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Clinical Characteristics, Outcomes, and Risk Factors of Patients Hospitalized for COVID-19 across the Latest Pandemic Waves: Has Something Changed?

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Abstract: Despite the availability of vaccines and antivirals and the biological evolution of SARS-CoV-2, the rate of hospitalizations and deaths from COVID-19 remains high in Italy. It is crucial to understand whether and how the clinical characteristics of patients hospitalized for COVID-19 have changed over 2021–2022 and which risk factors are currently associated with adverse outcomes to develop targeted interventions. In this study, we present and compare the characteristics and outcomes of 310 patients with COVID-19 who were hospitalized between 1 August and 9 December 2021, when the Delta SARS-CoV-2 variant was prevalent (Group A), and between 3 January and 30 June 2022, when the Omicron variant was predominant (Group B). Using Survival Analysis, we estimated the cumulative 28-day hazard ratio (H.R.) of Intensive Care Unit (ICU) admission/death of patients in Group B vs. A. We built uni- and multivariate Cox regression models for the overall population and each group to identify risk factors for ICU admission/death among patient features. We found that Group B had a comparable risk of ICU admission/death (HR 1.60, 95% Confidence Interval, C.I. 1.00–2.58, $p = 0.05$) but a higher prevalence of elderly and co-morbid subjects than Group A. Non-invasive ventilation requirement was associated with adverse outcomes in both Group A (HR 21.03, 95% C.I. 5.34–82.80, $p < 0.001$) and Group B (HR 4.53, 95% C.I. 2.39–8.59, $p < 0.001$), as well as in the overall population (HR 3.88, 95% C.I. 2.49–6.06, $p < 0.001$). During the Omicron wave, elderly and co-morbid subjects had the highest risk of hospitalization and poor outcomes.

Keywords: COVID-19; Omicron wave; Delta wave; real-life study

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1. Introduction

The clinical spectrum and outcome of COVID-19 depend on the complex interplay between the SARS-CoV-2 virus and the host.

While factors such as older age and underlying co-morbidities have been associated with a higher risk of severe disease [1,2], the evolution of the virus itself has also contributed to the emergence of variants of concern (VOCs). These variants are associated with enhanced transmissibility or virulence, reduction in neutralization by antibodies obtained through natural infection or vaccination, ability to evade detection by the immune system, and reduced susceptibility to antiviral treatments [3,4].

These unique challenges pose a threat to public health.

One such variant, B.1.1.529 (Omicron), has recently been associated with lower rates of hospitalization and death compared to the previously dominant B.1.617.2 (Delta) variant. This finding has been attributed to several factors, including a more significant reduction in

intrinsic viral pathogenicity of the new VOC, the significant number of people with previous SARS-CoV-2 infection (which may offer some protection against severe outcomes even in unvaccinated individuals), and ultimately, the high vaccine coverage, which has proven more effective than natural infection in protecting against death due to COVID-19 [5,6].

However, despite the apparent reduction in disease severity with the Omicron variant, the high transmissibility of the virus has led to a sustained burden on healthcare systems. Indeed, according to the latest report of the Centers for Disease Control, in the United States, the volume of visits to the emergency departments, the daily average number of hospitalizations, and the rate of deaths due to COVID-19 remain substantially the same [7].The same trend is being reported in Italy, where the number of new cases of Sars-CoV2 infection is about 30,000 per week [8].

To address this ongoing challenge, it is essential to understand the clinical features of patients at risk of infection and poor outcomes and to implement appropriate prevention strategies. Until now, only a few studies in Italy have attempted to describe the clinical features of patients hospitalized due to COVID-19 during the Omicron pandemic wave. Specifically, only one of these studies compared the characteristics and outcomes of patients hospitalized with Omicron infection to those infected with the Delta variant. The analysis found a similar rate of ICU admissions between these two groups of patients and between vaccinated and unvaccinated individuals. This may be due to a high prevalence of vulnerable patients with underlying medical conditions among those infected with the Omicron variant, who may have experienced reduced vaccine efficacy [9,10].

In this paper, we compare the demographic and clinical characteristics of patients hospitalized with COVID-19 during the Omicron pandemic wave in a single Italian center to those admitted during the Delta variant wave in 2021.

We aim to identify any changes in the clinical presentation, risk factors for poor outcomes, and potential strategies to mitigate the morbidity and mortality burden of COVID-19.

2. Materials and Methods

2.1. Study Design and Data Collection

The article describes a retrospective observational cohort study conducted at the Infectious Diseases Unit of Vittorio Emanuele Hospital in Bisceglie, Italy, from 1 August 2021, to 30 June 2022. The study aimed to investigate the clinical characteristics of all COVID-19 patients consecutively admitted to the hospital during that period.

Patients were diagnosed with SARS-CoV-2 infection through molecular testing, and demographic and clinical information was collected from their electronic medical records. This information included age, gender, body mass index (BMI), time from symptom onset to hospitalization, duration of hospital stay, and COVID-19 vaccine status, including the number of vaccine doses received. The Charlson Co-morbidity Index (CCI) was used to assess the burden of patients' co-morbidities, with a score of >=6 indicating a high risk of death due to co-morbid disease within the next year [11].

The study also identified and recorded the presence of any concomitant medical conditions that the patients had, based on International Diseases Classification (ICD) 9 coding. These conditions included hypertension, heart rhythm abnormalities, ischemic heart disease, chronic heart failure, peripheral vasculopathy, ischemic stroke, dementia, chronic obstructive pulmonary disease, autoimmune diseases, peptic ulcer, chronic liver disease, chronic kidney disease, solid tumors, hematologic malignancies, obesity, and type II diabetes mellitus.

During the course of the study, patients were treated for COVID-19 according to National Institute of Health (NIH) guidelines [12] based on the severity of their disease and their oxygen requirements. All patients received prophylactic treatment with the anticoagulant Enoxaparin at a single dose of 40 mg (20 mg if their estimated Glomerular Filtration Rate was $\leq$15 mL/min). In patients with early symptom onset (within one week) and low-flow oxygen, intravenous antiviral treatment with Remdesivir was administered at a dose of 200 mg, followed by 100 mg daily for the following four days, if not contraindicated.

Patients with severe SARS-CoV-2 pneumonia requiring supplemental oxygen were given Dexamethasone at a dose of 6 mg daily. Baricitinib, an immune suppressive treatment, was prescribed orally at a dose of 4 mg, in addition to Dexamethasone, on a case-by-case basis, to patients who required non-invasive ventilation or high-flow nasal cannula therapy or who experienced rapid respiratory deterioration.

Patients' outcomes were recorded and classified as (i) discharge with clinical stability, (ii) ICU admission, and (iii) death from any cause. The need for oxygen therapy and non-invasive ventilation (NIV) was also documented within the first 24 h of hospitalization. The latter variable was used to indicate severe SARS-CoV2 pneumonia with respiratory insufficiency. Oxygen therapy administers low-flow oxygen ($\leq$15 L/min) via nasal cannulas, Venturi masks, or reservoir masks.

In Italy, the prevalence of SARS-CoV-2 Variants of Concern (VOC) changed from the Delta variant, which was predominant in 2021, to the Omicron variant and its sub-lineages, which have been predominant in 2022 up to the time of writing. This change, along with an increase in the number of new infections in vaccinated individuals [8] and the availability of early treatments for mild/moderate COVID-19 [13–15], has led to significant changes in the clinical and epidemiological features of new SARS-CoV-2 infections over the study period. As a result, the study population was divided into two groups based on the date of hospital admission due to COVID-19:

- Group A: included patients hospitalized from 1 August to 9 December 2021;
- Group B: included patients hospitalized from 3 January to 30 June 2022.

The study did not routinely perform SARS-CoV2 RNA sequencing tests on all patients. However, data from the sequencing tests on nasal-pharyngeal swabs carried out randomly on patients of the department and data from the bulletins of the Italian Integrated Surveillance for COVID-19 [16] referring to the study period outline that the Delta variant was predominant in Italy and the region from June to December 2021 (Figure 1). The Omicron variant progressively replaced it until the end of the study period. The Delta variant had a prevalence of 100% in the region (Apulia) and higher than 90% nationwide during the enrollment period of Group A patients. The enrollment period of Group B patients recorded a prevalence of the Omicron variant in the Apulia region of 91.9% on 3 January and 100% since 17 January after that, and a prevalence in Italy of 98.8% on 17 January, and higher than 99% in the following surveys. Data of 18 patients hospitalized between 9 December 2021, and 2 January 2022, when the two variants co-existed, were not included in the analysis to avoid biases related to the overlapping of Delta and Omicron variants. Therefore, the two groups of patients in the study mirror the Delta (Group A) and Omicron (Group B) pandemic waves regarding symptoms manifestation and severity of COVID-19 progression.

2.2. Statistical Analysis

The study had two main objectives.

Firstly, it aimed to compare the clinical features and outcomes of patients hospitalized during two pandemic waves, one dominated by the Delta variant in 2021 and another by the Omicron variant in 2022. Descriptive statistics were performed for each group of patients, with categorical variables presented as absolute numbers and percentages and continuous variables as medians and Inter Quartile Ranges (IQRs). The null hypothesis of no differences between the two groups was tested using the Chi-square/Fisher's exact test for categorical variables and the independent samples Mann-Whitney U test for continuous variables collected before and during hospital admission.

The second objective was to investigate whether patients hospitalized more recently, during the Omicron wave and a period of widespread vaccination, had a different risk of adverse outcomes than those admitted in 2021. Survival analysis was conducted using Kaplan-Meier curves to estimate the two groups' relative 28-day risk of adverse outcomes. An adverse outcome was the cumulative probability of dying or being transferred to the

ICU during hospitalization. The two outcomes were considered together as the study population was small, and the probability of adverse events was low.

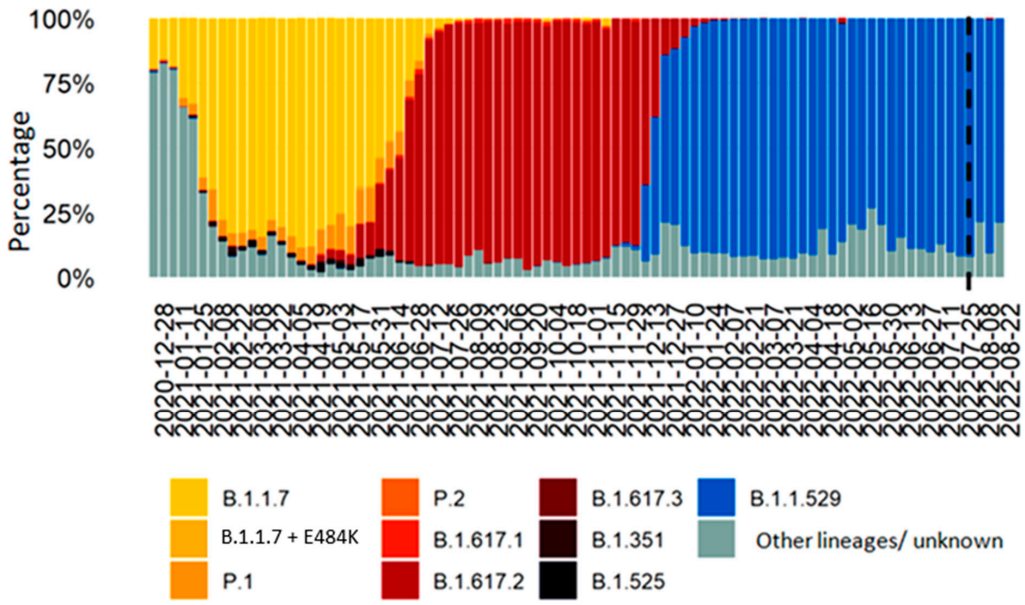

Figure 1. Distribution of the proportion of SARS-CoV2 lineages B.1.351 (Beta variant), P.1 (Gamma variant), B.1.617.2 (Delta variant) e B.1.1.529 (Omicron variant) monitored weekly by the Integrated Surveillance COVID-19, Italy, 28 December 2020–28 August 2022. Relative sublineages are included [16]).

Finally, Cox uni- and multivariate logistic regression models were built to identify ICU admission and death predictors based on patients' characteristics. To account for the study's retrospective nature, causal diagrams, such as directed acyclic graphs (DAGs), were used to understand the structural relationships between variables and distinguish causal effects from biases.

The analysis was conducted first on the entire study population, with potential predictors of adverse outcomes including male sex, age >65 years, symptom onset >7 days before hospitalization, CCI >=6, BMI >=30, and vaccine status. The administration of booster doses was also considered a potential predictor for patients in Group B, who were hospitalized during the Omicron wave. Separate regression models were built for Group A and B patients, considering the same clinical variables. The level of statistical significance was set at $p < 0.05$, and statistical tests were performed according to guidelines for medical research [17,18] and analyzed with the Jamovi 2.3.2 package [19].

3. Results

Overall, 310 patients were included in the analysis. Their clinical characteristics, divided according to the date of symptoms onset, are reported in Table 1.

Patients hospitalized during the year 2022 (Group B) were significantly older (median 78 (66–84) vs. 67 (56–80) years, $p < 0.001$) and presented with a significantly higher burden of co-morbidities (median CCI 5 (3–6) vs. 3 (2–4), $p < 0.001$) than those admitted during the year 2021. Specifically, subjects in Group B showed a higher prevalence of cardiovascular diseases (hypertension, heart rhythm abnormalities, chronic heart failure, peripheral vasculopathy), type 2 diabetes, chronic kidney disease, dementia, Chronic Obstructive Pulmonary Disease, and solid tumors.

Most of the population (229 patients, 74%) was vaccinated. Of them, 131 subjects (57%) had received the booster dose. As expected, they were all included in Group B, as in Italy, the administration of booster doses only started in October 2021 [15]. Notably, a median 12

(1–21) and 15 (3–23) weeks interval between the last vaccine dose and symptom onset was observed for patients in Group A and B, respectively ($p = 0.07$).

206 patients (66%) required oxygen administration, and 91 (30%) needed NIV support due to the onset of severe respiratory insufficiency.

Table 1. General features of the study population according to the time of COVID-19 symptoms onset (Group A: 1 August–9 December 2021; Group B 3 January–30 June 2022).

Variables	Overall (N = 310)	Group A § (N = 100)	Group B (N = 210)	*p*-Value
Median (IQR) age, years	75 (61–83)	67 (56–80)	78 (66–84)	***<0.001***
Male gender, n (%)	199 (64)	59 (59)	140 (67)	0.19
Co-existing conditions, n (%)				
Hypertension	119 (38)	7 (7)	112 (53)	**<0.001**
Heart rhythm abnormalities	55 (17)	8 (8)	47 (22)	**0.002**
Ischemic heart disease	38 (13)	8 (8)	30 (15)	0.08
Chronic heart failure	28 (9)	4 (4)	24 (11)	**0.03**
Type II Diabetes	43 (14)	6 (6)	37 (18)	**0.005**
Chronic Kidney disease	35 (11)	3 (3)	33 (16)	**<0.001**
Chronic Liver disease	8 (3)	1 (1)	7 (3)	0.23
Peripheral vasculopathy	19 (6)	2 (2)	17 (8)	0.03
Ischemic stroke	18 (6)	3 (3)	15 (7)	0.12
Dementia	41 (13)	4 (4)	37 (18)	**<0.001**
Chronic Obstructive Pulmonary Disease	53 (17)	8 (8)	45 (21)	**0.003**
Autoimmune Diseases	17 (5)	3 (3)	14 (7)	0.18
Peptic Ulcer	16 (5)	2 (2)	14 (7)	0.08
Solid Tumors	42 (13)	7 (7)	35 (17)	**0.02**
Hematologic malignancies	15 (5)	2 (2)	13 (6)	0.09
Bone fractures	16 (5)	3 (3)	13 (6)	0.23
BMI >= 30	27 (9)	12 (12)	15 (7)	0.15
Charlson Co-morbidity Index, median (IQR)	4 (2–6)	3 (2–4)	5 (3–6)	***<0.001***
Vaccine status				
0–1 dose	82 (26)	44 (44)	37 (18)	***<0.001***
2 doses	98 (32)	56 (56)	42 (20)	
2 doses + booster dose	131 (42)	0 (0)	131 (62)	
Oxygen * required >=24 after admission, n (%)	206 (66)	69 (69)	137 (65)	0.51
NIV required >=24 h after admission, n (%)	93 (30)	33 (33)	60 (29)	0.43
Median (IQR) time from symptom onset to hospitalization, days	4 (2–8)	5 (3–9)	4 (1–7)	0.56
Median (IQR) duration of hospital stay, days	14 (8–20)	14 (9–21)	14 (8–19)	0.05
Outcome, n (%)				
Discharged with clinical stability	220 (71)	77 (77)	143 (69)	0.23
Admitted in ICU	31 (10)	9 (9)	22 (10)	
Dead	59(19)	14 (14)	45 (21)	

§ Group A: patients hospitalized during B.1.617.2 (Delta) variant-related pandemic wave (1 August–9 December 2021). Group B: hospital admission during B.1.1.529 (Omicron) variant-related pandemic wave (3 January–30 August 2022). *IQR*: Inter Quartile Range; *BMI:* Body Mass Index; *NIV:* Non Invasive Ventilation; *ICU:* Intensive Care Unit. * *Oxygen*: low flow oxygen (≤15 L/min) administered in nasal cannulas, Venturi masks, or reservoir masks.

After a median of 14 (8–20) days of hospitalization, 220 patients (71%) were discharged. 31 patients (10%) were transferred to ICU during hospitalization: unfortunately, it was not possible to recall back their outcome. 59 (19%) subjects died.

Notably, despite the higher prevalence of patients vaccinated with three doses in Group B, the distribution of clinical outcomes of subjects in this group did not significantly differ from that of patients in Group A.

At Survival Analysis, a slightly non-significantly higher 28-day risk of unfavorable outcome was observed indeed for patients in Group B vs. A (HR 1.6, 95% C.I. 1.00–2.58, $p = 0.05$, Figure 2).

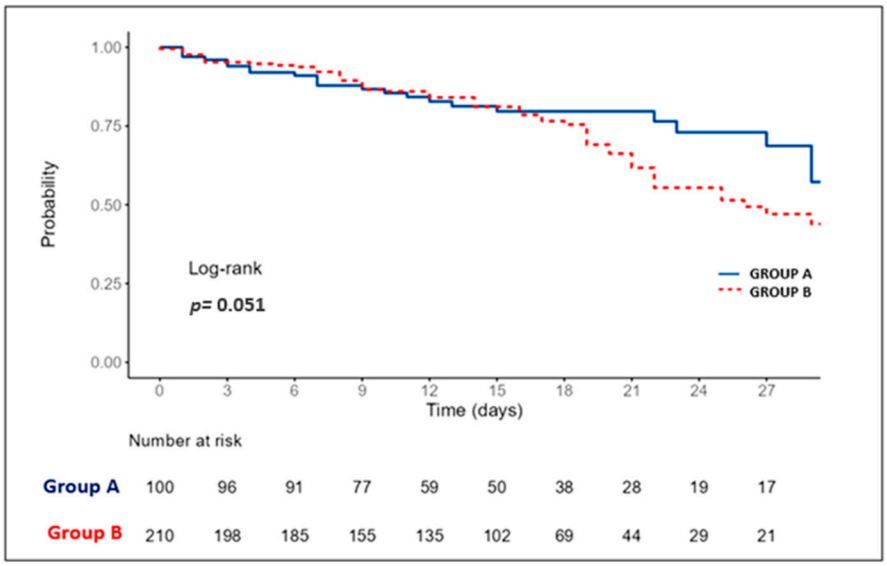

Figure 2. Kaplan Meier estimates the 28-day risk of ICU admission/death of 310 patients hospitalized due to COVID-19 according to the admission date. Group A: Patients hospitalized during B.1.617.2 (Delta) variant-related pandemic wave (1 August–9 December 2021). Group B: hospital admission during B.1.1.529 (Omicron) variant-related pandemic wave (3 January–30 August 2022).

Uni- and multi-variable Cox regression models were built for the overall population and are reported in Table 2. Having been hospitalized infected during the Omicron wave (HR 1.95 (1.09–3.5, $p = 0.02$) and having required NIV during the first 24 h of hospitalization (HR 3.98 95% C.I. 1.79–8.87, $p < 0.001$) related with a higher risk of adverse outcome

Table 2. Cox multivariate regression analysis predicts ICU admission/death risk factors among 301 patients hospitalized with COVID-19 at the Infectious Diseases Unit at Vittorio Emanuele Hospital, Bisceglie, Italy.

Variables	H.R. (95% C.I., *p*-Value)	aHR (95% C.I., *p*-Value)
Male sex	1.58 (1.00–2.49, $p = 0.05$)	1.27 (0.79–2.03, $p = 0.32$)
Age >= 65 years	2.15 (1.17–3.96, $p = 0.01$)	1.70 (0.86–3.34, $p = 0.12$)
Hospitalization during Omicron VOC pandemic wave	1.60 (1.00–2.58, $p = 0.05$)	***1.95 (1.09–3.5, p = 0.02)***
BMI >= 30	0.67 (0.27–1.64, $p= 0.38$)	0.89 (0.34–2.31, $p = 0.81$)
CCI >= 6	1.42 (0.93–2.18, $p= 0.11$)	1.03 (0.64–1.65, $p = 0.91$)
>=7 days before hospitalization	1.12 (0.71–1.76, $p= 0.62$)	0.93 (0.57–1.50, $p = 0.76$)
Vaccinate	1.03 (0.62–1.72, $p= 0.89$)	1.14 (0.62–2.09, $p = 0.69$)
Vaccinate with a booster dose	0.97 (0.63–1.49, $p= 0.90$)	0.69 (0.39–1.20, $p = 0.19$)
NIV < 24 h from admission	***3.83 (2.48–5.91, p < 0.001)***	***3.88 (2.49–6.06, p < 0.001)***

BMI: Body Mass Index; CCI: Charlson Co-morbidity Index; NIV: Non-Invasive Ventilation.

Early NIV requirement was strongly associated with adverse outcomes also in multi-variable models calculated separately for patients in Group A (HR 21.03, 95% C.I. 5.34–82.80, $p < 0.001$), and B (HR 4.53, 95% C.I. 2.39–8.59, $p < 0.001$).

As to vaccine status, while having received two vaccine doses was associated with a 75% lower risk of adverse outcomes for patients in Group A (HR 0.35 95% C.I. 12–0.98, $p = 0.04$, Table 3), no significant relation between vaccination (with 2 or even 3 doses) and poor outcomes was outlined for patients in Group B. (Table 4).

Table 3. Cox multivariate regression analysis predicts ICU admission/death risk factors among 100 patients hospitalized with COVID-19 from 1 August to 9 December 2021 (Group A).

Variables	H.R. (95% C.I., *p*-Value)	aHR (95% C.I., *p*-Value)
Male sex	1.35 (0.58–3.16, $p = 0.48$)	0.65 (0.26–1.61, $p = 0.35$)
Age >= 65 years	3.16 (1.06–9.40, $p = 0.04$)	***6.80 (1.71–27.04, p = 0.006)***
CCI >= 6	1.24 (0.29–5.35, $p = 0.77$)	0.58 (0.13–2.57, $p = 0.47$)
BMI >= 30	0.97 (0.29–3.27, $p = 0.96$)	2.30 (0.55–9.63, $p = 0.25$)
>=7 days until hospitalization	0.78 (0.32–1.93, $p = 0.59$)	0.81 (0.32–2.06, $p = 0.65$)
Vaccinate *	1.00 (0.42–2.38, $p = 0.99$)	***0.35 (0.12–0.98, p = 0.04)***
NIV < 24 h from admission	***14.14 (4.18–47.78, p < 0.001)***	***21.03 (5.34–82.80, p < 0.001)***

BMI: Body Mass Index; CCI: Charlson Co-morbidity Index; NIV: Non-Invasive Ventilation. * 2 vaccine doses vs. 0–1 doses.

Table 4. Cox multivariate regression analysis predicts ICU admission/death risk factors among 310 patients hospitalized with COVID-19 from 3 January to 30 June 2022 (Group B).

Variables	H.R. (95% C.I., *p*-Value)	aHR (95% C.I., *p*-Value)
Male sex	1.62 (0.93–2.81, $p = 0.09$)	1.45 (0.81–2.59, $p = 0.21$)
Age >= 65 years	1.73 (0.82–3.65, $p = 0.19$)	1.43 (0.62–3.31, $p = 0.40$)
CCI >= 6	1.20 (0.74–1.94, $p = 0.46$)	1.13 (0.66–1.91, $p = 0.66$)
BMI >= 30	0.64 (0.15–2.62, $p = 0.53$)	0.67 (0.16–2.85, $p = 0.59$)
>=7 days until hospitalization	1.25 (0.74–2.13, $p = 0.40$)	0.96 (0.55–1.70, $p = 0.90$)
Vaccinate *	1.05 (0.55–2.03, $p = 0.89$)	1.81 (0.83–3.92, $p = 0.13$)
Vaccinate with a booster dose	0.69 (0.43–1.13, $p = 0.14$)	0.58 (0.33–1.02, $p = 0.06$)
NIV < 24 h from admission	3.19 (1.94–5.26, $p < 0.001$)	3.36 (1.99–5.66, $p < 0.001$)

BMI: Body Mass Index; CCI: Charlson Co-morbidity Index; NIV: Non-Invasive Ventilation. * 2 vaccine doses vs. 0–1 doses.

4. Discussion

Italy is one of the European countries that has been hardest hit by the SARS-CoV-2 pandemic, with more than 25 million cases of infection and over 9000 deaths [20].

Since the first case was reported in Lombardy on 20 February 2020, significant financial and human resources have been invested to combat the health emergency. Three years later, healthcare workers are facing a completely different scenario, and there is some positive news to report.

According to data from the European Center for Diseases Control, as of 12 February 2023, there has been a noticeable improvement in the overall COVID-19 epidemiological situation in the European Union. Despite significant geographical differences, case notification rates, hospital admissions, and ICU admissions have generally declined throughout 2022. Similarly, COVID-19-related deaths have reached their lowest levels in the past year [21].

Our retrospective analysis reveals a similar trend, as the proportion of deaths (10%) and the number of ICU admissions during 2022 were comparable to those observed in 2021 (9% and 14%, respectively). This outcome is noteworthy and can be attributed to the early development of effective anti-COVID-19 vaccines and the high level of vaccination coverage among the Italian population [22]. However, it is surprising to see this trend persist despite the changes in the epidemiological landscape during the study period. Specifically, data from the Integrated Surveillance COVID-19 indicate that the Delta variant (B.1.617.2) dominated in Italy from the end of July to the end of December 2021, after which it was gradually replaced by the Omicron variant (B.1.1.529) and its sub-lineages [16].

It is well established that the Omicron variant of SARS-CoV-2, while more transmissible and capable of evading immunity in previously vaccinated individuals, generally poses a lower risk of severe outcomes than the Delta variant. This is due to a combination of intrinsic factors that make the infection less severe and the protection afforded by vaccination against hospitalization [6,23–25]. Thus, it was expected that patients hospitalized during the Omicron wave would have a better prognosis than those with Delta infection.

However, our analysis showed that hospitalized patients with Omicron were significantly older and in worse general condition upon admission than those with Delta infection.

The impact of age on COVID-19 is complex, as older age has been associated with adverse outcomes. However, co-existing co-morbidities that are more prevalent among the elderly may also worsen the effects of SARS-CoV-2 infection [26–28]. Our cohort observed a high prevalence of cardiovascular, neurological, renal, and pulmonary diseases among patients with Omicron infection. A significant proportion of patients required oxygen treatment, with 30% needing non-invasive ventilation within the first 24 h of hospitalization due to the development of severe pneumonia with respiratory insufficiency.

Early therapeutic intervention is crucial to prevent the development of systemic inflammatory syndrome and, ultimately, death, particularly for patients who require oxygen treatment. Unfortunately, elderly patients often have impaired liver and kidney metabolism, which can prevent antiviral treatments such as ritonavir-boosted nirmatrelvir and molnupiravir, which have been associated with a reduction in the severity of the disease. In addition, the Omicron subvariants currently in circulation are resistant to several monoclonal antibodies, making their use no longer recommended by international guidelines [12].

Focusing global efforts on achieving herd immunity through the widespread implementation of highly effective vaccines and promoting non-pharmaceutical interventions such as proper mask use, frequent hand washing, and social distancing to reduce viral transmission is the safest strategy to prevent SARS-CoV-2 infection and COVID-19 progression in vulnerable patients [29]. Our research highlights that, during the Delta wave, subjects who had completed at least the two doses vaccine schedule had almost 70% lower risk of adverse outcomes. However, this effect was lost in subjects hospitalized during the Omicron wave. This finding could explain the long time between the last vaccine doses and COVID-19 symptoms onset, which was nearly 4 months for subjects in Group B. This evidence underlines the importance, at least for elderly and co-morbid subjects, of following a vaccine schedule with regular doses that do not exceed 3 months [30].

In addition, the early identification of individuals who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines is advisable, as they could still benefit from Pre-exposure Prophylaxis with tixagevimab plus cilgavimab [12].

Our study has some limitations.

Firstly, the division of our study population into two groups is mainly based on an epidemiological criterion, as we did not perform SARS-CoV-2 RNA sequencing on all study patients. This limitation has prevented us from including the features of 18 subjects hospitalized during the overlapping period of the two viral variants in the study.

Secondly, the retrospective nature of our research has prevented us from collecting and analyzing data that could have influenced patients' outcomes, such as treatments administered before (mostly oral steroids and antivirals) or during hospitalization. Moreover, we could not recall patients' outcomes after their transfer to the ICU, which could have led to an underestimation of the number of deaths.

Lastly, it should be underlined that our experience applies to a local Italian context and cannot be generalized to a broader scenario.

However, our data will contribute to turning the spotlight again on COVID-19 hospitalizations, which still represent a heavy burden for the Italian economy and healthcare system. Despite the lower pathogenicity of the current variants, elderly and co-morbid subjects are still at risk of hospitalization and poor outcomes, especially in respiratory insufficiency. Further studies with larger cohorts of subjects and more extended follow-up periods are needed to conduct a deeper study of their features. The aim is to draw up new targeted preemptive and therapeutic strategies that could avoid, in these cases, the progression of COVID-19.

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Data Availability Statement: The manuscript has associated data that be shared with other researchers upon reasonable request (please contact the corresponding author at polisenomc@gmail.com).

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