

6 апреля в Jama network опубликована статья итальянских ученых о характеристиках и исходах лечения 1591 пациентов с SARS-CoV-2, поступивших в отделение реанимации в Ломбардии, Италия.

Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy

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Главные положения статьи

Цель исследования: определить, каковы характеристики и исходы у пациентов с лабораторным подтверждением заражения инфекцией коронавируса 2 (SARS-CoV-2), сопровождающейся тяжелым острым респираторным синдромом. Пациенты находились в отделении интенсивной терапии (реанимации).

Обнаружено: всего включены данные 1591 тяжело больных пациентов с 20 февраля по 18 марта 2020 г., **99%** пациентам (1287 of 1300) требовалась респираторная поддержка, в том числе в **88%** случаев эндотрахеальная интубация и ИВЛ, в **11%** - не инвазивная вентиляция. Летальность в отделении составила **26%**.

Характеристика пациентов при поступлении: средний возраст **63 года**, **82%** - мужчины, **68%** имели сопутствующие заболевания, **49%** - ИБС.

Abstract

Importance In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in China and has spread globally, creating a pandemic. Information about the clinical characteristics of infected patients who require intensive care is limited.

Objective To characterize patients with coronavirus disease 2019 (COVID-19) requiring treatment in an intensive care unit (ICU) in the Lombardy region of Italy.

Design, Setting, and Participants Retrospective case series of 1591 consecutive patients with laboratory-confirmed COVID-19 referred for ICU admission to the coordinator center (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy) of the COVID-19 Lombardy ICU Network and treated at one of the ICUs of the 72 hospitals in this network between February 20 and March 18, 2020. Date of final follow-up was March 25, 2020.

Exposures SARS-CoV-2 infection confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs.

Main Outcomes and Measures Demographic and clinical data were collected, including data on clinical management, respiratory failure, and patient mortality. Data

were recorded by the coordinator center on an electronic worksheet during telephone calls by the staff of the COVID-19 Lombardy ICU Network.

Results Of the 1591 patients included in the study, the median (IQR) age was 63 (56-70) years and 1304 (82%) were male. Of the 1043 patients with available data, 709 (68%) had at least 1 comorbidity and 509 (49%) had hypertension. Among 1300 patients with available respiratory support data, 1287 (99% [95% CI, 98%-99%]) needed respiratory support, including 1150 (88% [95% CI, 87%-90%]) who received mechanical ventilation and 137 (11% [95% CI, 9%-12%]) who received noninvasive ventilation. The median positive end-expiratory pressure (PEEP) was 14 (IQR, 12-16) cm H₂O, and FIO₂ was greater than 50% in 89% of patients. The median PaO₂/FIO₂ was 160 (IQR, 114-220). The median PEEP level was not different between younger patients (n = 503 aged ≤63 years) and older patients (n = 514 aged ≥64 years) (14 [IQR, 12-15] vs 14 [IQR, 12-16] cm H₂O, respectively; median difference, 0 [95% CI, 0-0]; *P* = .94). Median FIO₂ was lower in younger patients: 60% (IQR, 50%-80%) vs 70% (IQR, 50%-80%) (median difference, -10% [95% CI, -14% to 6%]; *P* = .006), and median PaO₂/FIO₂ was higher in younger patients: 163.5 (IQR, 120-230) vs 156 (IQR, 110-205) (median difference, 7 [95% CI, -8 to 22]; *P* = .02). Patients with hypertension (n = 509) were older than those without hypertension (n = 526) (median [IQR] age, 66 years [60-72] vs 62 years [54-68]; *P* < .001) and had lower PaO₂/FIO₂ (median [IQR], 146 [105-214] vs 173 [120-222]; median difference, -27 [95% CI, -42 to -12]; *P* = .005). Among the 1581 patients with ICU disposition data available as of March 25, 2020, 920 patients (58% [95% CI, 56%-61%]) were still in the ICU, 256 (16% [95% CI, 14%-18%]) were discharged from the ICU, and 405 (26% [95% CI, 23%-28%]) had died in the ICU. Older patients (n = 786; age ≥64 years) had higher mortality than younger patients (n = 795; age ≤63 years) (36% vs 15%; difference, 21% [95% CI, 17%-26%]; *P* < .001).

Conclusions and Relevance In this case series of critically ill patients with laboratory-confirmed COVID-19 admitted to ICUs in Lombardy, Italy, the majority were older men, a large proportion required mechanical ventilation and high levels of PEEP, and ICU mortality was 26%.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic due to the constantly increasing number of cases outside China.¹ Patients with SARS-CoV-2 infection can develop coronavirus disease 2019 (COVID-19), which has resulted in high rates of hospitalization and intensive care unit (ICU) admission.²

On February 20, 2020, the first patient diagnosed with COVID-19 in Italy developed respiratory failure and was admitted to one of the ICUs of Lombardy, a region of northern Italy. Since then, the increasing number of cases recorded in Lombardy, and subsequently throughout the country, led Italy to be the second most affected country in the world, after the US, as of March 27, 2020.³ Local health and government officials in Lombardy responded to the outbreak by creating a network of ICUs (COVID-19 Lombardy ICU Network) coordinated by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan. This network has managed an exponential surge of patients requiring ICU admission for respiratory support.²

Up through March 18, 2020, a total of 17 713 people had tested positive for the new SARS-CoV-2 coronavirus in Lombardy and 1593 (9%) had been admitted to the ICU.

Information on the incidence and clinical characteristics of critically ill patients diagnosed with COVID-19 is still limited. Among hospitalized patients with COVID-19 in China, the percentage of patients who required ICU care has varied from 5% to 32%.^{4,5}

The availability of ICU beds and the provision of intensive care varies among countries.⁶ Knowledge of the baseline characteristics and outcomes of critically ill patients is crucial for health and government officials engaged in planning efforts to address local outbreaks. This case series describes the clinical characteristics of patients with laboratory-confirmed COVID-19 admitted to ICUs of the COVID-19 Lombardy ICU Network in northern Italy.

Methods

This retrospective observational study was performed at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, which was the regional coordinating center for the COVID-19 Lombardy ICU Network. All consecutive patients with laboratory-confirmed SARS-CoV-2 infection, referred to Ospedale Maggiore Policlinico, and subsequently admitted to one of the ICUs among 72 hospitals in the network between February 20 and March 18, 2020, were enrolled. The institutional ethics board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, approved this study and due to the nature of retrospective chart review, waived the need for informed consent from individual patients.

According to the WHO guidance,⁷ laboratory confirmation for SARS-Cov-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. This guidance was implemented locally with the adjunct of using RT-PCR assay from lower respiratory tract aspirates as well.

Data were recorded by staff of the coordinator center on an electronic worksheet during daily telephone calls performed by intensivists of the hospitals of the COVID-19 Lombardy ICU Network.

Data Collection

Clinical data reported in this study were collected by phone within the first 6 to 24 hours following ICU admission. The recorded data included the following: age, sex, medical comorbidities, mode of respiratory support (invasive mechanical ventilation, noninvasive mechanical ventilation, oxygen mask), level of positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FIO₂), arterial partial pressure of oxygen (PaO₂), PaO₂/FIO₂ ratio, the use of extracorporeal membrane oxygenation (ECMO), and prone positioning. The number of patients who had died, had been discharged, and were still admitted in the ICU as of March 25, 2020, were recorded, and ICU length of stay also was determined.

Statistical Analysis

No statistical sample size calculation was performed a priori, and sample size was equal to the number of patients treated during the study period. Continuous variables are presented as median and interquartile range (IQR) with 95% CIs. Categorical variables are expressed as number of patients (percentage) with 95% CIs. Differences in distributions of patient characteristics by median age subgroups and by presence/absence of hypertension are reported using differences with 95% CIs.

Percentages of available data for the overall population are based on the total number of patients included in the study, distribution of available data over the age subgroups are based on the available data for that variable, and the other percentages are calculated using the number of available data for that subgroup.

Patients were grouped by age and by median age. Age groups were defined as follows: 0 through 20 years; 21 through 40 years; 41 through 50 years; 51 through 60 years; 61 through 70 years; 71 through 80 years; 81 through 90 years; and 91 through 100 years. Younger and older age were classified as age lower than the median age and age equal or higher than the median age.

Mann-Whitney rank sum test was used to compare nonparametric continuous variables between median age subgroups and patients with or without hypertension. χ^2 or Fisher exact test was used for categorical variables as appropriate. All statistical tests were 2-tailed, and statistical significance was defined as $P < .05$. Analyses were performed using SAS 9.4. The analyses have not been adjusted for multiple comparisons, and given the possibility of type I error, the findings should be interpreted as exploratory and descriptive.

Results

From February 20 to March 18, 2020, a total of 1694 patients with suspected or confirmed COVID-19 were referred to the coordinating center. A total of 77 patients had pending and 24 patients had negative test results for SARS-CoV-2; for 2 patients, data were not available. Thus, data from 1591 critically ill patients with laboratory-confirmed COVID-19 were included in this report.

Table 1 shows the demographic and clinical characteristics of the patients. Overall, 82% (1304 of 1591 patients [95% CI, 79.98%-83.82%]) were male, similarly distributed among all age groups. The median age was 63 years (IQR, 56-70) (range, 14-91 years [95% CI, 63-64]) among 1591 patients. A total of 363 patients (23% [95% CI, 21%-25%]) were aged 71 years and older, and 203 (13% [95% CI, 11%-15%]) were younger than 51 years. In this report, median age was used to stratify patients as younger (age ≤ 63 years) or older (age ≥ 64 years).

Sixty-eight percent (95% CI, 65%-71%) of patients had at least 1 comorbidity. Hypertension was the most common comorbidity, affecting 509 (49% [95% CI, 46%-52%]) of 1043 patients with available data. The second most common comorbidities were cardiovascular disease (223 patients, 21% [95% CI, 19%-24%]) and hypercholesterolemia (188 patients, 18% [95% CI, 16%-20%]). Only 42 patients (4% [95% CI, 3%-5%]) had a history of chronic obstructive pulmonary disease. All the patients older than 80 years had at least 1 comorbidity, and 496 of 650 patients (76% [95% CI, 73%-80%]) older than 60 years had at least 1 comorbidity.

Among 1300 patients with available respiratory support data, 1287 (99% [95% CI, 98%-99%]) who were admitted to the ICU needed invasive or noninvasive respiratory support. A total of 1150 patients (88% [95% CI, 87%-90%]) required endotracheal intubation and mechanical ventilation, and 137 patients (11% [95% CI, 9%-12%]) were treated with noninvasive ventilation. Invasive mechanical ventilation was used in 565 (88% [95% CI, 85%-90%]) of the 645 younger patients with available data and in 585 (89% [95% CI, 87%-92%]) of the 655 older patients (difference, -2% [95% CI, -5% to 2%]; $P = .33$). Noninvasive ventilation was used in 70 (11% [95% CI, 9%-14%]) of the

645 younger patients with available data and in 67 (10% [95% CI, 8%-13%]) of the 655 older patients (difference, -1% [95% CI, -4% to 3%]; $P = .71$).

The median (IQR) positive end-expiratory pressure (PEEP) was 14 (12-16) cm H₂O ($n = 1017$). PEEP levels as high as 22 cm H₂O were applied. Among a total of 999 patients with available data, 887 (89% [95% CI, 87%-91%]) required a fraction of inspired oxygen (FIO₂) of at least 50%, and 120 (12% [95% CI, 10%-14%]) required 100% FIO₂. The median PaO₂/FIO₂ ratio was 160 (IQR, 114-220 [95% CI, 152-166]) ($n = 781$). PEEP level grouped by median age was not significantly different (median, 14 [IQR, 12-15] cm H₂O in the group aged ≤ 63 years vs 14 cm H₂O [IQR, 12-16] in the group aged ≥ 64 years; median difference, 0 [95% CI, 0-0]; $P = .94$). FIO₂ was higher in older patients (median, 60% [IQR, 50%-80%] in the group aged ≤ 63 years vs 70% [IQR, 50%-80%] in the group aged ≥ 64 years; median difference, -10% [95% CI, -14% to -6%]; $P = .006$). PaO₂/FIO₂ was higher in the younger patients (163.5 [IQR, 120-230] in the group aged ≤ 63 years vs 156 [IQR, 110-205] in the group aged ≥ 64 years; median difference, 7 [95% CI, -8 to 22]; $P = .02$).

The [Figure](#) shows distribution of age, PEEP, FIO₂, and PaO₂/FIO₂. At admission, 240 of 875 patients (27% [95% CI, 25%-31%]) were treated with prone ventilation and 5 of 498 (1% [95% CI, 0.3%-2%]) required extracorporeal membrane oxygenation (ECMO).

Compared with patients without hypertension ($n = 526$), patients with hypertension ($n = 509$) were significantly older (median age, 66 [IQR, 60-72] years vs 62 [IQR, 54-68] years; median difference, 4 [95% CI, 2-6]; $P < .001$) and had higher PEEP levels (median [IQR], 14 [12-16] vs 14 [12-15] cm H₂O; median difference, 0 [95% CI, 0-0]; $P = .003$) and lower PaO₂/FIO₂ (median, 146 [IQR, 105-214] vs 173 [IQR, 120-222]; median difference, -27 [95% CI, -42 to -12]; $P = .005$). However, there was no statistically significant difference in FIO₂ (median, 70 [IQR, 50-80] in the group with hypertension vs 60 [IQR, 50-80] in the group without hypertension; median difference, 10 [95% CI, 6-14]; $P = .05$).

Among the 1581 patients with ICU disposition data available as of March 25, 2020, 920 patients (58% [95% CI, 56%-61%]) were still in the ICU, 256 (16% [95% CI, 14%-18%]) had been discharged from the ICU, and 405 (26% [95% CI, 23%-28%]) had died in the ICU. ICU mortality was higher in those who were older ([Table 2](#)). ICU mortality was significantly lower in younger patients (≤ 63 years) compared with older patients (≥ 64 years) (15% vs 36%; difference, -21% [95% CI, -26% to -17%]; $P < .001$). The percentage of patients discharged from the ICU was significantly higher among younger patients compared with older patients (21% vs 11%; difference, 9% [95% CI, 6%-13%]; $P < .001$).

As of March 25, 2020, the median (IQR) length of stay in the ICU was 9 (6-13 [95% CI, 9-9]) days ($n = 1591$). Among patients still in the ICU ($n = 920$), the median (IQR) length of stay was 10 days (8-14 [95% CI, 10-11]); among patients discharged from the ICU ($n = 256$), the median length of stay was 8 days (5-12 [95% CI, 8-9]); and among patients who died in the ICU ($n = 405$), the median length of stay was 7 (5-11 [95% CI, 7-8]) days.

The prevalence of hypertension was higher among patients who died in the ICU (63%, 195 of 309 patients) compared with those discharged from the ICU (40%, 84 of 212 patients) (difference, 23% [95% CI, 15%-32%]; $P < .001$) ([Table 2](#)).

Discussion

In this case series of critically ill patients admitted to ICUs in Lombardy, Italy, with laboratory-confirmed COVID-19 from February 20 to March 18, 2020, the majority were older men, a large proportion required mechanical ventilation and high levels of PEEP, and ICU mortality was 26%.

The majority of patients in this case series were admitted to the ICU because of acute hypoxemic respiratory failure that required respiratory support. Endotracheal intubation and invasive mechanical ventilation were needed in 88% of the patients, whereas only 11% could be managed with noninvasive ventilation. The need for invasive mechanical ventilation in this patient population was higher than that recently reported for other ICU patients: 71% (Washington State, US),⁸ 47% (Wuhan, China),⁹ 42% (Wuhan, China)¹⁰ and 30% (Wuhan, China; of note, half of these were treated with ECMO).⁵ The need for invasive mechanical ventilation in this critically ill Italian patient population was also higher compared with data reported by 2 Chinese studies from Wuhan, including all adult inpatients with laboratory-confirmed COVID-19 and patients hospitalized with severe disease (with rates of 17%¹¹ and 15%,⁴ respectively).

Conversely, in previously cited reports, noninvasive ventilation has been used much more frequently both inside and outside the ICU. For the ICU population, the use of noninvasive ventilation was reported as 19% (Washington State, US),⁸ 42% (Wuhan, China),⁹ 56% (Wuhan, China),¹⁰ and 62% (Wuhan, China; of note, this value included patients receiving high-flow nasal cannula).⁵ In previous reports, noninvasive ventilation was used in 14% of adult inpatients with laboratory-confirmed COVID-19¹¹ and 32% of hospitalized patients with severe laboratory-confirmed COVID-19.⁴

The higher rate of intubation in the current case series could be due to the severity of hypoxia (the median $\text{PaO}_2/\text{FIO}_2$ was 160), thus requiring high levels of PEEP. However, in one of the recent reports, the $\text{PaO}_2/\text{FIO}_2$ ratio upon ICU admission was even lower (136).⁹ Another potential explanation is that the majority of the patients requiring noninvasive ventilation in northern Italy were able to be managed outside the ICU and were thus not included in this report. Data regarding use of respiratory support were missing for some patients ($n = 291$, or 18.3%), which may also have influenced the rates of respiratory support reported in this study.

The population in this study consisted mostly of men (82%, which is higher than previously reported) and older individuals.^{4,9,10} The median age of the patients admitted to the ICU was 63 (IQR, 56-70) years old, which is the same as the median age of all the positive Italian cases with COVID-19¹² suggesting that, to date, older age alone is not a risk factor for admission to the ICU.

In this cohort of patients, 68% had at least 1 comorbidity, in line with that reported by Wang et al (72.2%),⁹ but much higher than in other reports.^{4,5} Similar to other previous reports,^{4,9} hypertension was the most common comorbidity, followed by cardiovascular disorders, hypercholesterolemia, and diabetes. Among older patients, comorbidities were common but a relatively small percentage of patients had pulmonary disease.

Previous reports described different mortality rates among patients requiring ICU admission, from 16%⁹ to 38%,⁵ 62%,¹⁰ 67%,⁸ and 78%.¹¹ In this study, at 5 weeks after the first admission in ICU, the majority of the patients (58%) were still in the ICU, 16% of the patients had been discharged from the ICU, and 26% had died in the ICU. The

death rate was higher among those who were older. However, these outcome data should be interpreted with caution because most patients were still hospitalized in the ICU and the minimum follow-up was 7 days; in particular, the mortality rate could eventually be higher.

To the best of our knowledge, this is the largest case series of patients with COVID-19 and severe illness who required admission to the ICU. Available data indicate considerable variability among different countries in both the proportion of severe cases of COVID-19 among those testing positive and in the proportion of severe cases of COVID-19 among those hospitalized with the disease. Among western countries, Italy seems to have a higher rate of severely ill patients and thus it is particularly relevant to report the demographic and clinical characteristics of this population upon admission to the ICU. The majority of the patients had moderate to severe respiratory failure and required invasive mechanical ventilation and high levels of PEEP.

These data could reflect a different organization of health care systems in the world. In Italy, for instance, noninvasive ventilation is delivered both in ICUs and in other hospital wards. The amount of intensive care support that has been provided by intensivists outside of previously existing ICUs and newly created ICUs was not quantified. While the final figures are not yet available, the number of level 2 ICU beds (providing high-flow oxygen, continuous positive airway pressure, or noninvasive ventilation) is estimated to be high with a large number of beds created to increase capacity to deal with severely ill patients during the COVID-19 outbreak. These data will be collected soon to provide a complete description of the critically ill patients with COVID-19.

These data also suggest that the need for organ support and intensive care, regardless of the reason, in the COVID-19 outbreak is substantial, with 9% of all positive cases being probably a conservative estimate. The volume of critically ill patients with COVID-19 infection that ICUs might be required to manage may be substantial, and adequate ICU capacity to deal with severe respiratory failure should be planned.

Limitations

This study has several limitations. First, this was a retrospective study, and data were acquired via telephone. Second, the critical nature of the Lombardy situation did not allow the coordinator to obtain more detailed information, such as baseline medication use. Third, the follow-up time is still relatively short compared with the course of the disease, and the reported mortality data and length of stay data reported in this study could change. Fourth, there were relatively large amounts of missing data for some outcomes.

Conclusions

In this case series of critically ill patients with laboratory-confirmed COVID-19 admitted to ICUs in Lombardy, Italy, the majority were older men, a large proportion required mechanical ventilation and high levels of PEEP, and ICU mortality was 26%.

[Back to top](#)

[Article Information](#)

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