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Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US

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IMPORTANCE The US is currently an epicenter of the coronavirus disease 2019 (COVID-19) pandemic, yet few national data are available on patient characteristics, treatment, and outcomes of critical illness from COVID-19.

OBJECTIVES To assess factors associated with death and to examine interhospital variation in treatment and outcomes for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study assessed 2215 adults with laboratory-confirmed COVID-19 who were admitted to intensive care units (ICUs) at 65 hospitals across the US from March 4 to April 4, 2020.

EXPOSURES Patient-level data, including demographics, comorbidities, and organ dysfunction, and hospital characteristics, including number of ICU beds.

MAIN OUTCOMES AND MEASURES The primary outcome was 28-day in-hospital mortality. Multilevel logistic regression was used to evaluate factors associated with death and to examine interhospital variation in treatment and outcomes.

RESULTS A total of 2215 patients (mean [SD] age, 60.5 [14.5] years; 1436 [64.8%] male; 1738 [78.5%] with at least 1 chronic comorbidity) were included in the study. At 28 days after ICU admission, 784 patients (35.4%) had died, 824 (37.2%) were discharged, and 607 (27.4%) remained hospitalized. At the end of study follow-up (median, 16 days; interquartile range, 8-28 days), 875 patients (39.5%) had died, 1203 (54.3%) were discharged, and 137 (6.2%) remained hospitalized. Factors independently associated with death included older age (≥80 vs <40 years of age: odds ratio [OR], 11.15; 95% CI, 6.19-20.06), male sex (OR, 1.50; 95% CI, 1.19-1.90), higher body mass index (≥40 vs <25: OR, 1.51; 95% CI, 1.01-2.25), coronary artery disease (OR, 1.47; 95% CI, 1.07-2.02), active cancer (OR, 2.15; 95% CI, 1.35-3.43), and the presence of hypoxemia (Pao_2:Fio_2<100 vs ≥300 mm Hg: OR, 2.94; 95% CI, 2.11-4.08), liver dysfunction (liver Sequential Organ Failure Assessment score of 2 vs 0: OR, 2.61; 95% CI, 1.30–5.25), and kidney dysfunction (renal Sequential Organ Failure Assessment score of 4 vs 0: OR, 2.43; 95% CI, 1.46–4.05) at ICU admission. Patients admitted to hospitals with fewer ICU beds had a higher risk of death (<50 vs ≥100 ICU beds: OR, 3.28; 95% CI, 2.16-4.99). Hospitals varied considerably in the risk-adjusted proportion of patients who died (range, 6.6%-80.8%) and in the percentage of patients who received hydroxychloroquine, tocilizumab, and other treatments and supportive therapies.

CONCLUSIONS AND RELEVANCE This study identified demographic, clinical, and hospital-level risk factors that may be associated with death in critically ill patients with COVID-19 and can facilitate the identification of medications and supportive therapies to improve outcomes.

Supplemental content

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Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection began in December 2019 in Wuhan, China, more than 6 million people have developed coronavirus disease 2019 (COVID-19), and more than 350 000 have died.[1] Critical illness from COVID-19 in China, Italy, and other countries has strained intensive care unit (ICU) resources and produced a wide spectrum of short-term mortality rates, ranging from 16% to 62%.[2-4]

As of June 19, 2020, approximately 2.2 million people in the US have been infected with SARS-CoV-2, and more than 100 000 have died. Although more people have died in the US than in any other country,[1] national data are lacking on the epidemiologic factors, treatment, and outcomes of critical illness from COVID-19. One study[5] of 24 patients in the Seattle, Washington, region reported frequent receipt of invasive mechanical ventilatory support and vasopressors and an in-hospital mortality of 50%. Local outbreaks of COVID-19 in New York City have been described in single-center and regional reports.[6,7] These studies[6,7] included primarily noncritically ill patients and had limited follow-up duration.

Granular data on patient characteristics, treatment, and outcomes of critical illness from COVID-19 are needed to inform decision-making about resource allocation, critical care capacity, and treatment of patients. Furthermore, nationally representative data across multiple hospitals are needed to assess interhospital variation in treatment and outcomes. To address this knowledge gap, we conducted the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID), a multicenter cohort study that examined the demographics, comorbidities, organ dysfunction, treatment, and outcomes of patients with COVID-19 admitted to ICUs across the US. The purposes of this study were to assess factors associated with death and to examine interhospital variation in treatment and outcomes in patients with COVID-19.

Key Points

Question What are the characteristics, outcomes, and factors associated with death among critically ill patients with coronavirus disease 2019 (COVID-19) in the US?

Findings In a cohort of 2215 adults with COVID-19 who were admitted to intensive care units at 65 sites, 784 (35.4%) died within 28 days, with wide variation among hospitals. Factors associated with death included older age, male sex, morbid obesity, coronary artery disease, cancer, acute organ dysfunction, and admission to a hospital with fewer intensive care unit beds.

Meaning This study identified demographic, clinical, and hospital-level factors associated with death in critically ill patients with COVID-19 that may be used to facilitate the identification of medications and supportive therapies that can improve outcomes.

Methods

Study Design and Oversight

In this multicenter cohort study, we enrolled adults with COVID-19 who were admitted to participating ICUs at 65 hospitals. The study was approved by the institutional review boards at each participating site with a waiver of informed consent. All data except dates were deidentified.

Study Sites and Patient Population

We included consecutive adult patients (≥18 years of age) with laboratory-confirmed COVID-19 (detected by nasopharyngeal or oropharyngeal swab) admitted to a participating ICU for illness related to COVID-19 between March 4 and April 4, 2020. Patients were considered to have been admitted to an ICU if they were admitted to a regular ICU or if they were in a non-ICU room that was functioning as an ICU room for surge capacity (defined further in the eMethods and eAppendix in the Supplement). We followed up patients until hospital discharge, death, or June 4, 2020, whichever came first. A complete list of participating sites is provided in eTable 1 and eFigures 1 and 2 in the Supplement. In this cohort, 98 patients were described in prior studies, including 58 reported in a single-center case series from New York City that included both critically ill and noncritically ill patients,[6] 28 reported in a single-center study focused on acute kidney injury,[8] and 12 reported in a case series of critically ill patients from the Seattle region.[5]

Outcomes

The primary outcome was death within 28 days of ICU admission. Patients who were discharged alive from the hospital before 28 days were considered to be alive at 28 days (we tested the validity of this assumption in a subset of patients, described in the eMethods in the Supplement). Secondary outcomes included development of respiratory failure, acute respiratory distress syndrome, congestive heart failure, myocarditis, pericarditis, arrhythmia, shock, acute cardiac injury, acute kidney injury, acute liver injury, coagulopathy, secondary infection, and thromboembolic events (definitions provided in eTable 2 in the Supplement). We also examined receipt of antivirals, antibiotics, anticoagulants, immunomodulating medications, mechanical ventilatory support, adjunctive and rescue therapies for hypoxemia, extracorporeal membrane oxygenation, mechanical cardiac support, vasopressors, and kidney replacement therapy.

Data Collection

Study personnel at each site collected data by manual review of electronic medical records and used a standardized case report form to enter data into a secure online database (eAppendix 2 in the Supplement). Patient-level data included baseline information on demographics, coexisting conditions, symptoms, medications before hospital admission, and vital signs; daily data for the 14 days after ICU admission on physiologic and laboratory values, medications, nonmedication treatments, and organ support; and outcome data on ICU and hospital length of stay and death. We also collected hospital-level data, including the city and state, main hospital vs satellite or affiliate hospital for the center, the number of ICU beds (not including surge capacity), and type of ICU to which the patients were admitted (medical, COVID specific, or other). All data were validated through a series of automated and manual verifications (eMethods in the Supplement).

Statistical Analysis

We aimed to generate a representative sample of critically ill adults by enrolling at least 2000 patients from at least 50 geographically diverse hospitals. To describe baseline characteristics, treatment, and outcomes, we express continuous variables as median (interquartile range [IQR]) and categorical variables as number (percentage).

To assess interhospital variation in treatments and outcomes, we used multilevel conditional logistic regression modeling with patients nested in hospitals to characterize hospital-level variation in treatment and to estimate hospital-specific rates of death at 28 days. This approach addresses the poor reliability of estimates stemming from hospitals that submitted few cases. To further improve the reliability of the estimates, we excluded hospitals that submitted data on fewer than 15 patients.

To account for differences in patient-level characteristics and illness severity among hospitals, we prespecified the following covariates for inclusion in the models: age, sex, race, hypertension, diabetes, body mass index (calculated as weight in kilograms divided by height in meters squared), coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, active cancer, duration of symptoms before ICU admission, and covariates assessed at ICU admission (lymphocyte count, ratio of the Pao_2 to the fraction of inspired oxygen [Fio_2], shock, and the kidney, liver, and coagulation components of the Sequential Organ Failure Assessment score).[9] We included the above characteristics and patient-level deviations from hospital means in the models. Finally, in a sensitivity analysis, we further adjusted for the number of ICU beds at each hospital before the COVID-19 pandemic (<50, 50-99, and ≥100 ICU beds).

To identify independent associations between patient and hospital characteristics and the primary outcome of 28-day mortality, we again used multilevel logistic regression modeling, with a random effect for hospital and fixed effects for each variable of interest. We included the same covariates as above. We also performed 2 sensitivity analyses. First, we repeated the above analysis but limited the patients to those who received invasive mechanical ventilatory support on ICU day 1. Second, we used a Cox regression model and all available follow-up data to assess the association between the above covariates and survival.

Data regarding body mass index were missing for 109 patients (4.9%). Data regarding the ratio of Pao_2:Fio_2 at ICU admission were missing for 273 of 1494 patients (18.3%). Additional details on missing data are provided in the eMethods and eTable 3 in the Supplement. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc) and Stata, version 16.1 (StataCorp LLC).

Results

Patient Characteristics at Baseline

From the 65 sites, 2215 of 2833 patients initially considered met eligibility criteria and were included in the analysis. The mean (SD) age was 60.5 (14.5) years, and 1436 (64.8%) were men. The median duration of symptoms before ICU admission was 7 days (IQR, 4-10 days). The most common symptoms before ICU admission were cough (1708 [77.1%]), dyspnea (1658 [74.9%]), and fever (1566 [70.7%]). A total of 1738 patients (78.5%) had at least 1 coexisting condition, including hypertension (1322 [59.7%]), diabetes (861 [38.9%]), and chronic lung disease (531 [24.0%]). On the day of ICU admission, 1494 patients (67.4%) received invasive mechanical ventilatory support, and 958 (48.3%) received vasopressors. The median Pao_2:Fio_2 ratio was 124 mm Hg (IQR, 86-188 mm Hg). Additional characteristics are provided in **Table 1** and eTables 3 and 4 and eFigures 3 and 4 in the Supplement.

Acute Organ Injury

In the 14 days after ICU admission, 1859 patients (83.9%) received invasive mechanical ventilatory support, 1635 patients (73.8%) developed acute respiratory distress syndrome, and 921 of the 2151 patients without end-stage kidney disease (42.8%) developed acute kidney injury. Other acute organ injuries were less frequent in this study, with only 230 patients (10.4%) experiencing a clinically detected thromboembolic event. The incidence of other acute organ injuries is shown in eFigure 5 in the Supplement.

The median time from symptom onset to each acute organ injury is shown in eFigure 5 in the Supplement. Respiratory failure, acute cardiac injury, and congestive heart failure occurred earlier in the illness, whereas secondary infection, acute liver injury, and thromboembolic events occurred later (eTable 5 in the Supplement). Longitudinal assessment of laboratory values and physiologic parameters is shown in eFigure 6 in the Supplement.

Treatment

The most commonly administered medications for COVID-19–related illness were hydroxychloroquine (1761 [79.5%]), azithromycin (1320 [59.6%]), and therapeutic anticoagulants (920 [41.5%]). Interventions for hypoxemia included neuromuscular blockade (909 [41.0%]), prone positioning (852 [38.5%]), inhaled epoprostenol (118 [5.3%]), and inhaled nitric oxide (94 [4.2%]). Additional medications and supportive therapies are listed in **Table 2**.

Risk- and reliability-adjusted use of medications and supportive therapies varied widely among hospitals (**Figure 1** and eTable 6 in the Supplement). For example, the risk- and reliability-adjusted proportion of patients who received hydroxychloroquine was 82.2% overall but ranged from 16.8% at the lowest use hospital to 98.1% at the highest. Similarly, the risk- and reliability-adjusted proportion of patients who received prone positioning was 35.1% overall but ranged from 4.6% at the lowest use hospital to 79.9% at the highest. Considerable interhospital variation in the use of therapies persisted in analyses further adjusted for the number of ICU beds (eTable 6 in the Supplement).

28-Day Mortality

Overall, 784 patients (35.4%) died within 28 days of ICU admission, 824 (37.2%) were discharged alive from the hospital within 28 days, and 607 (27.4%) remained hospitalized at 28

Table 1. Patient Characteristics at Baseline[a]

Characteristic	All patients (N = 2215)	Day 28	
		Alive (n = 1431)	Died (n = 784)
Demographics			
Age, mean (SD), y	60.5 (14.5)	57.4 (14.2)	66.0 (13.3)
Male	1436 (64.8)	900 (62.9)	536 (68.4)
Race/ethnicity			
White	837 (37.8)	549 (38.4)	288 (36.7)
Black	669 (30.2)	436 (30.5)	233 (29.7)
Asian	133 (6.0)	86 (6.0)	47 (6.0)
Other	576 (26.0)	360 (25.2)	216 (27.6)
Hispanic	445 (20.1)	288 (20.1)	157 (20.0)
BMI, median (IQR)[b]	30.5 (26.6-36.2)	30.7 (26.7-36.3)	29.9 (26.2-35.9)
Homeless	13 (0.6)	9 (0.6)	4 (0.5)
Symptoms before ICU admission			
Cough	1708 (77.1)	1146 (80.1)	562 (71.7)
Sputum production	287 (13.0)	195 (13.6)	92 (11.7)
Dyspnea	1658 (74.9)	1084 (75.8)	574 (73.2)
Fever	1566 (70.7)	1051 (73.4)	515 (65.7)
Fatigue or malaise	720 (32.5)	482 (33.7)	238 (30.4)
Nausea or vomiting	391 (17.7)	282 (19.7)	109 (13.9)
Diarrhea	461 (20.8)	323 (22.6)	138 (17.6)
Time from symptom onset to ICU admission, median (IQR), d	7 (4-10)	8 (5-10)	7 (3-9)
Coexisting conditions[c]			
Any	1738 (78.5)	1053 (73.6)	685 (87.4)
Diabetes			
Insulin dependent	305 (13.8)	170 (11.9)	135 (17.2)
Non-insulin dependent	556 (25.1)	339 (23.7)	217 (27.7)
Hypertension	1322 (59.7)	782 (54.6)	540 (68.9)
Chronic lung disease	531 (24.0)	334 (23.2)	197 (25.1)
COPD	173 (7.8)	86 (6.0)	87 (11.1)
Asthma	258 (11.6)	188 (13.1)	70 (8.9)
Other pulmonary disease	169 (7.6)	98 (6.8)	71 (9.1)
Current or former smoker	656 (29.6)	392 (27.4)	264 (33.7)
Coronary artery disease	288 (13.0)	130 (9.1)	158 (20.2)
Congestive heart failure	196 (8.8)	100 (7.0)	96 (12.2)
Chronic kidney disease	280 (12.6)	148 (10.3)	132 (16.8)
End-stage kidney disease	64 (2.9)	29 (2.0)	35 (4.5)
Active cancer	112 (5.1)	52 (3.6)	60 (7.7)
Immunodeficiency	65 (2.9)	38 (2.7)	27 (3.4)
Home medications			
Immunosuppressive medication	251 (11.3)	150 (10.5)	101 (12.9)
ACE-I	401 (18.1)	247 (17.3)	154 (19.6)
ARB	365 (16.5)	208 (14.5)	157 (20.0)
Mineralocorticoid receptor antagonist	65 (2.9)	29 (2.0)	36 (4.6)
Statin	840 (37.9)	476 (33.3)	364 (46.4)
NSAID	191 (8.6)	130 (9.1)	61 (7.8)
Aspirin	491 (22.2)	257 (18.0)	234 (29.8)
Anticoagulation	186 (8.4)	107 (7.5)	79 (10.1)
Vital signs on the day of ICU admission, median (IQR)			
Temperature, °C	38.1 (37.3-38.9)	38.1 (37.4-38.9)	38.0 (37.3-38.9)
Systolic blood pressure, mm Hg[d]	96 (86-111)	98 (87-111)	94 (83-109)
Heart rate, /min[e]	104 (90-119)	102 (90-116)	106 (92-123)

(continued)

Table 1. Patient Characteristics at Baseline[a] (continued)

Characteristic	All patients (N = 2215)	Day 28	
		Alive (n = 1431)	Died (n = 784)
Laboratory findings on the day of ICU admission, median (IQR)			
White blood cell count, /μL[f]	7900 (5800-11 200)	7700 (5800-10 600)	8300 (5900-12 000)
Lymphocyte count, /μL	811 (552-1144)	842 (582-1159)	747 (497-1091)
Hemoglobin level, g/dL[g]	12.7 (11.2-14.1)	12.8 (11.4-14.1)	12.6 (10.9-14.0)
Creatinine level, mg/dL[h]	1.0 (0.8-1.5)	1.0 (0.8-1.3)	1.2 (0.9-2.0)
D-dimer level, ng/mL[i]	1190 (690-2700)	1076 (652-2310)	1643 (877-3980)
C-reactive protein level, mg/L[j]	158 (94-237)	153 (87-228)	174 (104-258)
Severity of illness on the day of ICU admission			
Invasive mechanical ventilatory support, median (IQR)	1494 (67.4)	889 (62.1)	605 (77.2)
Fio_2[k]	0.8 (0.6-1.0)	0.8 (0.5-1.0)	1.0 (0.6-1.0)
PEEP, cm H_2O[l]	12 (10-15)	12 (10-15)	12 (10-15)
Pao_2:Fio_2, mm Hg[m]	124 (86-188)	131 (92-195)	113 (80-181)
Noninvasive mechanical ventilation	27 (1.2)	19 (1.3)	8 (1.0)
High-flow nasal cannula or nonrebreather mask	410 (18.5)	293 (20.5)	117 (14.9)
Vasopressor treatment	958 (48.3)	584 (40.8)	374 (47.7)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; Pao_2:Fio_2, ratio of Pao_2 over the fraction of inspired oxygen (assessed only in patients receiving invasive mechanical ventilation); PEEP, positive end-expiratory pressure.

SI conversion factors: to convert white blood cells and lymphocytes to $\times 10^9$/L, multiply by 0.001; hemoglobin to grams per liter, multiply by 10; creatinine to micromoles per liter, multiply by 88.4; D-dimer to nanomoles per liter, multiply by 5.476; and C-reactive protein to milligrams per liter, multiply by 10.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Data regarding BMI were missing for 109 patients (4.9%).

[c] The definitions of the coexisting conditions are provided in the eMethods in the Supplement.

[d] Data regarding systolic blood pressure were missing for 1 patient (0.05%).

[e] Data regarding heart rate were missing for 1 patient (0.05%).

[f] Data regarding white blood cell count were missing for 105 patients (4.7%).

[g] Data regarding hemoglobin level were missing for 110 patients (5.0%).

[h] Data regarding creatinine level were missing for 88 patients (4.0%).

[i] Data regarding D-dimer level were missing for 1186 patients (53.5%).

[j] Data regarding C-reactive protein level were missing for 917 patients (41.4%).

[k] Data regarding Fio_2 were missing for 178 of 1494 patients (11.9%) receiving invasive mechanical ventilatory support.

[l] Data regarding PEEP were missing for 185 of 1494 patients (12.4%) receiving invasive mechanical ventilatory support.

[m] Data regarding Pao_2:Fio_2 were missing for 273 of 1494 patients (18.3%) receiving invasive mechanical ventilatory support.

days. The unadjusted incidence of death within 28 days of ICU admission is displayed according to baseline patient and hospital characteristics in eFigures 3 and 4 in the Supplement and according to geographic region in eFigure 7 in the Supplement. The most common causes of death were respiratory failure (727 [92.7%]), septic shock (311 [39.7%]), and kidney failure (295 [37.6%]), with many patients having more than 1 cause.

Risk- and reliability-adjusted rate of death within 28 days varied widely across hospitals, from 6.6% to 80.8% (eFigure 8 and eTable 6 in the Supplement). After further adjustment for the number of ICU beds before the pandemic, this variation decreased, such that the risk- and reliability-adjusted rate of death ranged from 11.9% to 63.3% (eTable 6 in the Supplement).

In a multivariable model that examined the association between prespecified patient and hospital characteristics and 28-day mortality, older age was independently associated with higher risk of death (≥80 vs <40 years of age: odds ratio [OR], 11.15; 95% CI, 6.19-20.06) (ORs for other age categories are shown in **Figure 2**). Additional characteristics associated with death were male sex (OR, 1.50; 95% CI, 1.19-1.90), higher body mass index (≥40 vs <25: OR, 1.51; 95% CI, 1.01-2.25), coronary artery disease (OR, 1.47; 95% CI, 1.07-2.02), active cancer (OR, 2.15; 95% CI, 1.35-3.43), and the presence of hypoxemia (Pao_2:Fio_2<100 vs ≥300 mm Hg: OR, 2.94; 95% CI, 2.11-4.08), liver dysfunction (liver Sequential Organ Failure Assessment score of 2 vs 0: OR, 2.61; 95% CI, 1.30-5.25), and kidney dysfunction (renal Sequential Organ Failure Assessment score of 4 vs 0: OR, 2.43; 95% CI, 1.46-4.05) at ICU admission (Figure 2). Race (race other than White vs White race: OR, 1.11; 95% CI, 0.88-1.40), hypertension (OR, 1.06; 95% CI, 0.83-1.36), diabetes (OR, 1.14; 0.91-1.43), and lymphocyte count (OR, 1.11; 95% CI, 0.88-1.41) were not associated with death. Patients admitted to hospitals with fewer ICU beds had a higher risk of death (<50 vs ≥100 ICU beds; OR, 3.28; 95% CI, 2.16-4.99) (Figure 2). Interpretations were largely unchanged when restricted to patients who received invasive mechanical ventilatory support on ICU day 1 (eFigure 9 in the Supplement), although a body mass index greater than 40 was no longer associated with a higher risk of death.

Other Clinical Outcomes

Among patients discharged alive from the hospital within 28 days of ICU admission, the median ICU length of stay was 9 days (IQR, 5-14 days) and the median hospital length of stay

Table 2. Medications and Supportive Therapies for Coronavirus Disease 2019[a]

Treatment	Patients, No. (%)		
	All patients (N = 2215)	Day 28	
		Alive (n = 1431)	Died (n = 784)
Antibiotics and antivirals			
Hydroxychloroquine	1761 (79.5)	1130 (79.0)	631 (80.5)
Azithromycin	1320 (59.6)	863 (60.3)	457 (58.3)
Hydroxychloroquine and azithromycin	1117 (50.4)	729 (50.9)	388 (49.5)
Chloroquine	29 (1.3)	17 (1.2)	12 (1.5)
Remdesivir	134 (6.1)	101 (7.1)	33 (4.2)
Lopinavir and ritonavir	83 (3.8)	49 (3.4)	34 (4.3)
Therapeutic anticoagulation[b]			
Any	920 (41.5)	570 (39.8)	350 (44.6)
Heparin drip	573 (25.9)	349 (24.4)	224 (28.6)
Enoxaparin	302 (13.6)	206 (14.4)	96 (12.2)
Bivalirudin	25 (1.1)	19 (1.3)	6 (0.8)
Argatroban	24 (1.1)	16 (1.1)	8 (1.0)
Anti-inflammatory medications			
Corticosteroids	800 (36.1)	443 (31.0)	357 (45.5)
NSAIDs	99 (4.5)	76 (5.3)	23 (2.9)
Aspirin	377 (17.0)	205 (14.3)	172 (21.9)
Statins	519 (23.4)	336 (23.5)	183 (23.3)
Tocilizumab	378 (17.1)	265 (18.5)	113 (14.4)
Other interleukin 6 inhibitors	15 (0.7)	8 (0.6)	7 (0.9)
Vitamin C	196 (8.9)	120 (8.4)	76 (9.7)
Other medications			
Convalescent plasma	14 (0.6)	14 (1.0)	0 (0)
ACE-I	61 (2.8)	50 (3.5)	11 (1.4)
ARB	66 (3.0)	51 (3.6)	15 (1.9)
Tissue plasminogen activator	27 (1.2)	13 (0.9)	14 (1.8)
Specific interventions for hypoxemia			
Prone position	852 (38.5)	519 (36.3)	333 (42.5)
Neuromuscular blockade	909 (41.0)	524 (36.6)	385 (49.1)
Inhaled epoprostenol	118 (5.3)	62 (4.3)	56 (7.1)
Inhaled nitric oxide	94 (4.2)	71 (5.0)	23 (2.9)
Enrolled in a clinical trial[c]	398 (18.0)	298 (20.9)	100 (12.8)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Each of the interventions was assessed during the 14 days after ICU admission.

[b] Data on therapeutic anticoagulation were missing for 10 patients (0.5%).

[c] Data on enrollment in a clinical trial were missing for 8 patients (0.4%).

was 16 days (IQR, 11-22 days). Extracorporeal organ support included acute kidney replacement therapy (432 [20.1%]), extracorporeal membrane oxygenation (61 [2.8%]), and mechanical cardiac support (3 [0.1%]). Additional outcomes are provided in **Table 3**.

Mortality and Length of Stay Beyond 28 Days

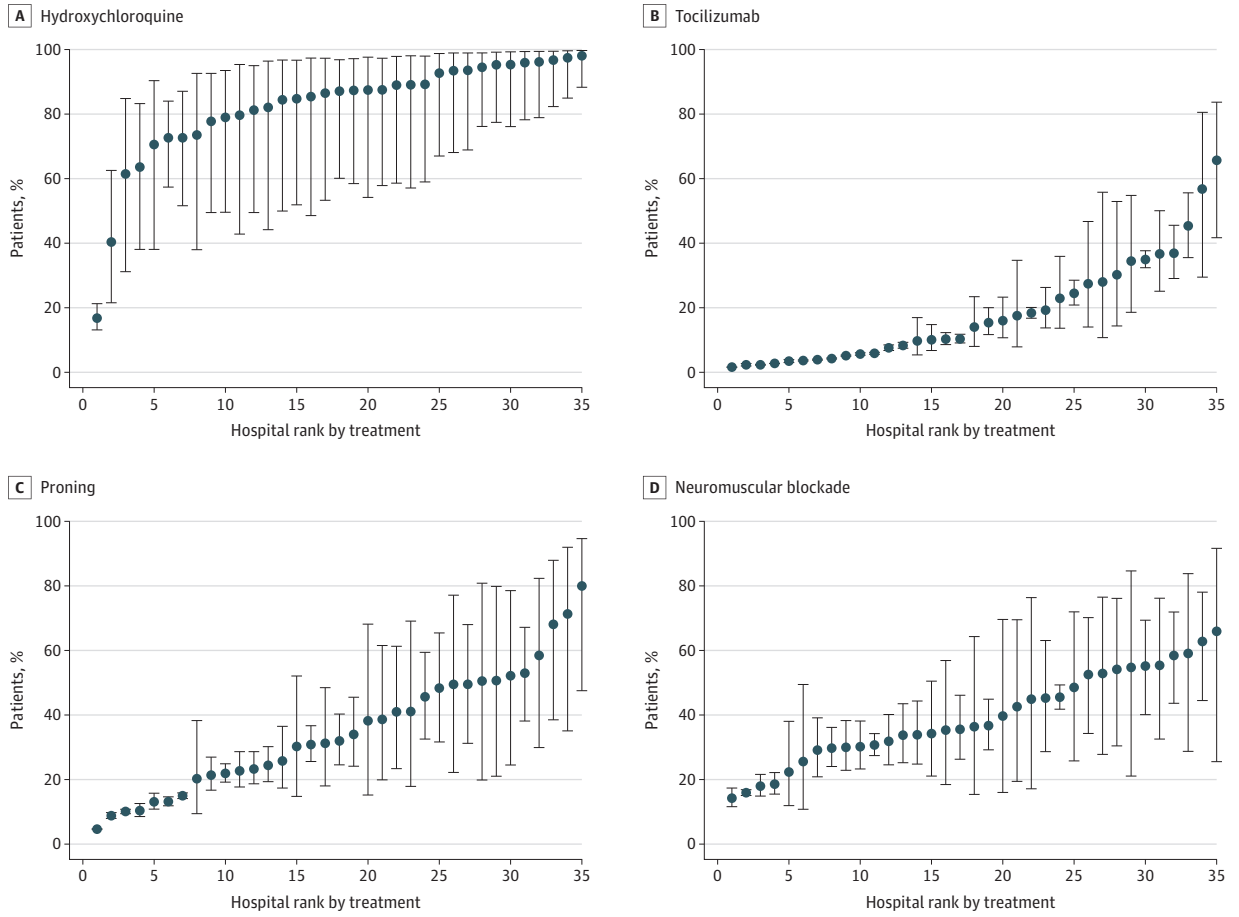
At the end of study follow-up (median, 16 days; interquartile range, 8-28 days), a total of 875 patients (39.5%) had died, 1203 (54.3%) were discharged alive from the hospital, and 137 (6.2%) remained hospitalized. Among patients discharged alive from the hospital, the median ICU length of stay was 12 days (IQR, 6-21 days), and the median hospital length of stay was 21 days (IQR, 13-33 days). Using a multivariable Cox regression model, we identified factors associated with death that were similar to those in the 28-day mortality model (eFigure 10 in the Supplement).

Discussion

This multicenter cohort study of 2215 critically ill adults with COVID-19 admitted to ICUs at 65 hospitals across the US found that 784 patients (35.4%) died in the 28 days after ICU admission. Older age, male sex, higher body mass index, coronary artery disease, and active cancer were independently associated with a higher risk of death, as was the presence of hypoxemia and liver and kidney dysfunction at ICU admission. Patients admitted to hospitals with fewer ICU beds also had a higher risk of death. Hospitals varied widely in the proportion of patients who received medications and supportive therapy for COVID-19 and in the proportion of patients who died.

Prior data on critical illness from COVID-19 derive from cohorts in China and Italy and small case series and regional reports from cohorts in the US.[3-6] Compared with a large cohort of critically ill patients with COVID-19 in Lombardy, Italy, the median age of patients in the cohort in the present study and the proportion who received invasive mechanical ventilatory support were similar.[4] The mortality in the cohort in the present study was higher than that of critically ill patients with COVID-19 in Italy (26%),[4] although 58% of the patients in that cohort were still in the ICU at the end of follow-up, but lower than that reported in single-center studies from Wuhan, China (62%)[3] and the Seattle region of the US (50%).[5] These com-

Figure 1. Interhospital Variation in Treatments



Risk- and reliability-adjusted estimates for use of hydroxychloroquine (A), tocilizumab (B), prone positioning (C), and neuromuscular blockade (D) across hospitals. Ranking of hospitals differed by treatment modality. Only 35 sites (and 1910 patients) were included in this analysis because the analysis was restricted to sites that submitted data on 15 patients or more. Errors bars indicate 95% CIs.

parisons are limited by different ICU admitting practices and duration of follow-up among studies.

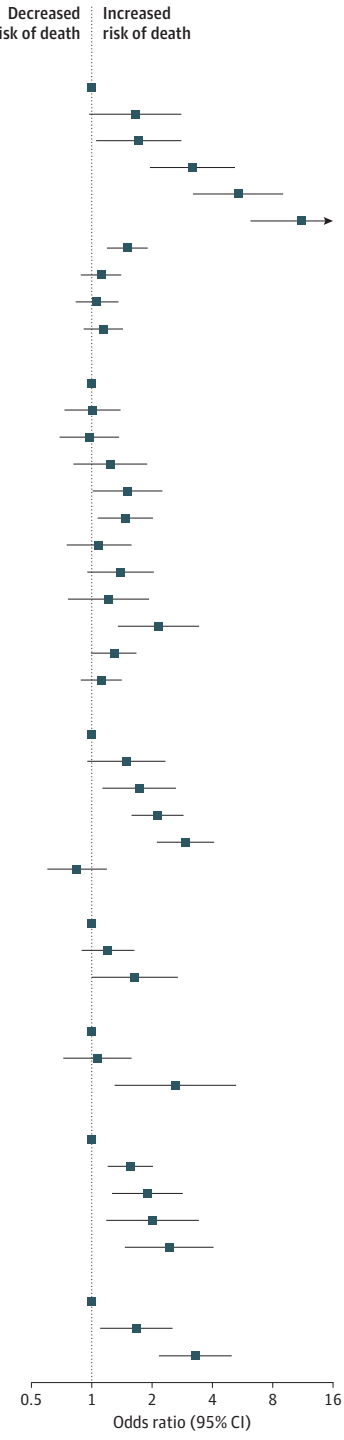
The most common acute organ injuries observed in the cohort in this study were respiratory failure, acute respiratory distress syndrome, and acute kidney injury. Other acute organ injuries were less frequent in this study, with only 230 patients (10.4%) experiencing a clinically detected thromboembolic event. This incidence of thromboembolic events is considerably lower than the 15% to 42% incidence reported in critically ill patients with COVID-19 in Europe[10-14] and is more consistent with the incidence reported in critically ill patients without COVID-19.[15] Understanding the reason for these differences will be important as hypercoagulability in COVID-19 is pursued as a potential therapeutic target.[16]

This study identified considerable interhospital variation in the administration of medications and supportive therapies intended to treat COVID-19 and associated organ injury. Sources of this variation may include the limited high-quality evidence on which to base clinical practice, variation in hospital resources to implement personnel-intensive interventions (eg, prone positioning), variation in the availability of certain medications (eg, remdesivir), or unmeasured variation in patient and practitioner characteristics across centers. These data support clinical equipoise for ongoing randomized clinical trials of therapies for COVID-19.

In this study, several patient characteristics were associated with a higher risk of death. Similar to previous reports,[17,18] older age was associated with a higher risk of death, although at least 15% of patients died in every age group, including those younger than 40 years. Two-thirds of the patients were men, and male sex was independently associated with a higher risk of death, supporting a prior report[19] of the association between male sex and adverse outcomes in patients with COVID-19. In addition, we found that higher body mass index was independently associated with a higher risk of death, extending the findings from prior reports[20-22] on the association between obesity and severe illness from COVID-19. We also identified several novel patient-level factors associated with death, including coronary artery disease and active cancer. Finally, we found that patients who were admitted to hospitals with fewer ICU beds had a higher risk of death.

Figure 2. Multivariable-Adjusted Risk Model for Death at 28 Days

Characteristic	Odds ratio (95% CI) for death
Age group, y	
18-39	1 [Reference]
40-49	1.65 (0.97-2.80)
50-59	1.71 (1.05-2.80)
60-69	3.18 (1.95-5.18)
70-79	5.36 (3.20-9.00)
≥80	11.15 (6.19-20.06)
Male sex	1.50 (1.19-1.90)
Race other than White	1.11 (0.88-1.40)
Hypertension	1.06 (0.83-1.36)
Diabetes	1.14 (0.91-1.43)
BMI	
<25	1 [Reference]
25-29.9	1.01 (0.73-1.39)
30-34.9	0.97 (0.69-1.37)
35-39.9	1.24 (0.81-1.89)
≥40	1.51 (1.01-2.25)
Coronary artery disease	1.47 (1.07-2.02)
Congestive heart failure	1.08 (0.75-1.58)
Chronic obstructive pulmonary disease	1.39 (0.95-2.04)
Current smoker	1.21 (0.76-1.93)
Active cancer	2.15 (1.35-3.43)
≤3 d From symptom onset to ICU day 1	1.29 (0.99-1.67)
Lymphocyte count <1000/μL on ICU day 1	1.11 (0.88-1.41)
PaO_2:FiO_2 on ICU day 1	
Not receiving IMV support	1 [Reference]
≥300	1.49 (0.95-2.33)
200-299	1.72 (1.13-2.63)
100-199	2.13 (1.58-2.87)
<100	2.94 (2.11-4.08)
Shock on ICU day 1	0.84 (0.60-1.19)
Coagulation component of SOFA score	
0	1 [Reference]
1	1.20 (0.89-1.63)
2	1.64 (1.00-2.69)
Liver component of SOFA score	
0	1 [Reference]
1	1.07 (0.72-1.58)
2	2.61 (1.30-5.25)
Renal component of SOFA score	
0	1 [Reference]
1	1.56 (1.20-2.02)
2	1.89 (1.26-2.84)
3	2.01 (1.18-3.42)
4	2.43 (1.46-4.05)
No. of ICU beds	
High (≥100)	1 [Reference]
Medium (50-99)	1.67 (1.10-2.53)
Low (<50)	3.28 (2.16-4.99)



To convert lymphocytes to $\times 10^9$/L, multiply by 0.001. BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICU, intensive care unit; IMV, invasive mechanical ventilation; PaO_2:FIO_2, ratio of the PaO_2 over the fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

Nearly 1 in 3 patients in the present cohort was Black compared with approximately 13.4% of the US population. Race, however, was not associated with death in multivariable models. These results are similar to those recently reported by a single-center study[23] in Louisiana, which found that Black patients were more likely to be hospitalized but had similar in-hospital mortality compared with White patients. The reasons for potential racial differences in the frequency of ICU admission with COVID-19 are likely multifactorial and may reflect differences in comorbidities, socioeconomic status, and other factors.

Strengths and Limitations

This study has several strengths. First, we collected comprehensive data from a large number of consecutive critically ill

Table 3. Clinical Outcomes and Organ Support[a]

Variable	All patients (N = 2215)	Day 28	
		Alive (n = 1431)	Died (n = 784)
Primary outcome			
Died within 28 d	784 (35.4)	NA	784 (100)
Causes of death[b]			
Respiratory failure	NA	NA	727 (92.7)
Heart failure	NA	NA	78 (9.9)
Septic shock	NA	NA	311 (39.7)
End-stage kidney disease	NA	NA	294 (37.5)
Liver failure	NA	NA	38 (4.8)
Other	NA	NA	116 (14.8)
Discharged alive from the hospital by day 28	824 (37.2)	824 (57.6)	NA
ICU length of stay, median (IQR), d	NA	9 (5-14)	NA
Hospital length of stay, median (IQR), d	NA	16 (11-22)	NA
Remained hospitalized	607 (27.4)	607 (42.4)	NA
Mechanical ventilatory support on days 1-14			
Received mechanical ventilatory support	1859 (83.9)	1126 (78.7)	733 (93.5)
Extubated, No./total No. (%)[c]	624/1859 (33.6)	506/1126 (44.9)	118/733 (16.1)
Length of mechanical ventilatory support, median (IQR), d	11 (7-14)	13 (9-14)	9 (5-13)
ECMO (days 1-14)			
Received ECMO	61 (2.8)	51 (3.6)	10 (1.3)
Decannulated from ECMO, No./total No. (%)[c]	9/61 (17.7)	9/51 (17.6)	0/10 (0)
Duration of ECMO, median (IQR), d	9 (7-12)	9 (8-12)	2.5 (1-9)
Acute kidney replacement therapy (days 1-14)[d]			
Received acute kidney replacement therapy	432/2151 (20.1)	204/1402 (14.6)	228/749 (30.4)
Kidney replacement therapy discontinued, No./total No. (%)[c]	124/432 (28.7)	55/204 (27.0)	69/228 (30.3)
Length of acute kidney replacement therapy, median (IQR), d	7 (3-11)	9 (6-12)	5 (2-9)
Vasopressor treatment on days 1-14			
Received vasopressors	1617 (73.0)	948 (66.2)	669 (85.3)
Vasopressor treatment discontinued, No./total No. (%)[c]	909/1617 (56.2)	691/948 (72.9)	218/669 (32.6)
Length of vasopressor treatment, median (IQR), d	6 (3-9)	6 (3-9)	6 (3-9)
Mechanical cardiac support (days 1-14)[e]	4 (0.2)	3 (0.2)	1 (0.1)

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Defined as per medical record review.

[c] Extubation, decannulation from ECMO, and discontinuation of kidney replacement therapy included both patients determined by treating practitioners to no longer require these therapies and patients for whom further supportive therapy was declined as a part of transition to comfort care.

[d] Patients with end-stage kidney disease (n = 64) were excluded from the denominator for analyses of acute kidney replacement therapy.

[e] Mechanical cardiac support included left ventricular assist device (n = 2) and right ventricular assist device (n = 2).

patients with laboratory-confirmed COVID-19 for 28 days, thereby minimizing selection or surveillance bias at each center. Second, we included patients from 65 geographically diverse sites from across the US, thereby maximizing generalizability. By including a large number of hospitals, we also identified considerable variation in risk-adjusted practice patterns and outcomes across sites. Third, we obtained all data by detailed medical record review rather than reliance on administrative or billing codes, which have well-described limitations.[24] Fourth, whereas prior studies[4-7] followed up patients for shorter periods, we followed up patients until the first occurrence of hospital discharge, death, or 28 days in our primary analyses and for up to 3 months in secondary analyses. By including additional follow-up, we were able to ascertain a definitive in-hospital mortality outcome (death or discharged) in 93.8% of the patients in our cohort. With the additional follow-up, the in-hospital mortality rate was 39.5%.

We acknowledge several limitations. Although health care center was included as a covariate in multivariable models, there may be unmeasured differences in patient populations among hospitals, explaining some of the observed variation in treatments and outcomes. Although some acute organ injuries (eg, acute kidney, liver, and cardiac injury) were assessed by objective laboratory-based definitions, others (eg, acute respiratory distress syndrome) relied on the clinical impression of the treating practitioner and may have differed from the true incidence. Although we assessed mortality and length of stay for 28 days, we assessed laboratory and physiologic parameters, acute organ injury, and organ support for the first 14 days only after ICU admission.

Our estimates of interhospital variation in risk- and reliability-adjusted rates of death may be affected by residual confounding because of differences in baseline risk and patient and physician characteristics across hospitals that were not accounted for by our measured covariates. For example, other than data on homelessness (0.6% prevalence in our cohort), we did not collect data on the socioeconomic status of the patients. Socioeconomic status is increasingly recognized as an important factor associated with health outcomes in patients with COVID-19[25] and could have influenced our findings with respect to variation in mortality across hospitals. We also did not collect detailed data on ventilator management strategies, hospital or ICU patient vol-

ume, or physician and nurse availability. Our models do not account for varying degrees of strain on the available resources across hospitals, such as the extent to which it may have increased the number of ICU beds beyond the baseline number before the pandemic. We did not collect data on do-not-resuscitate or do-not-intubate orders or the availability of palliative care for patients. These factors may have contributed to differing rates of intubation and ICU admission, and thus mortality, across centers. Accordingly, our findings should be interpreted cautiously. Further studies should build on our findings and seek to better understand the reasons for the considerable interhospital variation in outcomes that we observed.

Conclusions

In this multicenter cohort study of critically ill adults with COVID-19 in the US, more than 1 in 3 died within 28 days after ICU admission. We identified several patient- and hospital-level factors that were associated with death and found that treatment and outcomes varied considerably among hospitals. Future research should examine the patients with COVID-19 at greatest risk of adverse outcomes and seek to identify medications or supportive therapies that improve their outcomes.

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