BRIEF REPORT

Lombardy, Northern Italy: COVID-19 second wave less severe and deadly than the first? A preliminary investigation

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ABSTRACT

Background: The much-heralded second wave of coronavirus disease (COVID-19) has arrived in Italy. Right now, one of the main questions about COVID-19 is whether the second wave is less severe and deadly than the first wave. In order to answer this challenging question, we decided to evaluate the chest X-ray (CXR) severity of COVID-19 pneumonia, the mechanical ventilation (MV) use, the patient outcome, and certain clinical/laboratory data during the second wave and compare them with those of the first wave.

Methods: During the two COVID-19 waves two independent groups of hospitalised patients were selected. The first group consisted of the first 100 COVID-19 patients admitted to our hospital during the first wave. The second group consisted of another 100 consecutive COVID-19 patients admitted to our hospital during the second wave. We enlisted only Caucasian male patients over the age of fifty for whom the final outcome was available. For each patient, the CXR severity of COVID-19 pneumonia, the MV use, the patient outcome, comorbidities, corticosteroid use, and C-reactive protein (CRP) levels were considered. Nonparametric statistical tests were used to compare the data obtained from the two waves.

Results: The CXR severity of COVID-19 pneumonia, the in-hospital mortality, and CRP levels were significantly higher in the first wave than in the second wave (p ≤ .041). Although not statistically significant, the frequency of MV use was higher in the first wave.

Conclusions: This preliminary investigation seems to confirm that the COVID-19 second wave is less severe and deadly than the first wave.

KEYWORDS
SARS-CoV-2
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Introduction

Italy is one of the countries that has been most affected by the coronavirus disease (COVID-19) pandemic, and Lombardy is the region of Italy with the highest number of infected patients [1]. On December 28, 2020, the overall number of confirmed COVID-19 cases in Lombardy was 472,528, corresponding to about 23% of all cases in Italy [1].

During the COVID-19 first wave, the peak incidence in Italy was reached on March 21, 2020 [1]. After a progressive and significant descent, since late August 2020, the infections have started to rise again reaching a second peak on November 13, 2020 [1].

On March 21, 2020, the number of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Italy was 6557 [1]. On November 13, 2020, the number of new SARS-CoV-2 infections was 40,902 [1]. However, on March 21, the number of newly hospitalised patients with SARS-CoV-2 infection was 1890, with a hospitalisation rate (HR) of 28.8% (10.7% in intensive care units), whereas the number of new hospitalised patients with SARS-CoV-2 infection on November 13 was 1101 with a HR of 2.7% (5.4% in intensive care units) [1].

In addition, while on March 21, the number of new deaths was 793 with a daily case fatality rate (dCFR, calculated as the reported number of new COVID-19 deaths divided by the total number of positive cases) of 1.8%, the number of new deaths on November 13 was 550 with a dCFR of 0.08% [1].

Similarly, on March 21, the daily HR and dCFR in Lombardy were 17.4% and 3%, respectively, whereas the daily HR and dCFR on November 13 were 2.7% and 0.08%, respectively [1].

The thing worth highlighting is that Lombardy had a significantly higher dCFR than the rest of Italy only in the first COVID-19 wave.

According to these preliminary data, it would appear that in Italy, especially in Lombardy, the COVID-19 second wave is less severe (reduced daily HR) and deadly (reduced dCFR) than the first one was. In particular, it should be stressed that in Lombardy the dCFR in the COVID-19 second wave (calculated on November 13) was about 40 times lower than in the first one (calculated on March 21).

However, this difference could be affected by several factors, including the different number of swabs performed in the two waves. In fact, while on March 21, the number of nasal/pharyngeal swabs was 26,336 (with a 24.9% positivity rate), the number of nasal/pharyngeal swabs on November 13 was 254,908 (with a 16% positivity rate) [1]. Therefore, it is not yet clear whether the COVID-19 second wave in Italy, specifically in Lombardy, is less severe and deadly than the first one.

Considering the close relationship between pulmonary involvement, in-hospital mortality [2–4], and the need for ventilatory support [4,5], the main purpose of this study was to quantify the chest X-ray (CXR) severity of COVID-19 pneumonia during the second wave and compare it with that of the first one. To further test whether the severity and mortality of the second wave are indeed lower than that of the first wave, we compared the use of mechanical ventilation (MV), and the frequency of COVID-19-related mortality in the two waves. In addition, to determine whether the differences between the first and the second waves were real, we also considered comorbidities, corticosteroid use, and C-reactive protein (CRP) levels [6–8].

Materials and methods

To evaluate the CXR severity of COVID-19 pneumonia and the COVID-19-related mortality in both waves, we selected two independent groups of hospitalised patients with SARS-CoV-2 infection (confirmed by real-time polymerase chain reaction) for whom the final outcome (recovery or death) was available. The first group consisted of the first 100 male patients with COVID-19 admitted to our hospital during the first wave. The second group consisted of 100 consecutive male patients with COVID-19 admitted to our hospital during the second wave, from October 1 to November 30, 2020. For this study, we decided to enlist only Caucasian male patients over the age of fifty, as the literature reports that this subgroup of the population is more likely to develop severe lung disease [9]. Patients with previous interstitial lung disease or lung resection were excluded from this analysis. In addition, patients who died not as a result of the SARS-CoV-2 infection were also excluded.

The selected patients, retrospectively obtained through a search on our departmental digital archive, were also divided into four groups according to age: 50–59 years (group A), 60–69 years (group B), 70–79 years (group C), and ≥ 80 years (group D).

The radiographic severity of COVID-19 pneumonia was assessed using a dedicated CXR scoring system (Brixia score) [10]. For each patient, only the CXR examination showing the worst pneumonia was considered for comparison. The frontal chest projection of these
The data are presented as numbers (%) or medians (interquartile range). A. BORGHESI ET AL.

Table 1. Baseline characteristics of the study sample in the two COVID-19 waves.

| Characteristic                      | First (100 patients) | Second (100 patients) | p Value* |
|-------------------------------------|-----------------------|------------------------|----------|
| Patient age, years                  | 70 (61–78)            | 66 (59–77)             | .336     |
| Hypertension                        |                       |                        |          |
| No                                  | 43 (43)               | 51 (51)                | .258     |
| Yes                                 | 57 (57)               | 49 (49)                |          |
| Cardiovascular disease              |                       |                        |          |
| No                                  | 59 (59)               | 61 (61)                | .773     |
| Yes                                 | 41 (41)               | 39 (39)                |          |
| Diabetes                            |                       |                        |          |
| No                                  | 88 (88)               | 85 (85)                | .539     |
| Yes                                 | 12 (12)               | 15 (15)                |          |
| Chronic kidney disease              |                       |                        |          |
| No                                  | 90 (90)               | 92 (92)                | .622     |
| Yes                                 | 10 (10)               | 8 (8)                  |          |

Data are presented as numbers (%) or medians (interquartile range). *p Values obtained by means the Mann-Whitney U test or chi-square test.

examinations was independently evaluated by a thoracic radiologist (A.B.) with 15 years of experience in thoracic imaging who assigned the appropriate Brixia score. We also compared the use of MV and the in-hospital mortality in the two waves.

To further investigate differences between first and second COVID-19 waves, the presence of underlying comorbidities (hypertension, cardiovascular disease, diabetes, chronic kidney disease), the use of corticosteroids, and CRP levels were evaluated. For CRP levels, only the highest value measured during hospitalisation was considered for comparison.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the 2013 version of the Declaration of Helsinki. This preliminary investigation was notified to our local ethics committee as a retrospective analysis. Given the retrospective nature of this analysis, performed with data collected in an anonymous manner, and in accordance with the current legislation, the need for informed consent was waived.

**Statistical analysis**

The data are presented as numbers (%) or as median and interquartile range (IQR), because patient age, Brixia scores, and CRP levels in both waves were not normally distributed. To analyse differences between the two patient groups, baseline characteristics of the study sample (patient age, and underlying comorbidities) were compared by means of the Mann-Whitney U test, and the chi-square test.

The Mann–Whitney U test was also used to compare the Brixia scores between the first and second waves. The chi-square test was used to analyse significant differences in the frequency of MV use, corticosteroid use, and COVID-19-related mortality between the two waves. The Mann–Whitney U test was also used to compare the Brixia scores in the group of patients who needed MV. Additionally, differences in COVID-19-related mortality between the two waves were also tested using univariate and multivariable Cox regression analysis. For this analysis, patient- and treatment-related variables (patient age, underlying comorbidities, MV, and corticosteroid use) were also considered.

Finally, the Mann–Whitney U test was also applied to assess differences in CRP levels between the two COVID-19 waves.

Statistical analysis was performed using MedCalc® Statistical Software version 19.5.1 (MedCalc Software Ltd, Ostend, Belgium), and p values < .05 were considered statistically significant.

**Results**

No statistically significant differences were observed in the baseline characteristics of the two patient groups (p ≥ .258) (Table 1).

In the first wave, the Brixia score ranged from 1 to 16 (median, 10; IQR, 7.5–13). In the second wave, the Brixia score ranged from 1 to 15 (median 7; IQR, 4.5–9). The Brixia score was significantly higher in the first wave than in the second wave (p < .001). The Brixia scores of groups A, B, C, and D were also significantly higher in the first wave than in the second wave (Table 2, and Figure 1).

In the first wave 35/100 (35%) patients required the MV, whereas 26/100 (26%) patients required MV in the second wave (p = .168) (Figure 2). With regard to this group of COVID-19 patients, the Brixia score was significantly higher in the first wave than in the second wave (p = .006) (Table 2).

With regard to the corticosteroid therapy, we found that steroids were used more frequently in the second wave than in the first wave (p < .001) (Figure 2).

With regard to the COVID-19-related mortality, we found that the frequency of in-hospital death was significantly higher in the first wave (28%) than in the second one (16%) (p = .041) (Figure 2). On Cox regression analysis, the COVID-19 first wave, along with patient age, chronic kidney disease and MV use, was significantly associated with in-hospital mortality (Table 3, and Figure 3).

Finally, we also found that the levels of CRP were significantly higher in the first wave (median, 132 mg/L;
IQR, 69–199 mg/L) than in the second wave (median, 86 mg/L; IQR, 30–148 mg/L) (p = .001).

**Discussion**

The much-heralded second wave of COVID-19 has arrived in Italy [11–13]. Right now, one of the most challenging questions about COVID-19 in Italy is whether the second wave is less severe and deadly than the first. Currently, the answer to this question remains open, as the published data on COVID-19 were obtained almost exclusively from the first wave [14].

To the best of our knowledge, this is the first study to assess and compare the CXR severity of COVID-19 pneumonia, the use of MV, the use of corticosteroid, the in-hospital mortality, and CRP levels in the two COVID-19 waves.

In our study sample, consisting of two similar patient groups by age and underlying comorbidities, we found that the CXR severity index of COVID-19 pneumonia, the in-hospital mortality, and CRP levels were significantly higher in the first wave than in the second wave. Additionally, we found that the first wave, along with patient age, chronic kidney disease, and MV use, was strongly and independently associated with COVID-19-related death.

Although not statistically significant, the frequency of MV use was higher in the first wave than in the second wave. A thing worth pointing is that the patients who required MV had a significantly lower Brixia score in the second wave than in the first wave. This difference was probably due to the increased availability of ventilators in the second wave.

In our study, we also found that the frequency of steroid use was significantly higher in the second wave than in the first wave. However, we did not observe that the use of steroids was associated with a reduced risk of in-hospital mortality.

With regard to the corticosteroid therapy in COVID-19 patients, many authors report that steroids may have a positive effect in reducing the short-term mortality and the use of MV, specifically in severely ill COVID-19 patients [15–17]. Conversely, some authors argue that the use of corticosteroids may further increase mortality in patients with COVID-19 due to the possible prothrombotic effect of steroids [16–18]. Therefore, the role of

**Table 2.** Comparison of the Brixia scores by group in the two COVID-19 waves.

| Group                              | COVID-19 wave | Patients | Brixia score | Mann-Whitney U-test p Value |
|-----------------------------------|---------------|----------|--------------|-----------------------------|
| A (50–59 years old)               | First         | 22       | 9.5 (6–13)   | .001                        |
|                                  | Second        | 26       | 5.5 (3–8)    |                             |
| B (60–69 years old)               | First         | 27       | 10 (6.3–12)  | .026                        |
|                                  | Second        | 30       | 7.5 (5–9)    |                             |
| C (70–79 years old)               | First         | 34       | 10 (7–13)    | .021                        |
|                                  | Second        | 26       | 7.5 (5–11)   |                             |
| D (≥ 80 years old)                | First         | 17       | 10 (9–13)    | .029                        |
|                                  | Second        | 18       | 8 (5–11)     |                             |
| MV                                | First         | 35       | 13 (11.3–14) | .006                        |
|                                  | Second        | 26       | 11 (9–12)    |                             |

Data are presented as numbers (%) or medians (interquartile range). MV, group of patients who needed mechanical ventilation.
Corticosteroids in patients with COVID-19 still remain debated.

From a clinical point of view, the results of our study indicate a decreased severity and mortality of COVID-19 in the second wave, which should result in fewer hospitalisations, shorter hospitalisation stays, fewer life-threatening complications [19–23], lower infection-related morbidity and deaths [24].

Of course, the differences between the two COVID-19 waves could be influenced by several factors, such as the different number of swabs performed, the improved patient management, the different season (late winter/early spring for the first wave, autumn for the second wave), and the widespread use of face masks [25].

However, in our opinion, these factors cannot fully justify the results of this preliminary investigation and other factors could be taken into account. For example, mutations in SARS-CoV-2 that may have affected the severity and the mortality rate of COVID-19 [26,27].

The main limitations of this study include the retrospective nature of our analysis and the relatively large sample (100 patients per group). However, we would like to point out that for this study we only enlisted hospitalised male patients over the age of 50 for whom the final outcome (recovery or death) was available.

In conclusion, this study seems to confirm that the COVID-19 second wave is less severe and deadly than the first one. Although preliminary, this information, together with the beginning of the COVID-19 vaccination programs, is of particular interest not only for clinicians but also for the general population, as it allows us to look to the near future with more optimism.

**Disclosure statement**

The authors declare that they have no conflict of interest.

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**Table 3.** Univariate and multivariable Cox regression analysis in both COVID-19 waves.

| Variable                          | Univariate analysis | Multivariable analysis |
|-----------------------------------|---------------------|------------------------|
|                                   | HR                  | 95% CI                 | p Value | HR                  | 95% CI | p Value |
| Patient age*                      | 1.06                | 1.03–1.10              | <.001   | 1.07                | 1.03–1.11| <.001   |
| COVID-19 wave (first vs second)   | 3.03                | 1.60–5.77              | <.001   | 3.30                | 1.67–6.55| <.001   |
| MV (yes vs no)                    | 4.32                | 2.08–8.98              | <.001   | 6.23                | 2.90–13.38| <.001   |
| Chronic kidney disease (yes vs no)| 3.39                | 1.59–7.25              | .002    | 3.14                | 1.34–7.33| .008    |
| Cardiovascular disease (yes vs no)| 2.13                | 1.16–3.88              | .014    | 1.80                | 0.85–3.78| .124    |
| Hypertension (yes vs no)          | 0.53                | 0.28–1.00              | .049    | 1.04                | 0.51–2.13| .916    |
| Diabetes (yes vs no)              | 0.87                | 0.34–2.20              | .762    | –                   | –       | –       |
| Steroid therapy (no vs yes)       | 1.68                | 0.92–3.05              | .089    | –                   | –       | –       |

HR: hazard ratio; CI: confidence interval; MV: mechanical ventilation.

*Continuous variable.

**Figure 3.** Cox regression graph showing the recovery probability of patients with COVID-19 in the first (blue) and second (red) waves.
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