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Original article

COVID-19 long-term sequelae: Omicron versus Alpha and Delta variants

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ABSTRACT

Background: The study aimed to assess the association between three predominant SARS-CoV-2 variants (Alpha, Delta, and Omicron) and the risk of developing long COVID (persistence of physical, medical, and cognitive symptoms more than 4 weeks after infection), post-COVID-19 syndrome (symptoms extending beyond 12 weeks), and viral persistence (testing positive beyond 4 weeks despite clinical resolution).
Methods: Retrospective study of 325 patients hospitalized for COVID-19 with genomic sequencing information. For each SARS-CoV-2 variant, sample characteristics, frequency of symptoms, and long-term sequelae were compared using Chi-squared test, Fisher's exact test, Kruskal-Wallis test, and Dunn's test as appropriate. Odds ratios (OR) were calculated using logistic regression models to assess the association of risk factors and sequelae.
Results: The adjusted model showed that the Omicron (vs Alpha) variant (OR, 0.30; 95% CI 0.16–0.56), admission to ICU (OR, 1.14; 95% CI 1.05–1.23), and being treated with antiviral or immunomodulatory drugs (OR, 2.01; 95% CI 1.23–3.27) predicted long COVID and post-COVID-19 syndrome. Viral persistence showed no difference between variants.
Conclusions: The Omicron variant was associated with significantly lower odds of developing long-term sequelae from COVID-19 compared with previous variants, while severity of illness indicators increased the risk. Vaccination status, age, sex, and comorbidities were not found to predict sequelae development. This information has implications for both health managers and clinicians when deciding on the appropriate clinical management and subsequent outpatient follow-up of these patients. More studies with non-hospitalized patients are still necessary.

1. Introduction

SARS-CoV-2 infection causing mild or moderate COVID-19 typically presents with fever, cough, fatigue, shortness of breath, and muscle soreness that last for 1 or 2 weeks. Severe cases can present pneumonia with complications such as distress syndrome, septic shock, or multiple organ failure, which can take months to recover [1]. Long COVID syndrome has been defined when persistent physical, clinical, and cognitive sequelae remain at least 4 weeks after infection [2]. It is then classified as ongoing symptomatic COVID-19 when symptoms last from 4 to 12 weeks, and as post-COVID-19 when they persist for more than 12 weeks [2–5].

Although many studies have described the sequelae of COVID-19, the association between changes in the SARS-CoV-2 genetic code and development of long COVID has been little studied. According to Crook et al. [6], a specific variant may cause more harmful long-term effects than others, requiring faster and more intense treatment.

Moreover, the relation between patient characteristics and clinical variables (including vaccination status, previous conditions, and treatments) with increased risk of long COVID has been seldom studied. Wynberg et al. found no evidence to suggest that vaccination improves symptoms of post-acute sequelae of COVID-19 [7]. However, remdesivir is recommended in COVID-19 patients who do not require supplemental oxygen and are at high risk of progressing to severe disease, while dexamethasone plus immunomodulatory drugs (e.g., baricitinib or tocilizumab) are recommended for patients who require mechanical ventilation [8]. The effects of remdesivir, immunomodulators, and their combination in severe COVID-19 patients have been extensively studied, although their effects on sequelae remain unknown [9,10].

In summary, post-COVID-19 conditions have been extensively described but their association with SARS-CoV-2 variants has not been studied in depth. Knowing the effect of each variant on subsequent conditions in hospitalized patients can provide relevant information for clinical management decisions, as well as knowing further implications in terms of health costs and availability of

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resources. The aim of this study was to assess the association between the three predominant SARS-CoV-2 variants (Alpha, Delta, and Omicron) from January 2021 to June 2022 and the risk of developing long COVID or post-COVID-19 syndrome in hospitalized patients.

2. Materials and methods

2.1. Patients and design

Electronic health records of 354 patients who were hospitalized for COVID-19 between January 17, 2021 and June 16, 2022 in the Canary Islands, Spain, were retrospectively reviewed for this study. Patients were identified according to three steps using COVID-19 epidemiologic surveillance records. First, we selected patients whose records had whole genome sequencing information (n = 26,652). Second, we selected those who met the inclusion criteria (n = 1,482). Third, in order to get balanced arms, the final sample (n = 354) was identified by stratified random sampling. Strata were defined by variant (Alpha, Delta, Omicron); and sex (male, female) and age group (10-year intervals) based on the distribution of publicly available 2021 census data. Finally, 325 patients met the inclusion criteria for the analysis. The study was approved by the regional Research Ethics Committee (CHUC_2021_27), and all statistical analyses were performed on anonymized data.

2.2. Inclusion and exclusion criteria

Diagnostic confirmation of patients required a positive result either by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) or equivalent molecular techniques [11]. To be included in the study, patients had to: have genomic sequencing information available in their records; have been selected for sequencing at random according to the national strategy [11]; have required more than 48 hours of hospitalization caused by COVID-19; and be alive at the end of the 12-week follow-up period. Patients whose reason for admission was not COVID-19, or with hospitalization for less than 48 hours, or who had died before the end of the follow-up period were excluded.

2.3. Data description

Patient characteristics included sociodemographic variables (age, sex), date of diagnosis, and hospital and ICU admission and discharge dates. Obesity was categorized using BMI and standard references as non-obese, overweight, obesity, and severe obesity [12]. The following chronic comorbidities were assessed: diabetes, hypertension, cardiovascular diseases (ischemic cardiopathy, valvular cardiopathy, arrhythmia, myocardiopathy, heart failure, other), chronic liver disease (hepatic cirrhosis, chronic hepatitis), chronic respiratory diseases (chronic obstructive pulmonary disease, asthma, other lung conditions), chronic kidney disease, chronic neurological/neuromuscular disorders (epilepsy, Alzheimer's disease, other dementias, cerebrovascular diseases, migraine and other neurological disorders, multiple sclerosis, Parkinson's disease, neuroinfections), immunodeficiency (primary immunodeficiency, hematologic malignancy, solid-organ transplantation, people living with HIV, asplenia, biologics and targeted disease-modifying drugs), cancer, and osteoarthritis/arthritis [13,14].

Additionally, the following clinical management data were assessed: treatment with remdesivir, dexamethasone (or other systemic corticosteroids), baricitinib or tocilizumab, and their combinations; admission to ICU during hospitalization; invasive mechanical ventilation (IMV) requirement; and vaccination status against COVID-19 (not vaccinated; after diagnosis; >6 months prior to diagnosis; 3–6 months prior to diagnosis; <3 months prior to diagnosis).

Four groups of COVID-19 symptoms were assessed [2]: a) systemic and inflammatory symptoms, including tiredness or fatigue, post-exertional malaise and fever, joint or muscle pain, rash, changes in menstrual cycles, and temporary hair shedding; b) cardiorespiratory symptoms, including dyspnea or shortness of breath, cough, chest pain, and heart palpitations; c) central or neurological symptoms, including headache, sleep problems, dizziness (lightheadedness), pins-and-needles feelings, brain fog, and change in smell or taste; d) gastrointestinal symptoms, including diarrhea and stomach pain.

Three clinical outcomes were derived from COVID-19 sequelae. Viral persistence was defined as SARS-CoV-2 PCR persistently positive beyond 4 weeks despite clinical resolution [15]. Depending on the duration of symptoms, long COVID was divided into two stages: ongoing symptomatic COVID-19, when symptoms persisted beyond 4 weeks but less than 12 weeks, and post-COVID-19 when symptoms persisted beyond 12 weeks [2,3].

2.4. Statistical analysis

The required sample size was determined a priori using G*Power software (v. 3.19.4), to detect small-moderate effects — Odds Ratio (OR) equal or greater than 2— through logistic regression, assuming a two-tailed model with alpha 0.05, beta 0.80, and up to 50% common variance with other predictors. The Alpha variant was taken as the reference group to calculate the baseline rate of post-COVID-19, which was >25% in a pilot sample (n = 40). Consequently, the required sample size for between-variant differences was 84 participants per group. To account for possible patient exclusions, we increased the sample size by 40%, for a minimum of 118 participants per variant (n = 354).

For each SARS-CoV-2 variant (Alpha, Delta, Omicron), categorical variables were summarized as frequency and percentage, and Chi-squared or exact tests were used for comparisons as appropriate. Pearson's adjusted residuals were calculated to assess Bonferroni-adjusted individual differences when a statistically significant result was found. Continuous data were summarized using median and interquartile range (IQR). Medians were compared using Kruskal-Wallis test, and Dunn's test was used for Bonferroni-adjusted pairwise comparisons.

The association of each factor with both long COVID and post-COVID-19 development was assessed with OR and presented with 95% confidence intervals (CI). Crude OR were first estimated using simple logistic regression models. Adjusted OR were then estimated by adding the virus variant to the model, since this factor was the primary hypothesis of the study and statistically significant at the first step. All statistically significant factors at the second step were analyzed with a forward stepwise logistic regression method, where $p \leq 0.05$ was required to enter the model, and $p \geq 0.10$ removed variables. These analyses resulted in identical models for both long COVID and post-COVID-19, which included: variant, ICU length of stay, and treatment with either antiviral or immunomodulating drugs. Significance level was set at 0.05. The analyses were performed using Stata 15.1 (Stata Corp, College Station, TX, USA).

3. Results

We excluded 28 patients: seven patients who were hospitalized for other reasons, and 21 who died during the 12-week follow-up period. Consequently, 325 patients were included in the analysis. Dates of diagnosis were congruent with COVID-19 waves: Alpha,

from January 17 to July 18, 2021; Delta, from July 4 to January 9, 2022; and Omicron from December 15, 2021 to May 24, 2022.

Table 1 presents sample characteristics for each variant. No differences in age and sex distribution were found between variants. Among clinical variables, length of stay was found to be shorter in Omicron-infected patients compared to either Alpha or Delta. Although weight status showed differences between variants, no differences in obesity were found. Among comorbidities, only diabetes, chronic neurological diseases, neuromuscular disorders, and immunodeficiency presented statistically significant differences, and Omicron patients showed larger percentages in these risk factors. Around 40% of patients were treated with remdesivir regardless of the variant. However, differences in vaccination status were statistically significant between variants.

Systemic/inflammatory and cardiorespiratory symptoms were the most frequent in all variants, although significant differences between variants were observed. As shown in Table 2, while 42.9% of Alpha patients had tiredness or post-exertional fatigue, this rate decreased to 33% for Delta and 20% for Omicron patients. Joint/muscle pain and temporary hair shedding showed a similar pattern of significant differences between variants. No differences in other individual symptoms were observed.

Table 1
Patient characteristics by SARS-CoV-2 variant.

Characteristics	Alpha	Delta	Omicron	P value
Sample size, No.	105	115	105	
Sex, No. (%)				0.710
Male	50 (47.6)	58 (50.4)	56 (53.3)	
Female	52.38 (0)	49.57 (0)	46.67 (0)	
Age (years), median (IQR)	50 (36–66)	48 (35–62)	50 (32–67)	0.823
Age group (years), No. (%)				0.432
0 to 9	1 (1)	4 (3.5)	12 (11.4)	
10 to 19	3 (2.9)	9 (7.8)	5 (4.8)	
20 to 29	12 (11.4)	12 (10.4)	7 (6.7)	
30 to 39	18 (17.1)	18 (15.7)	12 (11.4)	
40 to 49	18 (17.1)	18 (15.7)	15 (14.3)	
50 to 59	18 (17.1)	18 (15.7)	19 (18.1)	
60 to 69	13 (12.4)	12 (10.4)	12 (11.4)	
70 to 79	12 (11.4)	12 (10.4)	12 (11.4)	
80 to 89	6 (5.7)	6 (5.2)	6 (5.7)	
90 and older	4 (3.8)	6 (5.2)	5 (4.8)	
Length of stay, median (IQR)	10 (7–13)	9 (6–14)	7.5 (5–10)	**0.002**
Admission to ICU, No. (%)	16 (15.8)	14 (13.3)	7 (7.7)	0.220
ICU length of stay, median (IQR)	10 (7–20.5)	12 (7–28)	4 (1–19)	0.260
Ventilator, No. (%)	6 (6.1)	7 (6.7)	2 (2.3)	0.220
Weight status, No. (%)				**0.033**
No	38 (36.2)	68 (59.1)	47 (44.8)	
Overweight	27 (25.7)	17 (14.8)	23 (21.9)	
Obesity	33 (31.4)	22 (19.1)	25 (23.8)	
Severe obesity	7 (6.7)	8 (7)	10 (9.5)	
Comorbidities, No. (%)				
Diabetes	18 (17.1)	19 (16.5)	30 (28.9)	**0.044**
Hypertension	39 (37.1)	38 (33)	44 (41.9)	0.398
Heart failure	9 (8.6)	13 (11.3)	17 (16.2)	0.227
Ischemic heart disease, arrhythmia	16 (15.2)	22 (19.1)	24 (22.9)	0.373
Chronic liver disease	5 (4.8)	8 (7)	10 (9.5)	0.404
Chronic lung disease	19 (18.1)	26 (22.6)	28 (26.7)	0.330
Chronic kidney disease	13 (12.4)	13 (11.3)	22 (21)	0.092
Chronic neurological diseases/Neuromuscular disorders	4 (3.8)	6 (5.2)	25 (23.8)	**< 0.001**
Immunodeficiency	2 (1.9)	5 (4.4)	13 (12.4)	**0.004**
Cancer	5 (4.8)	9 (7.8)	12 (11.4)	0.204
Osteoarthritis/arthritis	21 (20)	17 (14.8)	22 (21)	0.442
remdesivir, No. (%)	44 (41.9)	47 (40.9)	38 (36.2)	0.664
Vaccination, No. (%)				**< 0.001**
Unvaccinated	18 (17.1)	46 (40)	34 (32.4)	
After diagnosis	86 (81.9)	42 (36.5)	2 (1.9)	
>6 months before	0 (0)	4 (3.5)	26 (24.8)	
3–6 months before	0 (0)	13 (11.3)	31 (29.5)	
<3 months before	1 (1)	10 (8.7)	12 (11.4)	
Dose 1, No. (%)				0.962
BioNTech/Pfizer	1 (100)	19 (70.4)	48 (69.6)	
Moderna/Lonza	0 (0)	1 (3.7)	7 (10.1)	
J&J/Janssen	0 (0)	2 (7.4)	5 (7.3)	
Oxford/AstraZeneca	0 (0)	5 (18.5)	8 (11.6)	
BioNTech/Pfizer (pediatric)	0 (0)	0 (0)	1 (1.5)	
Dose 2, No. (%)				0.693
BioNTech/Pfizer	1 (100)	19 (79.2)	48 (77.4)	
Moderna/Lonza	0 (0)	1 (4.2)	7 (11.3)	
Oxford/AstraZeneca	0 (0)	3 (12.5)	7 (11.3)	
Gamaleya	0 (0)	1 (4.2)	0 (0)	
Dose 3, No. (%)				0.812
BioNTech/Pfizer	1 (100)	14 (77.8)	33 (82.5)	
Moderna/Lonza	0 (0)	4 (22.2)	7 (17.5)	

p-values were calculated from chi-squared or exact tests for frequencies as appropriate, and Kruskal-Wallis test for medians.
IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Length of stay, days from admission to discharge.

Table 2
Symptoms of long-term COVID sequelae.

	Alpha (n = 105)	Delta (n = 115)	Omicron (n = 105)	P value
Systemic/Inflammatory	54 (51.4)	43 (37.7)	28 (26.7)	**0.001**
Tiredness, fatigue, post-exertional malaise	45 (42.9)	38 (33)	21 (20)	**0.002**
Fever	6 (5.7)	3 (2.6)	9 (8.6)	0.159
Joint or muscle pain	19 (18.1)	16 (13.9)	7 (6.7)	**0.044**
Rash	6 (5.7)	6 (5.2)	1 (1)	0.151
Changes in menstrual cycles	0 (0)	0 (0)	0 (0)	–
Temporary hair shedding	9 (8.6)	5 (4.4)	0 (0)	**0.009**
Cardiorespiratory	44 (42.3)	46 (40)	26 (24.8)	**0.015**
Dyspnea, shortness of breath	35 (33.3)	34 (29.6)	20 (19.1)	0.055
Cough	21 (20)	17 (14.8)	10 (9.5)	0.101
Chest pain	6 (5.8)	6 (5.2)	4 (3.8)	0.796
Heart palpitations	3 (2.9)	4 (3.5)	1 (1)	0.458
Central/Neurological	22 (21)	25 (21.9)	12 (11.5)	0.096
Headache	6 (5.7)	6 (5.2)	3 (2.9)	0.571
Difficulty sleeping (insomnia)	11 (10.5)	9 (7.9)	5 (4.8)	0.299
Dizziness (lightheadedness)	4 (3.8)	2 (1.7)	0 (0)	0.121
Impaired balance and walking	2 (1.9)	6 (5.2)	5 (4.8)	0.403
Pins-and-needles feeling	2 (1.9)	5 (4.4)	1 (1)	0.242
Brain fog	2 (1.9)	2 (1.7)	1 (1)	0.835
Loss of smell or taste	3 (2.9)	2 (1.7)	0 (0)	0.237
Gastrointestinal	4 (3.8)	4 (3.5)	7 (6.7)	0.473
Diarrhea	1 (1)	1 (0.9)	1 (1)	0.997
Stomach pain	4 (3.8)	3 (2.6)	6 (5.7)	0.498
Diagnoses				
Viral persistence	9 (8.6)	8 (7)	9 (8.6)	0.877
Long COVID	53 (50.5)	49 (42.6)	22 (21)	**<0.001**
Ongoing symptomatic COVID	24 (22.9)	23 (20)	12 (11.4)	**0.081**
Post-COVID-19	29 (27.6)	26 (22.6)	10 (9.5)	**0.003**

Data are presented as frequency (percentage). p-values were calculated using chi-squared or exact tests as appropriate.
Viral persistence, ≥4 weeks with positive test; Long COVID, >4 weeks with symptoms; Ongoing symptomatic COVID, 4–12 weeks; Post-COVID-19, >12 weeks with symptoms.

Regarding viral persistence, no differences between variants were found. However, long-term sequelae showed differences between variants. Thus, long COVID rate was greater than expected with the Alpha variant ($p = 0.016$), and smaller than expected with the Omicron variant ($p < 0.001$). Despite overall differences were also found in post-COVID-19 rates, the adjusted residuals showed that only the Omicron variant was below the expected rate ($p = 0.011$).

Very similar results were found for the association between risk factors and either long COVID and post-COVID-19 (Table 3). Compared with the Alpha variant, the Omicron variant was individually associated with a reduction in post-COVID-19 (OR, 0.28; 95% CI 0.13–0.60). After adjusting for variant, other factors such as age, sex, length of stay, corticosteroids, and vaccination were not associated with the outcome. However, obesity (OR, 2.17; 95% CI 1.22–3.85), admission to the ICU (OR, 2.43; 95% CI 1.15–5.13), longer ICU length of stay (OR, 1.08; 95% CI 1.04–1.13), invasive ventilation requirement (OR, 2.90; 95% CI 1.18–7.08), treatment with antiviral drugs (OR, 2.14; 95% CI 1.22–3.76) or with immunomodulatory drugs (OR, 2.50; 95% CI 1.24–5.04) were associated with increased odds of post-COVID-19.

When all significant predictors were analyzed together, only the Omicron variant (OR, 0.31; 95% CI 0.14–0.70), admission to the ICU (OR, 1.08; 95% CI 1.03–1.12,) and treatment with either antiviral or immunomodulatory drugs (OR, 2.75; 95% CI 1.51–4.99) were retained in the model to predict post-COVID-19 (to account for 12.6% of variance).

4. Discussion

Our study shows that patients infected with the Omicron variant had lower odds of developing long-term sequelae from COVID-19 compared with patients infected with previous variants. Our results indicate a threefold difference compared with the Alpha variant, confirming previous hypotheses. In this sense, it has already been suggested that the severity of COVID-19 with the Omicron variant is milder compared with the Alpha and Delta variants identified by whole genome sequencing [16]. The lower severity of the Omicron-infected cases could explain the lower incidence of symptoms in the long term [17]. In our study, the Omicron variant was associated with a decreased risk for long-term symptoms regardless of severity. Antonelli et al., who studied variants by infection time period, also found a reduction in odds of long COVID in cases attributed to the Omicron variant, compared with cases attributed to the Delta variant [18]. Regarding post-COVID syndrome with earlier variants, another study found that the average count of long-term symptoms was higher in non-vaccinated hospitalized patients infected with the Wuhan variant compared with the Alpha or Delta variants [19]. The existence of different post-COVID syndromes depending on the SARS-CoV-2 variant has also been suggested [20]. Long-term cardiorespiratory symptoms tend to be less frequent after Omicron infection, while neurological symptoms remain prevalent [21,22]. In our study, the most frequently reported neurological symptoms were insomnia and impaired balance, although they did not present significant differences between variants. Due to the non-specificity of many of the neurological symptoms described (some of the most commonly described neurological manifestations are insomnia, fatigue/weakness, and myalgia) [22,23], it is also possible that patients did not mention all of them in the follow-up consultation or that the physician did not register them in the medical record.

Due to the different availability of vaccines, Alpha-infected patients were primarily vaccinated after diagnosis, while the majority of Omicron-infected patients were vaccinated prior to getting infected. Despite that, vaccination was not found to be associated with development of COVID-19 sequelae. Although a review by Mumtaz et al. showed that most of vaccinated patients reported beneficial effects on long COVID symptoms [24], the sys-

Table 3
Odds ratio of developing long COVID and post-COVID-19 for each risk factor.

	Long COVID (>4 weeks)			Post-COVID-19 (>12 weeks)		
	Crude OR (95% CI)	Adjusted by variant OR (95% CI)	Final model OR (95% CI)	Crude OR (95% CI)	Adjusted by variant OR (95% CI)	Final model OR (95% CI)
Variant						
Alpha (reference)						
Delta	0.73 (0.43, 1.24)	0.73 (0.43, 1.24)	0.75 (0.43, 1.31)	0.77 (0.42, 1.41)	0.77 (0.42, 1.41)	0.74 (0.39, 1.42)
Omicron	**0.26 (0.14, 0.48)**	**0.26 (0.14, 0.48)**	**0.30 (0.16, 0.56)**	**0.28 (0.13, 0.6)**	**0.28 (0.13, 0.60)**	**0.31 (0.14, 0.70)**
Age (years)	1.01 (1.00, 1.02)			1.00 (0.99, 1.01)		
Sex (female)	1.20 (0.77, 1.89)			1.34 (0.78, 2.31)		
Obese	**1.90 (1.18, 3.06)**	**1.98 (1.21, 3.26)**		**2.11 (1.21, 3.69)**	**2.17 (1.22, 3.85)**	
Length of stay (days)	1.00 (0.99, 1.01)			1.00 (0.99, 1.00)		
Admission to ICU	**3.94 (1.89, 8.20)**	**3.62 (1.69, 7.77)**		**2.69 (1.29, 5.60)**	**2.43 (1.15, 5.13)**	
ICU length of stay (days)	**1.15 (1.06, 1.25)**	**1.14 (1.05, 1.23)**	**1.14 (1.05, 1.23)**	**1.09 (1.04, 1.14)**	**1.08 (1.04, 1.13)**	**1.08 (1.03, 1.12)**
Invasive ventilation	**5.08 (1.94, 13.32)**	**4.43 (1.65, 11.92)**		**3.32 (1.38, 7.99)**	**2.90 (1.18, 7.08)**	
Antivirals	**1.63 (1.03, 2.57)**	**1.61 (1.00, 2.58)**		**2.17 (1.25, 3.76)**	**2.14 (1.22, 3.76)**	
Corticosteroids	0.75 (0.34, 1.65)			0.40 (0.12, 1.36)		
Immunomodulators	**4.26 (2.16, 8.42)**	**4.06 (2.01, 8.2)**		**2.71 (1.36, 5.38)**	**2.50 (1.24, 5.04)**	
Antivirals or immunomodulators	**2.18 (1.38, 3.44)**	**1.66 (1.04, 2.67)**	**2.01 (1.23, 3.27)**	**3.03 (1.71, 5.36)**	**2.91 (1.63, 5.20)**	**2.75 (1.51, 4.99)**
Vaccination						
Unvaccinated (reference)						
After diagnosis	**2.45 (1.41, 4.27)**	1.68 (0.89, 3.17)		**2.12 (1.08, 4.14)**	1.50 (0.71, 3.19)	
>6 months before	1.02 (0.42, 2.49)	1.90 (0.70, 5.19)		0.85 (0.26, 2.79)	1.60 (0.43, 5.97)	
3–6 months before	0.79 (0.35, 1.78)	1.20 (0.50, 2.88)		1.05 (0.39, 2.78)	1.60 (0.56, 4.59)	
<3 months before	1.53 (0.6, 3.93)	1.94 (0.72, 5.23)		0.83 (0.22, 3.15)	1.01 (0.26, 3.94)	

OR, odds ratio estimated using logistic regression; aOR, adjusted odds ratio; CI, confidence interval; Final model, the number of predictors was reduced for each outcome using forward stepwise method with $p < 0.05$ for addition and $p > 0.10$ for removal.
Long COVID, >4 weeks with symptoms; Post-COVID-19, >12 weeks with symptoms.

tematic review by Notarte et al. found mixed results: some studies reported improvement in long COVID symptoms after one dose of vaccine, while others reported no change or worsening of long COVID symptoms after vaccination [25].

Patients infected with the Omicron variant had shorter hospital length of stay, which is consistent with other studies [16], but some comorbidities (diabetes, chronic neurological diseases, neuromuscular disorders, and immunodeficiency) were significantly more frequent. These differences possibly indicate that the Omicron variant caused less morbidity compared with other variants, and only patients with the worst clinical condition required hospitalization.

For this study, the same number of hospitalized cases for each variant were included. Assuming that the Omicron variant causes milder cases in general [17], it is possible that cases were hospitalized after aggravation of their previous comorbidities or as a preventative measure [26]. In contrast, patients infected with the other variants were possibly hospitalized after having a more severe clinical course, due to the severity of the infection even without prior risk factors.

Some risk factors for long COVID have been previously identified in the literature, which include: age, pre-existing pulmonary conditions, obesity, ICU admission, and multiple symptoms at onset [27,28]; in addition, female patients are more likely to develop fatigue, anxiety, and depression [28,29]; and ICU admission, length of hospitalization, and treatment with remdesivir may predict long COVID [30]. In our study, no patient characteristic was associated with long-term sequelae. However, longer ICU stay and the need for treatment with either antivirals or immunomodulators confirmed the contribution of the overall increased illness severity as another significant predictor of long COVID. Remdesivir is an antiviral drug recommended during the pulmonary phase, when patients develop pneumonia and show decreased oxygen levels, and most of them require hospitalization. Immunomodulatory drugs (immunosuppressive agents) are used in the phase when inflammation extends beyond the lungs and evolves into a systemic hyperinflammatory syndrome [31], to inhibit proinflammatory cytokines that elevate as the disease progresses [32]. The usefulness of the different treatments for the management of COVID-19 has been extensively studied with very different results. While some authors found that the use of antiviral or immunomodulatory drugs reduced the risk of hospitalization [30], others found no effectiveness [33]. Considering that both antiviral and immunomodulatory treatments are recommended in patients at stages of the disease that require hospitalization, the increased clinical severity of these patients may explain the subsequent development of sequelae.

Despite the association found with sequelae, no association was found between variants and persistently positive testing for more than 4 weeks. Some variants have been reported to have spike protein mutations that could facilitate the persistence of SARS-CoV-2 in non-immunocompromised individuals [34]. However, according to Chang et al., host tolerance is a major contributor in defining disease severity besides the ability to clear the virus [35]. They showed that the prolonged presence of the virus is related to the severity of the disease and suggested that immunosuppressive treatments can alter viral clearance. Other authors have also suggested that immune responses may predict the persistence of SARS-CoV-2 [34]. In our study, we found no evidence that immunomodulatory treatment was associated with persistent positive testing; thus, further research is required to explain the individual susceptibility that influences viral clearance.

This study is not without limitations. Data on the symptoms and signs developed by the patients was extracted from the electronic medical records, including pneumology consultation — which was scheduled as routine follow-up of all hospitalized COVID-19 patients—, primary care physician's records, and any other medical consultations. In some cases, the patients did not attend the appointments, so it is possible that long COVID rates were underestimated.

In addition, the first pneumology follow-up consultation was sometimes scheduled several months after hospital discharge, so a certain memory bias cannot be ruled out. Many of the symptoms were self-reported by patients (i.e., tiredness, difficulty sleeping),

which in some cases could be attributed to other causes. Frequently, the difference between recovery from post-intensive care unit syndrome and an ongoing condition is not clearly defined [36]. However, in our study we verified that there was a medical diagnosis of post-COVID syndrome written by the physician in the medical record, or that there was no other cause that justified the symptoms (for instance, other acute or chronic conditions).

The positive interpretation of our results is that the Omicron variant reduced the risk for hospitalized patients to have chronic or persistent symptoms. The long COVID rate we found for Omicron-infected patients compares to previous estimates for the entire population (12%) [37], which is a significant improvement from the rates we found for other variants. However, it is too early to know whether successive mutations are turning variants less harmful in the long-term. On the one hand, although the Omicron variant reduced the acute effects of COVID-19 and the rate of hospitalized patients [16], it is difficult to predict the characteristics of future variants and their virulence. However, it has already been noticed that severe acute disease is not a prerequisite for long COVID [37]. Therefore, since our sample only included hospitalized patients, and the pathophysiological mechanism of long COVID still remains unknown [38,39], it is also possible that the Omicron variant produced similar rates of long-term sequelae among non-hospitalized patients that the study was unable to capture. Therefore, studies with patients who did not require hospital admission are still needed.

Our study showed a high prevalence of symptoms that were also characteristic of long-SARS [39,40], anticipating that full recovery could also be difficult to achieve for many long COVID patients. Currently, in addition to health costs relative to acute infection, there is an increasing burden derived from the treatment of long-term sequelae. Furthermore, specialized long COVID outpatient assessment clinics have been created to care for patients with no acute or life-threatening complications [41]. Although the health costs derived from COVID-19 have been extensively studied [42,43], new studies are needed to assess the costs of treating subsequent sequelae (physician consultations, pharmacotherapy, secondary care referrals, etc.) [37,44]. In addition to healthcare costs, many patients have been left out of the labor force due to long COVID, further noting that many of them disproportionately worked in service jobs, including health care, social care, and retail trade [37]. Our results suggest that the Omicron variant could potentially alleviate this burden.

Authors' contribution

Study conception and design: AHA and ELZ; data collection: AHA and AGH; analysis and interpretation of results: ELZ; draft manuscript preparation: AHA and ELZ.

All authors reviewed the results and approved the definitive version of the manuscript.

Ethical statement

The study was approved by the regional Research Ethics Committee (CHUC_2021_27), and all statistical analyses were performed on anonymized data.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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