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Severe COVID-19 pneumonia in Piacenza, Italy — A cohort study of the first pandemic wave

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ABSTRACT

Background: Piacenza is the closest city to the first coronavirus disease 2019 (COVID-19) cluster in Italy and has the highest national COVID-19 death rates per population. The objective of this study is to present characteristics and outcomes of patients admitted to medical departments of the Hospital of Piacenza during the first wave of the epidemic.

Methods: A total of 218 patients with confirmed or suspect COVID-19 and severe pneumonia were included from February 21st to May 15th, 2020. Routinely-collected clinical and laboratory data were retrospectively retrieved from electronic medical files. A Cox proportional-hazards model was fit to assess the association of treatment and other variables with death.

Results: Median age of patients was 68 years; 150 patients (69%) had comorbidities, mainly hypertension (107, 49%). Overall, 185 (85%) patients had acute respiratory distress syndrome (ARDS) on admission, including 103 (47%) with moderate or severe ARDS. Chest computed tomography scan showed bilateral disease in 201 (98%) and extensive lung involvement in 79 (50%) patients. Most patients received antiviral treatment (187, 86%) and corticosteroids (134, 61%). All patients received respiratory support and 64 (29%) were admitted to intensive care unit. As of June 30th, 100 patients (46%) died, 109 patients (50%) were discharged, and 9 patients (4%) were still hospitalized. In multivariable Cox analysis, age above 65 years, having more than one comorbidity, severe ARDS, low platelet counts, and high LDH levels at admission were associated with mortality, while having diarrhea at admission was associated with survival. The use of antivirals or corticosteroids was not associated with survival.

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Conclusions: Overall case fatality rates were high and associated with comorbidities, extensive lung involvement, ARDS at admission, and advanced age. The use of antivirals was not associated with increased survival.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), detected for the first time in Wuhan, China, in December 2019. COVID-19 is thought to have a favorable clinical course in most patients. However, in some cases, it may lead to severe pneumonia and eventually to acute respiratory distress syndrome (ARDS) [1]. To date, there is no established antiviral treatment for COVID-19. Many drugs are currently under investigation, while several are being employed in off-label use, and others are available via compassionate use or expanded access programs.

As of October 31st, 2020, 45 667 780 cases of COVID-19 and 1 189 499 deaths have been reported worldwide [2], with 594 472 cases and 37 781 deaths having occurred in Italy [3]. Italy, the first Western country reporting sustained COVID-19 transmission, has been disproportionately affected by the epidemic [4–6]. In areas of Northern Italy surrounding the first COVID-19 cluster in the town of Codogno, public healthcare systems have been overwhelmed by the abrupt caseload increase [7]. Limited availability of ventilatory support in intensive care units (ICUs) of many hospitals prompted the need to implement forms of patient triage. After the first months of the epidemic, the province of Piacenza, the closest to the initial cluster, had the highest COVID-19 death rates per population in the country [8]. In the Piacenza Hospital, the first proven case was reported on February 21st, 2020 [9]. As ICU capacity was quickly exhausted by COVID-19 patients, non-ICU medical departments, and in particular the Infectious Diseases Unit, had to admit increasing numbers of critically-ill patients who needed advanced respiratory support.

Multiple case series of COVID-19 patients have been published, mostly from China and the United States [10–18]. However, descriptions of the characteristics of patients in Italy are less common, excluding studies from the ICU setting [19,20]. Moreover, there is a need to characterize management and outcomes of severe cases admitted to non-ICU wards.

In this study, we present the characteristics of patients with severe COVID-19 pneumonia who were admitted to four medical departments of the Hospital of Piacenza during the first epidemic wave of the outbreak, aiming to describe treatment, case fatality rates, and factors associated with mortality.

Materials and methods

Study population and oversight

Consecutive patients admitted to four non-ICU medical departments (Infectious Diseases, Emergency Medicine, and two COVID-19 Units created during the epidemic) of the "Guglielmo da Saliceto" Hospital in Piacenza between February 21st, 2020, and May 15th, 2020, were included in this single-center, retrospective, observational study. Inclusion criteria for the study were the following: (1) confirmed COVID-19 cases with positive Sars-CoV-2 polymerase-chain-reaction (PCR) test, or suspect COVID-19 cases with highly suggestive radiologic evidence on chest high-resolution computed tomography (HRCT), in the absence of an alternative diagnosis, and (2) severe COVID-19 pneumonia. Children (<18 years

old) were not included. The study was approved by the local Ethics Committee (Area Vasta Emilia Nord). Requirement for informed consent was waived by the Ethics Committee.

Study definitions

Confirmed and suspect COVID-19 cases, and cases with severe COVID-19 pneumonia were defined according to WHO criteria [21,22]. Confirmed COVID-19 cases were defined as patients with a positive PCR test for SARS-CoV-2. Suspect COVID-19 cases were defined as patients with acute respiratory illness, chest HRCT evidence of lesions compatible with COVID-19, and residence in an area reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset. Severe COVID-19 pneumonia was defined as pneumonia with oxygen saturation on room air of 93% or less at hospital admission.

Study procedures

COVID-19 cases were confirmed using reverse transcriptase real-time PCR on nasopharyngeal swab specimen. HRCT scans were routinely performed at hospital admission to diagnose pulmonary COVID-19 and to assess the extent of lung involvement. HRCT scans were read by expert radiologists, who assessed optically the proportion of lung parenchyma involved by viral pneumonia (i.e. interstitial involvement, ground-glass opacities, crazy-paving pattern, etc.), as described previously [23]. Blood tests (including blood gas testing) were performed at the Clinical Laboratory of the Piacenza Hospital. Results from samples collected on admission or on the following day were considered as baseline results and included in the analysis.

Data collection

Routinely-collected data were retrieved retrospectively from electronic medical files, cross-checked and collated in an anonymized database. Collected data included demographic and clinical characteristics of patients, laboratory and radiologic examinations, treatment and oxygen support received, and outcomes. Treatment data were only available for the period of hospital stay at the medical departments, but not during the stay in the ICU. Data collection was completed and data were locked on June 30th, 2020.

Statistical analysis

Results of continuous data were reported as median and interquartile range (IQR), while categorical data were reported as counts and proportions. Missing data were not imputed. Survival analysis was performed to describe the time from hospitalization to death and Kaplan-Meier curves were estimated for probability of survival after hospitalization, overall and by various strata. Tests between strata were done by the log-rank test. The association of explanatory variables (patient characteristics, symptoms, comorbidities, laboratory and radiologic exams, and treatments) with death was analyzed using a multivariate Cox proportional hazards model. Variables were initially included into the multivariate Cox proportional hazards model if they predicted the outcome at

Table 1
Baseline clinical characteristics and comorbidities of 218 patients hospitalized with severe COVID-19 pneumonia.

	n (%)
Demographic characteristics	
Sex, male	172 (79)
Age, years, median (IQR) [range]	68 (59−76) [19−102]
Clinical presentation at hospital admission	
Fever	203 (93)
Dyspnea	159 (73)
Cough	111 (51)
Fatigue	36 (17)
Diarrhea	41 (19)
Time from symptoms to hospital admission, days, median (IQR)	7 (5−10)
Comorbidities	
Metabolic disease	
Obesity (BMI > 30)	52 (24)
Diabetes mellitus	46 (21)
Cardiovascular disease	
Hypertension	107 (49)
Other cardiovascular disease	56 (26)
Cerebrovascular disease	16 (7)
Pulmonary disease	
COPD	17 (8)
Bronchial asthma	6 (3)
Cancer	
Solid cancer	17 (8)
Onco-hematologic cancer	10 (5)
Chronic kidney disease	20 (9)
Chronic liver disease	3 (2)
HIV infection	2 (1)
Iatrogenic immunosuppression	5 (2)
Number of comorbidities	
None	68 (31)
One	59 (27)
More than one	91 (42)
Total number, median (IQR)	1 (0−4)

IQR = interquartile range; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

a p-value ≤ 0.20 in univariate analysis and if they fulfilled the proportional hazards assumption; a stepwise backwards hierarchical approach was applied for variable selection in the multivariable model. Hazard ratios (HRs) were reported with standard errors and 95%-confidence intervals (CI). No routine imputation of missing explanatory variables was done.

Statistical analysis was performed using Stata software version 15.0 (StataCorp).

Results

Overall, 245 proven or suspect COVID-19 cases were admitted to the four non-ICU medical departments of the Piacenza Hospital during the study period, out of which 218 had severe COVID-19 pneumonia and were included in the study.

Demographic and clinical characteristics of the patients

Baseline clinical characteristics are shown in Table 1. Median age of admitted patients was 68 years (IQR, 59−76; range, 19−102 years); 172 (79%) patients were male. Median time from first symptoms to hospital admission was 7 days (IQR, 5−10 days). Fever (203 patients, 93%), dyspnea (159 patients, 73%), and cough (111 patients, 51%) were the most common symptoms followed by fatigue (36 patients, 17%) and diarrhea (41 patients, 19%). One hundred and fifty patients (69%) had comorbidities with more than half of them (91 patients, 42%) having more than one known comorbidity. The most common comorbidity was hypertension (107 patients, 49%), followed by other cardiovascular diseases (56 patients, 26%), obesity (52 patients, 24%), and diabetes mellitus (46 patients, 21%).

Pulmonary disease was reported in 23 patients: chronic obstructive pulmonary disease (COPD) in 17 (8%) and bronchial asthma in 6 patients (3%). Other reported comorbidities included chronic kidney (20 patients, 9%) and liver (3 patients, 2%) disease, cerebrovascular disease (16 patients, 7%), solid cancer (17 patients, 8%), HIV infection (2 patients, 1%), and iatrogenic immunosuppression (5 patients, 2%).

Virology, radiology, and laboratory results on admission

As shown in Table 2, 216 (99%) patients had a positive PCR for SARS-CoV-2 from a nasopharyngeal swab. Two patients tested negative on admission, but had a HRCT scan showing bilateral interstitial disease and clinical and epidemiological history which was suggestive of COVID-19. The test could not be repeated since these patients died in the first day after admission. All 206 patients with available chest HRCT scan performed on hospital admission had signs of interstitial lung disease, 201 (98%) of them with bilateral involvement. The median proportion of lung parenchyma affected by viral pneumonia was 48% (IQR, 30–60; range, 5–90%), with 79 patients (50%) having extensive lung disease, defined as 50% or more of lung parenchyma affected. Twenty-five (12%) patients had pleural effusion. All patients had blood oxygen saturation of 93% or less on room air on admission. Arterial blood gas analysis found that 33 (15%) patients had an arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio higher than 300 mmHg, 82 patients (38%) had 200−300 mmHg, 50 patients (23%) had 100−200 mmHg, and 53 patients (24%) had less than 100 mmHg, corresponding to no ARDS, mild ARDS, moderate ARDS, and severe ARDS, respectively. Results of the baseline blood tests are shown in Table 2. Compared to reference values, median values of lymphocyte counts were decreased, while prothrombin time, lactate dehydrogenase, ferritin, C-reactive protein, D-dimer, and interleukin-6 were increased.

Treatment and respiratory support

Table 3 summarizes the treatment received by patients. Most patients (187, 86%) received antiviral treatment and 169 (78%) received a combination of two or more antivirals. Median time from onset of symptoms to the initiation of antiviral treatment was 8 days (IQR, 6–10 days); median duration of antiviral treatment was 6 days (IQR, 3–9 days). Overall, 181 patients (83%) received hydroxychloroquine, 118 patients (54%) received darunavir/cobicistat, 92 patients (42%) received lopinavir/ritonavir, and 5 patients (2%) received remdesivir. Additionally, 134 patients (61%) received corticosteroids. Median time from first symptoms to start of corticosteroid treatment was 10 days (IQR, 8–13 days) with a median treatment duration of 6 days (IQR, 3–10 days). Azithromycin was used as part of large-spectrum antibiotic treatment in 149 patients (68%), and tocilizumab was given to 14 patients (6%). Low molecular weight heparin was administered to 172 patients (79%) at a prophylactic dose and to 20 patients (9%) at a higher dose. Overall, 60 patients (28%) received ACE inhibitors, sartan, or both, for the treatment of hypertension. During hospitalization, all patients were administered respiratory support. Table 3 shows the highest level of respiratory support which was provided: any among nasal cannula, Venturi mask, or mask with reservoir for 58 patients (27%); high-flow nasal cannula for 14 patients (6%); non-invasive ventilation support with continuous positive airway pressure helmets for 88 patients (40%); tracheal intubation for 58 patients (27%). Overall, 64 patients (29%) were transferred from the Infectious Diseases ward to ICU; median time from hospitalization to ICU admission was 5 days (IQR, 3–9 days).

Table 2
Baseline diagnostic test results of 218 patients hospitalized with severe COVID-19 pneumonia.

	n (%)	N with available results
Positive PCR for SARS–CoV-2	216 (99)	218
Respiratory impairment at hospital admission		
Oxygen saturation≤93%	218 (100)	218
Arterial blood gas test		
PaO2/FiO2≥300 mmHg	33 (15)	218
PaO2/FiO2≥200 and <300 mmHg	82 (38)	218
PaO2/FiO2≥100 and <200 mmHg	50 (23)	218
PaO2/FiO2 < 100 mmHg	53 (24)	218
Chest HRCT scan at hospital admission		
Any interstitial lung disease	206 (100)	206
Bilateral lung involvement	201 (98)	206
Proportion of affected lung parenchyma (visual assessment), %, median (IQR) [range]	48 (30−60) [5−90]	158
Extended lung involvement (≥50%)	79 (50)	158
Any pleural effusion	25 (12)	206
Blood laboratory test, unit (reference range)		
Hematologic		
White blood cells, $\times 10^3/\mu l$, median (IQR) (4−10)	7.5 (6.0−9.8)	218
Hemoglobin, g/dl, median (IQR) (13−17)	13.6 (12.2−14.8)	218
Platelets, $\times 10^3/\mu l$, median (IQR) (150−450)	197 (157−265)	218
Lymphocytes, $\times 10^3/\mu l$, median (IQR) (1,5−4)	0.84 (0.62−1.11)	218
Biochemistry		
Blood creatinine, mg/dl, median (IQR) (0.6−1.2)	0.99 (0.83−1.25)	218
Total bilirubin, mg/dl, median (IQR) (0−1.1)	0.67 (0.51−0.90)	206
Prothrombin time, INR, median (IQR) (0.8−1.1)	1.29 (1.20−1.37)	207
Partial thromboplastin time, ratio, median (IQR) (0.8−1.2)	0.97 (0.89−1.05)	123
Lactate dehydrogenase, U/l, median (IQR) (0−248)	440 (325−574)	207
Ferritin, ng/mL, median (IQR) (12−300)	1033 (488−1991)	92
C-reactive protein, mg/dl, median (IQR) (0−0.5)	13.0 (7.7−18.8)	218
Procalcitonin, ng/mL, median (IQR) (<0.5)	0.38 (0.16−0.92)	100
D-dimer, ng/mL, median (IQR) (≤500)	1277 (733−4947)	55
Interleukin-6, pg/mL, median (IQR) (<6.4)	64 (13−205)	40

PCR = polymerase chain reaction; IQR = interquartile range; HRCT = high resolution computed tomography; PaO2 = arterial partial oxygen pressure; FiO2 = fractional inspired oxygen; INR = international normalized ratio.

Outcomes

As of June 30th, 2020, 209 (96%) out of 218 patients had a treatment outcome (Table 3). A total of 100 patients (46%) died, 93 (43%) within 28 days after admission to the hospital. Overall, 68 (31%) died in the ward and 33 (15%) in ICU. Fig. 1 shows Kaplan–Meier curves for mortality, overall and stratified by age (log-rank, p < 0.0001), extension of lung parenchyma affected by pneumonia at chest HRCT scan (log-rank, p < 0.0001), and PaO2/FiO2 ratio on admission (log-rank, p < 0.0001). One hundred-nine patients (50%) were discharged to a rehabilitation facility or sent home. Among these patients, median duration of hospitalization was 18 days (IQR, 11−27 days). Four patients (2%) were still in ICU and 5 patients (2%) were still in a non-ICU ward. Fig. 2 summarizes the time course of disease and treatment history of patients, stratified across four different groups according to final outcome (death or discharge) and to admission to ICU.

Association of treatment and other variables with mortality

Table 4 shows the results of multivariable Cox proportional-hazards model analysing the association of explanatory variables with death. Overall, the following variables were independently associated with death: age above 65 years at admission (HR 4.08; 95% CI 2.37−7.03), more than one comorbidity (HR 1.84; 95% CI 1.04−3.26), severe ARDS at admission (HR 3.66; 95% CI 1.47−9.07), platelet count <197 $\times 10^3/\mu l$ at admission (HR 2.23; 95% CI 1.42−3.48), and LDH > 440 U/l at admission (HR 1.98; 95% CI 1.19−3.29). Diarrhea at admission was associated with survival (HR 0.31; 0.13−0.72). Of note, antiviral treatment was not associated with increased survival, regardless of whether different drugs were entered as individual variables (hydroxychloroquine: HR 0.65; 95% CI 0.33−1.30; lopinavir/ritonavir: HR 0.66; 95% CI 0.41−1.08;

darunavir/cobicistat: HR 0.62; 95% CI 0.37−1.06) or grouped as a single variable (antiviral treatment: HR 0.81; 95% CI 0.43−1.53). Corticosteroid use was associated with survival and included in the final model, although the association did not reach statistical significance (HR 0.72; 95% CI 0.46−1.14).

Discussion

We hereby report high case fatality rates in patients affected by severe COVID-19 pneumonia who were hospitalized in non-ICU wards in Italy, despite the frequent use of antiviral drugs and access to non-invasive ventilation support.

In our study, 79% of patients were male, similarly to what has been described for ICU patients in Italy [20]. Overall, 85% of patients in our study had ARDS on admission, including 47% with moderate or severe ARDS. These rates of ARDS, much higher than in previous studies with a similar setting [10,17,18,24], are more comparable to ICU cohorts [11,12,16,20,25], and may account for the high mortality observed in our study (Fig. 1d). The median time from onset of symptoms to hospitalization was 7 days, suggesting that our patients developed severe illness in a short time. Median age was 68 years, which is higher compared to studies from Italy [20], China [10,13,15,24,25], Singapore [26], and the United States [11,12,14], and to surveillance data from Italy [3]. In addition, 69% of patients had at least one comorbidity, which is consistent with data from an ICU-based study from Italy [20], higher than in studies from China [10,13,17,18], although notably lower than in a cohort from the United States [14]. As in previous reports, the most common comorbidities were cardiovascular and metabolic diseases. Therefore, our observation confirms that older age (Fig. 1b) and comorbidities are associated with poor outcomes [16–18,24,27,28]. Another relevant finding was that, among patients who underwent HRCT on admission, half had 50% or more of lung parenchyma affected and 98%
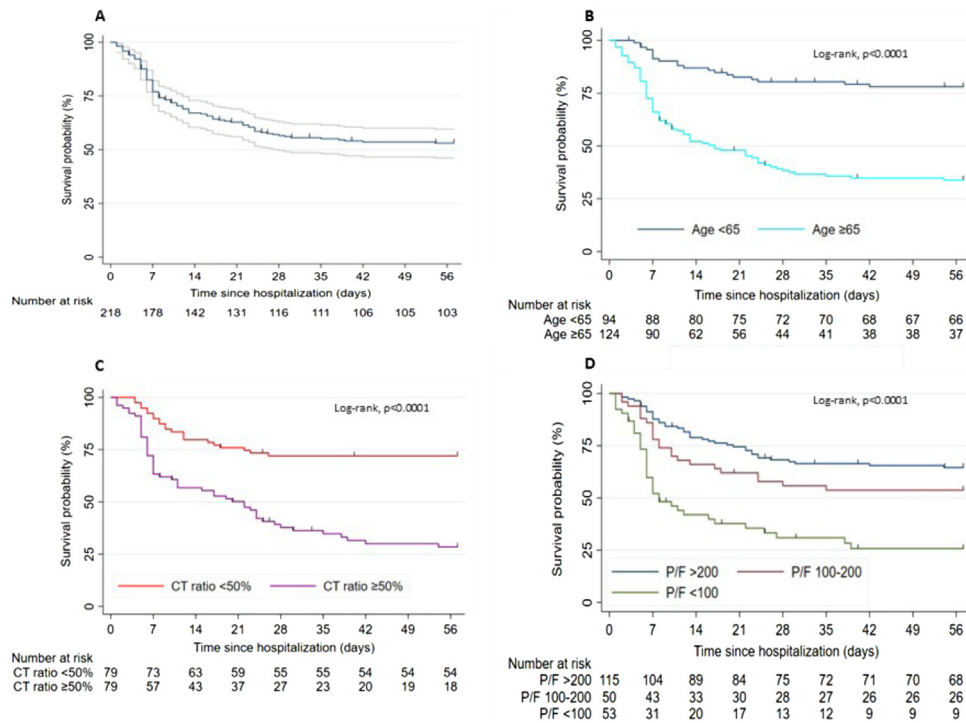
Fig. 1. Mortality of patients with severe COVID-19 pneumonia.
Kaplan-Meier curves of mortality over 56 days after hospital admission of 218 patients hospitalized with severe COVID-19 pneumonia. The figures represent: (a) overall mortality, with dashed line representing 95% confidence interval and a median time to death of 27 days; (b) mortality stratified by age (log-rank, p < 0.0001); (c) mortality stratified by the proportion of lung parenchyma affected by interstitial disease at chest computed tomography scan on admission (N = 158) (log-rank, p = 0.0001); (d) mortality stratified by P/F ratio on admission (log-rank, p < 0.0001). Dots indicate censoring.
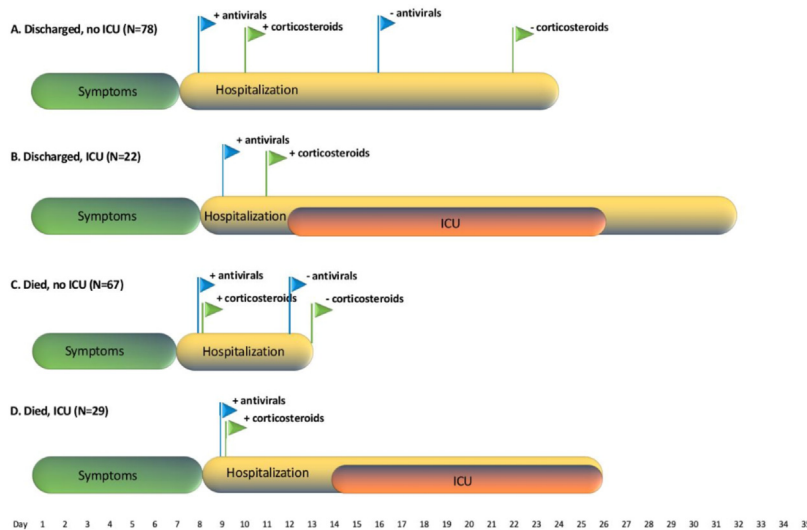CT = chest computed tomography; P/F = arterial partial oxygen pressure/fractional inspired oxygen.

Fig. 2. Time course of patients with severe COVID-19 pneumonia.
Time course of symptoms, hospital admission, intensive care unit (ICU) admission and discharge, initiation and discontinuation of antiviral and corticosteroid therapy, and death or discharge of patients hospitalized with severe COVID-19 pneumonia. Patients are divided in four groups according to their outcome and to intensive care unit admission: (a) patients who were not admitted to ICU and were discharged home or to a rehabilitation facility (N = 78); (b) patients who were admitted to ICU and were discharged home or to a rehabilitation facility (N = 22); (c) patients who were admitted to ICU and died (N = 67); (d) patients who were not admitted to ICU and died (N = 29). All durations represent median values for each group and are reported in days. Patients with no assigned outcome (N = 9) are not shown.
ICU = intensive care unit.
ICU = intensive care unit.

had bilateral disease. It has been shown that the score of pulmonary involvement is associated with ICU admission/death [23] and the results from our study support this conclusion, as well as the routine use of HRCT to assess the extension of pulmonary COVID-19 at hospital admission (Fig. 1c). On clinical grounds, almost all patients had fever, often associated with respiratory symptoms, while gastrointestinal symptoms were present in a minority of patients. This is in line with previous reports [10,12,24,26].

On admission, most patients had reduced lymphocyte counts and an increase in laboratory markers linked to inflammation, such

Table 3

Treatment, respiratory support received, and outcomes by June 30th, 2020, of 218 patients hospitalized with severe COVID-19 pneumonia.

	n (%)
Treatment[a]	
Antivirals	
Any antiviral	187 (86)
Combination of more than one antiviral	169 (78)
Time from symptoms to antiviral treatment start, days, median (IQR) (N = 187)	8 (6−10)
Antiviral treatment duration, days, median (IQR) (N = 187)	6 (3−9)
Hydroxychloroquine	181 (83)
Darunavir/cobicistat	118 (54)
Lopinavir/ritonavir	92 (42)
Remdesivir	5 (2)
Corticosteroids	
Any corticosteroid	134 (61)
Time from symptoms to corticosteroid treatment start, days, median (IQR) (N = 134)	10 (8−13)
Corticosteroid treatment duration, days, median (IQR) (N = 134)	6 (3−10)
Others	
Azithromycin	149 (68)
Tocilizumab	14 (6)
Low molecular weight heparin, prophylaxis	172 (79)
Low molecular weight heparin, high dose	20 (9)
Respiratory support	
Highest level of respiratory support during hospitalization	
Nasal cannula, Venturi mask, mask with reservoir	58 (27)
High-flow nasal cannula	14 (6)
CPAP helmet	88 (40)
Tracheal intubation	58 (27)
ICU	
Total admitted to ICU	64 (29)
Time from hospital admission to ICU admission, days, median (IQR) (N = 64)	5 (3−9)
Outcomes	
Death	
Total	100 (46)
At day 28 after hospital admission	93 (43)
Time from hospital admission to death, days, median (IQR) (N = 100)	8 (5−17)
Discharge from hospital (home or rehabilitation facility)	
Total	109 (50)
Time from hospital admission to discharge, days, median (IQR) (N = 109)	18 (11−27)
Outcome not assigned	
Total	9 (4)
Still in ICU at data lock	4 (2)
Still in hospital at data lock	5 (2)

IQR = interquartile range; CPAP = continuous positive airway pressure; ICU = intensive care unit.

[a] This table summarizes treatment received before and during admission at the medical departments (*i.e.* it does not include treatment received in the Intensive Care Unit).

as lactate dehydrogenase, ferritin, C-reactive protein, D-dimer, and interleukin-6. These findings are consistent with previous studies indicating the decrease of antiviral immune response and the trigger of the cytokine storm [10,13,14,24,28]

The vast majority of patients included in the study received at least one antiviral and most of them a combination of two, usually hydroxychloroquine and a boosted protease inhibitor (lopinavir/ritonavir or darunavir/cobicistat). In addition, 61% of patients were treated with corticosteroids. These high rates of treatment were based on local guidelines [29] and understandable in light of the clinical severity at presentation. To date, however, the evidence backing the efficacy of these drugs is limited. In two randomized controlled trials, lopinavir/ritonavir failed to show efficacy compared to standard-of-care [30,31]. The *in vivo* activity of hydroxychloroquine against COVID-19, despite high expectations, has not been confirmed in a large randomized, controlled clinical trial [32]. In our study, the use of these antivirals, often administered in combination, was not associated with increased survival, reinforcing the strong reserves on the efficacy of these drugs for treatment of severe COVID-19 pneumonia [33]. Corticosteroids are currently a mainstay of treatment of severe COVID-19 pneumonia: while no benefit had been found in the treatment of other coronaviruses [34], multiple randomized, controlled trials have shown that corticosteroids improve survival rates in patients who need oxygen support for COVID-19 [35]. More promising agents like remdesivir [36] and tocilizumab [37] were prescribed to small numbers of patients and could not be assessed in this study. In our study, corticosteroid use was associated with survival, but this finding did not reach statistical significance. This may be partially explained by the heterogeneous timing of start and duration of treatment with corticosteroids in our cohort, and by the small sample size.

The main finding from our study is an overall case fatality rate of 46%, similar to rates reported for ICU patients [11,12,16,20,25] and much higher than those reported in studies from non-ICU wards [10,13–15,24,26]. Mortality rates are often difficult to compare between these two groups of studies, also because indications for intensive care and mechanical ventilation may change greatly among different settings [38]. Indeed, most of our patients have characteristics that would have made them likely eligible for ICU directly at the *triage* level, had there not been a request overload due to the epidemic wave. Most deaths occurred quickly, half in the first 7 days of hospitalization and the majority within the first 28 days (Fig. 1a). There are multiple possible explanations for the high case fatality rate we observed. Above all, the characteristics of patients in our study are similar to those of ICU cohorts: high rates of comorbidities, extensive lung involvement, high proportion of ARDS at admission, and advanced age – all factors associated with mortality. As a matter of fact, during the peak of the epidemic in Piacenza Hospital, COVID-19 patients who needed ventilatory support were often allocated to non-ICU wards, like the Infectious Diseases or Emergency Medicine Units, which acted as a *de facto* sub-intensive care ward. This study describes the first wave of the epidemic, including the peak of COVID-19 admissions, and it is remarkable how non-ICU wards were quickly transformed to cope with the emergency, indicating a virtuous learning curve. Indeed, a high proportion of patients in our case series died without being admitted to the ICU, similarly to what has been reported previously in China [39], likely reflecting the lack of ICU resources. Finally, it

Table 4

Association of treatment and other variables with death, assessed using a multivariable Cox proportional-hazards model (N = 218).

	Hazard ratio	95% confidence interval	P value
Variables			
Age >65 years at admission	4.08	2.37–7.03	<0.001
Diarrhea at admission	0.31	0.13–0.72	0.007
More than one comorbidity	1.84	1.04–3.26	0.036
Severe ARDS at admission	3.66	1.47–9.07	0.005
Platelet count <197 × 10³/μl at admission	2.23	1.42–3.48	<0.001
LDH > 440 U/l at admission	1.98	1.19–3.29	0.008

Model adjusted by sex, presence of bilateral disease at computed tomography scan, and treatment with corticosteroids.
LDH = lactate dehydrogenase; ARDS = acute respiratory distress syndrome.

has been postulated that high pollution levels in the area may have increased fatality rates in Northern Italy [40] — an element which deserves future research.

This study has multiple limitations. As described above, the specific epidemic circumstances and patient selection must be taken into account. These findings may therefore not be representative of the overall characteristics and outcomes of COVID-19 cases in Piacenza and of severe COVID-19 pneumonia in general. In addition, 4% of patients were still hospitalized, without a final outcome, at data lock. Finally, the retrospective nature of the study explains the high rates of missing information for some laboratory tests.

In conclusion, this study describes the features of patients with severe COVID-19 pneumonia, their outcomes, and factors associated with mortality. These results warn about the consequences of hospital admission of large fluxes of patients that may overwhelm the healthcare system, despite swift response and optimal use of available resources. It seems therefore paramount to implement adequate prevention policies, while optimizing hospital preparedness, and increasing the capacities of medical and ICU wards for the management of future pandemic waves. Our results also highlight the dire need for an effective antiviral treatment for COVID-19 pneumonia. Hopefully, forthcoming randomized controlled clinical trials (NCT04315948, NCT04330690) will allow identifying promising treatment options.

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Competing interests

None declared.

Ethics approval

The study was approved by the local Ethics Committee (Area Vasta Emilia Nord). Requirement for informed consent was waived by the Ethics Committee.

Availability of data and material

Data may be made available by contacting directly the corresponding author.

Author contributions

LG made a substantial contribution to the conception and design of the work, to the acquisition, analysis and interpretation of data for the work, performed statistical analysis, wrote the manuscript, critically revised the manuscript for important intellectual content, gave final approval of the current version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

IK made a substantial contribution to the analysis and interpretation of data for the work, wrote the manuscript, critically revised the manuscript for important intellectual content, gave final approval of the current version to be published, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

GT and MC made a substantial contribution to the conception and design of the work, to the analysis and interpretation of data for the work, critically revised the manuscript for important intellectual content, gave final approval of the current version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All other authors gave a substantial contributions to the interpretation of data for the work, revised the manuscript for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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