Mortality rate among critically ill patients with COVID-19 in a medical system with adequate hospital resources: a prospective observational study

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Research

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Abstract

Background: For critically ill patients with coronavirus disease 2019 (COVID-19) who require intensive care unit (ICU) admission, mortality rates vary widely depending on many factors, among which hospital resources and clinical setting seem important. We sought to determine the outcome of critically ill patients admitted in the usual multidisciplinary ICUs of a big referral for COVID-19 tertiary-care hospital with adequate resources.

Methods: We performed a prospective observational study of all adult patients with COVID-19 consecutively admitted to four COVID-designated ICUs at Evangelismos Hospital, Athens, Greece, from March 11 to April 27, 2020.

Results: Among 50 critically ill patients, ICU and hospital mortality for the entire cohort was 32% (16/50), whereas 66% (33/50) of patients were discharged alive from the ICU and 2% (1/50) were still treated in the ICU until June 16, 2020. ICU and hospital mortality for those who received invasive mechanical ventilation was 39% (16/41). Patients who eventually died had already increased risk of death on ICU admission, as suggested by the high values of the Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, the presence of current malignancy and occurrence of cardiac arrest in 44% (7/16) of patients, and the general need for circulatory support by noradrenaline. Median PaO_2/FiO_2 on ICU admission for the entire cohort was 121 mmHg [interquartile range (IQR), 86-171 mmHg] and most patients had moderate and severe acute respiratory distress syndrome (ARDS) according to the Berlin Definition. The primary cause of death of all patients was multi-organ failure, most commonly due to sepsis, whereas none died from refractory hypoxemia, neurologic dysfunction or withdrawal of life support. Hospital stay was long in patients who survived [median 24 days (IQR, 15-35 days)] and was frequently complicated by bacteremias [36% (12/33)].

Conclusion: Severely ill COVID-19 patients with moderate and severe ARDS may have equal or even lower mortality rates compared to ARDS due to other causes, when they are admitted in general ICUs with experienced and adequate staff without limitations in hospital resources, where established ARDS therapies are used.

Background

The outbreak of coronavirus disease 2019 (COVID-19) emerged in China in December 2019 (1) and rapidly spread worldwide. The major clinical complication in patients with COVID-19 is acute respiratory distress syndrome (ARDS) requiring intensive care unit (ICU) admission. For those patients needing care in an ICU, mortality rates as high as 49 to 97% have been reported (2–9). However, there is report of lower mortality rates (30.9% for all patients admitted in the ICU and 35.7% for intubated patients) in areas where ICU capacity enabled the timely admission of all COVID-19 patients requiring critical care to a traditional ICU (10).

In Greece, the number of patients with confirmed COVID-19 and those who required hospital and ICU admission was rather limited, thus not overwhelming hospital resources (11). Therefore, we considered pertinent to investigate the outcome of critically ill patients with COVID-19 admitted to the general ICUs of a big referral for COVID-19 tertiary-care hospital with adequate resources.

Methods

Patients and Setting

This is a prospective observational study of all adult patients with COVID-19 consecutively admitted to four COVID-designated ICUs at Evangelismos Hospital, Athens, Greece, from March 11 to April 27, 2020. COVID-19 status was based upon positive severe acute respiratory syndrome coronavirus 2 real-time reverse transcriptase–polymerase chain reaction assay of nasopharyngeal-swab specimens. The study was approved by the hospital institutional review boards. Informed consent was waived.

During the study period, all patients with COVID-19 who required critical care were timely admitted to a COVID-ICU due to adequate ICU capacity. Additionally, all patients admitted to COVID-ICUs were treated by standard (i.e., pre-COVID) multidisciplinary ICU care teams with usual ICU staffing ratios. There was no lack of ventilators or other respiratory support devices, dialysis machines, medications, or other critical care supplies including personal protective equipment. Although there was an institutional recommendation against the routine use of non-invasive positive pressure mechanical ventilation, the routine use of high-flow nasal cannula oxygen therapy was not limited.

Clinical management occurred at the discretion of the critical-care trained attending physician. The management of mechanically ventilated patients was according to ARDS treatment guidelines (12, 13), including prone ventilation and conservative fluid management. Briefly, tidal volumes of approximately 6 ml/kg predicted body weight and a respiratory rate adjusted to maintain arterial pH above 7.30 were applied, targeting plateau pressure of less than 30 cmH_2O. Positive end-expiratory pressure (PEEP) was usually set according to the lower PEEP / higher FiO_2 ARDS network table (12) titrating for the best tidal respiratory system compliance.

Data Collection and Definitions

Data was collected through June 16, 2020. All patient data, clinical and laboratory, as well as ventilator settings and measurements were prospectively collected along with the ongoing pandemic. ARDS was defined according to the Berlin Definition criteria (14). Severity of illness was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II (15) and Sequential Organ Failure Assessment (SOFA) (16) scores. The severity of acute pulmonary damage in mechanically ventilated patients was graded by using the Lung Injury Score (17). Respiratory system compliance was computed as the tidal volume divided by the difference between plateau pressure and total PEEP. The last difference constituted the driving pressure. The evolution of organ dysfunction during the ICU stay was evaluated by calculating the SOFA score at admission and on ICU days 3, 5, 10, 14 and 21.

Statistical Analysis

Quantitative data is reported as median and interquartile range (IQR). Non-parametric statistics were applied. Comparisons between patients who survived versus those who died in the ICU were performed by using the Mann-Whitney U test. Differences between these two groups of patients in qualitative variables were assessed by Chi-square or Fisher's exact test when appropriate. Differences in group data for related samples were evaluated by the Friedman's ANOVA by ranks; when significant differences were found, post-hoc comparisons were performed by using the Wilcoxon matched-pair test. The SPSS statistical program (version 10, Chicago, IL, USA) was used for data analysis. Statistical significance was defined as a two-tailed p value of < 0.05.

Results

Patient Characteristics and ICU admission

During the study period 50 adults with COVID-19 infection were critically ill and admitted to the ICUs of our institution (Fig. 1A). Demographics and data on ICU admission are summarized in Table 1. The median patient age was 64 years (IQR, 58–72) and 24 patients (48.0%) were 65 years or older. The majority of patients were Caucasian (47 [94.0%]). Hypertension was the most common comorbidity (14 [28.0%]), followed by diabetes (9 [18.0%]). Five patients (10.0%) had hematologic malignancy, whereas 18 patients (36.0%) had at least two comorbidities.

Table 1

Demographics and clinical and laboratory data on ICU admission of patients with COVID-19[a]

	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
Age, years [median (IQR)]	64 (58–72)	61 (55–71)	70 (60–77)	0.065
≤ 64	26 (52.0)	20 (60.6)	5 (31.3)	0.054
≥ 65	24 (48.0)	13 (39.4)	11 (68.7)	
Gender, male	38 (76.0)	25 (75,8)	12 (75.0)	0.954
Race	47 (94.0)	30 (90.9)	16 (100)	0.542
Caucasian	3 (6.0)	3 (9.1)	0 (0)	
Asian				
Comorbidity	14 (28.0)	9 (27.3)	4 (25.0)	0.866
Hypertension	9 (18.0)	6 (18.2)	3 (18.8)	0.962
Diabetes mellitus	6 (12.0)	3 (9.1)	3 (18.8)	0.333
Cardiovascular[d]	5 (10.0)	1 (3.0)	4 (25.0)	**0.034**
Malignancy[e]	5 (10.0)	3 (9.1)	2 (12.5)	0.712
Obesity[f]	4 (8.0)	2 (6.1)	2 (12.5)	0.440
Chronic lung disease	1 (2.0)	0 (0)	1 (6.3)	0.327
Chronic renal failure	18 (36.0)	11 (33.3)	7 (43.8)	0.478
Comorbidities (≥ 2)				
Time from symptom onset to ICU admission, days [median (IQR)]	9 (8–11)	10 (8–12)	8 (8-10.5)	0.352

ICU, intensive care unit; IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation (16); SOFA, Sequential Organ Failure Assessment (17); PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CT, computed tomography; PEEP, positive end-expiratory pressure; LIS, Lung Injury Score (18).

[a]Data are expressed as n (%) unless otherwise indicated; [b]includes one patient who is still mechanically ventilated in the ICU; [c]Mann-Whitney U test and X^2 with Yates correction or Fisher exact test comparing those who survived versus died in the ICU; [d]coronary artery disease and/or congestive heart failure; [e]lymphoma, chronic lymphoid leukemia and acute myeloid leukemia had 3,1 and 1 patients, respectively (3 patients were under chemotherapy); [f]defined as BMI > 30 kg/m^2; [g]upper limit of normal 0.5 mg/dL; [h]upper limit of normal 0.1 ng/mL; [i]upper limit of normal 0.3 µg/mL; [j]upper limit of normal 14 pg/mL; [k]refers to 41 patients who received invasive mechanical ventilation.

	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
APACHE II score, median (IQR)	12 (8–17)	9 (6–12)	20 (17–26)	< 0.001
SOFA score, median (IQR)	7 (3–9)	6 (2–7)	11 (9–13)	< 0.001

ICU, intensive care unit; IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation (16); SOFA, Sequential Organ Failure Assessment (17); PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CT, computed tomography; PEEP, positive end-expiratory pressure; LIS, Lung Injury Score (18).

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	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
Laboratory data, median (IQR)				
Leukocyte count, x10^9/L	7.6 (5.9–11.2)	7.3 (5.9–10.8)	9.5 (6.0-17.3)	0.386
Lymphocyte count, x10^9/L	0.88 (0.61–1.13)	0.88 (0.65–1.13)	0.93(0.48–1.08)	0.855
Platelet count, x10^9/L	233 (193–318)	233 (200–322)	263 (211–329)	0.553
C-reactive protein, mg/dL[g]	14.2 (7.7–24.6)	13.6 (7.7–20.3)	21.7 (9.6–31.9)	0.092
Procalcitonine, ng/mL[h]	0.43 (0.12–0.94	0.34 (0.15–0.66)	1.41 (0.11–1.52)	0.503
Ferritin, µg/L	835 (353–1882)	835 (576–1710)	1509 (479–1740)	0.345
D-dimer, µg/mL[i]	1.23 (0.52–2.46)	1.30 (0.59–2.43)	1.17 (0.45–2.17)	0.987
Lactate dehydrogenase, IU/L	471 (403–611)	454 (363–604)	509 (428–574)	0.316
Albumin, g/dL	3.2 (3.0-3.6)	3.3 (3.1–3.7)	3.0 (2.8–3.4)	**0.038**
Creatinine, mg/dL	0.9 (0.7–1.1)	0.8 (0.7-1.0)	1.1 (0.7–1.8)	0.123
Troponin T, pg/mL[j]	15 (10–52)	12 (8–20)	31 (14–85)	**0.012**
Lactate, mmol/L	1.3 (1.0-1.8)	1.0 (0.9–1.3)	1.8 (1.3–2.1)	**< 0.001**
Bilateral infiltrates on chest x-ray/CT	49 (98)	32 (97)	16 (100)	1.000
Arterial blood gases, median (IQR)				

ICU, intensive care unit; IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation (16); SOFA, Sequential Organ Failure Assessment (17); PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CT, computed tomography; PEEP, positive end-expiratory pressure; LIS, Lung Injury Score (18).

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	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
PaO_2/FiO_2, mmHg	121 (86–171)	119 (89–157)	123 (75–243)	0.790
$PaCO_2$, mmHg	40 (33–45)	36 (29–42)	44 (42–50)	**0.002**
pH	7.39 (7.32–7.44)	7.42 (7.35–7.45)	7.30 (7.25–7.36)	**0.006**
Respiratory parameters at day of intubation, median (IQR)[k]				
PEEP, cmH_2O	14 (12–16)	14 (12–17)	13 (10–16)	0.436
Plateau pressure, cmH_2O	27 (25–29)	27 (26–29)	25 (24–29)	0.413
Driving pressure, cmH_2O	13 (11–15)	12 (10–14)	13 (12–15)	0.384
Static compliance, mL/cmH_2O	40 (32–50)	40 (33–50)	39 (33–42)	0.683
LIS	2.7 (2.5–3.2)	2.7 (2.5–3.2)	2.8 (2.5–3.5)	0.730
Noradrenaline	39 (78)	21 (64)	16 (100)	**0.004**

ICU, intensive care unit; IQR, interquartile range; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation (16); SOFA, Sequential Organ Failure Assessment (17); PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; CT, computed tomography; PEEP, positive end-expiratory pressure; LIS, Lung Injury Score (18).

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The median time from symptom onset to hospital admission was 7 days (IQR, 5.0-8.5 days). Twenty-three patients (46%) were admitted to the ICU within less than 24 hours after hospital admission. The remaining 27 patients (54%) had median hospitalization time in general wards prior to ICU admission 2 days (IQR, 1–4 days).

On ICU admission, the median APACHE II score was 12 (IQR, 8–17), and the median SOFA score was 7 (IQR, 3–9). Bilateral lung infiltrates were shown in 49 patients (98%), whereas the median PaO_2/FiO_2 was

121 mmHg (IQR, 86–171 mmHg). Thirty-nine patients (78%), all under invasive mechanical ventilation, were receiving noradrenaline for circulatory support. In none of the patients was the respiratory viral panel positive for a different viral infection or the respiratory samples positive for bacteria.

Invasive mechanical ventilation was applied in 41 patients (82%) (Fig. 1B). On the day of intubation, median static respiratory system compliance was 40 mL/cmH_2O (IQR, 32–50 mL/cmH_2O) and median Lung Injury Score was 2.7 (IQR, 2.5–3.2) (ARDS is identified when Lung Injury Score is higher than 2.5 [18]).

Interventions in the ICU

Interventions in the ICU are included in Table 2. A total of 14 patients (28%) received high-flow nasal cannula whereas only 2 patients (4%) were treated with non-invasive mechanical ventilation. Among those who received invasive mechanical ventilation, the median duration of mechanical ventilation was 13 days (IQR, 9–33 days), while 26 (52%) required neuromuscular blockade therapy for at least 24 hours, and prone position was used as rescue therapy in 6 patients (12%). Thirty-four patients (68%) required noradrenaline as vasopressor support for shock and 13 patients (26%) needed continuous renal replacement therapy. Most of the patients received hydroxychloroquine for at least 5 days.

Table 2

Interventions in the ICU and outcomes[a]

	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
High-flow nasal cannula	14 (28)	13 (39)	1 (6)	**0.019**
Non-invasive mechanical ventilation	2 (4)	2 (6)	0 (0)	0.551
Invasive mechanical ventilation (IMV)	41 (82)	24 (73)	16 (100)	**0.021**
Time to intubation, median (IQR)[d]	2 (0–3)	2 (0–4)	1 (0–3)	0.249
IMV days, median (IQR)	13 (9–33)	13 (10–32)	14 (7–27)	0.847
Neuromuscular blockade	26 (52)	14 (42)	12 (75)	0.066
Prone position	6 (12)	4 (12)	2 (13)	0.969
Noradrenaline	34 (68)	17 (52)	16 (100)	**< 0.001**
Noradrenaline days, median (IQR)	6 (2–13)	4 (1–8)	11 (5–15)	**0.009**
Renal replacement therapy	13 (26)	4 (12)	8 (50)	**0.003**
Renal replacement therapy days, median (IQR)	15 (11–24)	19 (15–24)	15 (9–26)	0.570
Selected inpatient medications	44 (88)	29 (88)	14 (88)	0.969
Hydroxychloroquine	38 (76)	26 (79)	12 (75)	0.765
Azithromycin	18 (36)	13 (39)	5 (31)	0.811
Lopinavir / Ritonavir	5 (10)	3 (9)	2 (13)	0.893
Anti-Interleukin-6 antibody	3 (6)	1 (3)	1 (6)	0.813
Remdesivir (or placebo)	5 (10)	2 (6)	3 (19)	0.382
Glucocorticoids				

ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

[a]Data are expressed as n (%) unless otherwise indicated; [b]includes one patient who is still mechanically ventilated in the ICU; [c]Mann-Whitney U test and X^2 with Yates correction or Fisher exact test comparing those who survived versus died in the ICU; [d]refers to 41 patients who received invasive mechanical ventilation; [e]among patients who did not have a tracheostomy; [f]patients who survived and were discharged alive from the ICU (n = 24) were the sum of patients who were successfully extubated (n = 17) and those who had a tracheostomy (n = 7).

	All (n = 50)[b]	Survived ICU (n = 33)	Died in ICU (n = 16)	p[c]
Outcomes	50 (29–88)	50 (29–84)	50 (30–88)	NA
Follow-up, days [median (range)]	17 (41)	17 (71)[f]	0 (0)	NA
Successful extubation[d,e]	9 (5–14)	9 (5–14)	NA	0.942
Time to successful extubation, days	12 (29)	7 (29)[f]	4 (25)	0.968
[median (IQR)[d,e]	22 (19–25)	21 (19–26)	22 (18–26)	0.847
Tracheostomy[d]	13 (9–33)	13 (10–32)	14 (7–27)	0.417
Time to tracheostomy, days	14 (9–31)	15 (10–30)	14 (7–27)	**< 0.001**
[median (IQR)][d]	21 (10–32)	24 (15–35)	14 (7–27)	NA
Mechanical ventilation days,	12 (24)	NA	NA	NA
median (IQR)[d]	12 (29)	NA	NA	
ICU days, median (IQR)				
Hospital days, median (IQR)				
28-day mortality				
28-day mortality in ventilated[d]				

ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

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ICU Outcomes

ICU outcomes are displayed in Fig. 1 and summarized in Table 2. As of data censoring on June 16, 2020, median patient follow-up was 50 days (range 29–88) (Table 2). Among 50 patients admitted in the ICU, 16 died (32.0%), 33 patients were discharged alive from the ICU (66.0%), and 1 patient remained in the ICU (2.0%) still receiving invasive mechanical ventilation; hospital mortality was 32.0% as well (16/50) (Fig. 1A), whereas 28-day mortality was 24% (12/50) (Table 2). Among 41 patients who received invasive mechanical ventilation, ICU and hospital mortality was 39.0% (16/41) (Fig. 1B); 24 patients were

discharged alive from the ICU (58.6%), 17 of them after a successful extubation and the remaining 7 patients with a tracheostomy in place (Table 2). Twenty-eight-day mortality was 29% (12/41) (Table 2).

Patients who died had a higher proportion of current malignancy, and on ICU admission, had higher APACHE II and SOFA scores, higher blood troponin T and lactate values, and were receiving noradrenaline for vasopressor circulatory support more frequently than those who survived (Table 1). Notably, among patients who died, 3 (19%) had suffered cardiac arrest during endotracheal intubation. Compared to those who survived, patients who died in the ICU rarely received high-flow nasal cannula oxygen therapy, and more commonly required invasive mechanical ventilation, noradrenaline infusion and continuous renal replacement therapy for renal failure management (Table 2). Duration of hospital stay was longer in patients who survived compared to those who died in ICU (Table 2).

SOFA score in patients who died was higher than in those who survived not only on ICU admission, but also on days 3–21 ($p < 0.01$ for all days) (Fig. 2). This difference could be attributed to higher cardiovascular and renal components of SOFA score in patients who died compared to those who survived ICU (data not shown). SOFA score in patients who survived was not significantly different from ICU admission to day 21. In contrast, SOFA score in patients who died did differ in the course of their ICU stay; post-hoc analysis showed that their SOFA scores on days 10, 15 and 21 were all significantly higher than on admission, day 3 or day 5 ($p < 0.05$ for all days) (Fig. 2). This difference was mainly due to the higher renal component of SOFA score (data not shown). The primary cause of death of all patients was multi-organ failure most commonly due to sepsis; none died from refractory hypoxemia, neurologic dysfunction or withdrawal of life support (18). Thrombotic events (i.e., deep venous thrombosis) occurred in 3 patients (6%) (2 patients survived and 1 died); in 1 patient who eventually survived, deep venous thrombosis was complicated by intermediate-risk pulmonary embolism. ICU-acquired bacteremia was detected in 12 patients who survived (36%) versus 4 patients who died (25%) ($p = 0.637$). Median number of bacteremias in patients who survived was 2.5 (IQR, 1.0-4.5) versus 1.5 (IQR, 1.0–4.0) in patients who died ($p = 0.770$). *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Enterococcus faecalis* were the most frequent bacteria, and were isolated in 6 (18%), 6 (18%) and 5 patients (15%), respectively, in patients who survived compared to 3 (19%), 2 (13%) and 2 patients (13%), respectively, in patients who died ($p = 0.729–0.926$).

Discussion

The main findings of the present study were: i) ICU and hospital mortality were 32% and 39% for the entire cohort of patients admitted to the ICU and for those who received invasive mechanical ventilation, respectively; ii) 28-day mortality was 24% and 29% for the whole group of patients admitted in the ICU and for those who required invasive mechanical ventilation, respectively; iii) patients who eventually died had already increased risk of death even on ICU admission, as suggested by the high values of APACHE II and SOFA scores, the presence of current malignancy and occurrence of cardiac arrest, and general need for circulatory support with noradrenaline; iv) the primary cause of death of all patients was multi-organ failure most commonly due to sepsis, whereas none died from refractory hypoxemia, neurologic

dysfunction or withdrawal of life support; and v) hospital stay was long in patients who survived, frequently complicated by bacteremias.

ICU and hospital mortality of 32% for overall ICU admissions observed in the present study was similar to that recently reported by Auld et al (10) in a large cohort of critically ill patients (n = 217) admitted in COVID-designated ICUs of 3 hospitals in Atlanta, Georgia, showing 28.6% ICU mortality and 31% hospital mortality. Moreover, ICU and hospital mortality of 39% for the approximately four-fifths of patients in our cohort who received invasive mechanical ventilation was also similar to that of Auld et al (10), reporting 33.9% ICU mortality and 35.7% hospital mortality. Notably, only 2.4% of patients in our cohort and 4.8% of patients in the previous study (10) still remained on the ventilator at the time of the report, and there was ample follow-up time (median 50 days, range 29–88 days, in our group of patients) (Table 2). Both patient cohorts, i.e., that of ours and that of Auld et al (10), seem comparable in terms of lung disease and patient illness severity, at least on ICU admission. Indeed, median PaO_2/FiO_2 was 121 mmHg (IQR, 86–171 mmHg) with median PEEP 14 cmH_2O (IQR, 12–16 cmH_2O) in our cohort versus median PaO_2/FiO_2 of 132 mmHg (IQR, 100–178 mmHg) (PEEP level was not reported) in the previous study (10); median SOFA score was 7 in both studies. Most of our patients had moderate and severe ARDS according to the ARDS Berlin Definition (14); the definition of ARDS was also fulfilled in most of our mechanically ventilated patients on the day of intubation, as the median Lung Injury Score was 2.7 (IQR, 2.5–3.2) (17) (Table 1). Our data, as well as that of Auld et al (10), provide evidence that mortality rates of severely ill COVID-19 patients with ARDS may be comparable or even lower to those reported in ARDS of different etiologies (19, 20) including Influenza A (21, 22). Indeed, hospital mortality for patients with moderate ARDS was 40.3% and for those with severe ARDS was 46.1% (19), whereas overall pooled mortality rate of all ARDS studies included in a comprehensive literature review was 43% (20). Moreover, mortality rate was 41.4% (21) and 46% (22) among ICU patients with Influenza A pneumonia, most of whom had ARDS.

Our findings differ from those of earlier studies in ICU patients with COVID-19 reporting overall mortality rates 49–62% (2, 7, 8) and mortality rates as high as 66–97% among patients requiring invasive mechanical ventilation in China (7, 23, 24). Similarly, mortality rate for our patients was substantially lower than that of subsequent reports from USA (4–6), showing mortality rates for patients requiring invasive mechanical ventilation ranging from 52% (5) and 67% (6) in the Seattle region to 88.1% in New York area (4), as well as from Italy demonstrating overall hospital mortality 53.4% for patients admitted in ICU (25). To interpret the observed differences in clinical outcomes, at least two general and/or local factors should be taken into account. Firstly and primarily, in our study all critically ill patients with COVID-19 were admitted to the ICU in time, because overwhelming stress on the healthcare system did not occur in our country (11). All these patients were admitted to preexisting multidisciplinary ICUs, were cared for by critical care teams with experience in the management of patients with severe acute respiratory failure at standard staffing ratios, and received full intensive care support, including renal replacement therapy. Secondly, the onset and peak of the COVID-19 pandemic in Greece occurred later than in many of the regions from earlier reports, including neighboring Italy (25). This delay gave time to

create organizational arrangements, purchase equipment, train personnel, make consensus-driven clinical protocols, and distribute supplies across the healthcare system.

Lung disease on ICU admission was not worse in patients who died than in those who survived as suggested by lack of any difference in blood oxygenation, respiratory system compliance and Lung Injury Score values; the same ventilatory protocol was also applied in both groups as implied by the presence of no difference in PEEP, plateau pressure and driving pressure levels (Table 1). Moreover, lung disease severity on admission and ICU days 3–21 did not contribute to the higher SOFA score in patients who died compared to those who survived (Fig. 2) and nobody died from refractory hypoxemia. The higher SOFA score on admission and ICU days 3–21 (Fig. 2) was mainly due to higher cardiovascular and renal components of SOFA score. Not surprisingly, patients who died compared to patients who survived, more commonly needed noradrenaline infusion for circulatory support on ICU admission (Table 1) and required noradrenaline use for shock treatment and continuous renal replacement therapy for renal failure management during ICU stay (Table 2).

We acknowledge the main limitation of this study, i.e., we reported findings and outcomes from a single center and included a rather limited number of patients compared to hundreds or thousands of patients incorporated in many studies from other countries with thousands victims of COVID-19 pandemic (2–4, 9, 23, 25, 26). However, our study included all consecutive patients admitted to four COVID-designated ICUs of the biggest referral center for COVID-19 in Greece and our study sample represents about 25% of the total number of patients admitted in Greek ICUs (27). Due to the relatively limited spread of the pandemic in Greece, our medical system was not overwhelmed, and this fact generated the purpose of the present study. Therefore, our findings might not be generalizable to different populations and medical systems, but might be relevant to other countries where the pandemic did not overwhelm the health system capacity.

Conclusions

Severely ill COVID-19 patients with moderate and severe ARDS may have equal or even lower mortality rates compared to ARDS due to other causes, when they are admitted in general ICUs with experienced and adequate staff without limitations in hospital resources, where established ARDS therapies (12, 13), including low tidal volume and conservative fluid management, are used. The reported hospital mortality rates of 32% overall and 39% for patients who received invasive mechanical ventilation could potentially be used as basis for future treatment protocols in similar clinical settings.

Abbreviations

COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; IQR: interquartile range

Declarations

Authors' contributions

All authors have contributed to the final version of the manuscript as follows: CR, EM, SK, IS, DZ, EI, SM, TD, CV, PK, LD, AS, IS, VM, AA, PT, AK, PP, ZM, ED, TT, IP, PG, AS, AM, EM, AK, AS, EG, and AK contributed to patients' inclusion; CR, EM, SK, and IS contributed to data collection; CR, SM, IK, VP, and SZ contributed to data analysis; SZ made the statistical analysis; CR, and SZ drafted and revised the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used/or analyzed in the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethical committee of 'Evangelismos' Hospital, Athens, Greece. The need of informed consent was waived because of the observational nature of the study.

Consent for publication

Not applicable

Competing interests

None

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Figures

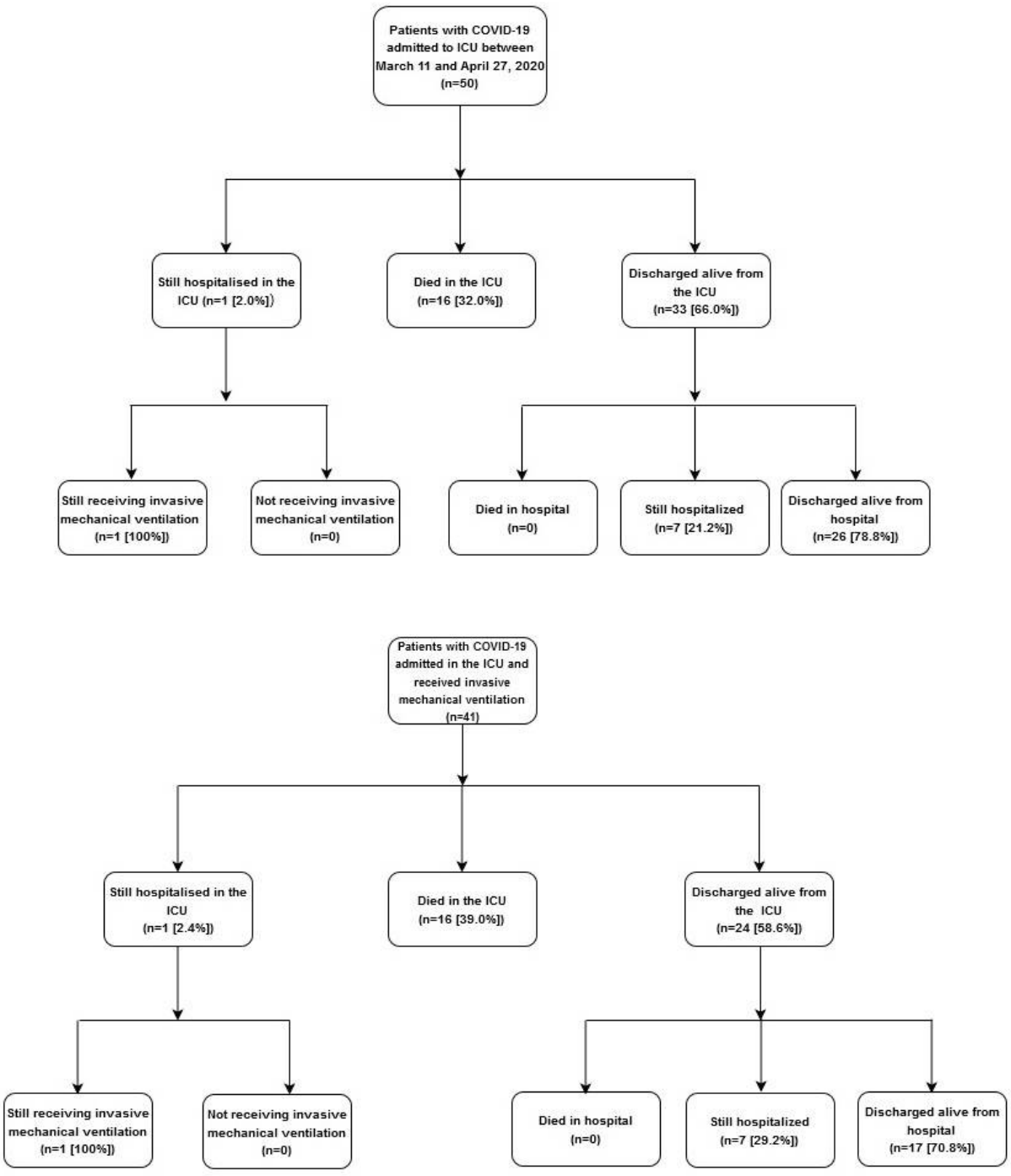

Figure 1

Flow diagram for study patients who were admitted to coronavirus disease 2019-designated ICUs (A), and received invasive mechanical ventilation (B). COVID-19 = coronavirus disease 2019; ICU = intensive care unit.

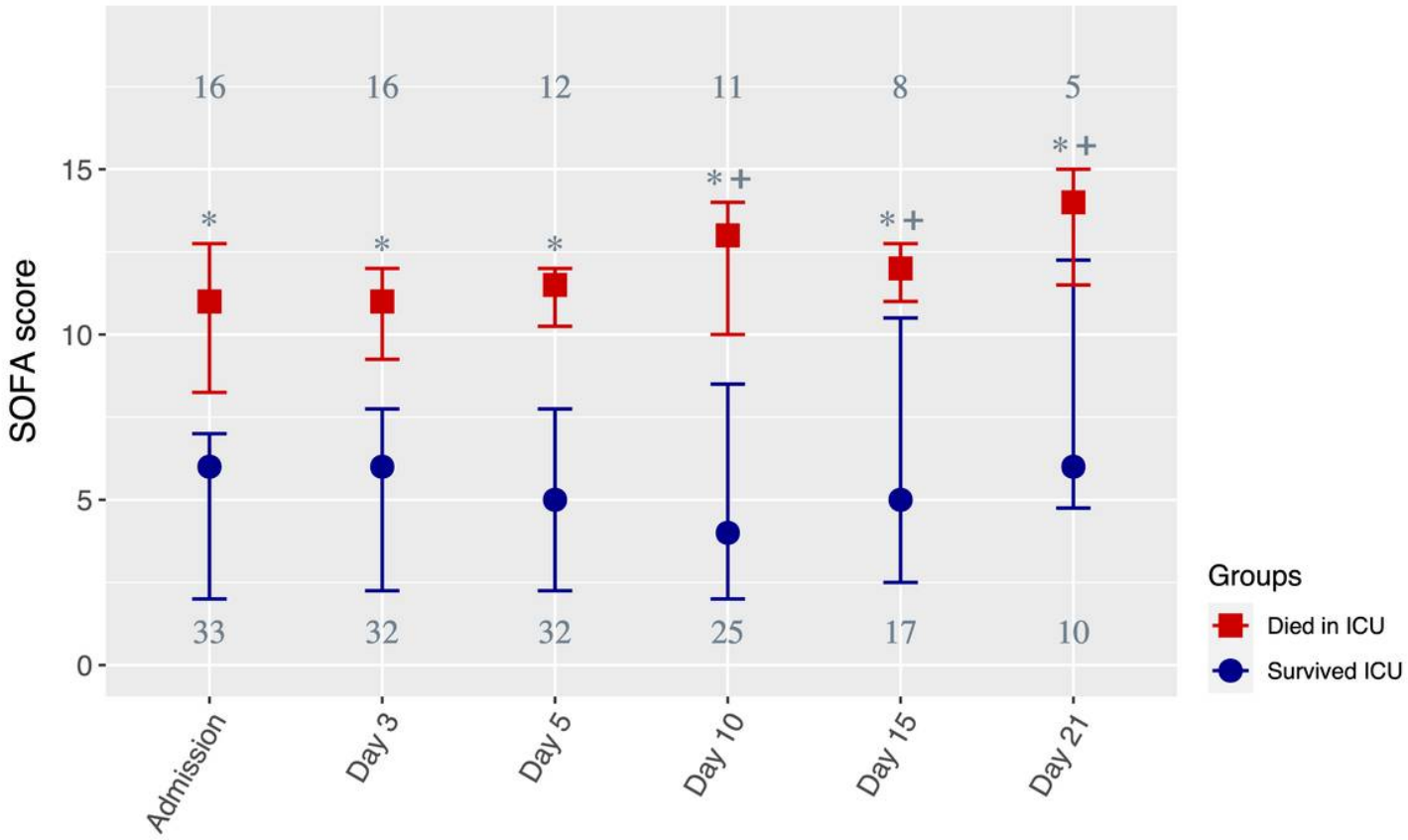

Figure 2

Serial SOFA score of patients admitted to the ICU and either survived or died in ICU. Days represent ICU days. Values are medians and error bars are interquartile ranges. Numbers represent the number (n) of patients on each day. Asterisks denote significant differences between died and survived on the same ICU day ($p<0.01$; Mann-Whitney U test), whereas crosses denote significant differences in patients who died between SOFA scores on days 10, 15 and 21 and SOFA scores on admission, day 3 or day 5 ($p<0.05$; Wilcoxon matched-pair test). SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit.

Supplementary Files

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- GraphicalAbstractImage.jpg