ORIGINAL ARTICLE

Seroprevalence and levels of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies among medical students: possible associated factors in Northeastern Brazil

Soroprevalência e níveis de anticorpos anti-síndrome respiratória aguda grave coronavírus 2 (SARS-CoV-2) entre estudantes de medicina: possíveis fatores associados no Nordeste do Brasil

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Abstract

Objective: we evaluated the seroprevalence and levels of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies among medical students and the possible associated factors. **Methods**: a survey was conducted using the data collected in November 2020 and February 2022 in Fortaleza, Northeast Brazil. A questionnaire was administered, and blood and nasopharyngeal swab samples were collected. The Abbott test was used for the assessment of humoral response to the SARS-CoV-2 spike (S) and nucleocapsid (N) proteins. The total antibodies were detected using a SARS-CoV-2 antibody test (Wodfo). Swab samples were subjected to qualitative detection of viral RNA. Chi-square test and multinomial logistic regression analysis were performed using SPSS and GraphPad Prism. **Results**: the seroprevalence rate in 2020 was 6.22% (40/643), and no difference in prevalence was observed between the semesters (p=0.520). The seroconversion rate was 51.1%. The seropositivity rates were 48.9% for N antibodies and 100% for S antibodies. The antibody response to N protein was higher in 2022 (p<0.001). Loss of smell was the most prevalent positive symptom (p=0.032). The adherence rate to protection measures was >75%. Most students reported a decrease in family income (63.7%), an increase in anxiety (82.6%), and a negative impact on their mental health (85.7%) regardless of the seroconversion status. The worst indicators of mental health quality were observed in students who attended classes up to the eighth semester (p<0.001). **Conclusion**: students showed lower immune response than the general population, with excellent adherence to the preventive and control measures. Medical schools played an important role in the formation but not transmission.

Keywords: covid-19; SARS-CoV-2; seroprevalence; medical students; survey.

Resumo

Objetivo: avaliamos a soroprevalência e os níveis de anticorpos anti-síndrome respiratória aguda grave coronavírus 2 (SARS-CoV-2) entre estudantes de medicina e os possíveis fatores associados. **Métodos**: foi realizada uma pesquisa com dados coletados em novembro de 2020 e fevereiro de 2022 em Fortaleza, Nordeste do Brasil. Um questionário foi aplicado e amostras de sangue e swab nasofaríngeo foram coletadas. O teste de Abbott foi utilizado para avaliação da resposta humoral às proteínas spike (S) e nucleocapsídeo (N) do SARS-CoV-2. Os anticorpos totais foram detectados usando um teste de anticorpos SARS-CoV-2 (Wodfo). Amostras de swab foram submetidas à detecção qualitativa de RNA viral. O teste qui-quadrado e a análise de regressão logística multinomial foram realizados utilizando SPSS e GraphPad Prism. **Resultados**: a taxa de soroprevalência em 2020 foi de 6,22% (40/643), e não foi observada diferença de prevalência entre os semestres (p=0,520). A taxa de soroconversão foi de 51,1%. As taxas de soropositividade foram de 48,9% para anticorpos N e 100% para anticorpos S. A resposta de anticorpos à proteína N foi maior em 2022 (p<0,001). A perda do olfato foi o sintoma positivo mais prevalente (p=0,032). A taxa de adesão às medidas de proteção foi >75%. A maioria dos estudantes relatou diminuição da renda familiar (63,7%), aumento da ansiedade (82,6%) e impacto negativo na saúde mental (85,7%), independentemente do estado de soroconversão. Os piores indicadores de qualidade em saúde mental foram observados nos alunos que frequentavam aulas até o oitavo semestre (p<0,001). **Conclusão**: os estudantes apresentaram resposta imunológica menor que a da população em geral, com excelente adesão às medidas preventivas e de controle. As escolas médicas desempenharam um papel importante na formação, mas não na transmissão.

Palavras-Chave: covid-19; SARS-CoV-2; soroprevalência; estudantes de medicina.

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Conflict of interesse: There is no conflict of interest on the part of any of the authors.
Received: 2024 Fev 1; Revised: 2024 Mar 13; Accepted: 2024 Mar 15

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in Wuhan, China, in late 2019 and soon spread to several countries[1,2]. On March 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (covid-19) as a global pandemic[3].

With the aim of reducing the speed of transmission and allowing healthcare systems to provide organized access and services, one of the main strategies adopted in Latin America was social isolation. Bars, malls, parks, schools, and universities were closed to reduce the contact between people[4,5]. After the initiation of covid-19 vaccination programs, several sectors of the economy gradually resumed operations. However, the reopening of schools and universities was not regarded as a top priority in developing and poorer countries[6,7].

Despite the high incidence of SARS-CoV-2 infection worldwide, the burden of disease in young adults during the first wave was considerably lower. This fact can lead to low concern regarding the susceptibility of the disease and decreased adherence to social distancing measures[8], thus favoring increased transmission.

At the beginning of the pandemic, the prevalence of cases among the university population was relatively high in some countries, including Brazil[9,10,11]. Addressing adherence to preventive measures against SARS-CoV-2 infection among university students may be particularly important, as existing evidence shows that the high prevalence of SARS-CoV-2 infection among individuals aged 18–24 years precedes the high prevalence of this infection in the rest of the population[12,13,14,15]. Furthermore, university medical students who begin training in the healthcare setting may be at increased risk. Thus, surveillance of antibody seropositivity in specific populations can be useful to target control measures.

This study mainly aimed to measure the seroprevalence of anti-SARS-CoV-2 antibodies among medical students before and after vaccination. We also assessed their mental health during the pandemic and identified the possible factors associated with this infection.

METHODS

Population, design and local of study

The study had two phases and involved medical students from a university center (Unichristus) located in Fortaleza, Northeastern Brazil, in different course periods.

First phase. From November 7 to 11th, 2020, the students were invited to answer an analytical cross-sectional survey with clinical, behavioral, and epidemiological data and underwent a collection of diagnostic tests for covid-19. Population characteristics investigated in the survey belong to demographic data, mental health status, housing conditions, and lifestyle. Data on the status of academic/professional activities, clinical data, and presence of covid-19 symptoms. Finally, they were asked about their knowledge of covid-19 transmission, individual protection measures, and prevention and care for the disease. This phase happened after the first wave, before vaccination, and before the resumption of face-to-face classes. An email explaining the aim and nature of the study was sent to approximately 1,400 students, with a link to the Google Form to be answered. Those who agreed to participate in the study were scheduled for blood sample collection and nasopharyngeal swabs.

Second phase. From February 17 to 23rd, 2022, a subsample of 10% of the first phase participants were randomly invited for new data collection. Humoral response for SARS-CoV-2 antigens was determined using blood, and nasopharyngeal swabs were collected again. This phase happened after the implementation of vaccination programs and the third wave of the disease.
Testings

Blood samples were centrifuged at 2,500 rpm for 10 min, frozen at −20°C and later transported to the Clinical Analysis Laboratory of the Unichristus University Center and to the laboratory of the covid-19 Diagnosis Support Unit of the Oswaldo Cruz Foundation (FIOCRUZ), in Fortaleza, where they were tested.

First phase. For reverse transcription polymerase chain reaction (RT-PCR), the samples were collected using nasal swabs, according to the protocol of the Brazilian Ministry of Health. For the detection of total antibodies, an immunochromatographic assay was used for rapid and qualitative detection of IgG/IgM antibodies against SARS-CoV-2 in whole blood, serum, or human plasma samples, using Wondfo brand SARS-CoV-2 antibody test (Wondfo Biotech Co., Guangzhou, China). A covid-19 case was defined as anyone who tested positive in at least one of these reactive or detection tests.

Second phase. As all the students were vaccinated in the second phase, they were tested against IgG against SARS-CoV-2 spike protein (S) (using samples of both phases), which can be positive after covid-19 or after a vaccine against covid-19. They were also tested using nasal swabs for RT-PCR. A subsample of the students also had IgG against SARS-CoV-2 nucleocapsid protein (N) determined in samples collected after the first and third waves, which can be positive only if the patient was exposed to SARS-CoV-2 in Brazil at that moment (as the vaccines used were not able to stimulate immunity against N protein). These assays were performed using Abbott Architect i2000SR (Abbott Diagnostics, Abbott Park, IL, USA).

Data analysis

The collected data were stored in the IBM SPSS Statistics for Windows version 20.0. The association between the frequency of seroconversion to covid-19 in the first wave

and other variables was assessed using Pearson's chi-square or Fisher's exact test. Variables with significant associations were included in the multinomial logistic regression model. The adjusted odds ratios and 95% confidence intervals (CIs) were used to determine the factors independently associated with IgG seroconversion to covid-19. In the antibody analysis, the data variables were considered non-normally distributed, and statistical analysis was performed using medians and interquartile ranges for continuous variables and frequency and percentage values for qualitative variables. Repeated measures analysis of variance was conducted to assess the differences in antibody titers over time. The Mann-Whitney U test was used for group comparisons. Statistical analyses were performed using GraphPad Prism (version 5.0). The matrix of antibodies was imported into the Morpheus program (https://software.broadinstitute.org/morpheus/), and the results were illustrated as a three-dimensional dendrogram (heat map). A p-value of <0.05 was considered significant.

Ethical aspects

The study was approved by the Research Ethics Committee of Christus University Center (CAAE 39691420.7.0000.5049).

RESULTS

A total of 749 online questionnaires were completed. Of these, 106 (14.2%) were excluded after removing duplicates, questionnaires that did not contain the examination results, and questionnaires that did not contain sufficient data. Data from 643 medical students were analyzed. Most students were women (65.2%), white (61.1%), with a median age of 21 years (range: 18–47), and single (88.6%). The study included participants from all over the course (Table 1).

Table 1. Socioeconomic conditions of medical students during the first wave of the covid-19 pandemic in the city of Fortaleza, Brazil

Variables	Total N (%)	Positive for covid-19		p-valor	Multinomial logistic regression	
		Yes N (%)	No N (%)		Ajusted OR (CI95%)	p value
Have a health plan						
No	88 (13.7)	82 (13.6)	6 (15.0)	0.803	-	-
Yes	555 (86.3)	521 (86.4)	34 (85.0)		RC	
Age						
<30 years	568 (88.5)	537 (89.1)	31 (79.5)	0.070	-	-
>30 years	74 (11.5)	66 (10.9)	8 (20.5)		RC	
Race/color						
Yellow	9 (1.4)	9 (100.0)	0 (0.0)	0.0842	-	-
White	393 (61.1)	370 (94.2)	23 (5.8)		-	
Brown	221(34.4)	205 (92.8)	16 (7.2)		-	
Black	13 (2.0)	12 (92.3)	1 (7.7)		-	
Ignored	7 (1.1)	7 (100.0)	0 (0.0)		RC	
Semester in progress						
1	56 (8.7)	50 (8.3)	6 (15.0)	0.001	0.97 (0.09-9.97)	0.986
2	68 (10.6)	66 (10.9)	2 (5.0)		-	
3	65 (10.1)	63 (10.4)	2 (5.0)		-	
4	84 (13.1)	80 (13.3)	4 (10.0)		-	
5	70 (10.9)	69 (11.4)	1 (2.5)		-	
6	80 (12.4)	72 (11.9)	8 (20.0)		-	
7	83 (12.9)	82 (13.6)	1 (2.5)		-	
8	61 (9.5)	51 (8.5)	10 (25.0)		-	
9	27 (4.2)	26 (4.3)	1 (2.5)		-	
10	31 (4.8)	26 (4.3)	5 (12.5)		-	
11	9 (1.4)	9 (1.5)	0 (0.0)		-	
12	9 (1.4)	9 (1.5)	0 (0.0)		RC	

Variables	Total N (%)	Positive for covid-19		p-valor	Multinomial logistic regression	
		Yes N (%)	No N (%)		Ajusted OR (CI95%)	p value
Transportation used to go to school						
Bicycle	4 (0.6)	4 (0.7)	0 (0.0)	0.521	-	-
Ride with college classmates	81 (12.6)	79 (13.1)	2 (5.0)		-	
Car alone	435 (67.7)	403 (66.8)	32 (80.0)		-	
Motorcycle with coworker	3 (0.5)	3 (0.5)	0 (0.0)		-	
Motorcycle alone	6 (0.9)	5 (0.8)	1 (2.5)		-	
Public transport	50 (7.8)	48 (8.0)	2 (5.0)		-	
Others	64 (10.0)	61 (10.1)	3 (7.5)		RC	
Type of housing						
House	179 (27.8)	167 (27.7)	12 (30.0)	0.753	-	-
Apartment	464 (72.2)	436 (72.3)	28 (70.0)		RC	
Living condition						
Living with college friends	11 (1.7)	11 (1.8)	0 (0.0)	0.689	-	-
Living alone	49 (7.6)	46 (7.6)	3 (7.5)		-	
Living with the family	583 (90.7)	546 (90.5)	37 (92.5)		RC	

* p<0.05, Fisher's exact test or Pearson's chi-square (n, %)

Most of the university students had private health plans (86.3%). Most of them lived with their families (90.8%), were residing in 81 different neighborhoods in Fortaleza (66.9%), and had an average family income of 12 minimum wages. All students had Internet access at home (100.0%), and most of them had full access to piped water (99.8%), systematic garbage collection services (99.5%), and basic sanitation services (98.9%). The most used means of transportation to go to school was their own car (45.9%), followed by public transport (31.9%) (Table 1).

In the first phase, students from all semesters were interviewed: 567 (99.2%) from the basic cycle (first to eighth semesters) and the other 76 (11.8%) belonging to the assistance cycle (9th to 12th semesters). A total of 40 students (6.22%) showed positive results in at least one of the tests, and no difference was observed in the positivity rate between different semesters (p=0.520). In the first phase of data collection, 11 students had detectable RT-PCR results, 24 were positive for IgG, 4 had positive rapid tests, and 1 had positive results on rapid and IgG tests. Most respondents reported not having anyone with covid-19 at home (57.6%), while 68.4% reported knowing someone who had died from covid-19.

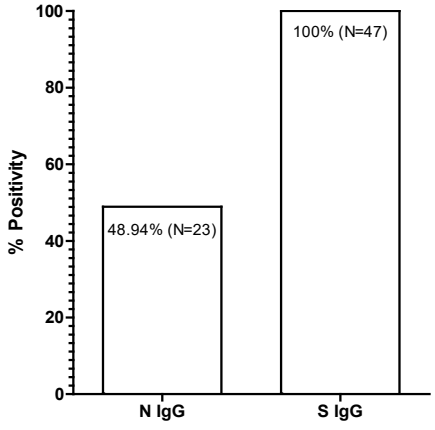
The students were vaccinated with the first dose between January 23 and August 21, 2021. The second dose was administered between March 20 and November 8. The students received Pfizer or AstraZeneca vaccines, and 28 tested negative for IgG and anti-N in the second phase of the research. All students in the second phase received at least two doses. As of February 23, 2022, 54.8% had already received a booster dose of the vaccine.

In the second phase, immediately after the peak of the third wave in Fortaleza, all students had IgG anti-S tests with positive results; among the 72 participants with positive test results, 63 (87.5%) initially yielded a negative result during the first survey. None of the RT-PCR was positive.

Antibody response

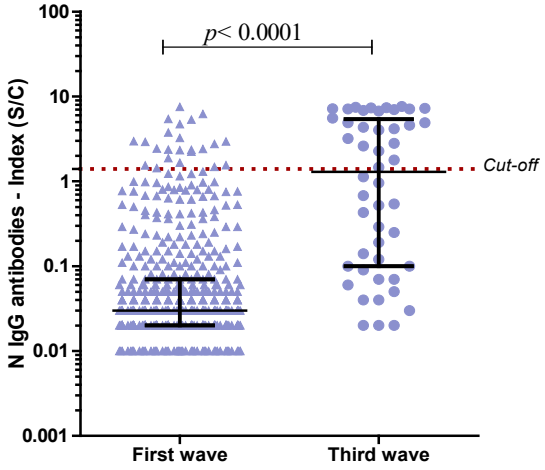
We evaluated the IgG antibody response to S and N proteins at two different time points after the first and third waves of the covid-19 pandemic. The seroconversion rate was 51.1% when the participants from both phases were included (n=47). The seropositivity rates were 48.9% for N antibodies (n=23) and 100% for S antibodies (n=47) after the third wave (Figure 1).

Figure 1. S and N IgG seropositivity in a cohort of students after the third wave of covid-19 in Fortaleza, Ceará, Brazil.



The antibody response to the N protein was higher after the third wave than after the first wave (p<0.0001) (Figure 2). The antibody levels against the N protein are shown in Figure 2.

Figure 2. Anti-N IgG levels in a cohort of students after the first and third waves of the covid-19 pandemic in Fortaleza, Ceará, Brazil. Black lines indicate the median levels, while error bars indicate the interquartile ranges; the horizontal dotted lines indicate the cutoff values. Statistical analysis was performed using the Mann-Whitney test. S/C, signal-to-cutoff ratio.



Clinical features of covid-19 symptoms

Most students believed that they did not have covid-19 (85.5%). The positivity rate was higher among those who believed they had covid-19 (p<0.001). However, among the 40 covid-19 positive students, 16 (40%) were unaware that they were previously infected.

The most reported symptoms in the first wave were headache, loss of smell, and taste (59.2%, 58.3%, and 49.5%, respectively). Only loss of smell was significantly more prevalent among covid-19-positive students (p=0.032).

Most patients did not seek medical assistance (56.0%), and the most commonly used drugs were dipyrone (54.4%), ivermectin (51.7%), and azithromycin (43.3%). Only zinc use was significantly associated with positive cases (p=0.001), while non-use of dipyrone was associated with positivity (p=0.007) (Table 2). In the multivariate analysis, seroconversion was inversely associated with dipyrone consumption (p=0.007) and directly related to loss of smell during the first wave of the pandemic (p=0.032).

Table 2. Signs, symptoms, and medications taken by medical students during the first wave of the covid-19 pandemic in the city of Fortaleza, Brazil

Variables	Total N (%)	Positive for covid-19		p-valor	Multinomial logistic regression	
		Yes N (%)	No N (%)		Ajusted OR (CI95%)	p value
Do you think you had covid-19?						
No	552 (85.8)	536 (88.9)	16 (40.0)	0.000	0.80 (0.15-2.16)	1.000
Yes	91 (14.2)	67 (11.1)	24 (60.0)			
Have any of the signs and symptoms						
Sore throat						
No	57 (55.3)	42 (52.5)	15 (65.2)	0.280	-	-
Yes	46 (44.7)	38 (47.5)	8 (34.8)		RC	
Skin rash or discoloration of fingers or toes						
No	98 (95.1)	76 (95.0)	22 (95.7)	0.898	-	-
Yes	5 (4.9)	4 (5.0)	1 (4.3)		RC	
Chest pain or pressure						
No	98 (94.2)	77 (96.3)	21 (87.5)	0.107	-	-
Yes	6 (5.8)	3 (3.8)	3 (12.5)		RC	
Dyspnea						
No	87 (84.5)	68 (85.0)	19 (82.6)	0.780	-	-
Yes	16 (15.5)	12 (15.0)	4 (17.4)		RC	
Difficulty breathing or shortness of breath						
No	83 (80.6)	65 (81.3)	18 (78.3)	0.749	-	-
Yes	20 (19.4)	15 (18.8)	5 (21.7)		RC	

Variables	Total N (%)	Positive for covid-19		p-valor	Multinomial logistic regression	
		Yes N (%)	No N (%)		Ajusted OR (CI95%)	p value
Loss of taste						
No	52 (50.5)	44 (55.0)	8 (34.8)	0.087	-	-
Yes	51 (49.5)	36 (45.0)	15 (65.2)		RC	
Headache						
No	42 (40.8)	34 (42.5)	8 (34.8)	0.507	-	-
Yes	61 (59.2)	46 (57.5)	15 (65.2)		RC	
Loss of smell						
No	43 (41.7)	38 (47.5)	5 (21.7)	0.027	4.72 (1.15-19.45)	0.032
Yes	60 (58.3)	42 (52.5)	18 (78.3)		RC	
Diarrhea						
No	74 (71.8)	57 (71.3)	17 (73.9)	0.802	-	-
Yes	29 (28.2)	23 (28.8)	6 (26.1)		RC	
Conjunctivitis						
No	101 (98.1)	79 (98.8)	22 (95.7)	0.343	-	-
Yes	2 (1.9)	1 (1.3)	1 (4.3)		RC	
Did you seek medical attention?						
No	61 (56.0)	51 (59.3)	10 (43.5)	0.175	-	-
Yes	48 (44.0)	35 (40.7)	13 (56.5)		RC	
Took some of the medications below						
Ivermectin						
No	43 (48.3)	34 (51.5)	9 (39.1)	0.306	-	-
Yes	46 (51.7)	32 (48.5)	14 (60.9)		RC	
Paracetamol						
No	73 (81.1)	54 (80.6)	19 (82.6)	0.832	-	-
Yes	17 (18.9)	13 (19.4)	4 (17.4)		RC	
Predinizone						
No	65 (72.2)	52 (77.6)	13 (56.5)	0.051	-	-
Yes	25 (27.8)	15 (22.4)	10 (43.5)		RC	
Zinc						
No	66 (73.3)	55 (82.1)	11 (47.8)	0.001	3.10 (0.72-13.38)	0.129
Yes	24 (26.7)	12 (17.9)	12 (52.2)			
Chloroquine						
No	81 (90.0)	62 (92.5)	19 (82.6)	0.171	-	-
Yes	9 (10.0)	5 (7.5)	4 (17.4)		RC	
Azithromycin						
No	51 (56.7)	41 (61.2)	10 (43.5)	0.139	-	-
Yes	39 (43.3)	26 (38.8)	13 (56.5)		RC	
Dipyrone						
No	41 (45.6)	25 (37.3)	16 (69.6)	0.007	0.09 (0.02-0.53)	0.007
Yes	49 (54.4)	42 (62.7)	7 (30.4)			

* p<0.05, Fisher's exact test or Pearson's chi-square (n, %)

Adherence to protective measures, lifestyle and mental health

The adherence rate to protective measures remained higher than 75%, and more than 90% knew the primary methods of protection. No variables related to adherence to control measures were associated with infection prevalence (p>0.05). More than half of the students (55.8%) had not received the flu vaccine at the time of research, regardless of whether they were positive for covid-19 or not (Table 3).

Table 3. Adherence to medical students' protection measures during the first wave of the covid-19 pandemic in the city of Fortaleza, Brazil

Variables	Total	Positive for covid-19		p-valor	Multinomial logistic regression	
		No N (%)	Yes N (%)		Ajusted OR (CI95%)	p value
Did you isolate yourself at home during the onset of symptoms?						
No	8 (8.8)	7 (10.4)	1 (4.2)	0.351	-	-
Yes	83 (91.2)	60 (89.6)	23 (95.8)		RC	
When you leave the house, do you wear a mask?						
Never	4 (0.6)	4 (0.7)	0 (0.0)	0.543	-	-
Sometimes	17 (2.6)	17 (2.8)	0 (0.0)		-	
Often	96 (14.9)	88 (14.6)	8 (20.0)		-	
Ever	526 (81.8)	494 (81.9)	32 (80.0)		RC	
How often do you wash your hands with soap and water?						
Never	2 (0.3)	2 (0.3)	0 (0.0)	0.789	-	-
Sometimes	115 (17.9)	110 (18.2)	5 (12.5)		-	
Often	336 (52.3)	313 (51.9)	23 (57.5)		-	
Ever	190 (29.5)	178 (29.5)	12 (30.0)		RC	
When social isolation measures were imposed by the health authorities, did you maintain social distancing?						
Very little	11 (1.7)	11 (1.8)	0 (0.0)	0.697	-	-
Little	16 (2.5)	14 (2.3)	2 (5.0)		-	
So-so	139 (21.6)	132 (21.9)	7 (17.5)		-	
Quite	353 (54.9)	330 (54.7)	23 (57.5)		-	
Virtually isolated from the world	124 (19.3)	116 (19.2)	8 (20.0)		RC	
What is your routine during isolation?						
Stay at home all the time	143 (22.4)	134 (22.4)	9 (22.5)	0.830	-	-
Go out only to buy essential items, like food or medications	345 (54.0)	325 (54.3)	20 (50.0)		-	
Go out every now and then to buy food and stretch your legs	104 (16.3)	97 (16.2)	7 (17.5)		-	
Go out every day to perform some activities	21 (3.3)	20 (3.3)	1 (2.5)		-	
Going out every day, all day, to work or to perform other routine activities	26 (4.1)	23 (3.8)	3 (7.5)		RC	
Thinking about your home routine, who has been entering the house during the isolation period?						
Only those who live in the house and no one else	198 (31.9)	185 (31.7)	13 (35.1)	0.750	-	-

Variables	Total	Positive for covid-19		p-valor	Multinomial logistic regression	
		No N (%)	Yes N (%)		Ajusted OR (CI95%)	p value
Some close relatives visit 1–2 times a week.	265 (42.7)	250 (42.9)	15 (40.5)		-	
Some close relatives visit almost every day.	37 (6.0)	35 (6.0)	2 (5.4)		-	
Friends, distant relatives, or others visit 1–2 times a week.	97 (15.6)	90 (15.4)	7 (18.9)		-	
Friends, distant relatives, or others visit every day.	23 (3.7)	23 (3.9)	0 (0.0)		RC	
Protective measures						
Younger age						
No	550 (85.5)	514 (85.2)	36 (90.0)	0.407	-	-
Yes	93 (14.5)	89 (14.8)	4 (10.0)		RC	
Wearing a facemask						
No	50 (7.8)	48 (8.0)	2 (5.0)	0.498	-	-
Yes	593 (92.2)	555 (92.0)	38 (95.0)		RC	
Avoidance of touching the mouth with bare hands						
No	64 (10.0)	58 (9.6)	6 (15.0)	0.271	-	-
Yes	579 (90.0)	545 (90.4)	34 (85.0)		RC	
Not being close to other people						
No	204 (31.7)	192 (31.8)	12 (30.0)	0.809	-	-
Yes	439 (68.3)	411 (68.2)	28 (70.0)		RC	
Avoiding direct contact with people with suspected covid-19						
No	154 (24.0)	142 (23.5)	12 (30.0)	0.355	-	-
Yes	489 (76.0)	461 (76.5)	28 (70.0)		RC	
Hand washing						
No	37 (5.8)	35 (5.8)	2 (5.0)	0.832	-	-
Yes	606 (94.2)	568 (94.2)	38 (95.0)		RC	
Application of alcohol gel to clean the hands						
No	76 (11.8)	72 (11.9)	4 (10.0)	0.713	-	-
Yes	567 (88.2)	531 (88.1)	36 (90.0)		RC	
Use of chloroquine						
No	626 (97.4)	587 (97.3)	39 (97.5)	0.953	-	-
Yes	17 (2.6)	16 (2.7)	1 (2.5)		RC	
Did you get the flu shot in 2020?						
No	359 (55.8)	334 (55.4)	25 (62.5)	0.381	-	-
Yes	284 (44.2)	269 (44.6)	15 (37.5)		RC	

* p<0.05, Fisher's exact test or Pearson's chi-square (n, %)

Most students reported a decrease in family income (63.7%), increased anxiety (82.6%), and a negative impact on their mental health (85.7%) during the first wave of the disease, regardless of the seroconversion status. Among those who had consumed alcohol before the pandemic, 36.1% reported an increase in their consumption. More than half of them knew someone who had covid-19 or who died of the disease. None of these variables was associated with seroconversion (Table 4).

Table 4. Change in life and mental health of medical students during the first wave of the covid-19 pandemic in the city of Fortaleza, Brazil

Variables	Total N (%)	Positive for covid-19		p-value	Multinomial logistic regression	
		No N (%)	Yes N (%)		Ajusted OR (CI95%)	p-value
Has your family income decreased after the new coronavirus pandemic?						
No	200 (36.3)	187 (36.5)	13 (34.2)	0.782	-	-
Yes	351 (63.7)	326 (63.5)	25 (65.8)		RC	
In this time of social isolation did you feel greater anxiety?						
No	112 (17.4)	107 (17.7)	5 (12.5)	0.397	-	-
Yes	531 (82.6)	496 (82.3)	35 (87.5)		RC	
Do you think your mental health has had an impact during social isolation?						
No	92 (14.3)	88 (14.6)	4 (10.0)	0.422	-	-
Yes	551 (85.7)	515 (85.4)	36 (90.0)		RC	
Do you think you caught covid-19 from someone you know?						
No	15 (16.5)	11 (16.4)	4 (16.7)	0.978	-	-
Yes	76 (83.5)	56 (83.6)	20 (83.3)		RC	
Do you live in the same house as people at risk for covid-19?						
No	224 (34.8)	213 (35.3)	11 (27.5)	0.315	-	-
Yes	419 (65.2)	390 (64.7)	29 (72.5)		RC	
Did someone in your household have laboratory-confirmed covid-19 shortly before you?						
No	490 (76.2)	468 (77.6)	22 (55.0)	0.001	2.95 (0.81-10.82)	0.102
Yes	153 (23.8)	135 (22.4)	18 (45.0)			
Has anyone in your class/class had laboratory-confirmed covid-19?						
No	76 (11.8)	68 (11.3)	8 (20.0)	0.098	-	-
Yes	567 (88.2)	535 (88.7)	32 (80.0)		RC	
Has anyone you know from college had laboratory-confirmed covid-19?						
No	66 (10.3)	59 (9.8)	7 (17.5)	0.119	-	-
Yes	577 (89.7)	544 (90.2)	33 (82.5)		RC	
Did you know someone who died due to covid-19?						
No	231 (35.9)	218 (36.2)	13 (32.5)	0.641	-	-
Yes	412 (64.1)	385 (63.8)	27 (67.5)		RC	
Smoker						
No	614 (95.5)	578 (95.9)	36 (90.0)	0.084	-	-
Yes	29 (4.5)	25 (4.1)	4 (10.0)		RC	

Variables	Total N (%)	Positive for covid-19		p-value	Multinomial logistic regression	
		No N (%)	Yes N (%)		Ajusted OR (CI95%)	p-value
Smoke frequency						
Non-smoker	606 (94.2)	571 (94.7)	35 (87.5)	0.002	0.32 (0.02-4.52)	0.397
Passive smoker	4 (0.6)	4 (0.7)	0 (0.0)		-	
Smoking when drinking alcohol	10 (1.6)	10 (1.7)	0 (0.0)		-	
Sporadically	16 (2.5)	11 (1.8)	5 (12.5)		RC	
Every day	4 (0.6)	4 (0.7)	0 (0.0)		-	
Many times a day	3 (0.5)	3 (0.5)	0 (0.0)		-	
Alcohol						
No	178 (27.7)	167 (27.7)	11 (27.5)	0.979	-	-
Yes	465 (72.3)	436 (72.3)	29 (72.5)		RC	
Pandemic increased alcohol consumption						
No	293 (63.4)	275 (63.5)	18 (62.1)	0.876	-	-
Yes	169 (36.6)	158 (36.5)	11 (37.9)		RC	
Physical activity						
No	191 (29.7)	177 (29.4)	14 (35.0)	0.449	-	-
Yes	452 (70.3)	426 (70.6)	26 (65.0)		RC	

* p<0.05, Fisher's exact test or Pearson's chi-square (n, %)

The worst indicators of a decline in mental health quality during the first wave were observed in students who attended up to the eighth semester compared with the students belonging to the assistance cycle (9th to 12th semesters) (p<0.001) (Table 5). The positivity rate was higher among the students in the front line of care and treated patients suspected of covid-19 in outpatient clinics or emergency rooms (p<0.001). Most positive students knew about the probable transmitter of the disease (p<0.001). However, the positivity rate was lower among those who received the flu vaccine (p<0.001).

Table 5. Mental health of medical students during the first wave of the covid-19 pandemic in the city of Fortaleza, Brazil

Variables	Total	Semester		p-value	Multinomial logistic regression	
		1 - 8	9 - 12		Ajusted OR (CI95%)	p-value
Have you ever returned to any in-person activities at college during the pandemic?						
No	39 (5.3)	8 (1.3)	31 (30.1)	<0.001	0.98 (0.09-9.80)	0.994
Yes	693 (94.7)	621 (98.7)	72 (69.9)		RC	
Have you returned to the practical activities that are carried out at UBS, CES, UPAS etc.?						
No	15 (2.0)	14 (2.2)	1 (1.0)	0.405	-	-
Yes	717 (98.0)	615 (97.8)	102 (99.0)		RC	
In the last 15 days, were you in a health unit that was a reference for the care of patients with covid-19? (as student)						
No	422 (57.7)	388 (61.7)	34 (33.0)	<0.001	0.01 (0.00-1.41)	0.067
Yes	310 (42.3)	241 (38.3)	69 (67.0)		RC	
COVID care as an outpatient student						
No	621 (84.8)	564 (89.7)	57 (55.3)	<0.001	1.77 (0.03-9.18)	0.777

Variables	Total	Semester		p-value	Multinomial logistic regression	
		1 - 8	9 - 12		Ajusted OR (CI95%)	p-value
Yes	111 (15.2)	65 (10.3)	46 (44.7)		RC	
COVID care as an emergency student						
No	680 (92.9)	592 (94.1)	88 (85.4)	0.001	1.08 (0.24-4.88)	0.221
Yes	52 (7.1)	37 (5.9)	15 (14.6)		RC	
COVID care as an ICU student						
No	702 (95.9)	602 (95.7)	100 (97.1)	0.513	-	-
Yes	30 (4.1)	27 (4.3)	3 (2.9)		RC	
COVID service as a UBS student						
No	511 (69.8)	430 (68.4)	81 (78.6)	0.035	3.69 (0.30-4.61)	0.143
Yes	221 (30.2)	199 (31.6)	22 (21.4)		RC	
COVID service as a UPA student						
No	715 (97.7)	619 (98.4)	96 (93.2)	0.001	0.33 (0.03-3.33)	1.000
Yes	17 (2.3)	10 (1.6)	7 (6.8)		RC	
COVID service as a student testing center						
No	730 (99.7)	627 (99.7)	103 (100.0)	0.567	-	-
Yes	2 (0.3)	2 (0.3)	0 (0.0)		RC	
Have you been on the front lines of caring for covid-19 patients?						
No	667 (91.1)	604 (96.0)	63 (61.2)	<0.001	1.16 (0.11-11.60)	0.993
Yes	65 (8.9)	25 (4.0)	40 (38.8)		RC	
Do you think you caught covid-19 from someone you know?						
No	23 (20.5)	16 (16.5)	7 (46.7)	0.007	1.03 (0.16-6.70)	0.972
Yes	89 (79.5)	81 (83.5)	8 (53.3)		RC	
Did you isolate yourself at home during the period of symptoms?						
No	9 (8.0)	5 (5.2)	4 (26.7)	0.004	0.72 (0.05-10.52)	0.808
Yes	103 (92.0)	92 (94.8)	11 (73.3)		RC	
Has anyone in your household had laboratory-confirmed covid-19?						
No	549 (75.0)	465 (73.9)	84 (81.6)	0.098	-	-
Yes	183 (25.0)	164 (26.1)	19 (18.4)		RC	
Has anyone in your class/class had laboratory-confirmed covid-19?						
No	86 (11.7)	78 (12.4)	8 (7.8)	0.176	-	-
Yes	646 (88.3)	551 (87.6)	95 (92.2)		RC	
Has anyone you know from college had lab-confirmed covid-19?						
No	72 (9.8)	70 (11.1)	2 (1.9)	0.004	0.40 (0.06-2.75)	0.352
Yes	660 (90.2)	559 (88.9)	101 (98.1)		RC	
Did you know someone who passed away from covid-19?						
No	258 (35.2)	231 (36.7)	27 (26.2)	0.038	1.16 (0.25-5.45)	0.848
Yes	474 (64.8)	398 (63.3)	76 (73.8)		RC	

Variables	Total	Semester		p-value	Multinomial logistic regression	
		1 - 8	9 - 12		Ajusted OR (CI95%)	p-value
Sleep problems						
I had sleep problems but they subsided.	11 (1.5)	10 (1.6)	1 (1.0)	0.227	-	-
I keep sleeping well	173 (23.6)	139 (22.1)	34 (33.0)		-	
did not affect anything	150 (20.5)	128 (20.3)	22 (21.4)		-	
With the pandemic, I started having sleep problems	168 (23.0)	148 (23.5)	20 (19.4)		-	
I already had sleep problems and they continued the same	95 (13.0)	85 (13.5)	10 (9.7)		-	
I already had sleep problems and they got a lot worse	135 (18.4)	119 (18.9)	16 (15.5)		RC	
During the social isolation decreed by the health authorities, were you able to do social distancing?						
Very little	13 (1.8)	9 (1.4)	4 (3.9)	0.060	-	-
Little	20 (2.7)	15 (2.4)	5 (4.9)		-	
So-so	156 (21.3)	132 (21.0)	24 (23.3)		-	
Quite	408 (55.8)	349 (55.6)	59 (57.3)		-	
Virtually isolated from the world	134 (18.3)	123 (19.6)	11 (10.7)		RC	
Isolation routine						
stay at home all the time	159 (21.8)	153 (24.5)	6 (5.8)	<0.001	0.88 (0.08-1.88)	0.992
Go out only for essentials, like shopping for food or a pharmacy	392 (53.8)	338 (54.1)	54 (52.4)		-	
Go out every now and then to buy food and stretch your legs	122 (16.8)	106 (17.0)	16 (15.5)		-	
Go out every day for some activity	23 (3.2)	16 (2.6)	7 (6.8)		-RC	
Going out every day, all day, to work or other regular activity	32 (4.4)	12 (1.9)	20 (19.4)			
Thinking about the routine of the house, who has been entering the house?						
Only those who live in the house and no one else	224 (31.6)	191 (31.4)	33 (32.7)	0.613	-	-
Some close relatives visit 1-2 times a week	301 (42.5)	259 (42.6)	42 (41.6)		-	
Some close relatives visit almost every day	44 (6.2)	35 (5.8)	9 (8.9)		-	
Friends, distant relatives or others who visit 1-2 times a week	112 (15.8)	97 (16.0)	15 (14.9)		-	
Friends, distant relatives or others who visit every day	28 (3.9)	26 (4.3)	2 (2.0)		RC	
Had the flu vaccine						
No	401 (54.8)	364 (57.9)	37 (35.9)	<0.001	0.46 (0.11-2.02)	0.306
Yes	331 (45.2)	265 (42.1)	66 (64.1)			

* p<0.05, Fisher's exact test or Pearson's chi-square (n, %)

DISCUSSION

Through this study, a group of students had behaviors, knowledge, symptoms, and mental health related to covid-19 measured. Furthermore, a seroprevalence study was carried out, which brought interesting conclusions about the behavior of the disease in students at different stages of the course.

Our results provide information on the prevalence of and factors associated with SARS-CoV-2 infection in university medical students shortly after the first wave of the disease and before returning to face-to-face classes. In the first phase of our study, the immune response related to this infection was lower in university medical students than in the general population

of Fortaleza, as previously described[16]. These findings can be compared with those of other prevalence studies; however, it is necessary to understand the local epidemiological scenario and the period after autochthonous transmission so the data can be compared fairly.

The highest levels of IgG-N were observed after the third wave when most of the participants were infected. IgG N appears to be induced mainly by infection, as reported by Fonseca et al.[17]. Viral N protein is a highly conserved nucleoprotein with functions associated with viral replication and is abundantly expressed during infection[18]. Thus, the high replication capacity of the Omicron variant could have allowed repeated exposure of immune cells to the N protein, explaining the high levels of N antibodies.

Among all symptoms reported during the first wave, loss of smell was the most likely to be associated with positivity for covid-19; students who were in the front line of care at the healthcare facilities were more likely to show positive results on first covid-19 testing. Students demonstrated sufficient knowledge of individual protective measures, strictly implemented social isolation rules, and had good adherence to control measures. Less than 2% of students were found to be infected after performing an RT-PCR between November 7 and 11, 2020. At that time, face-to-face classes had not yet been authorized, even with a >25% reduction in the cases and deaths in Ceará[19]. Certainly, this low positivity rate among the tested students, the reduction of cases and deaths in the general population, and the educational damage caused by the prolonged suspension of face-to-face classes in schools contributed, in an important way, to the decision to resume face-to-face classes in that period. The study conducted among students at the University of Cambridge, United Kingdom, in November 2020 also showed low positivity rates, suggesting that student participation in social events with large numbers of people was strongly linked to greater exposure to SARS-CoV-2[20].

Our study sample had a higher proportion of women, which was similar to that in other studies involving university medical students conducted in different countries[20,21]. However, no difference was observed in the positivity rates between the sexes. Furthermore, no difference was observed in terms of students' age; the majority of the sample were young people who demonstrated higher mobility and socialization, thus facilitating the spread of the disease as they tend to have milder symptoms when infected[11]. No difference was also found in the positivity rates between male and female students according to the semester, which suggests that the location of classes itself was not the main site of infection. This finding was not observed in other Brazilian cities when the undergraduates were compared with the medical residents[22]. It is probably due to the longer length of stay of residents in healthcare units compared with those still taking undergraduate courses, which increases the chance of exposure to the virus through greater contact with people known to be sick. A study conducted on medical students in Copenhagen showed that frequent participation in parties increased the risk of infection compared with the time spent in the classroom.

Another important aspect was the adherence of the public to individual protective measures, such as the use of masks and frequent hand washing. The students had an adherence rate of >90%. Similar data have been reported for university students from Guangdong, China[24]. However, the adherence rate varied. Medical students in Egypt showed low adherence to the use of masks, suggesting that adherence to the use of personal protective equipment (PPE) can be influenced by the local culture, the dissemination of educational information, the period of the pandemic, and the respective decrees implemented[24,25]. Another study conducted in Brazil showed that more than 10% of university students were hesitant to receive the vaccine[26], which is worrisome considering the high educational level of the interviewees.

When the rate of adherence to surveillance measures and physical contact restriction was assessed, we obtained more encouraging results compared with that in other Brazilian studies involving the general population[27]. It was probably due to the fact that we interviewed people with a higher level of education, as they are medical students and have sufficient knowledge about the proper use of PPE[28]. Another study conducted among university students in Brazil suggested that the suspension of face-to-face classes and the necessity of those students who lived in the university dormitories to return to their respective homes contributed to the increase in contact with infected people in the community and the greater spread of the virus. However, a survey conducted among English university students showed a higher risk of infection among those who stayed in university dormitories[29].

The most frequently reported symptoms were headache, loss of smell, and taste alteration. Our result was slightly different from those of other studies. It is due to the following factors: age of the investigated participants; sufficiency of data collected from surveys or healthcare facilities; non-determination of the severity of cases; whether any of the study participants were hospitalized; whether these events occurred during the first, second, or third wave of the disease; and vaccination status of the participants[7,21,27,28,29,30]. These situations can alter an individual's perception of reported symptoms. Reporting of symptoms may suggest the individual's ability to express self-reported sensations since education is also an important factor in understanding their symptoms and seeking treatment; that is, the individual's perception of illness is also important for the relevance of the analysis data on symptoms[31].

The use of online questionnaires and the fact that the participants were chosen through convenience sampling, even though it was considered a limitation, should not interfere with the results due to the strong desire of students to undergo the tests that were not readily available at that time. To further reduce the limitations of the application of remote questionnaires, they were only used within a short period of time. Moreover, the

tests performed can yield false negative results for individuals who were recently infected, especially in the first 15 days after developing the infection. In addition, when the samples were collected, P1 was still not widespread in Ceará.

In light of these findings, the medical schools seem to have played an important role in the formation, but not in the transmission, of SARS-CoV-2. A cautious interpretation, as suggested by a study that followed students in Germany, did not tend to support the closure of medical schools as a strategy to combat the pandemic in a low-prevalence scenario.

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How to cite this article/ Como citar este artigo:
Coelho TM, Saldanha AL, Julião MR, Brasil LF, Araújo FM, Fonseca MH, et al. Seroprevalence and levels of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies among medical students: possible associated factors in Northeastern Brazil . J Health Biol Sci. 2024; 12(1):1-15.