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Original Articles

Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital. A retrospective cohort study

Yasser Nassar[a], Ahmed Mokhtar[b], Amr Elhadidy[a], Marwa Elsayed[a], Farouk Mostafa[a], Ashraf Rady[b], Akram Eladawy[b], Mostafa Elshazly[c], Mohamed Saeed[c], Sherif Mokhtar[a], Samuel Buschbeck[d], Yasser Sakr[d,*]

[a] Critical Care Department, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt
[b] Department of Anesthesiology, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt
[c] Department of Chest Diseases, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt
[d] Dept. of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Am Klinikum 1, 07743 Jena, Germany

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ABSTRACT

Background: The characteristics, outcomes, and risk factors for in-hospital death of critically ill intensive care unit (ICU) patients with coronavirus disease-2019 (COVID-19) have been described in patients from Europe, North America and China, but there are few data from COVID-19 patients in Middle Eastern countries. The aim of this study was to investigate the characteristics, outcomes, and risk factors for in-hospital death of critically ill patients with COVID-19 pneumonia admitted to the ICUs of a University Hospital in Egypt.

Methods: Retrospective analysis of patients with COVID-19 pneumonia admitted between April 28 and July 29, 2020 to two ICUs dedicated to the isolation and treatment of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Cairo University Hospitals. Diagnosis was confirmed in all patients using real-time reverse transcription polymerase chain reaction on respiratory samples and radiologic evidence of pneumonia.

Results: Of the 177 patients admitted to the ICUs during the study period, 160 patients had COVID-19 pneumonia and were included in the analysis (mean age: 60 ± 14 years, 67.5% males); 23% of patients had no known comorbidities. The overall ICU and hospital mortality rates were both 24.4%. The ICU and hospital lengths of stay were 7 (25–75% interquartile range: 4–10) and 10 (25–75% interquartile range: 7–14) days, respectively. In a multivariable analysis with in-hospital death as the dependent variable, ischemic heart disease, history of smoking, and secondary bacterial pneumonia were independently associated with a higher risk of in-hospital death, whereas greater PaO_2/FiO_2 ratio on admission to the ICU was associated with a lower risk.

Conclusion: In this cohort of critically ill patients with COVID-19 pneumonia, ischemic heart disease, history of smoking, and secondary bacterial pneumonia were independently associated with a higher risk of in-hospital death.

Introduction

The coronavirus disease-2019 (COVID-19) pandemic, caused by infection with a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted healthcare systems worldwide. As of December 21, around 75 million infections have been documented around the globe with an overall mortality rate of 2.23% [1]. Although most patients with SARS-CoV-2 infections have been reported to develop mild to moderate symptoms, patients with severe respiratory insufficiency requiring admis-

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, Body mass index; COVID-19, Coronavirus disease-2019; CRP, C-reactive protein; ECMO, Extracorporeal membrane oxygenation; HFO, High flow oxygen therapy; FiO_2, Fraction of inspired oxygen; ICU, Intensive Care unit; IQ, Interquartile range; IU, International unit; LDH, Lactate dehydrogenase; PCO_2, Partial pressure of carbon dioxide; PO_2, Partial pressure of oxygen; SaO_2, Arterial oxygen concentration; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, Standard deviation.

* Corresponding author.
E-mail address: yasser.sakr@med.uni-jena.de (Y. Sakr).

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sion to the intensive care unit (ICU) are at a high risk of major morbidity and subsequently have high mortality rates [2–22]. Several cohort studies have reported the characteristics of and outcomes from COVID-19 pneumonia in these critically ill patients [2,4,5,11,12,20,23]. However, most of the studies published to-date, have reported on ICU cohorts from Europe [2,3,5,10,12,17,18], North America [4,6,7,24–26], and China [11,23,27–30], which may not reflect the global picture. Moreover, several studies have included relatively small number of patients, which may provide false estimates of outcome and disease burden in these patients [7,8,11,22,23,29,31]. In particular, data from Middle Eastern countries are scarce and little is known about the clinical characteristics of critically ill patients with COVID-19 in these countries. These data are crucial to provide insight about possible variability in the clinical presentation of severe SARS-CoV-2 infections and outcomes of COVID-19 disease in different geographic regions and healthcare systems.

Since the emergence of the epidemic, 126 273 patients with confirmed COVID-19 have been reported in Egypt with an overall mortality rate of 5.6% [1]. The aim of this study was to investigate the characteristics, outcomes, and risk factors for in-hospital death of critically ill patients with COVID-19 pneumonia admitted to the ICUs of a University Hospital in Egypt. Our hypothesis was that critically ill patients with COVID-19 pneumonia would have high morbidity and mortality rates in the ICU and that preexisting comorbid conditions and major complications during the ICU stay would be associated with a high risk of death in these patients.

Methods

Study design and setting

This was a retrospective observational cohort study of patients admitted to the two ICUs of Cairo University Hospitals that were dedicated to the isolation and treatment of patients with suspected or confirmed SARS-CoV-2 infections at the time of data collection: a16-bed medical and a 16-bed postoperative ICU.

Participants and case definition

We included all consecutive patients aged 18 years or more with confirmed SARS-CoV-2 infection who were admitted to the participating ICUs between April 28 and July 29, 2020. Diagnosis was confirmed in all patients using real-time reverse transcription polymerase chain reaction (rt-PCR) on respiratory samples and radiologic evidence of pneumonia. Patients with confirmed SARS-CoV-2 infection, but admitted to the ICU for medical conditions not related to COVID-19 pneumonia and those with incomplete records were excluded from the analysis.

Interventions

Patient records were reviewed by a senior intensivist (YN, AM, ME, or FM) to collect demographic data, comorbid conditions, initial symptoms, laboratory indices of organ failure, therapeutic interventions, major complications during the ICU stay, and vital status during the hospital stay. Routine laboratory investigations included parameters of liver and renal functions, complete blood picture, arterial blood gases, inflammatory parameters (C-reactive protein (CRP) and lactate dehydrogenase (LDH)), and D-dimer levels. These parameters were measured on admission to the ICU and at least once daily thereafter (at 7:00 am) in the ICU. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated from the data obtained within 24 h of admission to the ICU [32].

Ethics

The study was approved by the institutional review board of Cairo University Hospitals (Research Ethics Committee, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt, Protocol-ID: N-89-2020). Informed consent was waived due to the retrospective, anonymous nature of data collection.

End points

The primary end point was in-hospital mortality. Secondary end points included death in the ICU, ICU and hospital lengths of stay, and need for mechanical ventilation, renal replacement therapy or vasopressor therapy during the ICU stay.

Statistical analysis

All data were processed and analyzed in the departments of critical care medicine and anesthesiology of the new Kasr-El-Aini University Hospital of Cairo, Egypt in collaboration with Jena University Hospital, Jena, Germany. Data were analyzed using IBM® SPSS® Statistics software, v.21 for Windows (IBM, Somers, NY, USA) and summarized using means with standard deviation, medians and interquartile ranges (IQ), or numbers and percentages. Student's t test, Mann–Whitney test, Chi–square test and Fisher's exact test were used to compare between groups. The normality assumption was verified using Kolmogorov–Smirnov test and non-parametric tests were used as appropriate.

To identify independent risk factors for in-hospital death, we performed a forward stepwise multivariable logistic regression analysis, with in-hospital death as the dependent variable. Independent covariates were included stepwise with a cut-off p-value of 0.2 and excluded at a p-value of 0.1, including demographic variables (age, sex), referring facility, comorbid conditions, inflammatory parameters (white blood cell count, CRP (C-reactive protein), serum ferritin, and LDH), D-dimer levels, laboratory parameters of organ function, and major complications during the ICU stay (thrombocytopenia, secondary bacterial respiratory infection, atrial fibrillation, need for renal replacement therapy, need for blood transfusion, delirium, ischemic stroke, and pneumothorax). Colinearity between variables was ruled out before modeling. Goodness of fit was tested using a Hosmer and Lemeshow test, and odds ratios (OR) with 95% confidence interval (CI) were computed.

All reported p values are two-sided. A p value <0.05 was considered to be significant.

Results

Characteristics of the study group

During the period of observation, 850 patients were admitted to Cairo University Hospital with confirmed infection with SARS-CoV-2; 177 patients received medical treatment in one of the participating ICUs, of which 160 patients were included in the analysis; 85 to the general ICU and 75 to the postoperative ICU (Fig. 1). The characteristics of the study group are presented in Table 1. Patients were more commonly men (67.5%) and the mean age was 60 (SD: 14) years. The initial symptoms, most commonly fever, dyspnea, and cough, had occurred at a median of 7 (IQ: 5−10) days prior to ICU admission. The most common comorbid conditions were systemic hypertension, diabetes mellitus, and ischemic heart disease. Around 23% of patients had no known comorbidities. On admission to the ICU, the median SO_2 and PaO_2/FiO_2 ratio were 81% (IQ: 71−88) and 150 (IQ: 90−206), respectively, despite oxygen supplementation using a 10 L/min non-rebreathing face mask (Table 2). The inflammatory parameters, arterial blood gases, and laboratory

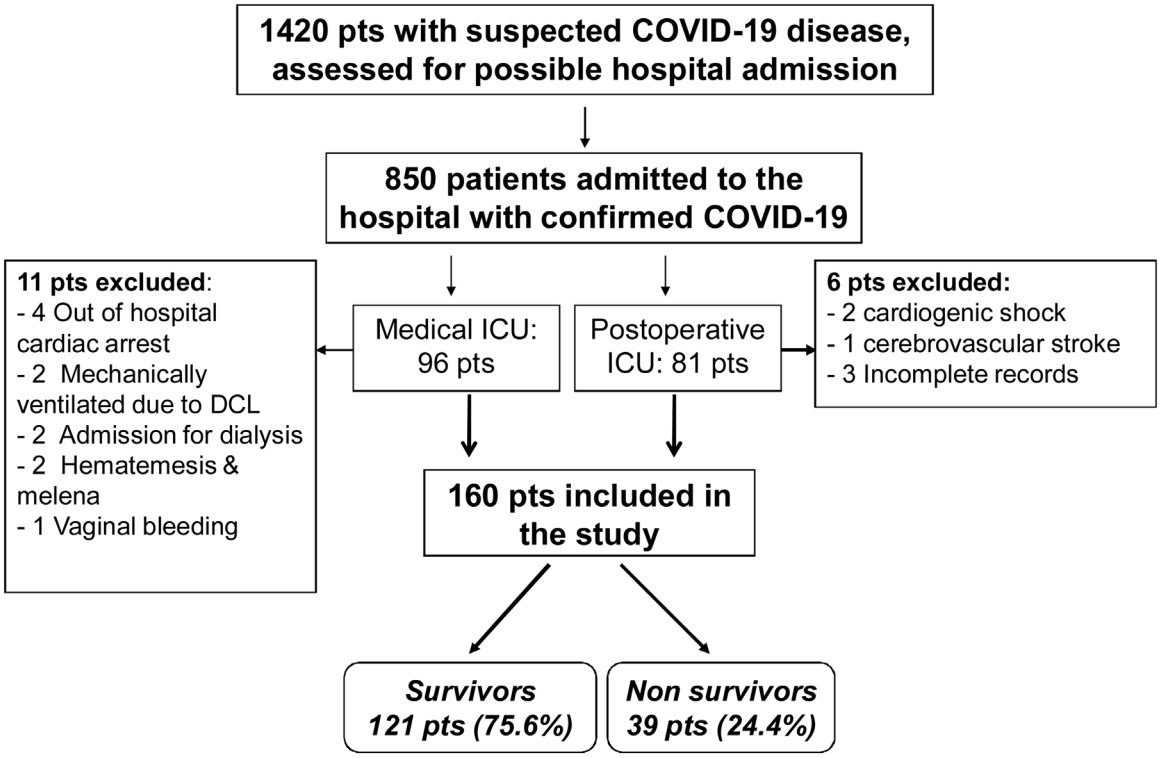

Fig. 1. Flow diagram showing patient inclusion. DCL: disturbed conscious level.

Table 1
Characteristics of the study cohort on admission to the ICU.

N	All patients 160	Survivors 121	Non-survivors 39	P value
Age, years, mean ± SD	60 ± 14	60 ± 14	65 ± 12	<0.001
Male, n (%)	108 (67.5)	80 (66.1)	28 (71.8)	0.501
BMI, kg/m^2, mean ± SD	27.9 ± 3.9	27.9 ± 4.0	28.3 ± 3.3	0.114
APACHE II score,mean ± SD	10 ± 5.7	9.1 ± 4.9	12.7 ± 6.9	<0.001
Onset of symptoms prior to admission, days, median (IQ)	7 (5–10)	7 (5–10)	7 (5–10)	0.169
Referral from another hospital	21 (13.1)	12 (9.9)	9 (23.1)	0.034
Initial symptoms, n (%)				
Fever	142 (88.8)	108 (89.3)	34 (87.2)	0.772
Dyspnea	114 (71.3)	84 (69.4)	30 (76.9)	0.368
Cough	85 (53.1)	65 (53.7)	20 (51.3)	0.791
Fatigue	13 (8.1)	6 (5)	7 (17.9)	0.01
Diarrhea	7 (4.4)	4 (3.3)	3 (7.7)	0.363
Anosmia	2 (1.3)	1 (0.8)	1 (2.6)	0.429
Number of comorbid conditions, n (%)				0.050
None	37 (23.1)	29 (24.0)	8 (20.5)	
1	42 (26.3)	33 (27.3)	4 (10.3)	
2	28 (17.5)	20 (24.8)	12 (30.8)	
>3	16 (10.1)	9 (22.3)	15 (38.4)	
Number of comorbidities, median (IQ)	2 (1–3)	1 (1–2)	2 (1–3)	0.047
Comorbidities, n (%)				
Systemic hypertension	89 (55.6)	64 (52.9)	25 (64.1)	0.22
Diabetes mellitus	73 (45.6)	54 (44.6)	19 (48.7)	0.656
Ischemic heart disease	33 (20.6)	16 (13.2)	17 (43.6)	<0.001
Chronic lung disease	17 (10.6)	13 (10.7)	4 (10.3)	1.000
Hyperlipidemia	17 (10.6)	12 (9.9)	5 (12.8)	0.564
Chronic kidney disease	15 (9.4)	11 (9.1)	4 (10.3)	0.761
Smoking	17 (10.6)	9 (7.4)	8 (20.5)	0.021
Arrhythmia	8 (5.0)	6 (5.0)	2 (5.1)	1.000
Cancer	5 (3.1)	5 (4.1)	0 (0)	0.336
Chronic liver disease	4 (2.5)	4 (3.3)	0 (0)	0.573
Immunosuppresssion	8 (5)	7 (5.8)	1 (2.6)	0.681
Pregnancy	1 (0.6)	1 (0.8)	0 (0)	1.000

APACHE II: acute physiology and chronic health evaluation, BMI: body mass index, IQ: interquartile range, ICU: intensive care unit, SD: standard deviation.

Table 2
Inflammatory parameters, arterial blood gases, blood picture, and parameters of organ function on admission to the ICU.

	Total patients 160	Survivors 121	Non-survivors 39	P value
Inflammatory parameters				
White blood cell count, $\times 10^9$/L	9.2 (6.0–12.7)	9.3 (6.3–12.5)	9.1 (5.8–14.5)	0.567
C-reactive protein, mg/L	124 (60–225.8)	112 (55–208)	150 (83–294)	0.073
Ferritin, ng/mL	859 (491–1538)	797 (465–1591)	879 (533–1461)	0.097
Lactate dehydrogenase, IU/L	591 (408–806)	591 (417–797)	579 (386–887)	0.905
D-dimer, µg/dl	0.73 (0.4–2.2)	0.6 (0.4–1.8)	1.3 (0.6–3.3)	<0.001
Arterial blood gases, median (IQ)				
SaO_2, %	81 (71–88)	83 (75–88)	72 (60–81)	<0.001
PCO_2, mmHg	33 (29–40)	32 (29–40)	37 (32–43)	0.002
HCO_3, mmol/L	23 (21–26)	23 (21–25)	24 (21–26)	0.445
pH	7.42 (7.39–7.46)	7.42 (7.39–7.46)	7.43 (7.36–7.46)	0.113
PO_2, mmHg	121 (70–154)	132 (74–166)	78 (67–132)	<0.001
Parameters of organ function				
Creatinine, mg/dl	1.1 (0.8–1.4)	1.0 (0.8–1.3)	1.3 (0.9–1.6)	<0.001
Urea, mg/dl	45 (30–68)	40 (28–59)	55 (39–76)	0.001
Total bilirubin, mg/dl	0.6 (0.4–0.8)	0.5 (0.4–0.8)	0.6 (0.4–0.9)	<0.001
Platelet count, $\times 10^9$/L	227 (161–292)	223 (163–280)	248 (141–311)	<0.001
ALT, IU/L	41.5 (29–58)	40 (27–59)	44 (30–58)	<0.001
AST, IU/L	37 (26–59)	34 (26–56)	42 (26–62)	0.001
PaO_2/FiO_2 ratio	150 (90–206)	170 (100–220)	100 (80–151)	<0.001

Values are presented in median (25–75% interquartile range).
ALT: alanine aminotransferase, AST: aspartate transaminase, FiO_2: fraction of inspired oxygen, IU: international unit, SaO_2: arterial oxygen concentration, PO_2: partial pressure of oxygen, PCO_2: partial pressure of carbon dioxide.

parameters of organ function on admission to the ICU are shown in Table 2.

Antimicrobial and adjuvant therapies

Patient management and ICU organizational aspects are detailed in Appendix 1. Hydroxychloroquine was given to151 (94.4%) patients, oseltamivir to 50 (31.3%), remdesivir to 11 (6.9%), and lopinavir/ritonavir to 5 (3.1%) patients. Therapeutic anticoagulation was carried out using low molecular weight heparin (LMWH) in 80 patients (50%), unfractionated heparinin 29 patients (18.1%), and fondaparinux in 30 (18.8%). In 21 patients (13.1%), therapeutic LMWH was replaced by fondaparinux because of profound thrombocytopenia. Only 5 patients (3.1%) received prophylactic doses of unfractionated heparin. Intravenous methylprednisolone (2 mg/kg/day) was given to 159 patients (99.4%), tocilizumab to 107 patients (66.9%), convalescent plasma to 49 (30.6%), and immunoglobulins (OCTAGAM®10%, Octapharma, Lachen, Switzerland 10%) to 6 patients (3.8%). Antibiotic therapy with azythromycin was given to 52 (32.5%) patients.

Morbidity and supportive therapy

During the ICU stay, invasive mechanical ventilation was required in 44 (27.5%) patients for a median of 4 (2–9) days. Repeated sessions of high flow oxygen therapy (HFO) and non-invasive mechanical ventilation were used in 135 (84.4%) and 95 (40.6%) patients for a median of 3 (2–4) and 3 (1–4) days, respectively. The most common complications during the ICU stay were need for vasopressor therapy, acute kidney injury, and thrombocytopenia (Table 3). Secondary bacterial respiratory infections occurred in 31 (19.4%) patients during the ICU stay. The most commonly isolated microorganisms were *Klebsiella pneumonia* (12 patients [7.5%]), *acinetobacter baumannii* (9 [5.6%]) and *Pseudomonas aeruginosa* (3 [1.9%]).

ICU and hospital lengths of stay were 7 (IQ: 4–10) and 10 (IQ: 7–14) days, respectively. ICU (10 (6–15) vs. 6 (4–9) days, p < 0.001) and hospital (12 (6–16) vs. 10 (8–14) days, p < 0.001) lengths of stay were higher in non-survivors than survivors.

Mortality and risk factors for in-hospital death

The overall ICU/hospital mortality rate was 24.4% (n = 39). Non-survivors were older (65 ± 12 vs. 60 ± 14 years, p < 0.001), had greater APACHE II score on admission to the ICU (12.7 ± 6.9 vs. 9.1 ± 4.9, p < 0.001), were more commonly referred from other hospital (23.1 vs. 9.9%, p = 0.034), and more frequently complained of fatigue at the onset of symptoms (17.9 vs. 5%, p = 0.01) than survivors (Table 1). The incidence of ischemic heart disease (43.6 vs. 13.2%, p < 0.001) and the total number of comorbid conditions (median 2 (1–3) vs. 1 (1–2), p = 0.047) were higher in non-survivors than in survivors. On admission to the ICU, SO_2, PO_2, and PaO_2/FiO_2 ratio were lower, whereas PCO_2, D-dimer levels, creatinine, urea, bilirubin, liver enzymes, and platelet count were higher in non-survivors than in survivors (Table 2). Invasive mechanical ventilation, vasopressor therapy, renal replacement therapy, and blood transfusion were more commonly required in non-survivors than in survivors. Non-survivors more frequently developed acute kidney injury, thrombocytopenia, secondary infection, atrial fibrillation, pneumothorax, and gastrointestinal hemorrhage than did survivors.

In a multivariable logistic analysis with in-hospital death as the dependent variable, ischemic heart disease (OR: 13.04, 95% CI: 3.66–46.43, p < 0.001), history of smoking (OR: 5.28, 95% CI: 1.19–23.41, p = 0.029), and the occurrence of bacterial pneumonia during the ICU stay (OR: 4.87, 95% CI: 1.67–14.24, p = 0.004) were independently associated with a higher risk of in-hospital death, whereas a greater PaO_2/FiO_2 ratio on admission to the ICU was associated with a lower risk (Table 4).

Discussion

The main findings of our study were that in this cohort of critically ill patients with COVID-19 admitted to two ICUs at a university hospital in Cairo, Egypt: 1) although there was a high prevalence of some comorbid conditions, including systemic hypertension, diabetes mellitus, and ischemic heart disease, around 23% of patients had no known comorbid conditions; 2) in patients needing ICU admission, SARS-CoV-2 infection was associated with a high rate of morbidity, with the most common complications being acute kidney injury, thrombocytopenia, and secondary bacterial infec-

Table 3
Procedures and complications during the ICU stay.

N	Total patients 160	Survivors 121	Non-survivors 39	P value
Respiratory support therapies, n (%)				
High frequency nasal oxygen	135 (84.4)	109 (90.1)	26 (66.7)	<0.001
Non-invasive ventilation	95 (40.6)	65 (53.7)	30 (76.9)	0.01
Invasive mechanical ventilation	44 (27.5)	7 (5.8)	37 (94.9)	<0.001
ECMO	2 (1.3)	0 (0)	2 (5.1)	0.058
Need for vasopressor therapy	42 (26.3)	6 (5)	36 (92.3)	<0.001
Complications, n (%)				
Acute kidney injury[a]	36 (22.5)	18 (14.9)	18 (46.2)	<0.001
Thrombocytopenia (<100 × 10^9/L)	35 (21.9)	21 (17.4)	14 (35.9)	0.015
Secondary respiratory infection	31 (19.4)	13 (10.7)	18 (46.2)	<0.001
Atrial fibrillation	22 (13.8)	11 (9.1)	11 (28.2)	0.003
Uncontrolled hyperglycemia	16 (10.0)	12 (9.9)	4 (10.3)	1.000
Need for renal replacement therapy	14 (8.7)	4 (3.3)	10 (25.6)	<0.001
Need for blood transfusion	13 (8.1)	5 (4.1)	8 (20.5)	0.003
Delirium	7 (4.4)	5 (4.1)	2 (5.1)	0.679
Ischemic stroke	5 (3.1)	3 (2.5)	2 (5.1)	0.596
Pneumothorax	4 (2.5)	0 (0)	4 (10.3)	0.003
Acute coronary syndrome	3 (1.9)	1 (0.8)	2 (5.1)	0.147
Gastrointestinal hemorrhage	3 (1.9)	0 (0)	3 (7.7)	0.014
Myocarditis	1 (0.6)	0 (0)	1 (2.6)	0.244
Cerebral hemorrhage	1 (0.6)	0 (0)	1 (2.6)	0.244

ECMO: extracorporeal membrane oxygenation.
[a] Defined as change in serum creatinine ≥0.3 mg/dL and/or urine output <0.5 mL/kg for more than 6 h.

Table 4
Summary of logistic regression analysis with in-hospital death as the dependent variable[a].

	OR (95% CI)	p value
APACHE II (per point)	1.09 (0.99–1.19)	0.063
Comorbid conditions		
Ischemic heart disease	13.04 (3.66–46.43)	<0.001
Smoking	5.28 (1.19–23.41)	0.029
Parameters of organ function on ICU admission		
PaO_2/FiO_2 ratio (per 20 mmHg)	0.81 (0.73–0.90)	<0.001
Major complications during ICU stay		
Bacterial pneumonia	4.87 (1.67–14.24)	0.004

APACHE: acute physiology and chronic health evaluation, CI: confidence interval, ICU: intensive care unit, OR: odds ratio.
[a] Forward stepwise multivariable logistic regression analysis, with in-hospital death as the dependent variable. Covariates were included stepwise with a cut-off p-value of 0.2 and excluded at a p-value of 0.1, including demographic variables (age, sex), referring facility, comorbid conditions, inflammatory parameters, D-dimer levels, laboratory parameters of organ function, and major complications during ICU stay (thrombocytopenia, secondary respiratory infection, atrial fibrillation, need for renal replacement therapy, need for blood transfusion, delirium, ischemic stroke, and pneumothorax). Colinearity between variables was ruled out before modeling. Hosmer & Lemeshow goodness of fit chi square: 4.48, p = 0.812.

tions; 3) 24% of patients died in-hospital within a median of 10 days after ICU admission; 4) ischemic heart disease, a history of smoking, and the occurrence of bacterial pneumonia during the ICU stay were independently associated with a higher risk of in-hospital death, whereas greater PaO_2/FiO_2 ratio on admission to the ICU was associated with a lower risk of in-hospital death.

To the best of our knowledge, this is the first study reporting characteristics of and outcomes from COVID-19 for patients requiring ICU admission in Egypt. Similar to previous studies from European [2,3,5,8,10,12,15–18,21,31,33–43], North American [4,6,7,24–26], and Asian [11,19,20,23,27–30,44] ICUs, more than two-thirds of our patients were male, with a high prevalence of preexisting comorbid conditions. Nonetheless, 23% of patients in our cohort did not have known comorbid conditions, suggesting that severe SARS-Cov-2 infections with a fatal outcome may also occur in otherwise healthy individuals.

Around 28% of patients in our cohort required invasive mechanical ventilation during the ICU stay. Higher rates of invasive mechanical ventilation, ranging from 69 to 87%, were reported in large European cohorts from countries with a relatively high prevalence of COVID-19 during the early months of their epidemics, including Italy, Spain, France, and the UK [3,10,12]. These earlier observations [3,10,12] triggered a more restrictive approach in initiating invasive mechanical ventilation in our institution to avoid the possible ventilator-associated morbidity in these patients, which may explain the rather liberal use of alternative oxygen supplementation strategies, such as HFO and non-invasive mechanical ventilation, and the routine implementation of prone positioning. However, 37 out of the 47 patients (84%) who received mechanical ventilation in our cohort died in the ICU. Restricting use of invasive mechanical ventilation to patients with high severity of illness after exhaustion of other therapeutic options may explain the high mortality rate of these patients.

In agreement with previous studies, SARS-CoV-2 infections were associated with a high morbidity rate in our cohort [2–4,11,12,29]; acute kidney injury was the most common complication. In 3988 consecutive critically ill patients with confirmed COVID-19 from Italian ICUs in Lombardy, Grasselli et al. [3] reported that acute kidney injury occurred in up to 55% of cases. The exhausted healthcare resources and relatively high admission rates at the time of that study [3] may explain the relatively high morbidity and mortality rates compared to later cohorts [12,13]. Thrombocytopenia was also common in our cohort, probably due to the well-known procoagulant effects of SARS-CoV-2 infection with subsequent platelet activation and increased consumption [45].

Although almost 1 in 4 of our patients with COVID-19 died in the ICU, the mortality rate in our cohort is lower than that reported in earlier large ICU cohorts [3–5,10]. A meta-analysis of 24 observational studies including 10,150 patients from centers across Asia, Europe and North America, reported that ICU mortality rates ranged from 0 to 84.6% [13]. However, in most of the included studies from the early months of the pandemic, complete follow-up data were not reported in 24.5–97.2% of patients [13]. Considering only patients with complete ICU admission data, the combined ICU mortality was 41.6% and was broadly consistent across the globe [13]. As the pandemic has progressed, mortality rates have decreased from above 50% to close to 40% [13]. Nonetheless, most of the large published cohorts [3–5,10,12,17,21,46] originated from countries with healthcare systems that were markedly overwhelmed during the epidemic with a subsequent negative impact on the

quality of the care provided. We may speculate, therefore, that the relatively low mortality rate in our cohort was related to the relatively low admission rate to our ICUs and the unstressed healthcare system in a university hospital setting that was able to maintain normal ICU management standards. In agreement with this supposition, Chew et al. [44] reported an overall mortality rate of no more than 9.1% in 22 patients with COVID-19 disease (13 requiring invasive mechanical ventilation), admitted to a "pandemic ready" ICU in Singapore with unstressed capacity. Garcia et al. [12] similarly reported an ICU mortality rate of 24% in 639 critically ill patients with confirmed SARS-CoV-2 infection admitted to ICUs in Switzerland, France, Netherlands, and Spain.

In our patients, secondary bacterial pneumonia was a common complication during the ICU stay and was independently associated with a higher risk of in-hospital death. This finding underscores the importance of timely diagnosis and appropriate therapy of these infections to avoid subsequent poor outcome. We also identified preexisting ischemic heart disease and smoking as independent risk factors for a higher risk of in-hospital death and greater PaO_2/FiO_2 ratio as a factor associated with a lower risk of death in our patients. These factors may be useful to identify patients at risk of poor outcome, who may require special care.

Our study has some limitations. First, our cohort may not be representative of patients with COVID-19 disease admitted to all Egyptian ICUs. Indeed, the healthcare system in Egypt is not uniform in terms of case-mix, available resources, and quality of care. The ICUs of Cairo University Hospitals are equipped with all organ support modalities and are staffed with trained specialists with considerable expertise in managing patients with respiratory insufficiency, which may not be the case in other ICUs in the country. Second, the multivariable analysis may be limited by the included variables and the possible influence of unmeasured confounders cannot be excluded. Finally, because of the lack of any strong evidence concerning therapeutic options in treating patients with COVID-19 disease, antiviral and adjunctive therapies were considered according to the discretion of the attending physician and local availability, so that a standardized approach concerning these therapies was not followed in all patients.

Conclusion

In this cohort of critically ill patients, COVID-19 pneumonia was associated with high morbidity and mortality rates. Ischemic heart disease, history of smoking, and secondary bacterial pneumonia were independently associated with a higher risk of in-hospital death, whereas a greater PaO_2/FiO_2 ratio on admission to the ICU was associated with a lower risk. Our data provide insight about the clinical presentation of severe SARS-CoV-2 infections and outcomes of COVID-19 disease in Egypt. Further studies are required to assess the possible impact of therapeutic interventions on outcome in this population which obviously differs from those admitted to the ICUs in other geographic areas.

Ethics approval and consent to participate

The report was approved by the institutional review board of Cairo University Hospitals, (Kasr-Al-Aini-Street, 11562, Cairo, Egypt, Protocol-ID: N-89 2020). Informed consent was waived due to the retrospective and anonymous nature of data collection. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and material

The dataset used and analyzed during the current report are available from the corresponding author on reasonable request. YN, AM, ME, and FM have complete access to patient data.

Authors' contributions

YN, AM, FM, AE, AA, SM, AR, AE, and YS designed the scientific work. YN, AM, ME, and FM contributed to data collection. YN, FM, SB, and YS contributed to data handling.SB, YN, and YS performed the statistical analysis. SB, YN, FM, and YN reviewed the literature. YN, SB, and YS wrote the first draft of the manuscript. All the authors reviewed, revised, and approved the submitted manuscript. YN, AM, FM have complete access to the clinical data of the reported cases and hold responsibility for integrity and correctness of data. SB and YS have access to the data set used for the current analysis.

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Competing interests

The authors declare that they do not have conflict of interests in relation to this manuscript.

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Appendix 1 Patient management and ICU organization

ICU organization

The two ICUs that participated in the study are closed-format ICUs. The intensivists have a background of critical care medicine (medical ICU) or anesthesiology (postoperative ICU) and are available 24-h/day. At least one ICU specialist with a minimum of 3 years' experience in managing critically ill patients and accredited by the Egyptian Medical Syndicate as a specialist in intensive care medicine was available on-site for each unit. Daily rounds were conducted by a team including attending physicians, nursing staff, and physiotherapists. Since the emergence of SARS-CoV-2 infection in Egypt, a multidisciplinary taskforce has been established in Cairo University Hospitals and held daily meetings to review, discuss, monitor clinical progress, and advise on individual patient management.

Patient management

All ICU patients with suspected or confirmed infection with SARS-CoV-2 received standard health care according to the best-known evidence at the time of admission, including isolation in single rooms, either on the hospital floor or in the ICU, and medical care with a 1:1 nurse: patient ratio. Infection control precautions were strictly implemented to prevent possible transmission of SARS-CoV-2 to other patients or to the healthcare staff. Patients were admitted to the ICU if they had persistent hypoxemia (>1 h), defined as SO_2 < 90% despite O_2 supplementation using 10

L/min non-rebreathing face mask oxygen, an imminent indication for invasive mechanical ventilation (rapid deterioration of respiratory function or impaired conscious level), hemodynamic instability necessitating initiation of vasopressor therapy or close monitoring of hemodynamic parameters, or the presence of associated comorbid conditions that necessitated close monitoring and therapy (e.g., uncontrolled hyperglycemia or severe hemorrhagic complications). Standard ICU supportive management was provided according to the standard operating procedures of the corresponding units and in accordance with the most recent Surviving Sepsis Campaign guidelines. Antiviral therapies (oseltamivir, remdesivir, and lopinavir/ritonavir), were prescribed at the discretion of the attending physician and availability of the product. Protective lung ventilation was used in mechanically ventilated patients. Prone positioning was standard of care in all patients with 16 h/day in patients requiring invasive mechanical ventilation, and during ventilation free intervals in patients requiring non-invasive ventilation and high flow oxygen therapy (HFO), provided that the patients were hemodynamically stable. Extracorporeal membrane oxygenation (ECMO) was considered as a last resort.

All suspected cases of SARS-CoV-2 infection were strictly isolated and nasopharyngeal swabs obtained for initial screening. Deep respiratory samples (tracheal aspirates or bronchoalveolar lavage fluid) were obtained from patients with suspected secondary respiratory infections, in addition to blood samples to perform BioFire® FilmArray® Panels (BioFire Diagnostics, Salt Lake City, Utah 84108 USA) for respiratory pathogens. Cultures of tracheal aspirates were not done in these patients due tothe undetermined biohazard risk during the early months of the epidemic.

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