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Vaccination status and outcomes in critical COVID-19 patients

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ABSTRACT

Objective: To analyze the clinical characteristics and outcomes of patients with COVID-19–related acute respiratory failure on the basis of their vaccination status at the time of ICU admission. **Methods:** We conducted a retrospective observational study using a prospective database of patients admitted to the ICU of a university hospital in the city of Murcia, in Spain, between January 1, 2021 and September 1, 2022. Clinical, analytical, and sociodemographic data were collected and analyzed on the basis of patient vaccination status. We adjusted for confounding variables using propensity score matching and calculated adjusted ORs and 95% CIs. **Results:** A total of 276 patients were included in the study. Of those, 8.3% were fully vaccinated, 12% were partially vaccinated, and 79.7% were unvaccinated. Although fully vaccinated patients had more comorbidities, partially vaccinated patients had higher disease severity. The proportion of patients with severe acute respiratory failure was higher in the unvaccinated group, followed by the partially vaccinated group. No significant differences were found among the different groups regarding complications, duration of ventilatory support, or length of ICU/hospital stay. In the sample selected by propensity score matching, the number of patients with severe complications and the in-hospital mortality rate were higher in unvaccinated patients, but the differences were not significant. **Conclusions:** This study failed to show a significant improvement in outcomes in critically ill COVID-19 patients vaccinated against SARS-CoV-2. However, the CIs were wide and the mortality point estimates favored patients who received at least one dose of COVID-19 vaccine.

Keywords: COVID-19; Vaccination; Critical care.

INTRODUCTION

Since the onset of the COVID-19 pandemic, successive epidemic waves have been primarily managed by social isolation measures and widespread adoption of barrier precautions to prevent transmission of SARS-CoV-2.[1] Toward the end of 2020, different vaccines were introduced with the aim of preventing transmission and mitigating the severity of disease.[2,3] Disease severity can be evaluated by the extent of pneumonia on chest CT scans,[4,5] need for hospital and/or ICU admission, need for respiratory support, and mortality.[6-11] Several meta-analyses have shown a relationship between vaccination and a reduction in disease severity, but the evidence regarding the effect of vaccination on viral transmission is less robust.[9-11] Messenger RNA vaccines have been the most administered around the world, and, despite their imperfect efficacy in preventing viral transmission, they have been associated with reductions in hospitalization, ICU admission, and mortality, although the underlying mechanisms have yet to be fully understood.[12]

The role of prior vaccination in patients presenting with critical COVID-19 and requiring ICU admission or developing ARDS is less clear. Several studies have analyzed the outcomes of ICU patients on the basis of their vaccination status, but the results are conflicting.[13-16] In a multicenter study conducted in Greece and involving 256 patients with ARDS, mortality was found to be lower in fully vaccinated individuals.[14] In a study conducted in an ICU in Spain, full vaccination was associated with fewer complications and lower mortality, although the differences were not significant.[13] In contrast, no difference in mortality was found between vaccinated and unvaccinated patients in multicenter studies conducted in Italy[15] and in Australia.[16] All of the aforementioned studies were conducted between June of 2021 and February of 2022, when the predominant SARS-CoV-2 variants were the Delta and then the Omicron. Comparison of results across studies is hindered by different classifications of vaccination status and the exclusion of patients with incomplete vaccination status in some studies.[15]

The objective of this study was to analyze the clinical characteristics and outcomes of patients with COVID-19–related acute respiratory failure (ARF) on the basis of their vaccination status at the time of ICU admission.

METHODS

We conducted a retrospective observational study using a prospective database of patients admitted to the

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ICU of a university hospital in the city of Murcia, in Spain. The study was approved by the local research ethics committee.

Patients

Our study included all patients ≥ 18 years of age consecutively admitted to the ICU between January 1, 2021 and September 1, 2022 because of COVID-19–related ARF. Diagnostic criteria included microbiological confirmation of COVID-19—a positive RT-PCR test (REALQUALITY RQ-2019-nCoV; AB ANALITICA s.r.l., Padova, Italy, or QuantiTect Probe RT-PCR Kit; QIAGEN, Hilden, Germany)—and the presence of pulmonary infiltrates on imaging.

Initial respiratory support was tailored to patient clinical status. High-flow nasal cannula oxygen therapy was preferentially used in patients with an RR of < 25 breaths/min and a PaO_2/FiO_2 ratio of 150-200 mmHg. In cases of severe hypoxemia (PaO_2/FiO_2 < 150 mmHg), noninvasive positive-pressure ventilation, particularly CPAP, was the approach of choice. Noninvasive ventilation (NIV) was delivered by VISION® and V60® ventilators (Philips Respironics, Murrysville, PA, USA). CPAP was initiated at a pressure of 10 cmH_2O and, if needed, progressively titrated up to 15 cmH_2O. When BiPAP was selected, the starting expiratory positive airway pressure (EPAP) was also set at 10-15 cmH_2O, the inspiratory positive airway pressure not exceeding the EPAP level by more than 5 cmH_2O. A full face mask was the interface of choice when initiating ventilatory support. Endotracheal intubation and invasive mechanical ventilation were the primary interventions used in order to prevent imminent cardiorespiratory arrest. Regardless of the respiratory support, the goal was to maintain an SpO_2 of 92-96% in cases of hypoxemic ARF and an SpO_2 of 88-92% in cases of hypercapnic ARF. For patients undergoing NIV, fentanyl was routinely administered to enhance tolerability. However, there were instances in which it became necessary to switch to another medication or supplement it with sedatives or neuroleptics, particularly in the presence of persistent intolerance or delirium. Protective ventilation settings and periodic prone positioning were used in patients undergoing endotracheal intubation and invasive mechanical ventilation.

Study variables and statistical analysis

Clinical and analytical data were collected at admission and during hospitalization. Sociodemographic variables, clinical variables (i.e., patient-reported signs and symptoms), and analytical variables were analyzed. Clinical status and disease severity were determined by the Simplified Acute Physiology Score II at admission[17] and the daily SOFA score.[18] Comorbidity burden was assessed by the Charlson Comorbidity Index.[19]

The COVID-19 waves were as follows: 1st wave, from November 3, 2020 to April 23, 2020; 2nd wave, from August 13, 2020 to December 8, 2020; 3rd wave, from December 23, 2020 to March 24, 2021; 4th wave, from April 6, 2021 to May 26, 2021; 5th wave, from July 9, 2021 to October 29, 2021; and 6th wave, from November 9, 2021 to March 23, 2022. After the 6th wave, there were only sporadic COVID-19 cases.

The main patient-related variables are detailed in Table S1 in the supplementary material. The primary outcomes of the study were in-hospital mortality and complications related to COVID-19 and the respiratory support used. We analyzed the following complications: hyperglycemia (≥ two consecutive blood glucose measurements ≥ 180 mg/dL and requiring insulin); severe bleeding (a drop of ≥ 2 g/L in the hemoglobin level); acute kidney injury (a ≥ 1.5-fold increase in creatinine levels from baseline accompanied by oliguria); agitation/hyperactive delirium (acute and fluctuating disturbance of consciousness and cognitive functions associated with muscle hyperactivity requiring medication for control); muscle weakness acquired in the ICU (electromyography showing critical illness polyneuropathy or myopathy); thromboembolic disease (one or more episodes of deep vein thrombosis or pulmonary embolism); atrial fibrillation (not present at admission); stroke (sustained neurological deficit caused by cerebral ischemic or hemorrhagic disease); barotrauma (presence of air in the pleural cavity or mediastinum during respiratory support); and nosocomial infection (catheter-related bloodstream infection, nosocomial pneumonia, or urinary tract infection).

Patients were categorized on the basis of their vaccination status at the time of infection with SARS-CoV-2, as follows: a) complete vaccination—patients who had received the required dose or doses of vaccine, including a booster dose or doses (if approved by health authorities), and who developed COVID-19 between 14 days and 5 months after the last dose; b) incomplete vaccination—patients who did not receive all recommended doses of vaccine, including a booster dose or doses if approved, or who developed COVID-19 less than 14 days or more than 5 months after the last dose; and c) no vaccination—patients who did not receive any COVID-19 vaccine. We determined vaccination status and type of administered vaccine (if any) using a web-based database available in the autonomous community of Murcia, in Spain.

Three types of comparisons were made. First, all three groups of patients were compared on the basis of their vaccination status (complete vaccination, incomplete vaccination, or no vaccination). Second, incompletely vaccinated patients and unvaccinated patients were grouped together and compared with fully vaccinated patients. Finally, patients with complete vaccination and those with incomplete vaccination were also grouped together and compared with those who did not receive any vaccination.

Quantitative variables are presented as mean ± standard deviation or median (interquartile range), whereas qualitative variables are presented as

absolute and relative frequencies. Comparisons between qualitative variables were performed with Pearson's chi-square test or Fisher's exact test. For comparisons between quantitative and qualitative variables with two categories, the Student's t-test or the Mann-Whitney test was employed. If a qualitative variable had three or more categories, comparisons were made by ANOVA or the Kruskal-Wallis test. Further analysis comparing unvaccinated patients and those who received at least one dose of vaccine was performed by means of propensity score matching (1:1 matching without replacement), matching within calipers being defined by the propensity score. The variables used for matching were present before the onset of COVID-19 and were selected to better assess the relationship between vaccination status and prognosis. They included age, sex, obesity, wave of the COVID-19 pandemic (grouping together patients admitted during waves 3 and 4, and those admitted during waves 5, 6, and later), the Charlson Comorbidity Index, and immunosuppression status. A caliper width of 0.1 of the standard deviation of the logit of the propensity score was used for the matching process. To assess the effectiveness of propensity score matching in minimizing differences between patients with and without vaccination, standardized mean differences were computed for each variable before and after matching. Standardized mean differences of < 10% were considered indicative of successful propensity score matching and balance between the two groups. Postmatching group comparisons were performed with the Student's t-test for paired data, the Wilcoxon test, or McNemar's test. Adjusted ORs and 95% CIs were calculated.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 25 (IBM Corporation, Armonk, NY, USA). All tests were two-tailed, and the level of significance was set at $p \leq 0.05$.

RESULTS

Between the start of the COVID-19 pandemic and September of 2022, 465 patients with positive RT-PCR results for SARS-CoV-2 were admitted to the ICU. Of those, 189 were excluded from the study. A flow chart of patient selection is shown in Figure S1. A total of 276 patients were included in the study. Of those, 204 (73.9%) were male, with a mean age of 58.8 ± 13.8 years. Of the 276 patients included in the study, 23 (8.3%) received complete vaccination and 33 (12%) received incomplete vaccination, whereas 220 (79.7%) did not receive any vaccination. Of the 33 patients with incomplete vaccination, 12 did not receive any booster that they were due to receive, 2 developed disease within two weeks of receiving the second dose of vaccine, and 19 developed disease more than 5 months after the last dose. The type of vaccine and number of doses received in the vaccinated groups are shown in Table 1.

Sociodemographic, background, and clinical characteristics of patients

As can be seen in Table 2, age was the only sociodemographic characteristic that differed among the three groups of patients (p = 0.009). Although patients with complete vaccination had more comorbidities, as assessed by the Charlson Comorbidity Index (p < 0.001), disease severity was higher in the incomplete vaccination group, followed by the complete vaccination and unvaccinated groups (p < 0.001). Dyspnea at diagnosis was less common in the fully vaccinated group (p = 0.009). These results held when we compared fully and partially vaccinated patients with unvaccinated patients, the exception being dyspnea, which did not differ significantly between the two groups.

First-line and further respiratory support did not differ among any of the groups. However, serum levels of D-dimer and LDH were significantly higher in the unvaccinated group, as opposed to C-reactive protein levels, which were higher in fully and partially vaccinated patients (Table 3). Although neither RR nor PaO_2/FiO_2 differed in the comparisons made, the proportion of patients with more severe ARF (PaO_2/FiO_2 < 100) was higher in unvaccinated patients, followed by partially vaccinated patients (p = 0.045). None of the variables related to respiratory/ventilatory pressures, EPAP/CPAP, PEEP, plateau pressure, or driving pressure differed among the groups.

Outcomes

No significant differences were found among the different groups regarding complications, duration of ventilatory support, or length of ICU/hospital stay (Table 4). Although the in-hospital mortality rate was higher in the incompletely vaccinated group (24.2%) than in the unvaccinated and fully vaccinated groups (20.5% and 17.4%, respectively), the difference was not significant (p = 0.813). There were no significant differences in the study outcomes between fully vaccinated patients and partially vaccinated or

Table 1. Type of vaccine and number of doses received.

Type of vaccine [manufacturer]	Complete vaccination			Incomplete vaccination		
	1st dose (n = 23)	2nd dose (n = 23)	3rd dose (n = 11)	1st dose (n = 33)	2nd dose (n = 19)	3rd dose (n = 8)
Viral vector [AstraZeneca®]	9 (39.1)	9 (39.1)	3 (27.3)	4 (12.1)	2 (10.5)	-
Messenger RNA vaccine [Pfizer®]	8 (34.8)	8 (34.8)	-	23 (69.7)	15 (71.4)	2 (75)
Viral vector [Jansen®]	5 (21.7)	-	-	2 (6.1)	4 (21.1)	-
Messenger RNA vaccine [Moderna®]	1 (4.3)	6 (26.1)	8 (72.7)	4 (12.1)	-	8 (72.7)

Table 2. Sociodemographic, background, and clinical characteristics of patients.[a]

Characteristic	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Male sex, n (%)	204 (73.9)	161 (73.9)	24 (72.7)	19 (82.6)	0.619	185 (73.1)	0.321	43 (76.8)	0.733
Age, years	58.8 ± 13.8	57.5 ± 13.8	64.1 ± 12.8	63.5 ± 12.1	0.009	58.4 ± 1392	0.090	63.8 ± 12.4	0.003
BMI, kg/m²	30.1 ± 5.7	30.1 ± 5.4	30.2 ± 7.5	29.9 ± 6.8	0.981	30.1 ± 5.7	0.860	30.1 ± 7.1	0.969
CURB-65 score	3 (2-3)	3 (2-3)	3 (2-3.5)	3 (2-3)	0.132	3 (2-3)	0,330	3 (2-3)	0.199
SAPS II	30.3 ± 9.2	29.2 ± 8.2	35.6 ± 12.8	32.8 ± 9.1	< 0.001	30.1 ± 9.2	0.169	34.5 ± 11.4	0.002
ICU admission from, n (%)					0.509		0.612		0.609
ER	82 (29.7)	66 (30.0)	11 (33.3)	5 (21.7		112 (26.7)		16 (28.6)	
Ward	155 (56.2)	125 (56.8)	18 (54.4)	12 (52.2)		231 (55.1)		30 (53.6)	
Another hospital	39 (14.1)	29 (13.2)	4 (12.1)	6 (26.1)		76 (18.1)		10 (17.9)	
Comorbidities, n (%)									
Obesity	117 (42.4)	94 (42.7)	13 (39.4)	10 (43.5)	0.931	107 (42.3)	0.912	23 (41.1)	0.823
Smoking	18 (5.5)	15 (6.8)	3 (9.1)	-	0.390	18 (7.1)	0.378	3 (5.4)	> 0.999
Hypertension	117 (42.4)	92 (41.4)	17 (51.5)	9 (39.1)	0.517	108 (42.7)	0.741	26 (46.4)	0.534
Dyslipidemia	100 (36.2)	74 (33.6)	15 (45.5)	11 (47.8)	0.202	89 (35.2)	0.227	26 (46.4)	0.087
Diabetes mellitus	76 (27.5)	55 (25)	13 (39.4)	8 (34.8)	0.162	68 (26.9)	0.416	21 (37.5)	0.062
Chronic lung disease	51 (18.5)	40 (18.2)	6 (18.2)	5 (21.7)	0.915	46 (18.2)	0.778	11 (19.6)	0.801
Chronic heart disease	26 (9.4)	18 (8.2)	3 (9.1)	5 (21.7)	0.106	21 (8.3)	0.051	8 (14.3)	0.163
Chronic kidney disease	12 (4.3)	7 (3.2)	3 (9.1)	2 (8.7)	0.170	10 (4)	0.263	5 (8.9)	0.072
Chronic liver disease	5 (1.8)	2 (0.9)	1 (3)	2 (8.7)	0.025	3 (1.2)	0.057	3 (5.4)	0.058
Active cancer	39 (14.1)	24 (10.9)	8 (24.2)	7 (30.4)	0.008	32 (12.6)	0.029	2 (3.6)	0.184
Stroke	6 (2.2)	4 (1.8)	2 (6.1)	-	0.225	6 (2.4)	> 0.999	2 (3.6)	0.352
Autoimmune disorder	9 (3.3)	4 (1.8)	3 (9.1)	2 (8.7)	0.028	7 (2.8)	0.167	5 (8.9)	0.019
Immunosuppression	27 (9.8)	11(5)	6 (26.1)	10 (30.3)	< 0.001	21 (8.3)	0.016	16 (28.6)	< 0.001
Charlson Comorbidity Index	0 (0-2)	0 (0-1)	1 (0-2)	2 (1-2)	< 0.001	0 (0-2)	< 0.001	2 (0-2)	< 0.001
Do-not-intubate order, n (%)	12 (4.3)	10 (4.5)	1 (3)	1 (4.3)	0.924	11 (4.3)	> 0.999	2 (3.6)	> 0.999

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Table 2. Sociodemographic, background, and clinical characteristics of patients.[a] (Continued...)

Characteristic	All (n = 276)	Group I No vaccination (n = 220)	Group II Incomplete vaccination (n = 33)	Group III Full vaccination (n = 23)	p*	Group IV No vaccination + Incomplete vaccination (n = 253)	p**	Group V Vaccination (n = 56)	p†
Symptoms, n (%)									
Dyspnea	272 (98.6)	218 (99.1)	33 (100)	21 (91.3)	0.009	251 (99.2)	0.036	54 (96.4)	0.184
Fever	206 (74.6)	160 (72.7)	26 (78.8)	20 (87)	0.277	186 (73.5)	0.156	46 (82.1)	0.226
Dry cough	233 (84.4)	186 (84.5)	29 (87.9)	18 (78.3)	0.617	215 (85)	0.374	47 (83.9)	0.910
Expectoration	29 (10.5)	22 (10)	4 (12.1)	3 (13)	0.857	26 (10.3)	0.720	7 (12.5)	0.586
Diarrhea	29 (10.5)	25 (11.4)	2 (6.1)	2 (8.7)	0.623	27 (10.7)	>0.999	4 (7.1)	0.358
Headache	84 (30.4)	60 (27.3)	14 (42.4)	10 (43.5)	0.077	74 (29.2)	0.156	24 (42.9)	0.029
Nausea/vomiting	18 (6.5)	18 (8.2)	-	-	0.086	18 (7.1)	0.378	-	0.029
Anosmia	22 (8)	17 (7.7)	4 (12.1)	1 (4.3)	0.548	21 (8.3)	> 0.999	5 (8.9)	0.791
Ageusia	20 (7.2)	17 (7.7)	1 (3)	2 (8.7)	0.600	18 (7.1)	0.677	3 (5.4)	0.774
Chest pain	15 (5.4)	12 (5.5)	1 (3)	2 (8.7)	0.655	13 (5.1)	0.361	3 (5.4)	> 0.999
Days from symptom onset to hospital admission	7 (5-10)	7 (5-10)	6.5 (4.5-10)	7 (5-11)	0.620	7 (5-10)	0.597	7 (5-10)	0.318
Days from symptom onset to ICU admission	9 (6-11)	9 (7-11)	8.5 (6-11)	8 (5-14)	0.680	9 (7-11)	0.722	8 (6-12)	0.370
COVID-19 wave					< 0.001		< 0.001		< 0.001
3rd	108 (39.1)	107 (48.6)	1 (3)	-		108 (42.7)		1 (1.8)	
4th	11 (4)	10 (4.5)	-	1 (4.3)		10 (4)		1 (1.8)	
5th	50 (18,1)	39 (17.7)	6 (18.2)	5 (21.7)		45 (17.8)		11 (19.6)	
6th	88 (31.9)	61 (27.7)	16 (48.5)	11 (47.8)		77 (30.4)		27 (48.2)	
After the 6th wave	19 (6.9)	3 (1.4)	10 (30.3)	6 (26.1)		13 (5.1)		16 (28.6)	
First chest X-ray in the ICU, n (%)					0.544		0.705		0.244
Affected quadrants, 3-4	22 (9.1)	22 (10)	2 (6.1)	1 (4.3)		24 (9.5)		53 (94.6)	
Affected quadrants, 1-2	251 (90.9)	198 (90)	31 (93.9)	22 (95.7)		229 (90.5)		3 (5.4)	
Increased infiltrates at 48 h	214 (77.5)	170 (77.3)	23 (69.7)	21 (91.3)	0.159	193 (76.3)	0.098	44 (78.6)	0.835

CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age = 65 years; and SAPS: Simplified Acute Physiology Score. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated.
*Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

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Table 3. Treatment, analytical, and respiratory variables.[a]

Variable	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Drugs, n (%)									
Antibiotics at ICU admission	113 (40.9)	83 (37.7)	18 (37.7)	12 (52.2)	0.129	101 (39.9)	0.253	30 (53.6)	0.031
Remdesivir	11 (4.0)	9 (4.1)	9 (4.1)	-	0.299	11 (4.3)	0.608	2 (3.6)	0.859
Tocilizumab	152 (55.1)	110 (50.5)	23 (69.7)	18 (78.3)	0.188	134 (53.0)	0.020	41 (73.2)	0.002
Corticosteroids	276 (100)	220 (100)	33 (100)	23 (100)	> 0.999	253 (100)	0.999	56 (100)	> 0.999
Respiratory support at ICU admission, n (%)					0.265		0.717		0.351
HFNC	3 (1.1)	3 (1.4)	-	-		3 (1.2)		-	
CPAP	207 (75)	167 (75.9)	21 (63.6)	19 (82.6)		188 (74.3)		40 (71.4)	
BiPAP	58 (21)	45 (20.5)	9 (27.3)	4 (17.4)		54 (21.3)		13 (23.2)	
IMV	8 (2.9)	5 (2.3)	3 (9.1)	-		8 (3.2)		3 (5.34)	
Respiratory support during the ICU stay, n (%)									
HFNC	235 (85.1)	190 (86.4)	25 (75.8)	20 (87.0)	0.270	215 (85.0)	> 0.999	45 (80.4)	0.220
CPAP	237 (85.9)	189 (85.9)	27 (81.8)	21 (91.3)	0.605	216 (85.4)	0.753	48 (85.7)	0.900
BiPAP	174 (63.0)	139 (63.2)	20 (60.6)	15 (65.2)	0.936	159 (62.8)	0.822	35 (62.5)	0.875
IMV	78 (28.3)	61 (27.7)	10 (30.3)	7 (30.4)	0.927	71 (28.1)	0.809	17 (30.4)	0.646
Lymphocytes, cells × 10^9/L	560 (400-800)	500 (400-775)	500 (400-775)	600 (225-1,275)	0.856	500 (400-700)	0.833	500 (300-1,000)	0.825
D-dimer, ng/mL	894 (595-1,500)	865 (572-1,362)	600 (400-900)	767 (543-2,230)	0.010	900 (596-1,492)	0.963	1,141 (738-2,734)	0.017
Ferritin, ng/mL	911 (532-1,427)	934 (520-1,423)	1,316 (879-3,347)	833 (421-1,476)	0.706	911 (524-1,423)	0.565	781 (555-1,444)	0.359
C-reactive protein, mg/L	10.7 (5.3-19.9)	9.6 (5.3-18.1)	17.8 (9.3-26.7)	15.4 (5.1-21.6)	0.007	10.7 (5.3-20)	0.396	15 (9.8-22-5)	0.004
LDH, U/L	630 (444-838)	592 (425-805)	422 (317-550)	381 (313-512)	< 0.001	570 (401-799)	< 0.001	403 (311-533)	< 0.001
RR, breaths/min	30 ± 6	30 ± 6	29 ± 6	28 ± 5	0.155	30 ± 6	0.173	29 ± 5	0.051
PaO_2/FiO_2 at ICU admission, mmHg	115 ± 24	116 ± 24	110 ± 26	117 ± 24	0.350	115 ± 24	0.636	113 ± 22	0.398
Worst value categorized level, n (%)									
< 100 mmHg	145 (52.5)	121 (55.0)	17 (51.5)	7 (30.4)		138 (54.5)		24 (42.9)	
101-150 mmHg	130 (47.1)	99 (45.0)	16 (48.5)	15 (65.2)	0.045	115 (45.4)	0.001	31 (55.4)	
151-200 mmHg	1 (0.4)	-	-	1 (4.3)		-		1 (1.8)	0.076
PEEP/EPAP/CPAP at start NIV/IMV, mmHg									
On the day of intubation	12.1 ± 1.1	12.1 ± 1.2	11.9 ± 0.7	12.0 ± 0.8	0.654	12.1 ± 1.2	0.774	11.9 ± 0.8	0.260
Worst value	12.7 ± 1.3	12.7 ± 1.3	12.7 ± 1.1	12.4 ± 0.9	0.542	12.7 ± 1.3	0.180	12.7 ± 1.3	0.373

Continue...▶

Table 3. Treatment, analytical, and respiratory variables.[a] (Continued...)

Variable	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Plateau pressure, cmH_2O									
On the day of intubation	24.9 ± 1.7	24.9 ± 1.6	25 ± 2.1	25.8 ± 1.3	0.343	24.9 ± 1.7	0.146	25.3 ± 1.8	0.342
Worst value during the ICU stay	27 ± 1.4	27 ± 1.3	26.8 ± 1.9	27.1 ± 1.6	0.862	26.9 ± 1.4	0.773	26.9 ± 1.7	0.836

HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; EPAP: expiratory positive airway pressure; and NIV: noninvasive ventilation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. *Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

unvaccinated patients, or between fully or partially vaccinated and unvaccinated patients.

After adjustment, the group of patients with at least one dose of vaccine and the group of unvaccinated patients showed a more balanced distribution of variables (Table 5). Although the numbers of patients with severe complications (OR = 1.49; 95% CI, 0.68-3.26), NIV failure (OR = 1.56; 95% CI, 0.68-3.59), and in-hospital mortality (OR = 1.59; 95% CI, 0.68-3.71) were higher in the unvaccinated group, none of these outcomes reached statistical significance. No significant differences were found between the two study groups regarding any of the complications analyzed in the present study (Table 6).

DISCUSSION

In this study, we found no relationship between vaccination status and outcomes in critically ill patients admitted to the ICU for ARF related to COVID-19.

Since the onset of the COVID-19 pandemic, an immense effort has been made to develop strategies to contain infection with SARS-CoV-2. The development of vaccines and their availability to the population was one of the priorities. Vaccines have shown high efficacy in preventing severe disease, resulting in lower rates of hospitalization, ICU admission, need for mechanical ventilation, and, ultimately, mortality.[7-11] These findings have been observed in different geographic settings.[20-24] However, in patients admitted to the ICU for critical COVID-19, the outcomes and their relationship with vaccination status are controversial.

In a small study conducted in 2021, Morales et al. showed no significant differences in length of stay or mortality between fully vaccinated, partially vaccinated, and unvaccinated patients.[13] Grapsa et al. analyzed patients with ARDS caused by COVID-19 and the need for invasive mechanical ventilation, finding lower mortality in patients with complete vaccination than in controls who were either unvaccinated or partially vaccinated.[14] Graselli et al. showed that although vaccination decreased the risk of ICU admission, vaccination status was not related to ICU or in-hospital mortality in patients admitted to the ICU.[15] Finally, in a multicenter study of patients admitted to ICU, Otto et al. showed that vaccinated patients had fewer days of invasive mechanical ventilation, ICU stay, and hospital stay.[16] Although crude mortality was higher in vaccinated patients, adjusted mortality by multivariate analysis showed no relationship between vaccination status and ICU or in-hospital mortality.

As in previous studies, we found that vaccinated patients were older and had more comorbidities,[13-16] probably because older individuals with comorbidities constitute the main target of vaccination campaigns. In the unvaccinated group, we found a higher proportion of patients with severe ARF (PaO_2/FiO_2 < 100 mmHg) at ICU admission, as well as increased levels of LDH and D-dimer, which are parameters related to worse clinical prognosis.[25] However, C-reactive protein

Table 4. Patient outcomes.[a]

Outcome	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
ARDS, n (%)	259 (93.6)	206 (93.6)	32 (97.0)	21 (91.3)		238 (94.1)		53 (94.6)	
Grade, n (%)					0.660		0.641		> 0.999
Moderate	96 (37.1)	76 (36.9)	12 (37.5)	8 (38.1)	0.993	88 (37.0)	0.919	20 (37.7)	0.910
Severe	163 (62.9)	130 (63.1)	20 (62.5)	13 (61.9)		150 (63.0)		33 (62.3)	
SOFA score at ICU admission									
Worst value during the ICU stay	3.6 ± 1.2	3.6 ± 1.1	4.1 ± 1.9	3.6 ± 0.9	0.058	3.7 ± 1.2	0.745	3.9 ± 1.6	0.157
	6.1 ± 3.7	5.9 ± 3.7	6.5 ± 3.7	6.2 ± 3.5	0.705	6.1 ± 3.7	0.816	6.4 ± 3.6	0.438
Hyperglycemia, n (%)	99 (35.9)	84 (38.2)	9 (27.3)	6 (26.1)	0.282	93 (36.8)	0.307	15 (26.8)	0.112
Severe bleeding, n (%)	10 (3.6)	10 (4.5)	-	-	0.267	10 (4.0)	> 0.999	-	0.221
Acute kidney injury, n (%)	67 (24.3)	50 (22.7)	10 (30.3)	7 (30.4)	0.493	60 (23.7)	0.472	17 (30.4)	0.234
Agitation/hyperactive delirium, n (%)	64 (23.2)	49 (22.3)	7 (21.2)	8 (34.8)	0.296	56 (22.1)	0.169	15 (26.8)	0.523
Weakness acquired in the ICU, n (%)	56 (20.3)	43 (19.5)	7 (21.2)	6 (26.1)	0.752	50 (19.8)	0.470	12 (23.2)	0.542
Thromboembolic disease, n (%)	21 (7.6)	16 (7.3)	3 (9.1)	2 (8.7)	0.915	19 (7.5)	0.690	5 (8.9)	0.777
Atrial fibrillation, n (%)	22 (8.0)	20 (9.1)	-	2 (8.7)	0.197	20 (7.9)	0.703	2 (3.6)	0.268
Stroke, n (%)	4 (1.4)	4 (1.8)	-	-	0.597	4 (1.6)	> 0.999	-	0.586
Barotrauma, n (%)	46 (16.7)	39 (17.7)	4 (12.1)	3 (13.0)	0.642	43 (17.0)	0.776	7 (12.5)	0.349
Nosocomial infection, n (%)	102 (37.0)	82 (37.3)	9 (27.3)	11 (47.8)	0.286	91 (36.0)	0.259	20 (35.7)	0.781
First-line NIV failure	79 (29.5)	64 (29.8)	7 (23.3)	8 (34.8)	0.649	71 (29.0)	0.559	15 (28.3)	0.849
First-line NIV failure with DNI order	70 (27,3)	56 (27,3)	7 (24,1)	7 (31,8)	0.830	63 (26.0)	0.622	14 (27,5)	0.985
Post-extubation NIV failure	5 (17.2)	4 (16.7)	1 (50.0)	-	0.344	5 (10.2)	> 0.999	1 (20.0)	> 0.999
NIV duration, days	6 (3-10)	5 (3-10)	7 (3-11)	6 (5-15)	0.865	5.5 (3-10)	0.852	6 (4-12)	0.813
IMV duration, days	13 (6-29)	13 (6-28)	7 (2-19)	35 (10-56)	0.051	13 (6-25)	0.055	11 (4-35)	0.811
Tracheotomy, n (%)	31 (11.2)	24 (10.9)	2 (6.1)	5 (21.7)	0.178	26 (10.3)	0.156	7 (12.5)	0.736
ECMO, n (%)	4 (1.4)	4 (1.4)	-	-	0.597	4 (1.6)	> 0.999	-	0.586
ICU stay, days	27 (14-43)	27 (15-45)	14 (6-31)	43 (26-87)	0.798	24 (13-43)	0.522	10 (6.0-16.5)	0.875
Hospital stay, days	32 (18-51)	39 (19-51)	17 (6-31)	50 (26-129)	0.583	30 (17-50)	0.300	18 (11-26)	0.628
ICU mortality	55 (19.9)	43 (19.5)	8 (24.2)	4 (17.4)	0.780	51 (20.2)	> 0.999	12 (21.4)	0.753
ICU mortality with DNI order	46 (17,4)	35 (16.7)	8 (25.0)	3 (13,6)	0.454	43 (17.8)	0.625	11 (20.3)	0.522

Continue...▶

Table 4. Patient outcomes.[a] (Continued...)

Outcome	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
In-hospital mortality	57 (20.7)	45 (20.5)	8 (24.2)	4 (17.4)	0.813	53 (19.3)	0.795	12 (21.4)	0.932
In-hospital mortality with DNI order	48 (18.2)	37 (17.6)	8 (25.0)	3 (13.6)	0.509	45 (18.6)	0.564	11 (20.4)	0.640

NIV: noninvasive ventilation; DNI: do-not-intubate; IMV: invasive mechanical ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. *Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

levels—a parameter related to the inflammatory process—were higher in vaccinated patients, especially fully vaccinated patients. Nevertheless, the main results regarding complications of COVID-19, length of ICU/hospital stay, and mortality were unrelated to vaccination status. We accounted for variations in the prevalence of different SARS-CoV-2 variants during the study period, which could have modified the vaccination results by adjusting for the variable "wave of the COVID-19 pandemic" (grouping together patients admitted during waves 3 and 4, and those admitted during waves 5, 6, and later) in the paired analysis.

Although previous studies have used different definitions of partially vaccinated patients, we have used the definition suggested by the U.S. Centers for Disease Control and Prevention, a definition that was also used in the aforementioned multicenter study in Greece.[14] This definition takes into account whether or not the booster dose has been received, as recommended by health authorities. In order to assess the potential impact of vaccination on clinical outcomes in critically ill patients, we made comparisons by dividing patients into three groups on the basis of their vaccination status. These comparisons were aimed at evaluating any differences or associations between vaccination status and clinical outcomes. Given the uncertainty about the role of incomplete vaccination in patient outcomes, we performed further analyses by grouping partially vaccinated patients and unvaccinated patients, and by comparing unvaccinated patients with those who had received at least one dose of vaccine. None of these analyses, including a propensity score-matched analysis comparing unvaccinated patients and patients who had received at least one dose of vaccine, showed a better prognosis in fully vaccinated or partially vaccinated patients. Multiple factors may contribute to the fact that vaccination does not protect against critical COVID-19, including age, vaccine type, virus variant, and immunosuppression.[26] In addition, other, unknown, factors may contribute to the lack of vaccine efficacy in vaccinated patients presenting with severe COVID-19. Despite these findings, in the absence of a statistically significant difference, it is important to note that the proportions of patients with severe complications, NIV failure, and in-hospital mortality were higher in unvaccinated patients than in those who had received at least one dose of vaccine in the propensity-matched sample. The presence of an OR of 1.93 for in-hospital mortality is relevant even in the absence of statistical significance and could provide further evidence for systematic vaccination against COVID-19, not only because it might reduce the risk of infection and severe disease but also because outcomes might be worse in unvaccinated patients who are critically ill.

Our study has several limitations. First, although the sample size was large (276 critically ill patients), the groups of patients with complete and incomplete

Table 5. Comparison of patient sociodemographic, clinical, and analytical characteristics matched by propensity score analysis.[a]

Variable	Vaccination (n = 52)	No vaccination (n = 52)	p	SMD, %
Male sex, n (%)	39 (75)	39 (75)	> 0.999	-
Age, years	63.1 ± 12.6	61.9 ± 13.7	0.551	8.3
Comorbidities, n (%)				
Obesity	22 (43.3)	20 (38.5)	0.845	5.4
Current smoking	3 (5.8)	2 (3.8)	> 0.999	6.2
Hypertension	24 (46.2)	22 (42.3)	0.832	5.9
Dyslipidemia	23 (44.2)	20 (38.5)	0.690	8.3
Diabetes mellitus	18 (34.6)	16 (30.8)	0.804	6.9
Chronic lung disease	11 (21.2)	11 (21.2)	> 0,999	-
Chronic heart disease	7 (13.5)	5 (9.6)	0.727	9.8
Chronic kidney disease	5 (9.6)	4 (7.7)	> 0.999	4.6
Chronic liver disease	3 (5.8)	2 (3,8)	> 0.999	6.2
Active cancer	2 (3.8)	3 (5.8)	> 0.999	6.5
Stroke	2 (3.8)	2 (3.8)	> 0.999	8.0
Autoimmune disorder	1 (1.9)	2 (3.8)	> 0.999	8.0
Immunosuppression	10 (19.2)	10 (19.2)	> 0.999	-
Charlson Comorbidity Index	2 (1-3)	2 (1-3)	0.963	6.3
COVID-19 wave, n (%)			> 0.999	3.3
3rd to 5th	13 (25.0)	14 (26.9)		
6th and later	39 (75.0)	38 (73.1)		
ICU admission from the ER, n (%)	12 (23.1)	12 (23.1)	> 0.999	-
CURB-65	3 (2-3)	3 (2-3)	0.204	17.1
SAPS II	33.4 ± 10.1	32.2 ± 7.2	0.328	13.7
Do-not-intubate order, n (%)	2 (3.8)	3 (5.8)	> 0.999	6.2
Days from symptom onset to hospital admission	7 (5-9)	7 (5-10)	0.337	11.1
Days from symptom onset to ICU admission	8 (6-12)	8 (7-12)	0.795	2.0
3-4 quadrants affected on the first chest X-ray in the ICU, n (%)	49 (94.2)	47 (90.4)	0.727	9.8
Increased infiltrates at 48 h, n (%)	42 (80.8)	35 (67.3)	0.167	22.6
Respiratory support at ICU admission, n (%)				
CPAP	37 (71.2)	39 (75.0)	0.851	5.2
BiPAP	12 (23.1)	13 (25.0)	> 0.999	2.7
Other (HFNC/IMV)	3 (5.8)	1 (4.5)	0.625	13.9
Drugs, n (%)				
Antibiotics at ICU admission	27 (51.9)	17 (32.7)	0.076	28.0
Remdesivir	2 (3,8)	2 (3.8)	> 0.999	-
Tocilizumab	36 (69.2)	33 (63.5)	0.648	9.5
Corticosteroids	52 (100)	52 (100)	> 0.999	-
D-dimer, ng/mL	1,281 (756-2,884)	1,068 (771-2,103)	0.278	2.3
C-reactive protein, mg/L	12.8 (5.2-21.3)	15.0 (9.5-20.8)	0.006	31.6
LDH, U/L	399 (302-535)	531 (393-783)	0.003	44.8
RR, breaths/min	29 ± 5	30 ± 7	0.557	8.2
PaO_2/FiO_2 at ICU admission, mmHg	112 ± 21	114 ± 17	0.554	8.3

SMD: standardized mean difference; CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age = 65 years; SAPS: Simplified Acute Physiology Score; HFNC: high-flow nasal cannula; and IMV: invasive mechanical ventilation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated.

vaccination were relatively small. This may have impacted the statistical significance of the differences among groups. Second, because this was a single-center study with a working protocol based mainly on the treatment of ARF with NIV, the results may be more closely related to patient management than to vaccination status. Finally, we analyzed all patients admitted since vaccination began, regardless of the predominant variant. The Delta variant predominated during the first few months after initiation of vaccination, with the Omicron variant predominating from September of 2021 onward. However, correlation studies conducted in Europe showed that, although vaccination did not significantly improve the infection rate in the first four months of 2022, it had an impact on health care systems, hospitalizations, ICU admissions, and mortality.[27] This benefit diminished in the last month of 2022, a finding that is consistent with previous observations and indicates that, although a booster dose temporarily restores antibody levels

Table 6. Comparison of patient outcomes matched by propensity score analysis.[a]

Variable	Vaccination (n = 52)	No vaccination (n = 52)	p	SMD, %
Respiratory support during the ICU stay, n (%)				
HFNC	41 (78.8)	47 (90.4)	0.109	0.27
CPAP	44 (84.6)	45 (86.5)	> 0.999	3.5
BiPAP	33 (63.5)	36 (69.2)	0.678	8.6
IMV	16 (30.8)	16 (30.8)	-	-
SOFA score at ICU admission	4.0 ± 1.6	3.9 ± 0.9	0.659	6.2
Worst value during the ICU stay	6.4 ± 3.5	6.4 ± 3.9	0.878	2.1
Patients with complications, n (%)	28 (53.8)	33 (63,5)	0.487	12.0
Hyperglycemia, n (%)	14 (26.9)	15 (28.8)	> 0.999	3.0
Severe bleeding, n (%)	-	3 (5.8)	-	24.5
Acute kidney injury, n (%)	15 (28.8)	13 (25.0)	0.815	6.5
Agitation/hyperactive delirium, n (%)	15 (28.8)	13 (25.0)	0.804	6.9
Weakness acquired in the ICU, n (%)	12 (23.1)	8 (15.4)	0.424	14.7
Thromboembolic disease, n (%)	5 (9.6)	3 (5.8)	0.727	9.8
Atrial fibrillation, n (%)	2 (3.8)	5 (9.6)	0.453	15.8
Barotrauma, n (%)	6 (11.5)	4 (7.7)	0.754	8.7
Nosocomial infection, n (%)	18 (34.6)	20 (38.5)	0.815	6.5
First-line NIV failure[b], n (%)	14 (28.6)	19 (36.5)	0.664	9.3
NIV duration, days	5 (3-7)	4 (3-7)	0.824	1.5
IMV duration, days	14 (8-21)	13 (9-22)	0.927	5.2
Tracheotomy, n (%)	6 (11.5)	3 (5.8)	0.508	13.9
ECMO, n (%)	-	1 (1.9)	-	13.9
ICU stay, days	10.5 (6-19.5)	10 (6-16.5)	0.912	7.8
Hospital stay, days	19 (12-26.5)	18 (11-26)	0.725	10.7
ICU mortality, n (%)	12 (23.1)	16 (30.8)	0.503	12.4
In-hospital mortality, n (%)	13 (25.0)	18 (34.6)	0.405	14.5

SMD: standardized mean difference; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. [b]In 101 patients receiving first-line NIV or after failure of HFNC (49 patients in the vaccination group and 52 patients in the no vaccination group).

and boosts cell-mediated immunity, protection from different outcomes of Omicron infection begins to wane 3-4 months after administration.[27]

It is well demonstrated that vaccines prevent hospitalization, severe disease, and death from COVID-19.[28] What is not as clear is how vaccinated or partially vaccinated patients fare in comparison with unvaccinated patients once COVID-19–related ARF is established. This study failed to show a significant improvement in outcomes in critically ill COVID-19 patients vaccinated against SARS-CoV-2. However, the CIs were wide and the mortality point estimates favored patients who received at least one dose of COVID-19 vaccine. Further, larger, studies are needed in order to determine the connection between vaccination status and prognosis of critical COVID-19, as well as to match patient-related factors, vaccine type, and virus variant with their effects on these patients.

AUTHOR CONTRIBUTIONS

Pedro Nogueira Costa planned the study, interpreted the data, and wrote the article. The remaining authors participated in data collection and interpretation, having reviewed the final draft of the article.

CONFLICTS OF INTEREST

None declared.

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