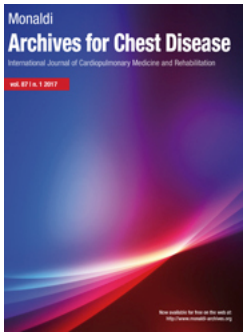

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Retrospective analysis of epidemiologic features and clinical course of COVID-19 patients and comparison between vaccinated and unvaccinated patients

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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 (IW, IIW, and IIIW). In addition, we looked at the link between vaccination and clinical presentation and hospitalization outcome. The average age and comorbidities of patients increased, as did the worsening of respiratory conditions at admission (PaO_2/FiO_2 median 207 in IW, 95.5 in IIW, and 99 in IIIW). Continuous positive airway pressure (CPAP) was the primary respiratory support during the first wave, but an increase in the use of high flow nasal cannula and noninvasive 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 V-group *vs* 44.7% in NV-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.

Key words: COVID-19; COVID-19 vaccines; respiratory insufficiency; SARS-CoV2.

Introduction

The first infection of COVID-19 was detected in China in December 2019, with the virus spreading rapidly across the world leading WHO to declare the outbreak as a pandemic on March 11th, 2020. Since then, 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, fatigue while many people are asymptomatic. SARS-CoV-2 infection may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction (MOF) [2]. The risk of severe disease

increases with age and/or the presence of underlying 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 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 of mechanical ventilatory support via endotracheal intubation (ETI), which often exceed available resources. Later, improved organization of the health facilities and the increase in knowledge on the respiratory physiopathology and therapeutic management [7] allowed a 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 at 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 reverse-transcriptase-PCR (RT-PCR) 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, CT findings, hospitalization length, comorbidities, hemogasanalytic data at admission, onset of complications, respiratory support provided [continuous oxygen therapy (COT), high-flow

nasal cannula (HFNC), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV)], clinical course and outcome.

They were divided into three groups on the basis of the time of their hospital admission: IW (first wave) from March 2020 to June 2020), IIW (second wave) from October 2020 to June 2021) and IIIW (third wave) 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 (PaO_2/FiO_2 ratio) and outcome (discharge, intubation, mortality) in COVID-19 patients.

Statistical analysis

The normal distribution of all continuous data was tested by 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 Kruskal-Wallis test among different groups and Mann–Whitney test was used between 2 groups for continuous variables; χ^2 tests 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 CCI. 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 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, 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 IIIW (the median age 75 years-old; IQR, 14) and younger in 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 a mild respiratory failure (PaO_2/FiO_2median 207 [IQR 234]), during IIW patients presented mainly with a severe respiratory failure (PaO_2/FiO_2median 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 (Fi02 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, onset of pneumothorax/pneumo-mediastinum, thromboembolic complications (including pulmonary embolism) and haemorrhage 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). Outcomes of hospitalization considered were discharge, need for intubation, death. The discharge rate was significantly different during the three period, 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.Mortality rate was higher during 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 underwent vaccination). Characteristics of the two group 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 V-group *vs* 8.6% in NV-group), atrial fibrillation (20.4% in V-group *vs* 6.4% in NV-group) and cancer (both haematological and solid tumour, 30.6% in V-group *vs* 10.3% in NV-group). On the other hand, hypertension was more represented in NV-group (26.5% in V-group *vs* 46.9% in NV-group). NV patients showed a lower PaO_2/FiO_2 at presentation (PaO_2/FiO_2 median 140 [IQR 170] in V-group *vs* 103 [IQR 92] in NV-group) and requested higher oxygen administration for adequate oxygenation (FiO_2 median 60 [IQR 55] in V-group *vs* 80 [IQR 40] in NV-group).According to the severity of respiratory failure, we observed higher use of CPAP in non-vaccinated patients (CPAP use rate 22.4% in V-group *vs* 62.4% in NV-group). About outcomes of hospitalization, we observed no difference in mortality rate (28.6% in V-group vs 27.8% in 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 V-group vs 44.7% in NV-group). Adjusted multivariate analysis showed that PaO_2/FiO_2 at admission (p<0.001, 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.

Discussion

As many health care facilities, we experienced three different Covid-waves founding 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, the respiratory support, also in accordance with the recommendations of the time, was mainly provided by CPAP.

As the waves followed, SARSCoV2 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 pathogenic mechanisms of SARS-CoV-2 [13,14] and the pathophysiological mechanisms of COVID-19 [7], 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 the reduction in the rate of intubation, that are especially evident during the third wave.

The higher mortality rate observed in IIIW can be explained with 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 smaller need to use positive pressure respiratory supports and high oxygen flows to compensate the respiratory failure.

We observed an increase in home discharge rates in vaccinated patients, in line with international literature regarding the effectiveness of anti-SARSCoV2 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 patients' management probably resulted in better outcomes. Moreover, the advent of vaccines and the consequent vaccination campaign, was 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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Table 1. Demographics and comorbidities.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p-value
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*

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

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p-value
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*
Noninvasive 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*

Table 3. Study population COVID-19 complications.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p-value
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

Table 4. Length of hospitalization and outcome.

	IW (n=40)	IIW (n=310)	IIIW (n=57)	p-value
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*

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

	V-group (n=49)	NV-group (n= 407)	p-value
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*
Noninvasive 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
Outcome			

	V-group (n=49)	**NV-group (n= 407)**	**p-value**
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*