Retrospective analysis of epidemiologic features and clinical course of COVID-19 patients and comparison between vaccinated and unvaccinated patients

Domenica Di Costanzo,[1] Mariano Mazza,[2] Andreina Carbone,[3] Anna Pratillo,[1] Felice Di Perna,[1] Vittoria Graziani,[1] Cristina Casals Marin,[1] Stefania Tartaglione,[1] Antonio Ponticiello[1]

[1]Pneumology Department, Sant'Anna and San Sebastiano Hospital, Caserta; [2]ASL Caserta, Distretto 23, Mondragone (CE); [3]Cardiology Unit, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

Correspondence: Domenica Di Costanzo, Pneumology Department, Sant'Anna and San Sebastiano Hospital, via Ferdinando Palasciano, 81100 Caserta, Italy.
Tel. +39.0823.232630.
E-mail: domenica.dicostanzo@libero.it

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Abstract

At our Pneumology Department, we dealt with three waves of COVID-19 pandemics. The purpose of this study is to compare patients' epidemiological and clinical characteristics across waves and to assess the effect of vaccination on clinical presentation, course, and prognosis. From March 2020 to March 2022, a retrospective cohort study was conducted to compare patient characteristics. Based on the time of hospital admission, data from 456 patients were collected and divided into three groups [first wave (IW), second wave (IIW), and third wave (IIIW)]. In addition, we looked at the link between vaccination, clinical presentation and hospitalization outcome. The average age and comorbidities of patients increased, as did the worsening of respiratory conditions at admission (partial pressure of oxygen/fraction of inspired oxygen ratio median 207 in IW, 95.5 in IIW, and 99 in IIIW). Continuous positive airway pressure was the primary respiratory support during the first wave, but an increase in the use of high-flow nasal cannula and non-invasive ventilation was later observed, resulting in a higher hospital discharge rate and a lower intubation rate. Vaccinated patients had less severe COVID-19-related respiratory failure, a better clinical course, and a higher hospital discharge rate (71.4% in the vaccinated group *vs.* 44.7% in the non-vaccinated group, $p<0.001$). Patients' characteristics changed over the three waves, possibly due to virus mutations. The advancement of clinical and therapeutic management knowledge has contributed to a reduction in the severity of respiratory failure. The vaccination campaign improved the clinical course and reduced mortality.

Introduction

The first infection of COVID-19 was detected in China in December 2019, with the virus spreading rapidly across the world leading the World Health Organization to declare the outbreak as a pandemic on March 11th, 2020. Since then, the COVID-19 pandemic has been responsible for the death of over 2 million people in the European Region [1].

The symptoms are usually fever, sore throat, dry cough, breathlessness, and fatigue, while many people are asymptomatic. SARS-CoV-2 infection may progress to pneumonia, acute respiratory distress syndrome and multi-organ dysfunction [2]. The risk of severe disease increases with age and/or the presence of under-

lying medical conditions such as heart disease, diabetes, oncological, or lung disease.

Most of the countries experienced multiple waves of SARS-CoV-2 outbreaks. Currently, several studies are available showing that, over the course of each wave, patients' characteristics and clinical course varied, leading caregivers to face different challenges requiring different approaches [3-6]. At the beginning of the pandemic, with the exponential rise in the number of cases, hospitals had to face an increasing number of patients presenting with hypoxemic respiratory failure, with a higher demand for mechanical ventilatory support *via* endotracheal intubation, which often exceeded available resources. Later, improved organization of the health facilities and the increase in knowledge on respiratory physiopathology and therapeutic management [7] allowed greater use of non-invasive respiratory supports.

Finally, on December 27th, 2020, "Vaccine Day" marked the official start of the COVID-19 vaccination campaign across Europe. Vaccine distribution in Italy began on December 31st, 2021 [8].

From March 2020 to March 2022, we faced three waves of COVID-19 pandemics in our Pneumology Department. The term "wave" refers to the rising and falling trends of infections over a long period of time. The current study's goal is to characterize the epidemiological and clinical characteristics of infected patients and to assess the efficacy of various therapeutic approaches. The secondary goal was to look at how vaccination affected the clinical presentation, course, and prognosis of patients with COVID-19 pneumonia.

Materials and Methods

We conducted a single-center, observational, retrospective study. We collected data from COVID-19 patients who were admitted to our Department of Respiratory Disease from March 2020 to March 2022. All patients were diagnosed with SARS-CoV-2 infection using a reverse-transcriptase-polymerase chain reaction assay of a specimen collected on a nasopharyngeal swab or throat swab.

We selected patients with complete epidemiologic and clinical data: demographic data such as age, gender, and associated comorbidities; symptoms at presentation, computed tomography findings, hospitalization length, comorbidities, hemogasanalytic data at admission, onset of complications, respiratory support provided [continuous oxygen therapy, high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV)], clinical course and outcome.

They were divided into three groups based on the time of their hospital admission: first wave (IW) from March 2020 to June 2020), second wave (IIW) from October 2020 to June 2021, and third wave (IIIW) from December 2021 to March 2022. To evaluate differences in the epidemiological and clinical characteristics during the three waves and establish their impact on the course of the disease, we excluded vaccinated patients and analyzed data from non-vaccinated patients only. To achieve the secondary endpoint, we evaluated the relationship between vaccination/non-vaccination and clinical presentation [partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2)] and outcome (discharge, intubation, mortality) in COVID-19 patients.

Statistical analysis

The normal distribution of all continuous data was tested by the Kolmogorov-Smirnov test. In the descriptive analysis, frequency and percentage were reported for the categorical variables; mean, standard deviation, median, and interquartile range (IQR) were used to summarize continuous variables. Comparisons were conducted using the Kruskal-Wallis test among different groups; the Mann-Whitney test was used between two groups for continuous variables; and χ^2 tests were used for categorical variables. Univariate and multivariate logistic regression was used to investigate factors independently associated with vaccination. The variables included in the multivariate model were male gender, age, atrial fibrillation, neurological and gastroenteric disorders, hypertension, coronary artery disease, cancer, and Charlson Comorbidity Index. We included variables with $p<0.05$ by the univariable test as a candidate for the multivariable analysis, with a forward variable selection, testing the addition of each variable, and repeating this process until none improves the model to a statistically significant extent.

It was considered to be statistically significant when the p-value was less than 0.05. All calculations were made using SPSS 18.0 (SPSS Inc., Chicago, USA).

Results

Primary endpoint

The total number of analyzed patients was 456. We analyzed data from 407 non-vaccinated patients (IW: 40 patients, IIW 310 patients, and IIIW 57 patients). Patient demographics and comorbidities are described in Table 1.

We observed a significant difference in the median age of the patients among the three waves ($p<0.001$), with older patients in the IIIW group (median age of 75 years old; IQR, 14) and younger in the IW group (median age 58 years old; IQR, 16). Comorbidities varied during the three waves, showing a higher value of Charlson Comorbidity Index in IIIW compared to IW and IIW [0.5 (IQR 1) in IW *vs.* 1 (IQR 1) in IIW *vs.* 2 (IQR 2) in IIIW]. The rate of patients' comorbidities did not differ between the three waves except for chronic kidney disease (2.5% IW, 6.1% IIW, 14% IIIW) and previous stroke/transient ischemic attack (IW 0%, IIW 1.3%, IIIW 17.5%). Patients presented with different degrees of hypoxemia at admission during the three periods. The degree of respiratory impairment (*i.e.*, severity of respiratory failure measured by PaO_2/FiO_2) at hospital admission and the respiratory support administered are summarized in Table 2. During IW, patients presented mainly with mild respiratory failure [PaO_2/FiO_2 median 207 (IQR 234)], during IIW, patients presented mainly with severe respiratory failure [PaO_2/FiO_2 median 95.5 (IQR 55)], as well as during IIIW [PaO_2/FiO_2median 99 (IQR 79)]. Simultaneously, oxygen administration requested for adequate oxygenation was higher [FiO_2 median 80 (IQR 30)] during IIW and IIIW [FiO_2 median 80 (IQR 40)] while lower values were administered during IW [FiO_2 median 37.5 (IQR 59)]. Patients were treated with different oxygen and ventilator support: CPAP, NIV, or HFNC. Provided that the same patient could receive more than one type of respiratory support, according to the hemogasanalytic and clinical characteristic, we observed a different trend in their use. CPAP was mainly used during the second wave (patients treated with CPAP IIW 69.7% *vs.* IW 32.5% *vs* IIIW 43.9%). The use of NIV increased progressively during the three waves (patients treated with NIV IW 12.5% *vs*. IIW 30.3% *vs*. IIIW 56.1%). A similar trend was observed for the use of HFNC (patients treated with HFNC during IW 0 *vs*. IIW 3.5% *vs*. IIIW 19.3%). We also recorded major complications arising during hospital admission, including atrial fibrillation, the onset of pneumothorax/pneumo-mediastinum, thromboembolic complications (including pulmonary embolism), and hemorrhage complications. There were no

significant differences in complication rates during the three waves (Table 3). The length of hospitalization and outcome are summarized in Table 4. The median length of hospitalization was similar during the three waves (IW 7 days, IQR 13; IIW 9 days, IQR 10; IIIW 11 days; IQR 9). The outcomes of hospitalization considered were discharge, need for intubation, and death. The discharge rate

Table 1. Demographics and comorbidities.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p
Age (years), median (IQR)	58 (16)	69 (18)	75 (14)	<0.001
Sex (males), n (%)	28 (70)	190 (61.3)	32 (56.1)	0.38
Pregnant, n (%)	0 (0)	1 (0.3)	0 (0.0)	0.85
Type 2 diabetes mellitus, n (%)	10 (25)	77 (24.8)	14 (24.6)	0.99
Hypertension, n (%)	13 (32.5)	148 (47.7)	30 (52.6)	0.12
Chronic kidney disease, n (%)	1 (2.5)	19 (6.1)	8 (14)	0.049
Dialysis, n (%)	0 (0)	0 (0)	0 (0.)	—-
Neurological disorders, n (%)	3 (7.5)	27 (8.7)	5 (8.8)	0.96
Stroke/transient ischemic attack, n (%)	0 (0)	4 (1.3)	10 (17.5)	<0.001
Thyroid disease, n (%)	3 (7.5)	24 (7.7)	5 (8.8)	0.96
Coronary artery disease, n (%)	2 (5)	47 (15.2)	13 (22.8)	0.056
Atrial fibrillation, n (%)	1 (2.5)	22 (7.1)	3 (5.3)	0.499
Pacemaker/implantable cardioverter-defibrillator, n (%)	0 (0)	8 (2.6)	2 (3.5)	0.52
Heart transplantation, n (%)	0 (0)	0 (0)	0 (0.0)	—
Peripheral artery disease, n (%)	1 (2.5)	6 (1.9)	0 (0)	0.54
Liver disease, n (%)	0 (0)	5 (1.6)	1 (0.9)	0.65
Kidney or liver transplantation, n (%)	0 (0)	5 (1.6)	1 (1.8)	0.7
Gastrointestinal disease, n (%)	0 (0)	4 (1.3)	2 (3.5)	0.317
Chronic obstructive pulmonary disease/asthma, n (%)	0 (0)	40 (12.9)	6 (10.5)	0.052
Cancer, n (%)	2 (5)	35 (11.3)	5 (8.8)	0.43
Charlson comorbidity index, median (IQR)	0.5 (1)	1 (1)	2 (2)	<0.001

IQR, interquartile range; IW, first wave; IIW, second wave; IIIW, third wave.

Table 2. Severity of respiratory failure and respiratory support provided during hospitalization.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p
PaO_2/FiO_2, median (IQR)	207 (234)	95.5 (55)	99 (79)	<0.001
Continuous positive airway pressure, n (%)	13 (32.5)	216 (69.7)	25 (43.9)	<0.001
Non-invasive ventilation, n (%)	5 (12.5)	94 (30.3)	32 (56.1)	<0.001
High flow nasal cannula, n (%)	0 (0)	11 (3.5)	11 (19.3)	<0.001
FiO_2, median (IQR)	37.5 (59)	80 (30)	80 (40)	<0.001

IQR, interquartile range; IW, first wave; IIW, second wave; IIIW, third wave; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

Table 3. Study population COVID-19 complications.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p
Atrial fibrillation, n (%)	0 (0)	13 (4.2)	2 (3.5)	0.41
Pneumothorax/mediastinum, n (%)	0 (0)	11 (3.5)	2 (3.5)	0.48
Thromboembolism, n (%)	1 (2.5)	17 (5.5)	5 (8.8)	0.40
Hemorrhagic events, n (%)	1 (2.5)	10 (3.2)	1 (1.8)	0.82

IW, first wave; IIW, second wave; IIIW, third wave.

Table 4. Length of hospitalization and outcome.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p
Days of hospital, median (IQR)	7 (13)	9 (10)	11 (9)	0.34
Death, n (%)	1 (2.5)	84 (27.1)	28 (49.1)	<0.001*
Intubation/intensive care, n (%)	8 (20)	104 (33.3)	0 (0)	<0.001*
Discharged home, n (%)	31 (77.5)	122 (39.4)	29 (50.9)	<0.001*

IQR, interquartile range; IW, first wave; IIW, second wave; IIIW, third wave.

was significantly different during the three periods, showing a higher percentage during the first wave (patients discharged home IW 77.5%) and during the third wave (patients discharged home IIIW 50.9%), while the lower rate was observed during the second wave (patients discharged home IIW 39.4%). To note, the number of patients who required intubation and mechanical ventilation was different in the first two waves (20% in IW *vs.* 33.3% in IIW), while during the third wave, no patient was intubated. The mortality rate was higher during the third wave compared to the first and second wave (IIIW 49.1%; 2.5% in IW *vs.* 27.1% in IIW; p<0.001).

Secondary endpoint

To evaluate a relationship between vaccination and clinical presentation (PaO_2/FiO_2 ratio) and outcome (discharge, intubation, mortality) in COVID-19 patients, the totality of patients was divided into two groups: V-group (patients who underwent at least one dose of SARSCoV2 vaccine) and NV-group (patients who did not undergo vaccination). Characteristics of the two groups are summarized in Table 5. There were no differences between the two groups in median age and global burden of comorbidities (Charlson Comorbidity Index). However, in the V-group, some comorbidities were more represented like neurological disorders (previous stroke or transient ischemic attack, 20.4% in the V-group *vs.* 8.6% in the NV-group), atrial fibrillation (20.4% in the V-group *vs.* 6.4% in the NV-group) and cancer (both hematological and solid tumor, 30.6% in the V-group *vs.* 10.3% in the NV-group). On the other hand, hypertension was more represented in the NV-group (26.5% in the V-group *vs.* 46.9% in the NV-group). NV patients showed a lower PaO_2/FiO_2 at presentation [PaO_2/FiO_2 median 140 (IQR 170) in the V-group *vs.* 103 (IQR 92) in the NV-group] and requested higher oxygen administration for adequate oxygenation [FiO_2 median 60 (IQR 55) in the V-group *vs.* 80 (IQR 40) in the NV-group]. According to the severity of respiratory failure, we observed a higher use of CPAP in non-vaccinated patients (CPAP use rate 22.4% in the V-group *vs.* 62.4% in the NV-group). About outcomes of hospitalization, we observed no difference in mortality rate (28.6% in the V-group *vs.* 27.8% in the NV-group), and no patients, both vaccinated and unvaccinated, were intubated while the rate of discharge was significantly higher for vaccinated patients (71.4% in the V-group *vs.* 44.7% in the NV-group). Adjusted multivariate analysis showed that PaO_2/FiO_2 at admission [p<0.001, odds ratio (OR) 1.01], FiO_2 required (p<0.001, OR 0.96), use of CPAP (p<0.001, OR 0.17) and discharge rate (p<0.001, OR 4.9) were independently associated with vaccination.

Table 5. Characteristics of vaccinated and non-vaccinated patients.

	V-group (n=49)	NV-group (n=407)	p
Demographics and comorbidities			
Age (years), median (IQR)	73 (16)	69 (19)	0.789
Sex (males), n (%)	23 (46.9)	250 (61.4)	0.051
Charlson comorbidity index, median (IQR)	2 (2)	1 (1)	0.116
Type 2 diabetes mellitus, n (%)	10 (20.4)	101(24.8)	0.49
Hypertension, n (%)	13 (26.5)	191 (46.9)	0.007*
Chronic kidney disease, n (%)	6 (12.2)	28 (6.9)	0.177
Dialysis, n (%)	1 (2)	0 (0)	0.107
Neurological disorders, n (%)	10 (20.4)	35 (8.6)	0.014 *
Stroke/ transient ischemic attack, n (%)	2 (4.1)	14 (3.4)	0.52
Thyroid disease, n (%)	3 (6.1)	32 (7.9)	0.46
Coronary artery disease, n (%)	12 (24.5)	62 (15.2)	0.07
Atrial fibrillation, n (%)	10 (20.4)	26 (6.4)	0.002*
Pacemaker/implantable cardioverter-defibrillator, n (%)	1(2)	10 (2.5)	0.66
Heart transplantation, n (%)	1 (2)	0 (0)	0.107
Peripheral artery disease, n (%)	0 (0)	7 (1.7)	0.44
Liver disease, n (%)	0 (0)	6 (1.5)	0.50
Kidney or liver transplantation, n (%)	1 (2)	6 (1.5)	0.55
Gastrointestinal disease, n (%)	3 (6.1)	6 (1.5)	0.06
Chronic obstructive pulmonary disease/asthma, n (%)	6 (12.2)	46 (11.3)	0.49
Cancer, n (%)	15 (30.6)	42 (10.3)	<0.001*
Clinical presentation			
PaO_2/FiO_2 median (IQR)	140 (170)	103 (92)	<0.001*
FiO_2 median (IQR)	60 (55)	80 (40)	<0.001*
Continuous positive airway pressure, n (%)	11 (22.4)	254 (62.4)	<0.001*
Non-invasive ventilation, n (%)	12 (24.5)	131 (32.2)	0.176
High-flow nasal cannula, n (%)	5 (10.2)	22 (5.4)	0.152
Complications			
Atrial fibrillation, n (%)	4 (8.2)	15 (3.7)	0.136
Pneumothorax/mediastinum, n (%)	0 (0)	13 (3.2)	0.22
Thromboembolism, n (%)	5 (10.2)	23 (5.7)	0.17
Hemorrhagic events, n (%)	0 (0)	12 (2.9)	0.251
Outcomes			
Days of hospital., median (IQR)	9 (14)	9 (11)	0.478
Death, n (%)	14 (28.6)	113 (27.8)	0.9
Intubation/intensive care, n (%)	0 (0)	112 (27.5)	<0.001*
Discharged home, n (%)	35 (71.4)	182 (44.7)	<0.001*

IQR, interquartile range; V, vaccinated; NV, non-vaccinated; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

Discussion

As many healthcare facilities, we experienced three different COVID-19 waves, finding a progressive increase both in the average age of hospitalized patients and the average Charlson score detected at the entrance. We also found worse respiratory conditions at the admission, according to PaO_2/FiO_2 ratio, during the second wave, in line with what was also observed in the other Italian studies by Radovanovic *et al*. and Bensai *et al*. [9,10]. In these patients, respiratory support, also in accordance with the recommendations of the time, was mainly provided by CPAP.

As the waves followed, COVID-19 underwent countless mutations [11,12], which made it less pathogenic in the general population while maintaining its lethality and ability to determine severe pictures in older age groups and patients with multiple comorbidities. However, the increased awareness of the pathogenic mechanisms and the pathophysiological mechanisms of COVID-19 [7,13,14], led to a change in not only pharmacological therapy but also in the respiratory support used in these patients. We observed a progressive increase in the use of HFNC and early NIV and a progressive reduction of the CPAP mask. The improved management with different respiratory aids probably resulted in a significant increase in the discharge rate and a reduction in the rate of intubation, which is especially evident during the third wave.

The higher mortality rate observed in IIIW can be explained by the increase in the average age between the three waves and by a greater comorbidity load and fragility of older patients, and this is also in line with the results of other Italian studies [15,16].

Lastly, no significant differences were observed in length of hospitalization and complication rates.

Analysis of subpopulations of vaccinated and unvaccinated patients found that vaccinated patients had less severe respiratory impairment (higher values of PaO_2/FiO_2 at the time of admission). These patients also showed a more favorable clinical course with a smaller need to use positive pressure respiratory supports and high oxygen flows to compensate for the respiratory failure.

We observed an increase in home discharge rates in vaccinated patients, in line with international literature regarding the effectiveness of anti-SARS-CoV-2 vaccines [17-21]; however, our data showed no differences in mortality rates, probably as already stated regarding age and comorbidities of patients in IIIW.

Conclusions

In conclusion, during the three waves, SARS-CoV-2 underwent countless mutations, which made it less pathogenic in the general population while maintaining its lethality and ability to determine severe pictures in older age groups and patients with multiple comorbidities. However, during the three waves, the improvement in patient management probably resulted in better outcomes. Moreover, the advent of vaccines and the consequent vaccination campaign were able to reduce the severity of respiratory failure due to COVID-19 and make the clinical course more favorable, reducing the burden on the resources of the Italian health system.

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