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PII: S1876-0341(23)00469-0

DOI: https://doi.org/10.1016/j.jiph.2023.12.026

Reference: JIPH2345

To appear in: *Journal of Infection and Public Health*

Received date: 6 June 2023

Revised date: 29 December 2023
Accepted date: 31 December 2023

Please cite this article as: Andrea Lombardi, Simone Villa, Marta Colaneri, Giovanni Scaglione, Francesca Bai, Benedetta Varisco, Valeria Bono, Antonio Vena, Chiara Dentone, Chiara Russo, Mauro Tettamanti, Giulia Renisi, Giulia Viero, Cecilia Azzarà, Marco Mantero, Flora Peyvandi, Matteo Bassetti, Giulia Marchetti, Antonio Muscatello, Alessandro Nobili, Andrea Gori and Alessandra Bandera, Clinical characteristics and outcomes of vaccinated patients hospitalised with SARS-CoV-2 breakthrough infection: Multi-IPV, a multicentre study in Northern Italy, *Journal of Infection and Public Health,* (2023) doi:https://doi.org/10.1016/j.jiph.2023.12.026

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Abstract

Background:
Despite the well-known efficacy of anti-COVID-19 vaccines in preventing morbidity and mortality, several vaccinated individuals are diagnosed with SARS-CoV-2 breakthrough infection, which might require hospitalisation. This multicentre, observational, and retrospective study aimed to investigate the clinical characteristics and outcomes of vaccinated vs. non-vaccinated patients, both hospitalised with SARS-CoV-2 infection in 3 major hospitals in Northern Italy.

Methods:
Data collection was retrospective, and paper and electronic medical records of adult patients with a diagnosed SARS-CoV-2 infection were pseudo-anonymised and analysed. Vaccinated and non-vaccinated individuals were manually paired, using a predetermined matching criterion (similar age, gender, and date of hospitalisation). Demographic, clinical, treatment, and outcome data were compared between groups differing by vaccination status using Pearson's Chi-square and Mann-Whitney tests. Moreover, multiple logistic regression analyses were performed to assess the impact of vaccination status on ICU admission or intra-hospital mortality.

Results:
Data from 360 patients were collected. Vaccinated patients presented with a higher prevalence of relevant comorbidities, like kidney replacement therapy or haematological malignancy, despite a milder clinical presentation at the first evaluation. Non-vaccinated patients required intensive care more often than their vaccinated counterparts (8.8% vs. 1.7%, p=0.002). Contrariwise, no difference in intra-hospital mortality was observed between the two groups (19% vs. 20%, p=0.853). These results were confirmed by multivariable logistic regressions, which showed that vaccination was significantly associated with decreased risk of ICU admission (aOR=0.172, 95%CI: 0.039-0.542, p=0.007), but not of intra-hospital mortality (aOR=0.996, 95%CI: 0.582-1.703, p=0.987).

Conclusions:

This study provides real-world data on vaccinated patients hospitalised with COVID-19 in Northern Italy. Our results suggest that COVID-19 vaccination has a protective role in individuals with higher risk profiles, especially regarding the need for ICU admission. These findings contribute to our understanding of SARS-CoV-2 infection outcomes among vaccinated individuals and emphasise the importance of vaccination in preventing severe disease, particularly in those countries with lower first-booster uptake rates.

Keywords
Vaccination, Breakthrough infection, SARS-COV-2

Introduction

Although there are still questions about the impact of SARS-CoV-2 variants and the duration of the immune response, messenger RNA (mRNA)-based and adenoviral-vectored vaccines have shown an overall efficacy of 70-95%, being the most effective way to prevent morbidity and mortality from SARS-CoV-2 [1].

While breakthrough infections, defined as a positive nasopharyngeal swab at least one week after the vaccine schedule, can be expected[2], more attention should be paid to vaccinated patients who experience a progression of COVID-19 to a severe form that requires hospitalisation after being infected[3]. Some studies have already explored the nature and course of SARS-CoV-2 among vaccinated individuals, guiding us in public health preparedness[4–6]. However, despite Italy being the first European country to be heavily affected by the spread of the SARS-CoV-2 pandemic, with a burden of excess mortality[7], real-life data on clinical, laboratory and sociodemographic parameters of patients hospitalised for SARS-CoV-2 despite being fully or partially vaccinated are still scarce[8].

With this in mind, the main objective of this multicentre retrospective observational study was to investigate risk factors and clinical, immunological, and infection characteristics of vaccinated hospitalised patients with SARS-CoV-2 infection in 3 major hospitals in Northern Italy.

Materials and methods

Study design and participants

This study (Multi-IPV study) was a multicentre, observational, retrospective cohort study of hospitalised patients with a confirmed diagnosis of SARS-CoV-2 conducted in Northern Italy (IRCCS Ospedale Maggiore Policlinico, Milan; ASST Santi Paolo e Carlo, Milan; Ospedale Policlinico San Martino, Genoa) from February 2021 to November 2021. The three centres are all university hospitals with around 1,000 beds.

Medical records of all adult patients with clinical and virological diagnosis of SARS-CoV-2 infection were pseudo-anonymised and abstracted on standardised data collection forms. Data were retrospectively extracted from paper and electronic medical records only of the patients with complete information regarding their vaccination status by 1 data entry person per hospital.

Patients' consent

This research project was carried out following a research plan and according to the current version of the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects).

The sponsor (IRCCS Ospedale Maggiore Policlinico, Milan) ensured that approval from a Competent Ethics Committee (CEC) was sought for the study. Before the initiation of treatment and data collection, all participants signed an informed consent. The study was approved by

the IRCCS Ospedale Maggiore Policlinico Foundation Institutional Review Board (1191_2021bis).

Patients' characteristics

The demographic data included sex and age. Clinical data included symptoms at presentation, including the use of a clinical presentation score (i.e., WHO Ordinal Scale[9]), and comorbidities among the following: diabetes, obesity (i.e., body mass index equal to 25 kg/m^2 or above), chronic obstructive pulmonary disease (COPD), kidney disease, liver disease, dialysis, haematological malignancy, solid-organ transplant.

Treatment data included the use of remdesivir, monoclonal antibodies (mAbs), and invasive and non-invasive respiratory support therapies, such as low-flow oxygen, Venturi masks, continuous positive airway pressure (CPAP) helmets, high flow nasal cannula (HFNC), and mechanical ventilation.

Genotyping analysis of SARS-CoV-2 isolates, the COVID-19 vaccine type, and the immunological status were finally considered.

Main exposure

Vaccination status was considered the primary exposure of interest. This was defined as being vaccinated or not if the patient received at least one COVID-19 vaccine dose.

Outcomes

The primary outcome was to describe the clinical characteristics of the patients vaccinated for COVID-19 and admitted to the three considered hospitals with a breakthrough infection.

The secondary outcome was to compare the proportions of admissions to intensive care unit (ICU), intra-hospital mortality and type of respiratory support needed, if any, between vaccinated and non-vaccinated individuals hospitalised for SARS-CoV-2.

Finally, we wanted to assess the impact of the COVID-19 vaccine on ICU admission and intra-hospital mortality.

Statistics

Qualitative variables were described as counts and percentages of each category. Quantitative variables were summarised as median and interquartile range (IQR).

The primary author manually paired all the vaccinated and non-vaccinated individuals based on predetermined matching criteria. Non-vaccinated individuals were matched to vaccinated ones of a similar age (± 5 years compared to the age of the vaccinated patient), same gender, and hospitalised in the same period (± 7 days concerning the date of hospitalisation of the vaccinated patient).

Demographic, clinical, treatment, and outcome data were compared between groups differing by vaccination status using Pearson's Chi-square (χ^2) tests and Mann-Whitney tests.

Two multiple logistic regression analyses were conducted to examine the relationship between vaccination status, ICU admission, and intra-hospital death. In both cases, the relationship was adjusted for patient gender, age, and the number of comorbidities.

The results are expressed in odds ratio (OR) and 95% confidence interval. A significance threshold of 0.05 was used.

Statistical analyses were conducted using R (version 4.1.2).

Results

Overall, 360 patients were included in the study, mainly from ASST Santi Paolo e Carlo, which provided data from 192 patients (53%), while 126 (35%) and 42 (12%) patients were from Ospedale Policlinico San Martino of Genoa and IRCCS Ospedale Maggiore Policlinico of Milan, respectively. Patients' demographic characteristics and comorbidities at admission, stratified by vaccination status, are reported in Table 1.

Baseline characteristics	N	Overall N = 360	Non-vaccinated N = 181	Vaccinated N = 179	p-value
Hospital	360				0.959
PC-MI		42 (12%)	22 (12%)	20 (11%)	
SM-GE		126 (35%)	63 (35%)	63 (35%)	
SPC-MI		192 (53%)	96 (53%)	96 (54%)	
Sex	360				0.989
Male		203 (56%)	102 (56%)	101 (56%)	
Female		157 (44%)	79 (44%)	78 (44%)	
Age (years)	360	68 (51, 80)	67 (51, 79)	68 (50, 81)	0.554
Diabetes	359				0.140
No		278 (77%)	146 (81%)	132 (74%)	
Yes		81 (23%)	35 (19%)	46 (26%)	
Unknown		1	0	1	
Obesity	309				0.321
No		284 (92%)	141 (90%)	143 (93%)	
Yes		25 (8.1%)	15 (9.6%)	10 (6.5%)	
Unknown		51	25	26	
COPD	359				0.451
No		295 (82%)	146 (81%)	149 (84%)	
Yes		64 (18%)	35 (19%)	29 (16%)	
Unknown		1	0	1	
Liver disease	359				>0.999
No		354 (99%)	178 (98%)	176 (99%)	
Yes		5 (1.4%)	3 (1.7%)	2 (1.1%)	
Unknown		1	0	1	
Kidney disease	359				0.220
No		331 (92%)	170 (94%)	161 (90%)	
Yes		28 (7.8%)	11 (6.1%)	17 (9.6%)	
Unknown		1	0	1	
Dialysis	359				0.014
No		353 (98%)	181 (100%)	172 (97%)	
Yes		6 (1.7%)	0 (0%)	6 (3.4%)	
Unknown		1	0	1	
Haematological malignancy	130				0.047
No		117 (90%)	61 (95%)	56 (85%)	
Yes		13 (10%)	3 (4.7%)	10 (15%)	
Unknown		230	117	113	

Solid-organ transplant	322				0.086
No		305 (95%)	155 (97%)	150 (93%)	
Yes		17 (5.3%)	5 (3.1%)	12 (7.4%)	
Unknown		38	21	17	
Number of comorbidities*					0.011
None		175 (49%)	100 (55%)	75 (42%)	
More than 1		185 (51%)	81 (45%)	104 (58%)	

Table 1. Demographic characteristics and comorbidities of enrolled patients at admission.

Most of the patients were males (203, 56%), had a mean age of 68 (IQR: 51-80) years, and had at least one comorbidity (185, 51%). Overall, we observed a high prevalence of comorbidities such as diabetes (23%), chronic obstructive pulmonary diseases (18%), obesity (8.1%) and kidney disease (7.9%). By stratifying the study population for vaccination status, those vaccinated against COVID-19 had a higher frequency of suffering from at least one other disease (58% vs. 45%, P=0.011), especially being on dialysis (3.4% vs. 0.0%, P=0.014) and had a history of haematological malignancy (15% vs 4.7%, P=0.047).

At admission, as presented in Table 2, patients generally presented fever (187, 52%), dyspnoea (147, 41%), and cough (140, 39%). Overall, the clinical presentation at admission was scored 5 (IQR: 4-5) using the WHO Ordinal Scale, and vaccinated patients were generally less affected by dyspnoea (35% vs 46%, P=0.030).

Symptoms at presentation	**N**	**Overall** N = 360	**Non-vaccinated** N = 181	**Vaccinated** N = 179	**p-value**
Fever	360				0.836
No		173 (48%)	86 (48%)	87 (49%)	
Yes		187 (52%)	95 (52%)	92 (51%)	
Coryza	360				0.724
No		352 (98%)	176 (97%)	176 (98%)	
Yes		8 (2.2%)	5 (2.8%)	3 (1.7%)	
Cough	360				0.343
No		220 (61%)	115 (64%)	105 (59%)	
Yes		140 (39%)	66 (36%)	74 (41%)	
Dyspnoea	360				0.030
No		213 (59%)	97 (54%)	116 (65%)	
Yes		147 (41%)	84 (46%)	63 (35%)	
Loss of smell/taste	359				>0.999
No		350 (97%)	175 (97%)	175 (98%)	
Yes		9 (2.5%)	5 (2.8%)	4 (2.2%)	
Unknown		1	1	0	
Gastrointestinal symptoms	360				0.704
No		322 (89%)	163 (90%)	159 (89%)	
Yes		38 (11%)	18 (9.9%)	20 (11%)	

Symptoms at presentation	N	Overall N = 360	Non-vaccinated N = 181	Vaccinated N = 179	p-value
WHO Ordinal Scale					
• **Admission**	168	5.00 (4.00, 5.00)	5.00 (4.00, 5.00)	5.00 (3.50, 5.00)	0.038
		192	96	96	

Table 2. Clinical presentation and characteristics of enrolled patients at admission.

The clinical presentation at discharge, measured using the WHO ordinal scale, was 1 (IQR: 0-1), with no differences between groups (Table 3). Overall, 19 (5.3%) patients were admitted to ICU, and 69 (19%) died. Non-vaccinated individuals were more frequently admitted to ICU than those vaccinated (8.8% vs. 1.7%, P=0.002). On the other hand, no difference was observed in intra-hospital mortality (19% vs 20%, P=0.853).

Therapies	N	Overall N = 360	Non-vaccinated N = 181	Vaccinated N = 179	p-value
WHO Ordinal Scale					
• **Discharge**	167	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.705
		193	96	97	
ICU admission	360				0.002
No		341 (95%)	165 (91%)	176 (98%)	
Yes		19 (5.3%)	16 (8.8%)	3 (1.7%)	
Death	360				0.853
No		291 (81%)	147 (81%)	144 (80%)	
Yes		69 (19%)	34 (19%)	35 (20%)	

Table 3. Clinical presentation at discharge and outcomes.

Focusing on treatment (Table 4), 251 (70%) patients required respiratory support. Overall, 100 patients (60%) required HFNC. Pharmacological treatment was provided in 108 (30%) and 117 (32%) patients with remdesivir and mABs, respectively. No significant differences were observed among those vaccinated and non-vaccinated.

Therapies	N	Overall N = 360	Non-vaccinated N = 181	Vaccinated N = 179	p-value
Respiratory support[§]	358				0.611
No		107 (30%)	56 (31%)	51 (29%)	
Yes		251 (70%)	124 (69%)	127 (71%)	
Unknown		2	1	1	
HFNC	168				0.616
No		68 (40%)	36 (42%)	32 (39%)	
Yes		100 (60%)	49 (58%)	51 (61%)	
Unknown		192	96	96	
Venturi mask	167				0.367
No		162 (97%)	80 (95%)	82 (99%)	

Therapies	N	Overall N = 360	Non-vaccinated N = 181	Vaccinated N = 179	p-value
Yes		5 (3.0%)	4 (4.8%)	1 (1.2%)	
Unknown		193	97	96	
CPAP	167				>0.999
No		166 (99%)	84 (99%)	82 (100%)	
Yes		1 (0.6%)	1 (1.2%)	0 (0%)	
Unknown		193	96	97	
Remdesivir	360				0.765
No		252 (70%)	128 (71%)	124 (69%)	
Yes		108 (30%)	53 (29%)	55 (31%)	
Monoclonal Antibodies	360				0.681
No		243 (68%)	124 (69%)	119 (66%)	
Yes		117 (32%)	57 (31%)	60 (34%)	

Table 4. Respiratory support and pharmacological therapies administered to the enrolled patients.

A small subset of patients was further investigated for their immunological profile and SARS-CoV-2 variant, as described in Table 5. The most common variant detected was the Delta (24/31, 77%), followed by the Omicron (4, 13%), with no difference based on patients' vaccination status. Conversely, the median of anti-S antibody titres at admission was 18 (IQR: 0-1,702) U/mL, with those vaccinated with 6,380 (IQR: 71-12,500) U/mL against 0 (IQR: 0-5) U/mL among non-vaccinated patients (P=0.001).

Variable	N	Overall N = 42	Non-vaccinated N = 22	Vaccinated N = 20	p-value
Anti-S antibodies (U/mL)	29	18 (0 - 1,702)	0 (0 - 5)	6,380 (71 - 12,500)	0.001
Missing	13	7	6	13	
VOCs	31				0.521
Beta		1 (3.2%)	0 (0%)	1 (7.1%)	
Delta		24 (77%)	13 (76%)	11 (79%)	
Gamma		2 (6.5%)	2 (12%)	0 (0%)	
Omicron		4 (13%)	2 (12%)	2 (14%)	
Unknown		11	5	6	

Table 5. Immunological profile against SARS-CoV-2's Spike protein and SARS-CoV-2 variants of concern.

In the multivariable logistic models, we observed no relationship between vaccination status and intra-hospital deaths (OR=1.051, 95%CI: 0.621-1.780, P=0.853), also when adjusted for age, gender, and the number of comorbidities (aOR= 0.996, 95%CI: 0.582-1.703, P=0.987). Conversely, patients vaccinated were found to have a lower probability of being admitted to the ICU (OR=0.176, 95%CI: 0.040-0.539, P=0.007) and remained so when controlled for confounders (aOR=0.172, 95%CI: 0.039-0.542, P=0.007).

Variables	Categories	OR (95%CI)	p-value	aOR (95%CI)*	p-value
COVID-19 vaccine status	Non-vaccinated	1	0.850	1	0.987
	Vaccinated	1.051 (0.621-1.780)		0.996 (0.582-1.703)	
Sex	Female	1	0.017	1	0.011
	Male	0.525 (0.307-0.889)		0.494 (0.285-0.847)	
Age (years)	*continuous*	1.002 (0.988-1.018)	0.749	1.004 (0.989-1.019)	0.646
Number of comorbidities	*continuous*	1.236 (0.969-1.564)	0.082	1.308 (1.014-1.679)	0.036

* Adjusted for all other variables included in the table.
Acronyms: CI, confident interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

Table 6. Crude odds ratio (OR) (95%CI) for the association with intra-hospital death and adjusted OR (aOR) (95%CI) for potential confounders of the association between intra-hospital death and COVID-19 vaccination status (n=360).

Variables	Categories	OR (95%CI)	p-value	aOR (95%CI)*	p-value
COVID-19 vaccine status	Non-vaccinated	1	0.006	1	0.007
	Vaccinated	0.176 (0.040-0.539)		0.172 (0.039-0.542)	
Sex	Female	1	0.010	1	0.010
	Male	7.083 (1.990-45.117)		7.165 (1.985-45.953)	
Age (years)	*continuous*	0.986 (0.960-1.011)	0.266	0.986 (0.955-1.018)	0.385
Number of comorbidities	*continuous*	0.956 (0.574-1.461)	0.849	0.953 (0.556-1.511)	0.847

* Adjusted for all other variables included in the table.
Acronyms: CI, confident interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

Table 7. Crude odds ratio (OR) (95%CI) for the association with ICU admission and adjusted OR (aOR) (95%CI) for potential confounders of the association between ICU admission and COVID-19 vaccination status (n=360).

Discussion

This study investigated the differences in clinical outcomes between vaccinated and non-vaccinated individuals hospitalised for COVID-19. Based on real-world data, our findings revealed that vaccinated patients had a lower risk of being admitted to the ICU, whereas no relationship was found between vaccination status and intra-hospital death.

Firstly, vaccinated patients were more frequently affected by comorbidities notoriously linked to greater severity of SARS-CoV-2 infection, such as dyalisis[10] and haematological malignancy[11].
Nonetheless, these patients presented significantly less dyspnoeic at admission and had reduced median WHO Ordinal Scales scores, potentially implying a lower risk of progression to a severe form of SARS-CoV-2 infection[9]. However, the differences mentioned above in

clinical characteristics did not lead to a difference in treatments administered regarding respiratory support and pharmacological therapies.

Secondly, we found a significant difference in the number of patients admitted to ICU, with non-vaccinated patients requiring intensive care more often than their vaccinated counterparts. Differently, no difference in intra-hospital mortality was observed between the two groups. These results are also confirmed by the multivariable logistic regressions, which showed that vaccination was significantly associated with decreased ICU admission risk but not intra-hospital mortality, as further supported by current evidence [8,12]. However, it is essential to note that the sample in this study was not fully balanced in terms of comorbidities. This imbalance is reasonably expected, as vaccinated individuals mostly had specific recommendations for the COVID-19 vaccine.

However, the increased likelihood of ICU admission for non-vaccinated individuals was often associated with their younger age and fewer comorbidities. As a result, these patients were more likely to be eligible for intensive care and had a higher chance of survival. This partly explains the lack of difference in intra-hospital mortality compared to the vaccinated individuals. A higher burden of comorbidities among vaccinated patients might explain their lower admission to the ICU[13]. Our findings suggest that the COVID-19 vaccine has a protective role in individuals with higher risk profiles, as defined by dyspnoea rates and WHO ordinal scale scores, especially regarding the need for ICU admission. This study adds to the growing body of evidence demonstrating the benefits of COVID-19 vaccination, even without booster vaccine doses, against a very aggressive COVID-19 variant such as Delta [4,14].

However, our study has several limitations. It has a retrospective design and a relatively small sample size. Additionally, Multi-IPV was performed during the Delta-dominant period, characterised by a virulent and aggressive variant and relatively low vaccine coverage in Italy. Most of the Italian population had received only 1 or 2 vaccine doses, if any. Therefore, our findings cannot be directly compared to more recent studies that evaluated the disease course of patients infected with the Omicron variant or subvariants who had already received booster doses of the COVID-19 vaccine. As we discussed earlier, considering the imbalance in terms of comorbidities between vaccinated and non-vaccinated individuals, the findings of this study may not be generalisable to populations with different comorbidity profiles. Lastly, data on SARS-CoV-2 variants and the prognostic role of anti-S antibody titres were unfortunately incomplete, preventing us from drawing any relevant conclusions.

However, we believe that our findings have important implications for public health and provide further support for vaccination efforts against the SARS-CoV-2 pandemic in Italy, where people who have received only two doses of vaccine are now estimated to be around 2 to 3 million[16]. Similarly, these findings might be relevant in other European countries where the first-booster uptake rates are below 50%[17].

Our study calls for prospective data on patients with SARS-CoV-2 infection who were hospitalised despite having received the COVID-19 vaccination.

Conclusions

Although a complete COVID-19 vaccine course is recommended, it does not guarantee immunity against adverse outcomes. Therefore, it is strongly recommended, especially for those with underlying health conditions, to receive vaccinations and booster shots to prevent severe consequences from SARS-CoV-2.

Data availability statement

Anonymised participant-level data will be made available upon requests directed to the corresponding author. Proposals will be reviewed and approved by the competing Ethical

Committee and investigators based on scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

Acknowledgements

None

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Declaration of Competing Interest

All authors declare no competing interests.