

A comparative analysis of the first and second COVID-19 wave in Italy: evaluation of mortality in the Infectious Disease Unit of Genoa University Hospital

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SUMMARY

This retrospective study describes demographics and outcomes of adult patients with SARS-CoV-2 infection admitted to our ward during the first wave (from February 25 to May 30, 2020) and during the second wave (from August 5 to November 30, 2020). The primary study objective was to evaluate overall in-hospital mortality, which was 21.1% (60/285) vs 10.3% (27/261) ($p=0.006$). This study seems to corroborate and expand the concept that the second wave of COVID-19 was less deadly than the first. Despite some limitations, the clinical and managerial experience gained during the first wave trained us to handle and control the second one.

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COVID-19 (coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) has become a global pandemic, occurring and forming several peaks in waves (Vahidy *et al.*, 2020; Fan *et al.*, 2020). This infection forced the national health system to reorganize emergency, infectious diseases and intensive care units (Inayat *et al.*, 2020). Up to now, there are more than 3.9 million people in Italy with confirmed infection, with 117,000 deaths (case/fatality rate 3%) (Epicentro ISS, 2021). Throughout the summer, after cases decreased in both the number of infections and in the seriousness of the illness (De Natale *et al.*, 2020), Europe faced a COVID-19 second wave. In this context, the Italian situation appeared to be “strange”: compared with the other selected countries, the Italian infection cases seemed to be lower in the same analysed period (Bontempi, 2020). In Genoa, SARS-CoV-2 had two peaks in waves - a winter wave and an early fall wave. Data obtained from the first wave of the pandemic were used to evaluate the burden and severity of the disease associated with SARS-CoV-2 (Vena *et al.*, 2020). However, we soon realized that patients in-

fectured with SARS-CoV-2 during the second wave of illness experienced a better outcome. The aim of this report is to evaluate overall in-hospital mortality during the first and second wave of COVID-19 patients hospitalized at the Infectious Diseases (ID) Unit of San Martino University Hospital in Genoa, Italy.

This is a retrospective study comparing demographics and outcomes of adult patients with SARS-CoV-2 infection admitted to our Infectious Diseases (ID) ward during the first wave (from February 25 to May 30, 2020) to those admitted during the second wave (from August 5 to November 30, 2020). A confirmed case of SARS-CoV-2 infection was defined by a positive result of a real-time polymerase chain reaction (RT-PCR) assay of a respiratory sample.

The primary study objective was to evaluate overall in-hospital mortality.

In both periods, patients were admitted to the ID ward if they presented PaO₂ ≤60 mmHg at rest in ambient air and were hospitalized following WHO criteria (WHO, 2020).

During the first wave, our standard of care consisted of:

- 1) methylprednisolone (1 mg/kg for 5 days intravenously, then 0.5 mg/kg for 5 days-10 days) for severe patients with SARS-CoV-2 infection;
- 2) remdesivir (200 mg loading dose and then 100 mg/day for 4 days) as compassionate use for progressive severe disease;
- 3) tocilizumab was allowed for intravenous admin-

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istration at the dose of 8 mg/kg (maximum 800 mg) for patients with severe inflammation or rapid respiratory deterioration. Other drugs of proven ineffectiveness (hydroxychloroquine, darunavir/ritonavir, oseltamivir) were also prescribed during the early phase of the pandemic. During the second wave, dexamethasone at the dosage of 6 mg/day for 10 days was administered to all severely ill patients who were on supplemental oxygen or ventilator support. Remdesivir was also administered to all hospitalized patients with symptoms onset <10 days who required supplemental oxygen. In both waves, all patients received low molecular weight heparin as prophylaxis or treatment, depending on the d-dimer value (< or \geq times the normal value, respectively). Short-term antibiotic coverage was prescribed at admission if there was clinical or radiological suspicion of bacterial co-infection.

No sample size calculations were done for this descriptive and comparative analysis. Categorical variables were summarized by means of numbers and percentages, whereas continuous variables were summarized through median values and interquartile ranges (IQR). Normal distribution variables and non-normal distribution continuous variables were compared using *t*-test or Mann-Whitney test. Categorical variables were compared by the Chi-square test. $P \leq .05$ was considered statistically significant. To calculate overall mortality and to optimize the correct estimated probability of death at each time point we also used Kaplan-Meier curve survival analysis techniques. The study was approved by the Ethics

Committee of the Liguria Region (N. CER Liguria 114/2020 - ID 10420).

Overall, a total of 1138 and 1663 patients with proven SARS-CoV-2 infection were hospitalized at San Martino hospital in the first and second wave, respectively. Of those, 285 (25.0 %) and 261 (15.7%) patients were admitted to the ID ward in both periods and are the subjects of the present study.

In *Table 1* we report the main features of COVID-19 percentages in the two different periods, as defined above. The median age, the arterial oxygen partial pressure/fractional inspired oxygen (PaO₂/FiO₂), the number of patients ventilated with Continuous Positive Airway Pressure (CPAP) or with invasive mechanical ventilation were the same during the two waves.

As for treatment, a higher percentage of patients received treatment with corticosteroids (52.9% vs 87.3%, $p < 0.0001$) and remdesivir (2.4% vs 37.9%, $p < 0.00001$) during the second wave.

Median time from first positive to first negative nasal swab of SARS-CoV-2 was longer in the first period than in the second one (11 vs 9 days, $p = .0083$). Overall mortality in the first period was 21.1% (60/285) vs 10.3% (27/261) ($p = .0006$). As shown in *Figure 1*, using the Kaplan-Meier curve, overall in-hospital mortality during the first and second wave was statistically significant (Log Rank = < 0.001), and increased during the first wave. In-ward raw mortality was not significantly different in the two periods ($p = .0953$). No differences were observed in median age of deceased patients (81 vs 80 years; IQR 78-87 vs IQR 75-85).

Our study shows that, in a sample consisting of two

Table 1 - Clinical features, laboratory findings and treatment of hospitalized COVID-19 patients during first vs second wave.

	First wave N= 285 (25.0%)	Second wave N= 261 (15.7%)	P value
Sex, Male (%)	188 (65.9)	167 (63.9)	.6279
Age, years, median (IQR ¹)	68 (57-78)	66 (55-78)	.2543
Days from the onset of symptoms to ID Unit admission, median (IQR)	7 (4-10)	8 (5-12)	.0238
PaO ₂ /FiO ₂ ² at hospital admission median (IQR)	250 (155-310)	265 (187-300)	.4237
Helmet CPAP ³ required (%)	101 (35.4)	86 (32.9)	.5405
IMV ⁴ required (%)	22 (7.7)	27 (10.3)	.2836
Remdesivir treatment	7 (2.4)	99 (37.9)	<.00001
Corticosteroids treatment	151 (52.9)	228 (87.3)	<.00001
Overall In-Hospital mortality	60 (21.1)	27 (10.3)	.0006
7-day	35 (12.3)	14 (5.4)	.0047
30-day	58 (20.3)	27 (10.3)	.0013
Length of ID ⁵ Unit hospitalization median (IQR)	11 (7-17)	8 (5-12)	<.00001
Days from the first nasal swab positive to the first negative median (IQR)	11 (7-20)	9 (6-13)	.0083

Abbreviations: ¹IQR: Interquartile Range, ²PaO₂/FiO₂: arterial oxygen partial pressure/ fractional inspired oxygen, ³CPAP: Continuous Positive Airway Pressure, ⁴IMV: Invasive mechanical ventilation, ⁵ID: Infectious Diseases.

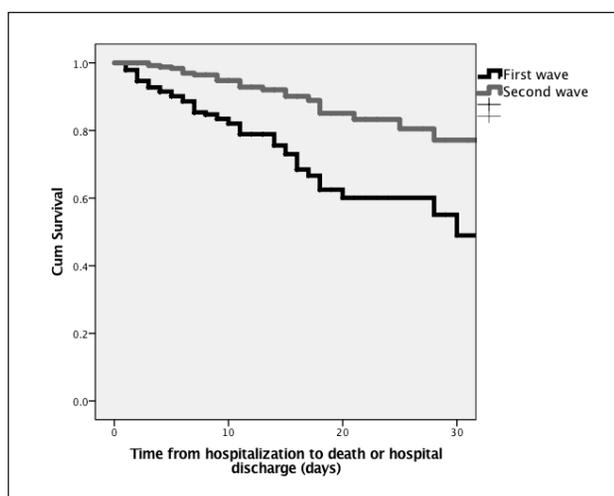


Figure 1 - Overall in-hospital mortality of COVID-19 patients during the first and second wave.

Log Rank= <0.001 .

group of COVID-19 patients similar in age, sex and disease severity, overall in-hospital mortality decreased significantly during the second wave.

The issue regarding trends in mortality of severe SARS-CoV-2 patients during the second wave is strongly debated in the medical literature and is still unresolved (Olivieri *et al.*, 2021).

Consistent with many reports coming from Europe and from other parts of the world (de Brouwer *et al.*, 2020), our study shows that the mortality rate halved from the first to the second wave (from 21.1% to 10.3%). We speculate that several factors may have contributed to this observation, including the wide availability of antiviral therapy, the systematic administration of corticosteroids, and improved medical knowledge. In this sense, the role of effective treatment is further suggested by the shorter viral shedding observed during the second wave (11 vs 9 days). Other factors, not considered in the study, might also have affected shorter viral shedding during the second wave, for example the higher viral load values. Unfortunately, the data concerning quantitative viral load, RT-PCR cycle threshold, and virus sequencing are missing in this report. Furthermore, shorter viral shedding could be explained by a different circulating virus variant during the two different waves.

There are some limitations of our study. First, we did

not collect underlying medical conditions of our patients; second, we cannot exclude that the lower mortality rate observed in the second wave may reflect changes in demographic characteristics of the patients, with the vulnerable population (e.g., nursing home residents) likely to have died in the first wave. Lastly, we calculated the mortality rates based upon patients hospitalized in the ID ward only, and not in the Intensive Care Unit or in the other wards of the hospital, which may not reflect and could underestimate mortality among all patients admitted to our hospital or during the pandemic.

In conclusion, this study seems to corroborate and expand the concept that the second wave of COVID-19 was less deadly than the first one. Despite some limitations, clinical and managerial experience during the first wave trained us to handle and control the second one.

The data concerning the in-hospital mortality rate during the third wave are ongoing, with consideration of the impact of new variants and vaccinated people.

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