Retrospective Multicenter Study of COVID-19 Patients Admitted to Non-ICU Wards during the Omicron (B.1.1.529) Variant Surge: Assessment of Clinical Characteristics and Outcomes by Vaccination Status

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ABSTRACT

Background: The benefits of prior vaccination in patients hospitalized for moderate to severe COVID-19 during the Omicron surge are not well defined. We assessed characteristics and outcomes of a cohort of COVID-19 inpatients by their vaccination status.

Methods: Patients admitted with moderate to severe COVID-19 between December 20, 2021 and March 31, 2022 were divided into 3 groups: 1) unvaccinated, 2) vaccinated with 2 doses, and 3) vaccinated with 3 doses. The main outcome was a composite of ICU transfer, mechanical ventilation or in-hospital death (poor outcome).

Results: We enrolled 446 patients (median age 78 years, IQR 65-85.3), of which 168 (37.7%) unvaccinated, 113 (25.3%) vaccinated with 2 doses and 165 (37%) vaccinated with 3 doses. Vaccinated patients had a higher comorbidity burden and were older (3-dose vaccinees) compared to unvaccinated ones. The rate of poor outcome was not significantly different between groups (19.6%, 15% and 22.4% for unvaccinated, 2-dose and 3-dose vaccinated patients, respectively). Multivariable regression analysis did not show a protective effect of vaccination, either with 2 or 3 doses. In the subset of 205 patients over 80 years, a 3-dose vaccination was inversely associated with poor outcome (OR 0.47 [95% CI 0.23-0.95], p=0.04).

Conclusion: The rate of poor outcome was not associated with vaccination status and was similar between study groups, despite a higher risk profile displayed by 2-dose and 3-dose vaccinees. Prior vaccination with 3 doses reduced the risk of poor outcome compared to no vaccination in the subset of patients older than 80 years.

Keywords: COVID-19; Vaccination; In-hospital death; Third dose; Non-ICU setting

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ICU: Intensive Care Unit; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; MV: Mechanical Ventilation; IQR: Interquartile Ranges; SD: Standard Deviation; OR: Odds Ratio; CI: Confidence Interval

INTRODUCTION

Since its first detection in early November 2021, the Omicron (B.1.1.529) variant of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide becoming dominant and causing, in winter 2021-2022, the largest surge in COVID-19 cases to date [1]. Millions of cases of Omicron infection have been registered, even among naturally immunized and vaccinated individuals (breakthrough infections), due to increased transmissibility and immune evasion capacity, and waning of immunity in the population over time [1-6].

Several studies have shown that the protection offered by COVID-19 vaccines against infection or mild disease by Omicron

is substantially lower than previously reported for earlier variants [4,6-8]. Nevertheless, vaccine effectiveness against COVID-19-related hospitalization and death remained relatively high, especially in individuals who received a booster dose (third dose) after completion of the primary regimen [3,4,6,9-13].

In those individuals developing breakthrough Omicron infection and requiring hospitalization, the benefits of prior vaccination (with or without a booster dose) in preventing further disease progression and complications are not well defined. This study aimed to assess the clinical characteristics and outcomes of patients hospitalized for moderate to severe COVID-19 by their vaccination status, during a period of dominant Omicron circulation.

MATERIALS AND METHODS

This retrospective study was carried out at 4 large Italian acute care hospitals in the Tuscany region. The participants were enrolled from 4 COVID-19 non-Intensive Care Unit (ICU) wards, located respectively in the San Giovanni di Dio hospital and the Careggi university hospital of Florence, in the San Jacopo hospital of Pistoia and in the San Giuseppe hospital of Empoli. The study was conducted in the winter 2021-2022, during the fourth wave of COVID-19 cases registered in Italy, caused by the spread of the Omicron (B.1.1.529) variant. All patients with a laboratory confirmed diagnosis of moderate to severe COVID-19 admitted between December 20, 2021 and March 31, 2022 were enrolled. The diagnosis of SARS-CoV-2 infection was confirmed by a real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay on nasopharyngeal swab. COVID-19 severity was defined according to the National Institute of Health guidelines. Patients with unknown vaccination status, patients who received a vaccine not authorized by EMA, patients with a known history of previous SARS-CoV-2 infection, and those with asymptomatic to mild SARS-CoV-2 infection admitted for other medical reasons were excluded.

Participants were divided into 3 groups according to vaccination status: unvaccinated, vaccinated with 2 doses (primary series), and vaccinated with 3 doses (primary series plus booster). The unvaccinated group included patients who had not received any dose of COVID-19 vaccine and patients who had received just 1 dose of a 2-dose primary regimen. The 2-dose vaccinated group included patients who had received the primary vaccination course (included patients vaccinated with a single dose of Ad26.COV2.S [Janssen] vaccine) ≥ 14 days prior to symptom onset, without receiving a booster. The 3-dose vaccinated group included those patients who completed the primary series and received a booster dose ≥ 14 days prior to symptom onset.

Demographics and clinical characteristics of the enrolled patients were retrieved from electronic medical records and recorded on an Excel spreadsheet.

The main outcome of the study was a composite of ICU transfer, Mechanical Ventilation (MV) or in-hospital death, and was defined as "poor outcome". The characteristics and outcomes were compared between unvaccinated and vaccinated patients with either 2 or 3 doses, and between 2-dose and 3-dose vaccinees. A single subgroup analysis was conducted, which included patients older than 80 years.

The study was approved by the institutional review board of the department of internal medicine and the hospital management of each participating hospital and was performed in accordance with the principles embodied in the Declaration of Helsinki. Due to the retrospective design, informed consent requirement was waived.

Statistical analysis

Variables were compared among the study groups (2-dose vaccinated *vs.* unvaccinated patients, and 3-dose vaccinated *vs.* unvaccinated and 2-dose vaccinated patients) and between patients with favorable or poor outcome.

Continuous variables were expressed as medians and Interquartile Ranges (IQR) or means and Standard Deviation (SD) and compared by T-test, or Mann-Whitney, according to Kolmogorov-Smirnov test for normality. Categorical variables were expressed as numbers and percentages and compared by Chi-square test or Fisher exact test, as appropriate. A multivariable logistic regression model was used to determine the adjusted association between vaccination status and the study outcome. Odds Ratio (OR) and its 95% Confidence Interval (CI) were reported. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Analysis was performed using GNU PSPP Statistical Analysis Software (https://www.gnu.org/software/pspp/), and Excel (Microsoft).

RESULTS

During the study period, 470 patients with moderate to severe COVID-19 were admitted to non-ICU COVID-19 wards of participant hospitals. After excluding 24 patients (7 patients with a history of past SARS-CoV-2 infection, 1 patient vaccinated with an EMA unauthorized vaccine, and 16 patients with unknown vaccination status), a total of 446 were enrolled. Viral genome sequencing was obtained in 5 (1.1%) participants: Omicron B.1.1.592 infection was confirmed in all cases.

The median age of the enrolled patients was 78 (IQR 65-85.3) years and 249 (55.8%) were males. One hundred sixty-eight patients (37.7%) were unvaccinated for COVID-19, 113 (25.3%) were vaccinated with 2 doses (primary series), and 165 (37%) with 3 doses (primary series plus booster dose). One hundred one of 113 (89.4%) patients vaccinated with 2 doses received the second dose ≥ 120 days prior to symptom onset. All patients vaccinated with 3 doses received the booster dose within 150 days of symptom onset.

Overall, 15 (3.4%) patients required ICU transfer or MV and 77 (17.3%) died during hospital stay. Eighty-seven (19.5%) patients had a poor outcome (ICU transfer, MV, or in-hospital death). The median length of stay was 7 (IQR 4-11) days.

Table 1 illustrates demographics, clinical characteristics and outcomes of participants by vaccination status. Patients in the 2-dose group were not significantly older (78, IQR 63-81 *vs.* 73.5, IQR 62-83, p=0.73) and had a higher comorbidity burden compared to unvaccinated ones (median Charlson comorbidity index [CCI] 5, IQR 3-6 *vs.* 4, IQR 2-5, p=0.008), being characterized by a higher rate of cancer, chronic lung disease and immunosuppression. Patients in the 3-dose group were significantly older (84, IQR 76-88.5 *vs.* 73.5, IQR 62-83, p<0.001), had a higher comorbidity burden (CCI 6, IQR 4-7 *vs.* 4, IQR 2-5, p<0.001) and, specifically, a higher frequency of cancer, cardiovascular disease, chronic liver disease, chronic lung disease, chronic renal failure and hypertension with respect to those in the unvaccinated group. Compared to 2-dose vaccinated patients, 3-dose vaccinees were older (84, IQR 76-88.5 *vs.* 78, IQR 63-81, p<0.001), had a higher CCI (6, IQR 4-7 *vs.* 5, IQR 3-6, p<0.001) and a higher rate of cardiovascular disease and chronic renal failure.

Table 1: Demographics, clinical characteristics and outcomes of participants by vaccination status: comparison between unvaccinated, 2-dose or 3-dose vaccinated patients. **Note:** BMI: Body Mass Index; CCI: Charlson Comorbidity Index; NIV: Non-Invasive Ventilation; ICU: Intensive Care Unit; MV: Mechanical Ventilation.

Characteristic	Unvaccinated	Vaccinated with 2 doses	P value (0 vs. 2 doses)	Vaccinated with 3 doses	P value (0 vs. 3 doses)	P value (2 vs. 3 doses)
n (%)	168 (37.7)	113 (25.3)	-	165 (37)	-	-
Demographics and clinical characteristics	-	-	-	-	-	-
Median age, years (range)	73.5 (62-83)	78 (63-81)	0.73	84 (76-88.5)	<0.001	<0.001
Male, n (%)	90 (53.6)	72 (63.7)	0.09	87 (53.4)	0.88	0.07
Cancer, n (%)	5 (3)	15 (13.3)	<0.001	31 (18.8)	<0.001	0.22
Cardiovascular disease, n (%)	39 (23.2)	37 (32.7)	0.08	79 (47.9)	<0.001	0.01
Cerebrovascular disease, n (%)	20 (11.9)	16 (14.2)	0.58	22 (13.3)	0.69	0.84
Chronic liver disease, n (%)	5 (3)	3 (2.7)	1	13 (7.9)	0.04	0.07
Chronic lung disease, n (%)	20 (11.9)	25 (22.1)	0.02	47 (28.5)	<0.001	0.23
Chronic renal failure, n (%)	11 (6.5)	9 (8)	0.65	32 (19.4)	<0.001	0.008
Dementia, n (%)	23 (13.7)	15 (13.3)	0.92	34 (20.6)	0.09	0.12
Diabetes mellitus, n (%)	34 (20.2)	34 (30.1)	0.06	48 (29.1)	0.06	0.86
Hypertension, n (%)	73 (43.5)	59 (52.2)	0.15	92 (55.8)	0.02	0.56
Immunosuppression, n (%)	5 (3)	10 (8.8)	0.03	12 (7.3)	0.07	0.63
Obesity (BMI>30), n (%)	22 (13.1)	15 (13.3)	0.97	15 (9.1)	0.25	0.27
Median CCI, n (range)	4 (2-5)	5 (3-6)	0.008	6 (4-7)	<0.001	<0.001
COVID-19 Treatments	-	-	-	-	-	-
Dexamethasone, n (%)	158 (94)	106 (93.8)	0.93	147 (89.1)	0.1	0.18
Remdesivir treatment, n (%)	34 (20.2)	36 (31.9)	0.03	59 (35.8)	0.002	0.5
Second immunomodulant, n (%)	17 (10.1)	8 (7.1)	0.38	6 (3.6)	0.02	0.2
Conventional oxygen therapy, n (%)	111 (66.1)	72 (63.7)	0.68	106 (64.2)	0.73	0.93
NIV, n (%)	46 (27.4)	32 (28.3)	0.86	40 (24.2)	0.51	0.45
Outcomes	-	-	-	-	-	-
Median length of stay, days (range)	7 (4-11)	8 (4-13)	0.12	6 (4-10)	0.54	0.03
ICU transfer or MV, n (%)	7 (4.2)	5 (4.4)	0.91	3 (1.8)	0.34	0.28
In-hospital death, n (%)	27 (16.1)	14 (12.4)	0.39	36 (21.8)	0.18	0.04
ICU transfer, MV, or in-hospital death, n (%)	33 (19.6)	17 (15)	0.32	37 (22.4)	0.53	0.13

Regarding treatments, remdesivir was more frequently used among 2-dose (31.9% *vs.* 20.2%, p=0.03) and 3-dose vaccinated patients (35.8% *vs.* 20.2%, p=0.002) compared to unvaccinated ones; 3-dose vaccinees received a second immunomodulant less frequently than unvaccinated patients (3.6% *vs.* 10.1%, p=0.02).

Thirty-three (19.6%) patients in the unvaccinated, 17 (15%) in the 2-dose and 37 (22.4%) in the 3-dose group experienced a poor outcome, with no statistically significant difference between unvaccinated patients and 2-dose (p=0.32) or 3-dose vaccinees (p=0.53), and between 2-dose and 3-dose vaccinees (p=0.13).

To identify predictors of poor outcome, we performed a univariate comparison of patients with favorable *vs.* poor outcome within the subpopulations of unvaccinated or 2-dose vaccinated patients Table 2, unvaccinated or 3-dose vaccinated patients Table 3, and 2-dose or 3-dose vaccinated patients Supplementary Table 1, respectively. Next, we performed multivariate logistic regression analysis to explore the association between vaccination status and study outcome controlling for potential confounders (Tables 4 and 5 and Supplementary Table 2). The multivariate regression did not show a significant protective effect of vaccination, either with 2 or 3 doses compared to no vaccination (2 doses *vs.* no vaccination: OR 0.65, 95% CI 0.32-1.34, p=0.25; 3 doses *vs.* no vaccination: OR 0.65, 95% CI 0.35-1.23, p=0.19, respectively), and with 3 doses compared to 2 doses (OR 1.13, 95% CI 0.56-2.31, p=0.73). Among the unvaccinated or 2-dose vaccinated patients, dementia was identified as an independent risk factor for poor outcome (OR 3, 95% CI 1.32-6.83, p=0.009). Among the unvaccinated or 3-dose vaccinated patients, age (OR 1.04, 95% CI 1.01-1.07, p=0.01), cancer (OR 3.05, 95% CI 1.18-7.91, p=0.02) and dementia (OR 2.06, 95% CI 1.02-4.16, p=0.04) were confirmed as independent predictors for poor outcome. Cancer was the only independent predictor of poor outcome identified among the subpopulation of 2-dose or 3-dose vaccinees (OR 3.49, 95% CI 1.47-8-27, p=0.004).

Table 2: Univariate comparison of patients unvaccinated or 2-dose vaccinated with favorable *vs.* poor outcome (ICU transfer, MV or in-hospital death). **Note:** BMI: Body Mass Index; CCI: Charlson Comorbidity Index; NIV: Non-Invasive Ventilation.

Characteristic	Favorable outcome	Poor outcome	P value
n (%)	231 (100)	50 (100)	-
Demographics and clinical characteristics	-	-	-
Median age, years (range)	73 (61-80)	82 (72.8-89)	<0.0001
Male, n (%)	134 (58)	28 (56)	0.79
Cancer, n (%)	14 (6.1)	6 (12)	0.14
Cardiovascular disease, n (%)	60 (26)	16 (32)	0.38
Cerebrovascular disease, n (%)	29 (12.6)	7 (14)	0.78
Chronic liver disease, n (%)	8 (3.5)	0 (0)	0.36
Chronic lung disease, n (%)	39 (16.9)	6 (12)	0.39
Chronic renal failure, n (%)	14 (6.1)	6 (12)	0.14
Dementia, n (%)	21 (9.1)	17 (34)	<0.0001
Diabetes mellitus, n (%)	55 (23.8)	13 (5.6)	0.74
Hypertension, n (%)	101 (43.7)	31 (62)	0.019
Immunosuppression, n (%)	11 (4.8)	4 (8)	0.32
Obesity (BMI>30), n (%)	31 (13.4)	6 (12)	0.79
Median CCI, n (range)	4 (2-5)	5 (4-6)	0.0001
COVID-19 Treatments	-	-	-
Dexamethasone, n (%)	217 (93.9)	47 (94)	0.99
Remdesivir, n (%)	61 (26.4)	9 (18)	0.21
Second immunomodulant, n (%)	19 (8.2)	6 (12)	0.4
Conventional oxygen therapy, n (%)	166 (71.9)	17 (34)	<0.0001
NIV, n (%)	47 (20.3)	31 (62)	<0.0001
Vaccination status	-	-	-
2-dose vaccinated, n (%)	96 (41.6)	17 (34)	0.32

Table 3: Univariate comparison of patients unvaccinated or 3-dose vaccinated with favorable *vs.* poor outcome (ICU transfer, MV or in-hospital death). **Note:** BMI: Body Mass Index; CCI: Charlson Comorbidity Index; NIV: Non-Invasive Ventilation.

Characteristic	Favorable outcome	Poor outcome	P value
n (%)	263 (100)	70 (100)	-
Demographics and clinical characteristics	-	-	-
Median age, years (range)	77 (65-86)	84 (79.8-91)	<0.0001
Male, n (%)	137 (52.1)	40 (57.1)	0.45
Cancer, n (%)	23 (8.7)	13 (18.6)	0.019
Cardiovascular disease, n (%)	88 (33.5)	30 (42.9)	0.14
Cerebrovascular disease, n (%)	34 (12.9)	8 (11.4)	0.74
Chronic liver disease, n (%)	15 (5.7)	3 (4.3)	0.77
Chronic lung disease, n (%)	52 (19.8)	15 (21.4)	0.76
Chronic renal failure, n (%)	28 (10.6)	15 (21.4)	0.017
Dementia, n (%)	34 (12.9)	23 (32.9)	<0.0001
Diabetes mellitus, n (%)	65 (24.7)	17 (24.3)	0.94
Hypertension, n (%)	126 (47.9)	39 (55.7)	0.25
Immunosuppression, n (%)	11 (4.2)	6 (8.6)	0.14
Obesity (BMI>30), n (%)	31 (11.8)	6 (8.6)	0.45
Median CCI, n (range)	4 (3-6)	5 (4-6.3)	<0.0001
COVID-19 Treatments	-	-	-
Dexamethasone, n (%)	237 (90.1)	68 (97.1)	0.06
Remdesivir, n (%)	81 (30.8)	12 (17.1)	0.024
Second immunomodulant, n (%)	17 (6.5)	6 (8.6)	0.54
Conventional oxygen therapy, n (%)	193 (73.4)	24 (34.3)	<0.0001
NIV, n (%)	42 (16)	44 (62.9)	<0.0001
Vaccination status	-	-	-
3-dose vaccinated, n (%)	128 (48.7)	37 (52.9)	0.53

Table 4: Predictors of poor outcome (ICU transfer, MV or in-hospital death) within the subpopulation of unvaccinated or 2-dose vaccinated patients, multivariate analysis. **Note:** CCI: Charlson Comorbidity Index.

Characteristic	Odds ratio	95% CI	P value
Age	1.04	1.00-1.08	0.06
Dementia	3	1.32-6.83	0.009
Hypertension	1.63	0.82-3.25	0.16
CCI	1.14	0.92-1.41	0.23
Vaccination with 2 doses	0.65	0.32-1.34	0.25

Table 5: Predictors of poor outcome (ICU transfer, MV or in-hospital death) within the subpopulation of unvaccinated or 3-dose vaccinated patients, multivariate analysis. **Note:** CCI: Charlson Comorbidity Index.

Characteristic	Odds ratio	95%CI	P-value
Age	1.04	1.01-1.07	0.01
Cancer	3.05	1.18-7.91	0.02
Chronic renal failure	1.81	0.77-4.26	0.18
Dementia	2.06	1.02-4.16	0.04
CCI	1.03	0.85-1.26	0.74
Remdesivir	0.62	0.30-1.29	0.2
Vaccination with 3 doses	0.65	0.35-1.23	0.19

After assessing the whole study population, we performed a subgroup analysis of participants with age over 80 years (Supplementary Tables 3-7). Patients in this subgroup were 205 (46% of the whole population), of whom 57 (27.8%) were unvaccinated, 34 (16.6%) vaccinated with 2 doses and 114 (55.6%) with 3 doses. They had a higher median age (86, IQR 83-90 *vs.* 78, IQR 65-85.3, p<0.001) and CCI (6, IQR 5-7 *vs.* 5, IQR 3-6, p<0.001), and experienced a poor outcome more frequently (61 of 205, 29.8% *vs.* 87 of 446, 19.5%, p=0.004) than the whole population. Multivariable regression analysis showed that, among patients older than 80 years, prior vaccination with 3 doses was inversely associated with poor outcome compared to no vaccination (OR 0.47, 95% CI 0.23-0.95, p=0.04), while cancer and dementia were independent predictors of poor outcome (OR 3.60, 95% CI 1.31-9.89, p=0.01 and OR 2.24, 95% CI 1.10-4.56, p=0.03, respectively).

DISCUSSION

In this retrospective multicentre study of patients admitted to non-ICU setting for moderate to severe COVID-19 during a period of Omicron (B.1.1.529) variant dominance, a considerable proportion of enrolled patients were vaccinated with 2 (25.3%) or 3 doses (37%), being affected by a breakthrough SARS-CoV-2 infection. Two-dose vaccinated patients had a higher comorbidity burden and similar age compared to those unvaccinated; 3-dose vaccinated patients had a higher comorbidity burden and were older than unvaccinated and 2-dose vaccinated ones. Although participants vaccinated with 2 or 3 doses had a higher risk profile for progression of COVID-19 disease, the rate of ICU transfer, MV or in-hospital death was similar between study groups (19.6% in unvaccinated, 15% in 2-dose and 22.4% in 3-dose vaccinated patients). The multivariate regression analysis failed to demonstrate a significant protective effect of vaccination with either 2 or 3 doses in the whole population, while identifying higher age and a diagnosis of dementia or cancer as independent risk factors for poor outcome. Receipt of a third dose of vaccine had a protective effect in the high-risk subgroup of patients aged over 80 years.

The Omicron variant has been associated with reduced vaccine effectiveness against infection or mild disease, due to immune evasion and rapid waning immunity. Evidence on protection against severe disease is mixed, with some studies suggesting substantially reduced effectiveness against hospitalization compared to the Delta variant, and other studies suggesting high levels of effectiveness (close to 90%) after a third vaccine dose [3,14]. Time elapsed since receipt of vaccination is associated with reduction in effectiveness, while vaccine booster doses have been shown to restore it [1,3,8,15]. The US VISION network evaluated the effectiveness of mRNA vaccinees in the period December 2021-June 2022, in comparison with no vaccination. During the Omicron BA.1 period, vaccine effectiveness against COVID-19-associated hospitalization 14-149 days and ≥ 150 days after receipt of the second vaccine dose was 68% and 61%, respectively; after receipt of the third dose, a considerable increase in the effectiveness against hospitalization was registered (92% 7-119 days and 85% ≥ 120 days after receipt of dose 3, respectively) [1].

In the present study, the high 2-dose (25.3%) and 3-dose (37%) vaccination rate among patients hospitalized for Omicron infection could suggest a suboptimal performance of vaccination against COVID-19-related hospitalization. However, it should be considered that, at the time of study initiation, the rate of vaccination coverage in the Italian population was remarkably higher than that found in our study population. The percentage of primary vaccination was 93.3% and 95.7% in the 70-79 and over 80 age individuals, respectively, while the percentage of booster vaccination was 51.1% and 68.4%, respectively. Furthermore, the higher comorbidity burden (2-dose and 3-dose vaccinees) and age (3-dose vaccinees) registered in vaccinated participants compared to unvaccinated ones appear as an indirect proof of vaccination effectiveness in preventing COVID-19-related hospitalization in younger and healthier individuals. As already demonstrated by previous studies, our results seem to confirm that the protective effect of vaccination against COVID-19-related hospitalization is weakened in patients with advanced age and high rate of comorbidities [15,16-18]. In addition, the inability of vaccination to prevent hospitalization in 2-dose vaccinated patients could be due to waning immunity, since almost 90% of them in our study had received the second dose over 120 days prior of hospitalization.

With regards to the benefits of prior vaccination in hospitalized patients, the results of our study indicate that, once a patient requires admission to non-ICU setting for moderate to severe COVID-19, the rate of progression to worst outcomes (ICU transfer or MV requirement, or in-hospital death) is not different between unvaccinated and 2-dose or 3-dose vaccinated patients, even after controlling for potential confounders. While several studies have described a protective effect of prior vaccination against disease progression in patients hospitalized for COVID-19, in agreement with our research, other studies have found no association between vaccination status and outcomes in patients admitted for COVID-19 [3,15,17-20]. In the study conducted by Grasselli et al. during a period of Delta variant predominance, vaccinated patients admitted to an ICU for COVID-19 were older and had more comorbidities than unvaccinated patients; after controlling for age and comorbidities, mortality was similar between vaccinated and unvaccinated patients [17]. Similar results

were obtained by Brosh-Nissimov in a cohort of patients admitted with severe/critical COVID-19 during an Omicron-dominant period. The authors found that, compared to unvaccinated patients, 3-dose vaccinees had a higher frequency of hypertension, chronic renal failure, cancer and immunosuppression, and similar rates of MV and death (49% *vs.* 51%, p=0.72). No association was found between 3-dose vaccination and outcome after adjusting for confounders. However, the study also demonstrated that the risk of a poor outcome was reduced among patients who received a fourth vaccine dose [15].

Patients older than 80 years represented a considerable part of our study population (46%). In this study subgroup the median age and burden of comorbidities were higher and the rate of poor outcome significantly exceeded that recorded in the entire population (29.8% *vs.* 19.5%). Multivariate analysis demonstrated a protective effect of vaccination with 3 doses -but not with 2 doses- in this high-risk category of COVID-19 patients, confirming the usefulness of updating vaccination status by booster dose in these vulnerable individuals.

This study has several limitations. The retrospective design reduces the reliability of our findings. The type of vaccinees used by participants was not recorded; as a consequence we were unable to explore potential effectiveness differences. The precise timing of vaccine receipt with respect to SARS-CoV-2 infection acquisition was not available for most participants and we could not calculate the mean time elapsed between receipt of the second or third vaccine dose and Omicron infection acquisition. The Omicron variant (B.1.1.592) infection was confirmed by viral genome sequencing in only about 1% of participants; however, as estimated by national reports, during the study period Omicron was the predominant SARS-CoV-2 variant.

CONCLUSION

In this cohort of patients with Omicron infection admitted to non-ICU setting for moderate to severe COVID-19, participants vaccinated with 2 or 3 doses had a similar rate of poor outcome compared to unvaccinated ones, despite displaying a higher risk profile for progression to most serious COVID-19 complications. Adjusting for age, comorbidities and treatments, vaccination status was not associated with ICU transfer, MV or in-hospital mortality. Only among the high-risk subgroup of patients older than 80 years, previous 3-dose vaccination was protective against adverse outcome compared to no vaccination. These findings underscore the need for continued efforts in improving vaccination coverage and restoring vaccine effectiveness by booster dose, in order to maintain a high protection against the most severe outcomes of the SARS-CoV-2 infection, especially among older individuals.

DISCLOSURE STATEMENT

The authors report no potential conflicts of interest. No financial support.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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