.57)
Respiratory diseases	1.51 (1.31-1.73)	1.47 (1.29-1.69)	2.04 (1.71-2.43)	1.24 (1.03-1.51)	2.84 (1.71-4.69)	1.30 (1.20-1.43)
Osteoporosis	1.86 (1.52-2.28)	1.59 (1.28-1.97)	2.25 (1.73-2.93)	1.25 (0.89-1.77)	3.21 (1.56-6.59)	1.44 (1.26-1.63)
Rheumatic diseases	1.76 (1.52-2.03)	1.50 (1.28-1.74)	1.91 (1.56-2.33)	1.46 (1.18-1.80)	2.55 (1.46-4.45)	1.39 (1.27-1.52)
HAS	1.42 (1.25-1.61)	1.26 (1.11-1.44)	1.43 (1.20-1.71)	1.22 (1.02-1.45)	1.74 (1.04-2.89)	1.22 (1,13-1.32)
Diabetes	1.27 (1.06-1.52)	1.08 (0.89-1.31)	1.51 (1.20-1.90)	1.09 (0.85-1.41)	1.89 (0.99-3.57)	1.13 (1.01 (1.27)
Cardiopathy	1.34 (1.11-1.61)	1.32 (1.10-1.58)	1.65 (1.30-2.08)	1.22 (0.94-1.57)	1.94 (1.00-3.78)	1.15 (1.02-1.29)
Cancer	0.92 (0.56-1.42)	0.77 (0.48-1.24)	1.32 (0.82-2.12)	0.92 (0.53-1.60)	1.36 (0.34-5.46)	1.02 (0.80-1.30)

Mobirdade						
0-1	Ref	Ref	Ref	Ref	Ref	Ref
2	1.65 (1.40-1.95)	1.41 (1.20-1.67)	1.45 (1.13-1.85)	1.25 (0.99-1.56)	1.86 (0.86-3.99)	1.36 (1.23-1.51)
3 or more	2.10 (1.82-2.41)	1.93 (1.69-2.20)	2.56 (2.11-3.09)	1.65 (1.37-1.98)	3.96 (2.19-7.13)	1.60 (1.47-1.73)

Note: *Poisson regression [a]muscle pain, joint pain, fatigue, [b]headache, memory loss, loss of attention, [c]shortness of breath, dry cough, cough with phlegm, pain in breathing, sore throat, runny nose, nasal obstruction, [d]changes in sensation, loss of smell and loss of taste, [e]nausea and diarrhoea. Respiratory diseases: Asthma/bronchitis/emphysema/COPD; Rheumatic diseases: Arthritis/arthrosis/rheumatism; Cardiopathy:Heart failure, weak heart, large heart

Table 2: Crude analysis of long COVID and previous morbidities and multimorbidity (n=2.919).

In the adjusted analysis, it was found that symptoms of anxiety, respiratory diseases, rheumatic diseases and depression increased the likelihood of long COVID by up to 33.0%. There was a linear trend, where individuals with either two and three morbidities or more were 1.22 (95% CI 1.07-1.39) and 1.40 (95% CI 1.24-1.57), respectively, times more likely to develop long COVID. Regarding the grouped symptoms of long COVID, an increase in the probability of musculoskeletal symptoms of long COVID was observed in individuals with two, three or more previous diseases. For the other grouped symptoms of long COVID, there was a higher probability among those with three or more previous illnesses, to present with respiratory (PR:2.09; 95% CI 1.57-2.78) and digestive (PR:4.34; 95% CI 1.94-9.70) symptoms of long COVID (Table 3).

Previous morbidities	**Musculoskeletal[a] % (IC 95%)**	**Neurological[b] % (IC 95%)**	**Respiratory[c] % (IC 95%)**	**Sensory[d] % (IC 95%)**	**Digestives[e] % (IC 95%)**	**Long COVID % (IC 95%)**
Depression	1.31 (1.09-1.57)	1.42 (1.20-1.68)	1.21 (0.92-1.59)	1.08 (0.85-1.37)	1.79 (0.85-3.76)	1.17 (1.05-1.30)
Anxiety	1.42 (1.20-1.68)	1.44 (1.24-1.69)	1.41 (1.11-1.79)	1.38 (1.12-1.70)	1.92 (1.00-3.69)	1.33 (1.21-1.47)
Respiratory diseases	1.44 (1.20-1.73)	1.34 (1.12-1.61)	1.70 (1.31-2.19)	1.08 (0.84-1.40)	2.48 (1.21-5.07)	1.23 (1.10-1.37)
Osteoporosis	1.23 (0.88-1.72)	1.08 (0.75-1.55)	1.42 (0.88-2.30)	0.91 (0.52-1.58)	2.82 (0.73-10.8)	1.02 (0.81-1.30)
Rheumatic diseases	1.31 (1.05-1.63)	1.21 (0.97-1.52)	1.68 (1.23-2.29)	1.26 (0.93-1.71)	2.91 (1.28-6.62)	1.18 (1.02-1.35)
HAS	1.14 (0.94-1.38)	1.01 (0.83-1.23)	1.10 (0.84-1.44)	1.13 (0.89-1.45)	1.62 (0.80-3.26)	1.09 (0.97-1.22)
Diabetes	1.11 (0.87-1.42)	1.09 (0.83-1.42)	1.25 (0.87-1.81)	1.05 (0.73-1.49)	1.93 (0.72-5.18)	1.12 (0.96-1.31)
Cardiopathy	1.22 (0.94-1.59)	1.30 (1.01-1.67)	1.63 (1.17-2.27)	1.28 (0.92-1.79)	1.97 (0.78-5.00)	1.08 (0.91-1.28)
Cancer	1.20 (0.74-1.93)	0.75 (0.40-1.43)	1.23 (0.62-2.44)	1.15 (0.61-2.17)	4.41 (2.66-7.30)	1.04 (0.75-1.43)
Morbidity						
0-1	Ref	Ref	Ref	Ref	Ref	Ref
2	1.36 (1.09-1.70)	1.14 (0.92-1.42)	1.10 (0.77-1.56)	1.02 (0,76-1,36)	1.68 (0.64-4.41)	1.22 (1.07-1.39)
3 or more	1.75 (1.44-2.13)	1.60 (1.33-1.94)	2.09 (1.57-2.78)	1.41 (1,08-1,82)	4.34 (1.94-9.70)	1.40 (1.24-1.57)

Note: *Poisson regression [a]muscle pain, joint pain, fatigue, [b]headache, memory loss, loss of attention, [c]shortness of breath, dry cough, cough with phlegm, pain in breathing, sore throat, runny nose, nasal obstruction, [d]changes in sensation, loss of smell and loss of taste, [e]nausea and diarrhoea. Respiratory diseases: Asthma/bronchitis/emphysema/COPD; Rheumatic diseases: Arthritis/arthrosis/rheumatism; Cardiopathy: Heart failure, weak heart, large heart. Adjusted for: Gender, age, skin color, marital status, education, economic class, health insurance, and physical activity.

Table 3: Adjusted analysis of long COVID, previous morbidities and multimorbidity (n=2.919).

Discussion

The results of this study revealed that the prevalence of long COVID symptoms was higher among individuals with previous morbidities, with an emphasis on the significant association between depression, anxiety, respiratory diseases, previous rheumatic diseases and long COVID symptoms. The presence of multimorbidity was associated with the occurrence of long COVID symptoms, in a dose-response manner.

Regarding the symptoms of long COVID, in a meta-analysis that covered 11,598 patients with persistent symptoms of COVID-19, it was highlighted that the prevalence of fatigue was 29.2% (95% CI 21.5-39.4); muscle pain was 13.3% (95% CI 7.4-23.6); joint pain was 28.2% (95% CI 14.7-54.0), loss of smell or taste and headaches were 14.7% and 10.4%, respectively, dyspnea was 21.4% (95% CI 14.3-21.2), cough was 17.8% (95% CI 13.3-23.8), and gastrointestinal problems was 6.2% (95% CI 4.6-8.3) over a period of four to eight months, which is in line with the results of our study.

Regarding mental health, several studies have pointed to a relationship between depression, anxiety and stress and the number of symptoms of long COVID. In a study conducted in Mexico, the main symptoms were headache (62.1%); memory problems (58.6%); diarrhea (48.3%); mental confusion (48.3%); and dyspnea, arthralgia and myalgia (41.4%). There is evidence of a range of long-term adverse effects of other viral infections, such as SARS-CoV-1 and MERS-CoV and studies have verified the presence of chronic fatigue and long-term mental health changes 31 to 50 months after these infections.

Although the mechanisms of interaction between mental health morbidities and symptoms of long COVID are currently not well understood, there are some hypotheses on how COVID-19 may affect the nervous system, including neuroinflammation caused by the involvement of the respiratory system by the immune response to SARS-CoV-2 by increasing cytokines, chemokines and immune cells in the brain, inducing reactive states in brain cells; an autoimmune response against the nervous system; the reactivation of viruses such as the Epstein-Barr virus, which can lead to neuropathology; ischemia of neural cells due to interruption of cerebral blood flow caused by cerebrovascular and thrombotic diseases; and lung and multi-organ dysfunction during the severe acute phase of the disease that can impair the functioning of neural cells.

Regarding respiratory morbidities, some studies corroborated our findings, finding an association between COPD/asthma and long COVID. In one study, there was an association between COPD (RR=1.55; 95% CI 1.47; 1.64), asthma (RR=1.15; 95% CI 1.12; 1.18) and long COVID. In another study, there was an association between longer duration of long COVID symptoms lasting ≥ 28 days (15.8%) and ≥ 56 days (18.0%) and asthma.

In a survey conducted in Suriname, 26.4% of the respondents had SAH, 13.2% had a previous diagnosis of heart disease, 56.6% experienced mild COVID-19 and 39.6% experienced at least one persistent symptom after recovery from acute SARS-CoV-2 infection.

One of the most distinguished mechanisms in the literature for the emergence of long COVID is mitochondrial dysfunction, which can have cytopathic effects on the central nervous, respiratory, circulatory, immune, renal and digestive systems. After infection with SARS-CoV-2, the binding between a viral protein and mitochondrial complexes can lead to mitochondrial dysfunction, which in turn increases oxidative stress and causes immune cells to overreact, this exacerbated reaction leads to inflammation and potentially persistent symptoms of COVID-19.

Corroborating the results of the present study, was found an association between rheumatologic diseases and long COVID, wherein 74.0% had this outcome. For musculoskeletal diseases such as osteoporosis, which was highlighted in our study, some suggestions for the involvement of the musculoskeletal system, COVID-19 and long COVID have been proposed, including the interaction of the SARS-CoV-2 spike protein with Angiotensin-Converting Enzyme 2 (ACE2), which, in addition to being present in lung tissue, is present in other tissues such as smooth muscle, cartilage and kidneys, which are also affected by the cytokine inflammation cascade, hypoxia and muscle catabolism.

Some studies have demonstrated the impact of the coronavirus pandemic on the management of osteoporosis, both for the performance of control and diagnostic tests, as well as in drug therapy, including significant reductions in the performance of bone densitometry examinations (49.0%) when compared to the first semesters of 2019 and 2020. There was also a reduction in the contact of health professionals for recommended treatment, with a range of only 29.0% and 51.7% of professionals dealing with individuals with osteoporosis reported delays in starting treatment during the COVID-19 pandemic.

Regarding cancer, they found that 60.0% of people with neoplasms reported symptoms of long COVID, with an average duration of 7-14 months after infection; fatigue (82%), sleep disturbances (78%), myalgia (67%) and gastrointestinal symptoms (61%), followed by dyspnea (47%) and cough (46%) were the most reported symptoms.

Regarding multimorbidity, a study conducted with older adults in Canada showed that having two or more morbidities had a 1.90 (95% CI 1.02-3.49) times higher risk of developing long COVID. In a multicenter, population-based survey conducted in China with 2,712 patients with a history of mild-to-severe COVID-19, a relationship was found between the presence of three or more morbidities (Odds Ratio (OR)=2.71, 95% CI 1.54-4.79) and long COVID.

Hypotheses point to the mechanism of long COVID through long-term tissue damage to organs such as the lungs, brain and heart and a pathological inflammation due to viral persistence, immune dysregulation and autoimmunity, among others, which may likely contribute to the hyperactivation of monocyte-derived macrophages in the acute and post-acute phases of the disease.

Finally, the present study had some limitations. The diagnoses of morbidities and symptoms of long COVID were self-reported, which may have underestimated the occurrence of data due to recall bias. The lack of inclusion of some important variables for adjustment, such as behavioral factors, generates residual confusion. Notably, 19 diseases included in the list of multimorbidities were not investigated; however, morbidities with the highest prevalence in the literature were investigated.

The strengths of the study include the fact that this is a population-based study with a representative sample that were mostly non-hospitalized, which reveals the relationship between morbidities and long COVID in individuals who did not develop the severe form of the disease, the mechanism of which is still poorly understood. Thus, the findings of this study reinforce the greater vulnerability of individuals with morbidities and multimorbidity to long COVID and the importance of considering that morbidities and multimorbidity should be monitored and included in strategic health plans for the population, especially in those with COVID-19.

Conclusion

It is concluded that the existence of previous morbidities and infection by the SARS-CoV-2 virus, may predispose individuals to long-term symptoms of long COVID and this experience is accentuated according to the number of preexisting morbidities. Thus, the interaction of long COVID with prior morbidities requires active investigation so that all individuals diagnosed with long COVID can access targeted health strategies. The data from this study can help us to understand the mechanisms that explain the strong relationship between morbidities/multimorbidity and long COVID.

Ethical Approval and Consent to Participate

This research involved human participants and was conducted in accordance with the pertinent guidelines and regulations of the

Declaration of Helsinki and this study protocol was approved by the Health Research Ethics Committee of the Federal University of Rio Grande (Certificate of Submission for Ethical Evaluation No. 39081120.0 .0000.5324). This study complied with the specific resolution of the National Health Council (466/2012) and informed consent was obtained from all participants in accordance with the resolution of the Free and Informed Consent Form of the National Health Council.

Consent to Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Competitive Interests

The authors declare that they have no competing interests.

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Authors' Contributions

All coauthors contributed to the manuscript's design, acquisition, analysis, and interpretation of the data, and reviewed and approved the content of the manuscript.

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