Outcomes of patients with COVID-19 hospitalized during the fourth pandemic wave in relation to their clinical features and vaccination status

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ABSTRACT

This study aims to observe the clinical characteristics and outcomes of recovered patients from coronavirus disease 2019 (COVID-19) related to the vaccination status. We examined results of 205 COVID-19-recovered patients from 15 December 2021 to 1 March 2022 in two hospitals of Local Health Authority of Alessandria (Italy) during the fourth pandemic wave. 77% of patients were hospitalized for acute respiratory failure (ARF) with radiological pneumonia pattern (recovered for COVID), 23% for other causes with occasional positivity finding (recovered with COVID). 32% of patients were not vaccinated for SARS-CoV-2, 37% had three doses, 25% two doses, 5% only one dose. All patients without vaccination were hospitalized for ARF and they had a 7 times higher risk of hospitalization than the vaccinated. 60% of all patients had ≥3 comorbidities, of these 50% was vaccinated with three doses. In the fourth pandemic wave compared to the other not all patients were hospitalized for ARF and pneumonia and the presence of comorbidities ≥3 is a risk factor for hospitalization regardless of vaccination status. This justifies the administration of the fourth dose to frail patients.

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Introduction

On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 disease caused from the new severe acute respiratory coronavirus syndrome-coronavirus 2 (SARS-CoV-2) a Public Health Emergency of International Concern.[1]

On 12 March 2020, the WHO has declared the COVID-19 outbreak a global pandemic. As of 11 July 2022, 19.439.501 infected subjects are counted in Italy, and 169.106 subjects died since the start of the pandemic. At the end of December 2020, the vaccine administration has begun on the Italian territory and as of 11 July 2022 91.51% of the population over the age of 12 received at least one administration, 90.12% completed the course of vaccinations and 83.52% of the first booster dose eligible population completed the course for at least 4 months.[2]

Differently from the other pandemic waves, the fourth occurred in the presence of a high percentage of

vaccinated subjects in the Italian adult population. An analysis performed by the Italian National Institute of Health (ISS), updated as of 23 February 2022, relating to the impact of vaccination in the prevention of new infections, intensive care hospitalizations, and deaths, highlighted that: i) the vaccine effectiveness in terms of percentage risk reduction of infection compared to unvaccinated subjects was equal to 63% within 90 days of completing the vaccination course, 52% between 91 and 120 days, and 43% over 120 days from the completion of the vaccination course; and ii) the prevention of severe disease was equal to 86% for vaccinated subjects who have completed the course of vaccinations for less than 90 days, 88% in subjects with a complete course from 91 to 120 days, and 83% in subjects who had completed the vaccination course for more than 120 days.

From 7 January to 6 February 2022 in the population over 12 years, for the unvaccinated subjects the hospitalization rate was about 4 times higher than vaccinated subjects with a full course from ≤120 days and about 9 times higher than vaccinated subjects with additional dose/booster (361 hospitalizations per 100,000 *versus* 89 per 100,000 *versus* 40 per 100,000, respectively).[2]

At the same time, the number of hospitalizations in Intensive Care Unit (ICU) for the unvaccinated subjects was about 6 times higher than vaccinated with a full course from ≤120 days and about 17 times higher than vaccinated with additional dose/booster (30 hospitalizations in ICU per 100,000 *versus* 5 per 100,000 *versus* 2 per 100,000, respectively).[2]

From 31 December 2021 to 30 January 2022, the mortality rate of unvaccinated subjects was about 6 times higher than in vaccinated subjects with a complete course from ≤120 days and approximately 17 times higher than vaccinated subjects with dose additional/booster (114 deaths per 100,000 *versus* 23 per 100,000 *versus* 7 deaths per 100,000, respectively).[2]

Materials and Methods

The VIENNA study

Based on these observations we decided to analyze the clinical features and COVID-19 outcomes (*i.e.*, death, use of invasive and non-invasive mechanical ventilation) in relation to: i) vaccination status; and ii) any other gender differences of 205 patients consecutively hospitalized from 15 December 2021 to 1 March 2022 at COVID-19 wards of the 'Monsignor Galliano' Hospital in Acqui Terme (Alessandria, Italy) and the 'Santo Spirito' Hospital in Casale Monferrato (Alessandria, Italy) both of the Alessandria Local Health Unit (Azienda Sanitaria Locale, Piedmont Region).

The VIENNA observational study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and subsequent revisions (Legislative Decree No. 211 of 24.06.03). The study protocol was approved by the Intercompany Ethics Committee SS. Antonio and Biagio and Cesare Arrigo Hospital, Alessandria.

Statistical analysis

Descriptive statistics were used to analyze the possible correlation among the variables of interest and the covariates collected in the dataset. Categorical variables were expressed as numbers and percentages. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using Epi Info 4.3 version.

Results

Clinical features

The average age of the patients was 74.4 years, 95 (46%) were women and 110 (54%) men. Sixty-six (32%) patients were not vaccinated, 75 (37%) were vaccinated with three doses, 51 (25%) with two doses, 11 (5%) with a single dose. At the hospitalization 125 (60%) patients had a number of comorbidities ≥3. The prevalent comorbidity was arterial hypertension (present in 59% of all hospitalized patients and 97% of patients with comorbidities ≥3). Twenty (10%) hospitalized patients did not present pathologies, 70% of them was not vaccinated. Figure 1 shows clinical features of hospitalized patients in relation to the vaccinal status. It can be noted that hospitalized patients with three doses of vaccine were significantly older than unvaccinated patients (80 years *versus* 72 years) than vaccinated with two doses and one dose (80 years *versus* 73 and 69 years) and they had more comorbidities compared to unvaccinated, vaccinated patients with one dose and two doses (unvaccinated n=52, 34.52%, vaccinated with three doses n=59, 79%, vaccinated with two doses n=37.73%, vaccinated with a dose n=7.64%). Unvaccinated patients or vaccinated with one dose only were hospitalized more frequently even in the absence of pathologies (unvaccinated n=14, 21%, vaccinated with three doses n=1, 1.1%, vaccinated with two doses n=3, 3.6%, vaccinated with a dose n=2.18%).

Clinical course

One hundred fifty-eight (77%) hospitalized patients were admitted for COVID positivity with a 1:3.3 ratio among patients hospitalized with COVID and for COVID. Forty-one (20%) hospitalized patients died and 12 (6%) were transferred to ICU due to the worsening of their clinical conditions. In patients transferred to ICU the mortality rate was 90%. Among the patients transferred to ICU, 46% was unvaccinated while 27% was vaccinated with three doses and the remaining 27%

with two doses. 73% presented a number of comorbidities ≥3 while 80% of unvaccinated hospitalized in ICU presented only one comorbidity (arterial hypertension).

Figure 2 shows the correlation between vaccination status, comorbidities, deaths, and hospitalization in ICU. It is clear that comorbidities represent a statistically significant risk factor for the hospitalization (Table 1) (comorbidities ≥3 were present in 79% and 73% of patients vaccinated with three and two doses, respectively). In the multiple regression model, we observe a greater risk due to the presence of comorbidities with an ODDS of over 4 times, statistically significant at 90% (90% CI 1.64-10.8). Thirty-three (16%) patients received non-invasive ventilation (NIV) with a mortality rate equal to 42.5% (n=14). The average age was 72.7 years. 55.5% of these pa-

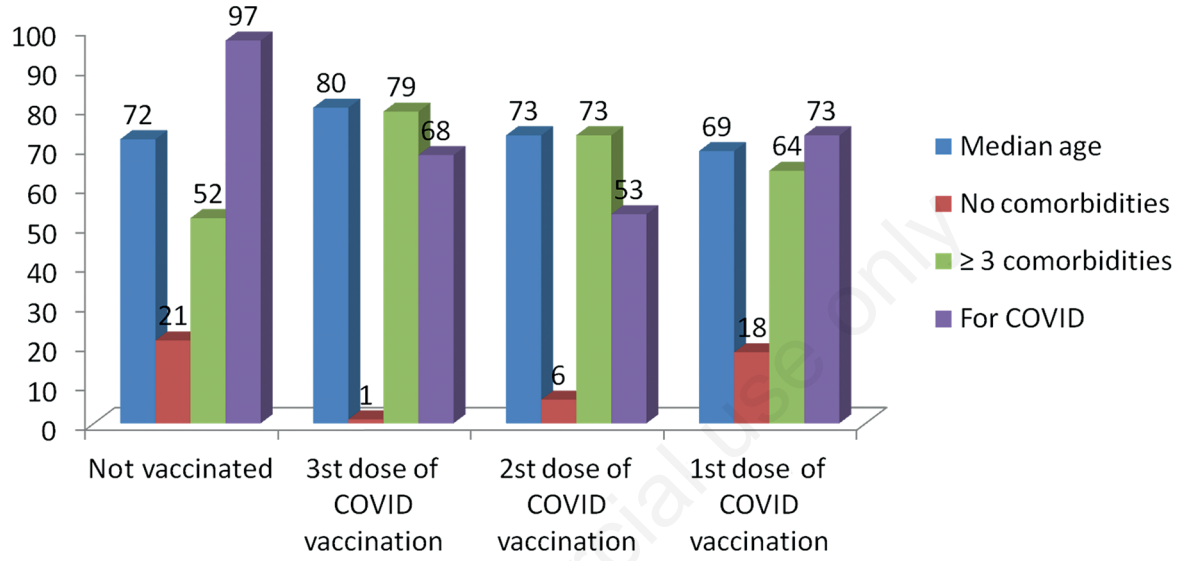

Figure 1. Patient's features related to vaccination status.

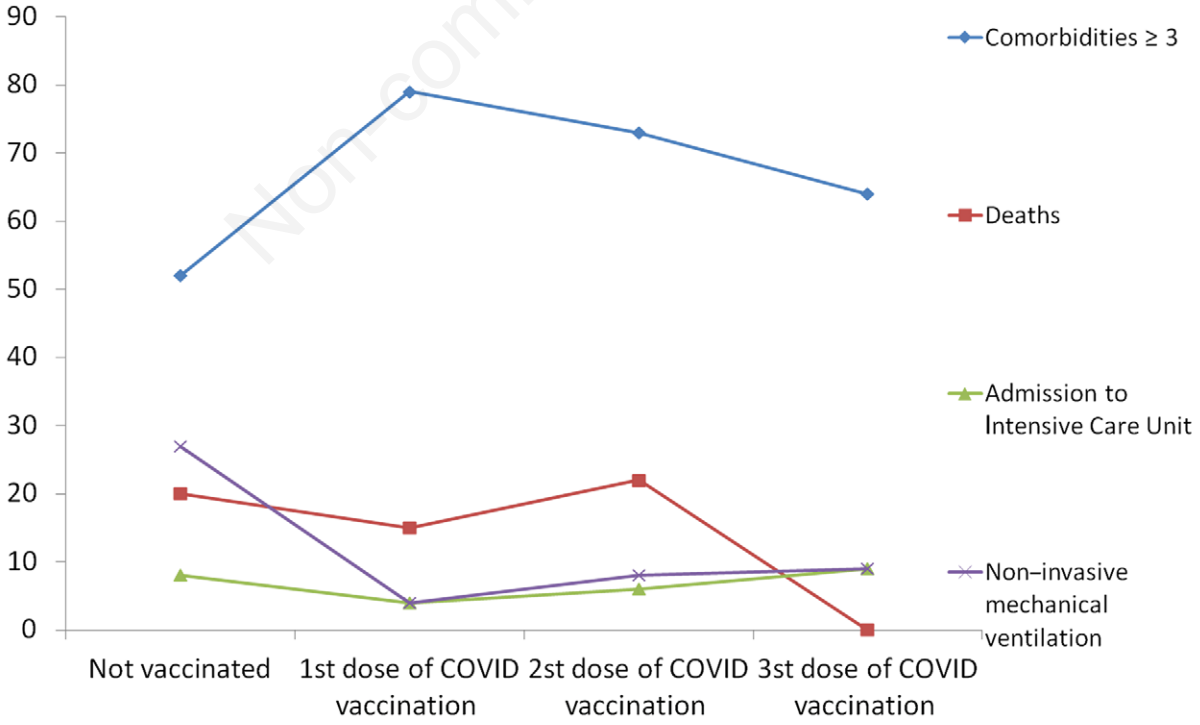

Figure 2. Correlation between vaccination status, comorbidities ≥3, deaths, admission to Intensive Care Unit and non-invasive mechanical ventilation (%).

tients was unvaccinated. Nineteen (58%) had a number of comorbidities ≥3.

Gender differences during the fourth wave pandemic

The differences between gender of the patients admitted during the fourth pandemic wave are highlighted in Figure 3. Women were mostly hospitalized for COVID compared to men (98%, n=93, *versus* 74%, n=81). They were mostly unvaccinated (41%, n=39, *versus* 26%, n=28) and they had fewer comorbidities than men (52%, n=49, *versus* 59% n=65). The average age was higher in women (77.75) than in men (71.7) with a similar death rate (21% in women, n=20, 23%, n=25, in men).

Table 1. Unconditional logistic regression.

Term	Odds ratio	90%	C.I.	Coefficient	S.E.	Z-statistic	P-value
Comorbidities (yes/no)	4.2255	1.6431	10.8662	1.4411	0.5742	2.5097	0.0121
Dead (yes/no)	1.5753	0.7338	3.3819	0.4544	0.4645	0.9784	0.3279
Age	1.0138	0.9955	1.0323	0.0137	0.011	1.2401	0.215
Pneumonia (yes/no)	0.3364	0.1766	0.6408	–1.0895	0.3918	–2.7805	0.0054
Intensive Care Unit (yes/no)	0.4914	0.147	1.6424	–0.7105	0.7336	–0.9685	0.3328
Constant	*	*	*	–0.8248	0.8417	–0.98	0.3271
Convergence	Converged						
Iterations	5						
Final –2*Log-Likelihood	237.862						
Cases included	206						
Test	**Statistic**	**D.F.**	**P-value**				
Score	21.6136	5	0.0006				
Likelihood ratio	22.0104	5	0.0005				

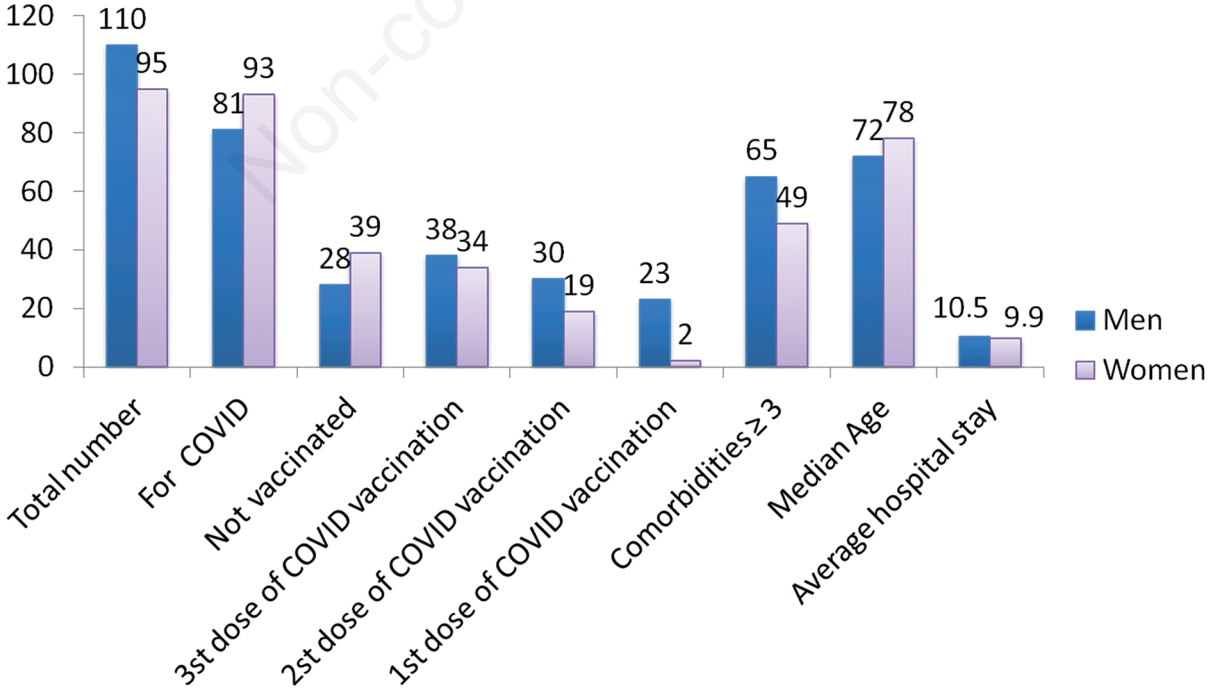

Figure 3. Gender difference in VIENNA study.

Comparison between the first, second and fourth waves pandemic

Compared to the first pandemic wave it is clear that the average age of hospitalized patients has increased (from 67 to 75 years) but the number of deaths (31% *versus* 32% and 20%) and the use of non-invasive mechanical ventilation (*i.e.*, continuous positive airway pressure, CPAP) (29% *versus* 21% and 17%) have decreased (Figure 4).

Discussion

The picture of the fourth pandemic wave in our territory (pertaining to the Monsignor Galliano Hospital in Acqui Terme and the Santo Spirito Hospital in Casale Monferrato) is in line with the ministerial data (2) which show that unvaccinated patients have a 4 times higher risk of being hospitalized than vaccinated subjects. Data relating to vaccination coverage as of 31 December 2021 (Table 2) at the Acqui Terme and Ovada district demonstrate as 46,402 patients were vaccinated with three doses, 50,998 with two doses, 53,748 with one dose and 10,938 subjects were not vaccinated, while in the Casale Monferrato district 52,941 patients were vaccinated with three doses, 56,813 with two doses, 63,193 with one dose and 12,364 subjects were unvaccinated.

The unvaccinated subjects were 23,302 with a hospitalization rate of 0.3%, 7 times higher compared to vaccinated who had a hospitalization rate of 0.044%. Comparing the hospitalization rate between unvaccinated subjects and vaccinated with one dose, two doses and three doses we note that: i) vaccinated with one dose had 30 times less risk of hospitalization compared to unvaccinated (younger patients with less comorbidities); ii) vaccinated with two doses had 6 times lower; iii) and vaccinated with 3 doses 4 times lower.

Comorbidities ≥3 are an independent risk factor for hospitalization and there where comorbidities ≥3 in 97% of hospitalized vaccinated patients with three doses. The vaccination has a protective effect on hospitalization risk; therefore, it is justified the administration of the fourth dose to frail patients with comorbidities ≥3.

Table 2. Vaccination coverage as of 31 December 2021 at Acqui Terme-Ovada district and Casale Monferrato district.

Residents	First dose	Second dose	Third dose	Total population	Population >50 years
Acqui Terme-Ovada district	53.748	50.998	46.402	67.772	64.686
Casale Monferrato district	63.193	56.813	52.941	79.477	75.557

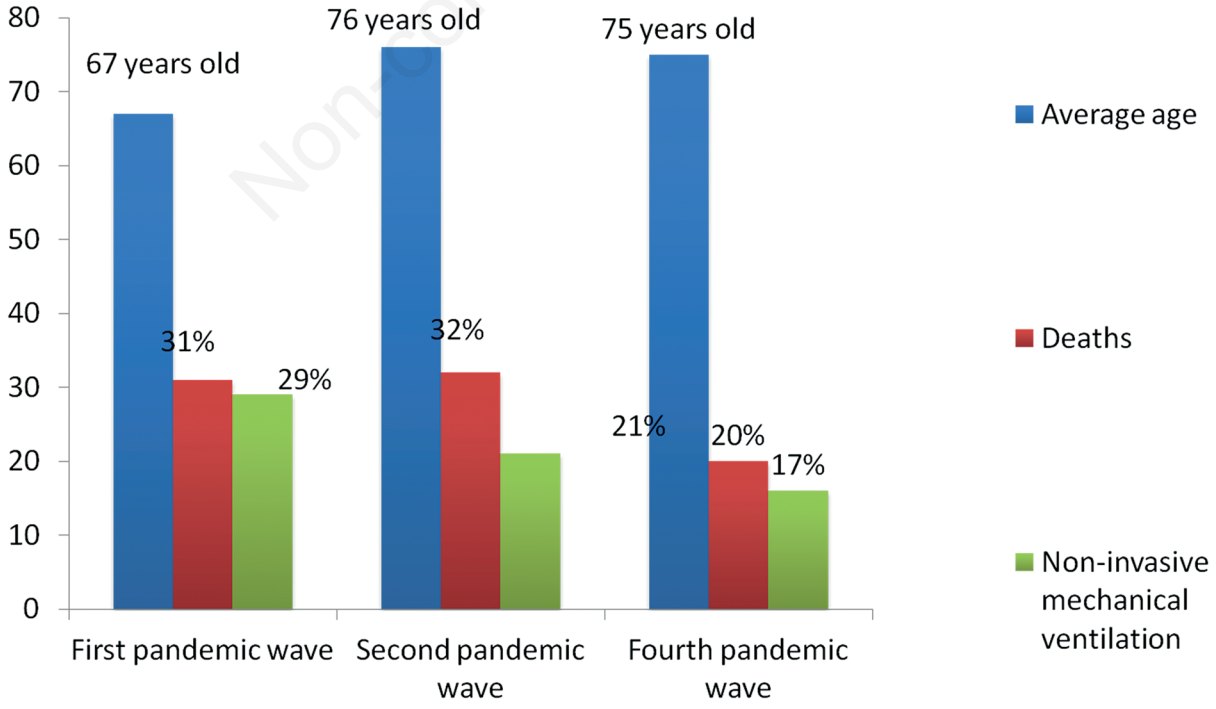

Figure 4. Comparison of different waves during the COVID-19 pandemic.

Conclusions

Our analysis shows an admission ratio of hospitalized patients for COVID-19 and with COVID-19 equal to 3:1 and it highlights the need to implement multidisciplinary areas in each hospital for the management of COVID-19 patients hospitalized for others causes.

Finally, the comparison between the pandemic waves underlines as, unlike previous waves, in the fourth mainly elderly patients with multiple comorbidities have been hospitalized, proving the effectiveness of vaccination in the younger population with few comorbidities. Moreover, the ability of clinicians to manage patients is improved given the reduction in mortality and in the use of non-invasive mechanical ventilation.

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