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Risk Factors for Critical Coronavirus Disease 2019 and Mortality in Hospitalized Young Adults: An Analysis of the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS) Coronavirus Disease 2019 Registry

IMPORTANCE: Even with its proclivity for older age, coronavirus disease 2019 has been shown to affect all age groups. However, there remains a lack of research focused primarily on the young adult population.

OBJECTIVES: To describe the epidemiology and outcomes of coronavirus disease 2019 and identify the risk factors associated with critical illness and mortality in hospitalized young adults.

DESIGN, SETTINGS, AND PARTICIPANTS: A retrospective cohort study of the Society of Critical Care Medicine's Viral Infection and Respiratory Illness Universal Study registry. Patients 18–40 years old, hospitalized from coronavirus disease 2019 from March 2020 to April 2021, were included in the analysis.

MAIN OUTCOMES AND MEASURES: Critical illness was defined as a composite of mortality and 21 predefined interventions and complications. Multivariable logistic regression was used to assess associations with critical illness and mortality.

RESULTS: Data from 4,005 patients (152 centers, 19 countries, 18.6% non-U.S. patients) were analyzed. The median age was 32 years (interquartile range, 27–37 yr); 51% were female, 29.4% Hispanic, and 42.9% had obesity. Most patients (63.2%) had comorbidities, the most common being hypertension (14.5%) and diabetes (13.7%). Hospital and ICU mortality were 3.2% (129/4,005) and 8.3% (109/1,313), respectively. Critical illness occurred in 25% ($n = 996$), and 34.3% ($n = 1,376$) were admitted to the ICU. Older age ($p = 0.03$), male sex (adjusted odds ratio, 1.83 [95% CI, 1.2–2.6]), and obesity (adjusted odds ratio, 1.6 [95% CI, 1.1–2.4]) were associated with hospital mortality. In addition to the above factors, the presence of any comorbidity was associated with critical illness from coronavirus disease 2019. Multiple sensitivity analyses, including analysis with U.S. patients only and patients admitted to high-volume sites, showed similar risk factors.

CONCLUSIONS: Among hospitalized young adults, obese males with comorbidities are at higher risk of developing critical illness or dying from coronavirus disease 2019.

KEY WORDS: coronavirus disease 2019; intensive care; mortality risk; outcomes; young adults

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DOI: 10.1097/CCE.0000000000000514

Coronavirus disease 2019 (COVID-19) has established itself as the first modern pandemic. Most people who die of COVID-19 are more than 65 years old, and age seems to be one of the most critical risk factors

for adverse outcomes (1). The odds of death in patients who are greater than or equal to 60 years have been estimated to be 18.8 times that of patients less than 60 years old (2). However, there have been reports of deaths from COVID-19, even in young, otherwise healthy adults, particularly healthcare workers (3). There has been an increase in all-cause mortality among young adults since the start of the pandemic (4). A review of the Centers for Disease Control and Prevention (CDC) data on April 01, 2021, demonstrated that 9.1 million cases of COVID-19 had been reported in patients 18–40 years old in the United States, with 6,859 deaths (5). Within the first 9 months of the COVID-19 pandemic, the demographics had shifted, with the occurrence rate increasing 2.1-fold among very young adults (18–22 yr). Furthermore, young adults may be less likely than other age groups to adhere to COVID-19 prevention measures (e.g., social distancing) (6, 7) and have shown higher rates of vaccine hesitancy (8).

Even though the published literature on the COVID-19 pandemic is growing exponentially, there remains a lack of research focused primarily on the young adult population, that is, persons 18–40 years old. Most of the data on young adults are derived from studies on healthcare workers (9). The largest reported information in this age group comes from an administrative database (10). There have also been a couple of single-center reports (11, 12), but so far, there has been no comprehensive study focusing on the risks and outcomes of young adults hospitalized with COVID-19.

Since transmission rates may be higher among young adults, understanding the clinical aspects of their hospitalization is crucial. This study's primary objective was to describe the epidemiology, disease characteristics, and outcomes of COVID-19 in hospitalized young adults. Our secondary objective was to identify risk factors associated with critical illness and mortality in this population.

MATERIALS AND METHODS

A retrospective cohort study was performed for adults 18–40 years old admitted to 152 hospitals participating in the Society of Critical Care Medicine (SCCM) Discovery Network's Viral Infection and Respiratory Illness Universal Study (VIRUS) registry from March 2020 to April 2021. SCCM VIRUS registry is a prospective, cross-sectional, observational study of all eligible adult and pediatric patients admitted to the hospital. The VIRUS study was approved by the Mayo Clinic Institutional Review Board (number 20-002610) and by all participating sites, with a waiver of informed consent. Each site collected deidentified data through manual chart abstraction or automation and entered it into a centralized Research Electronic Data Capture (REDCap) database (13) hosted by the Mayo Clinic. Inclusion criteria for the VIRUS registry encompass any patient admitted with COVID-19 in participating hospitals with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or high clinical suspicion of COVID-19. Patients with non–COVID-19-related admissions and repeat admissions are excluded. In this report, we excluded patients who did not have laboratory confirmation of SARS-CoV-2 infection.

Study Variables

The variables extracted from the database included demographics (age, sex, race, ethnicity, source of admission, healthcare worker status, pregnancy), clinical characteristics (signs and symptoms at presentation, comorbidities), hospital and ICU management (respiratory and hemodynamic support), and outcomes (complications, length of stay, and mortality). Race and ethnicity were self-reported separately. These were later categorized as composite index as non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, non-Hispanic others, and Hispanic as per the current CDC reporting on race/ethnicity disparities pertaining to COVID-19 (14). The number of comorbidities (of 36 discrete options) and the number of signs/symptoms at presentation (of 27 discrete options) were summated. Patients were further characterized as having greater than or equal to two comorbidities at presentation. Obesity was analyzed separately and was not included in the composite of comorbidity. All patients with a history of smoking, current smokers, chewing tobacco, vaping, and cigar-smoking were classified as "exposure to smoking/tobacco." Body mass index (BMI) was calculated based on the patient's weight and height and categorized into standard BMI categories (15). Patients with biologically implausible weight (< 30 kg; $n = 4$), height (< 4 feet; $n = 26$), and BMI (> 100; $n = 3$) values were counted as missing.

Definition of Critical Illness

The investigators defined critical COVID-19 by consensus. It was specified to capture patients using

variables in the VIRUS registry, which would meet the National Institutes of Health (NIH) definition of critical COVID-19 (respiratory failure, shock, and/or multiple organ dysfunction), with the additional inclusion of mortality (16). It was defined as a composite of 1) disease outcome: mortality, and/or 2) severe organ system involvement identified by the requirement of higher level respiratory support (invasive or noninvasive ventilation, nitric oxide, high-flow nasal cannula [HFNC]), patients who required inotropes, vasopressors, extracorporeal membrane oxygenation (ECMO), or had complications of septic shock, cardiac arrest, new-onset cardiac arrhythmia, congestive heart failure, cardiomyopathy, endocarditis, myocarditis or pericarditis (cardiac), or required continuous renal replacement therapy/hemodialysis or had complications of acute kidney failure (renal), complications of meningitis/encephalitis or seizures or cerebrovascular accident (CNS), or disseminated intravascular coagulation (thrombotic disease). All other patients were classified as having a noncritical illness. Acute renal failure was a discreet complication option in the VIRUS registry. Acute renal failure diagnosis was not further adjudicated by us using laboratory values. A summary of the distribution of each of the variables for this composite outcome is provided in the supplemental digital content (**SDC 1**, http://links.lww.com/CCX/A752).

Missing Data Analysis

Missing data analysis was performed for primary outcome variables (ICU admission status, hospital length of stay, and mortality) and independent variables used in the regression models (age, sex, race and ethnicity, and comorbidities). Missing data analysis, in the subset of patients meeting inclusion criteria (18–40 yr old patients in VIRUS registry with laboratory-confirmed SARS-Co-V-2 infection; n = 4,714), showed missing BMI in 27.8% patients (1,310/4,714) and missing ICU status in 13% patients (624/4,714). Sex, race and ethnicity, and hospital length of stay were missing in less than 1% and were excluded from further analysis (**SDC 2**, http://links.lww.com/CCX/A752). Both BMI and ICU admission status appeared to be missing not at random (MNAR). Patients with obesity (using obesity comorbidity variable) were less likely to be missing BMI, and patients with critical illness were less likely to be missing ICU admission status. Since the obesity comorbidity variable acted as a good proxy to the missing BMI, a composite variable (obesity as diagnosed with BMI or as comorbidity diagnosed by a physician) was used for analysis. The final analysis cohort of 4,005 had 1,076 patients (26.8%) with missing BMI values. Due to the lack of a suitable surrogate, patients with missing ICU status were excluded from the analysis; however, a sensitivity analysis was performed after including patients with missing ICU admission variable (total n for this analysis 4,608). The number and percentage of missing data were calculated and reported for all other variables (ICU length of stay, ICU mortality, hospital admission source, healthcare worker status, etc.).

Statistical Analysis

Descriptive statistics were performed for continuous and categorical variables and reported as median with interquartile range (IQR) and number with percentages, respectively. Nonparametric Wilcoxon rank-sum test was used for comparison of continuous variables. Categorical variables were compared using the Fischer exact test or chi-square test as appropriate. The effect size of the difference (Cohen's D for continuous variables and Cramer's V for categorical variables) (17) was calculated using the open-source statistical program R (V4.0.0; R Foundation for Statistical Computing, Vienna, Austria). Cohen's D value of less than 0.2 was considered small effect, and Cohen's D value of 0.5 and 0.8, medium and large effects, respectively (18). For "Cramer's V," the effect size of less than or equal to 0.2 was deemed to be weak, 0.2–0.6 as moderate, and greater than or equal to 0.6 as a strong association (19). Separate multivariable logistic regression was performed to assess the factors associated with critical COVID-19 and mortality. Odds ratios (ORs) and 95% CIs are reported. Variables for inclusion into the multivariable model were determined a priori based on theoretical understanding of risk factors and included demographics (race and ethnicity, age, and sex) and clinical characteristics (six most common comorbidities). Collinearity was assessed using the variance inflation factor (VIF). Only variables with VIF less than 5 were included in the model. Five sensitivity analyses were performed: 1) inclusion of patients only from sites which had greater than 10 patients and patients from both ICU and general floor (n = 3,358), 2) inclusion of patients only from U.S. sites (n = 3,260), 3) including the status as a healthcare worker (yes/no) in the model (n = 2,564), 4) including patients who had missing ICU

admission status in the model (n = 4,608), and 5) conservative definition of critical illness using requirement of organ support therapies and mortality as criteria (n = 955 patients met critical illness criteria with this definition). A p value of less than 0.05 was considered statistically significant. All analysis was performed using JMP Pro V 16.0 (SAS Institute, Cary, NC) and open-source statistical program R (V4.0.0; R Foundation for Statistical Computing). This report conforms to the Strengthening The Reporting of Observational Studies in Epidemiology statement (20) (**SDC STROBE Checklist**, http://links.lww.com/CCX/A754).

RESULTS

During the study period, a total of 65,301 patients were entered into the registry, of which 4,867 (≈ 7.5%) were between 18 and 40 years old. Eight-hundred sixty-two patients were excluded (no COVID-19 test available or missing data on essential data fields). The final analysis included 4,005 patients from 152 centers (3,260 patients from the United States and 745 patients from 18 international non-U.S. countries) (**Fig. 1**). The median number of patients per hospital was 6 (IQR, 2.5–20). Detailed characteristics of sites are provided in **SDC 3** (http://links.lww.com/CCX/A752).

Demographics

The median age was 32 years (IQR, 27–37 yr); 51% were female, and 29.4% were Hispanic. A total of 1,376 patients (34.3%) required ICU admission, and 996 (24.8%) met the criteria for critical illness. A total of 235 of 996 patients (23.6%) with critical illness were not admitted to the ICU, whereas 615 of 1,376 patients (44.7%) admitted to the ICU did not meet critical illness criteria. ICU admission source was from the hospital emergency department in 59.5% and another inpatient unit in 28.1%. The majority of young adults who required hospitalization for COVID-19 had medical comorbidity (n = 2,532; 63.2%), with 28.2% (n = 1,128) having

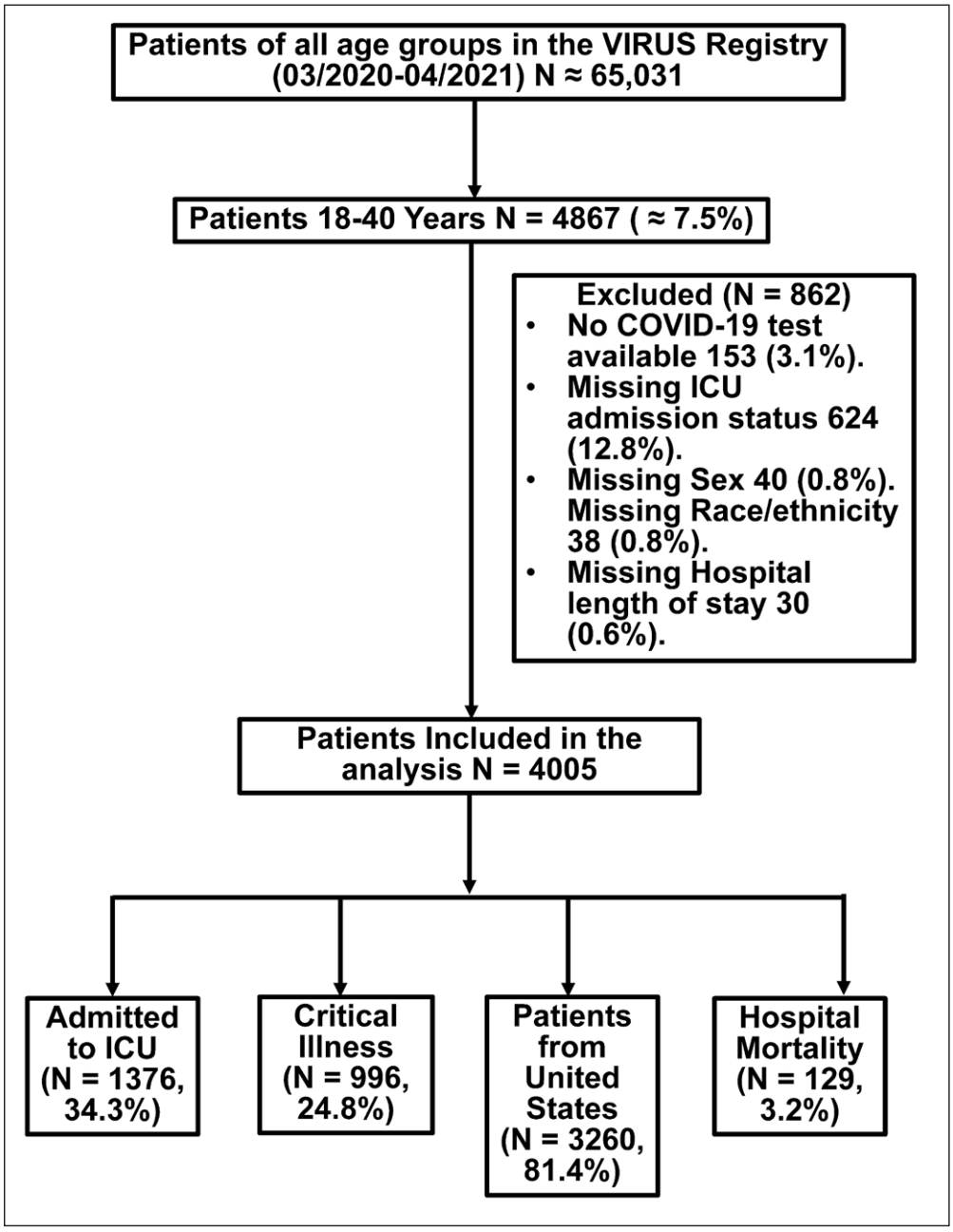

Figure 1. Consort flow diagram of the study cohort. (The total number of patients is approximate as it reflects the number of entries in the registry on the week of data extraction for analysis.) COVID-19 = coronavirus disease 2019, VIRUS = Viral Infection and Respiratory Illness Universal Study.

TABLE 1.
Demographics, Clinical Characteristics of Young Adult Patients Admitted to the Hospital With Coronavirus Disease 2019

Category	Subcategory	*N*	Values, Median (IQR) or *n* (%)
Median age (yr)		4,005	32 (27–37)
Sex	Female	4,005	2,043 (51.0)
Race and ethnicity	Non-Hispanic White	4,005	1,020 (25.5)
	Non-Hispanic Black		880 (21.9)
	Non-Hispanic Asian		600 (14.9)
	Non-Hispanic other		329 (8.2)
	Hispanic		1,176 (29.4)
Country[a]	United States	4,005	3,260 (81.4)
Healthcare worker[b]	Yes	2,564	159 (6.2)
Pregnant patient[c]	Yes	539	191 (35.4)
Hospital admission source[d]	ED	3,538	1,795 (50.7)
	Home		1,138 (32.2)
	Other		273 (7.7)
	Transfer from another facility		221 (6.3)
	Outside ED		88 (2.5)
	Nursing home		23 (0.6)
ICU admission (yes)		4,005	1,376 (34.3)
Critical illness (yes)[e]			996 (24.8)
ICU admission source[f]	Hospital ED	1,078	642 (59.5)
	Hospital floor/ward		303 (28.1)
	Outside ED/hospital		68 (6.3)
	Outside ICU		47 (4.3)
	Other		10 (0.9)
	Operating room		6 (0.6)
	Nursing home		2 (0.02)
Obesity (yes)		4,005	1,722 (42.9)
Comorbidity (yes)[g]		4,005	2,532 (63.2)
Two or more comorbidities[h]		4,005	1,128 (28.2)
Median number of comorbidities		4,005	1 (0–2)

ED = emergency department, IQR = interquartile range.

[a]India (411; 10.2%), Turkey (96; 2.4%), Russia (33; 0.8%), Pakistan (32; 0.8%), Saudi Arabia (30; 0.7%), Nigeria (20; 0.5%), Serbia (14; 0.4%), Spain (19; 0.5%), Belgium (14; 0.4%), Honduras (12; 0.3%), Japan (15; 0.4%), Kuwait (14; 0.4%), Mexico (10; 0.3%), Bolivia (7; 0.2%), Colombia (7; 0.2%), Iran (5; 0.1%), Egypt (5; 0.1%), and Canada (1; 0.03%).

[b]Healthcare worker status missing 1,441 (35.9%).

[c]Pregnancy status missing in very large proportion of female patients (1,504/2,043; 73.6%).

[d]Hospital admission source missing 467 (11.6 %).

[e]Two-hundred thirty-five of 996 patients (23.6%) with critical illness were not admitted to the ICU. Six-hundred fifteen of 1,376 ICU admissions (44.7%) did not have critical illness. Of 615 patients admitted to ICU without critical illness, 308 (50.1%) were not from United States.

[f]ICU admission source missing 298 (21.6%).

[g] Does not include obesity.

[h]Two comorbidities 511 (12.8%), three comorbidities 283 (7.0%), four comorbidities 161 (4.0%), and five comorbidities 96 (2.4%).

greater than or equal to two comorbidities. A total of 1,722 patients (42.9%) were obese (**Table 1**). The common comorbidities of the study population were hypertension (*n* = 579; 14.5%), diabetes mellitus (*n* = 549; 13.7%), and asthma (*n* = 391; 9.7%). Fever (*n* = 1,642; 40.9%), cough (*n* = 1,592; 39.7%), and shortness of breath (*n* = 1,470; 36.7%) were the three most common presenting signs and symptoms. A total of 338 patients (8.4%) had smoking/tobacco exposure (**Table 2**).

Hospital Management and Outcomes

Overall, 64.7% patients (2,590/4,005) required respiratory support (invasive or noninvasive ventilation,

TABLE 2.
Presenting Signs and Symptoms and Comorbidities of Young Adult Patients Admitted to the Hospital With Coronavirus Disease 2019

No.	Signs/Symptoms	*n* (%)	Comorbidity	*n* (%)
1	Fever	1,642 (40.9)	Hypertension	579 (14.5)
2	Cough (productive or dry)[a]	1,592 (39.7)	Diabetes mellitus	549 (13.7)
3	Dyspnea/shortness of breath	1,470 (36.7)	Asthma	391 (9.7)
4	Myalgia/fatigue	875 (21.8)	Smoking/tobacco exposure[c]	338 (8.4)
5	Nausea/vomiting	641 (16.0)	Depression	260 (6.5)
6	Diarrhea	453 (11.3)	Substance abuse	201 (5.0)
7	Chest pain/tightness	429 (10.7)	Chronic kidney disease	132 (3.2)
8	Chills/rigors	492 (12.3)	Chronic pulmonary disease (not asthma)	101 (2.5)
9	Headache	498 (12.4)	Obstructive sleep apnea/home continuous positive airway pressure	105 (2.6)
10	Abdominal pain	251 (6.3)	Iron deficiency anemia	147 (3.6)
11	Sore throat/throat pain	283 (7.1)	Alcohol addiction	82 (2.0)
12	Malaise	228 (5.7)	Hypothyroidism	119 (2.9)
13	Loss of taste/smell[b]	240 (5.9)	Stroke or other neuro disorder	81 (2.0)
14	Anorexia (loss of appetite)	209 (5.2)	Psychosis	65 (1.6)
15	Nasal congestion/rhinorrhea	185 (4.6)	Venous thromboembolism/pulmonary embolism	88 (2.2)
16	Dizziness/lightheadedness	97 (2.4)	Congestive heart failure	73 (1.8)
17	Arthralgia	51 (1.3)	Dyslipidemia/hyperlipidemia	133 (3.3)
18	Confusion/delirium	48 (1.2)	Liver disease	83 (2.0)
19	Night sweats	31 (0.7)	Chronic dialysis	62 (1.5)
20	Rash	17 (0.4)	Hematologic malignancy	54 (1.3)

[a]Cough with sputum 365 (9.1%) and dry cough 1,286 (32.1%).

[b]Loss of taste 147 (3.6%) and loss of smell 194 (4.8%).

[c]Current smoker 157 (3.9%), past smoker 171 (4.2%), vaping 15 (0.4%), cigars 12 (0.3%), pipes 2 (0.05%), and chewing tobacco 6 (0.15%).

Hemoptysis 23 (0.6%), seizures 14 (0.4%), sneezing 12 (0.3%), conjunctival congestion 9 (0.2%), lymphadenopathy 6 (0.1%), and other 454 (11.3%). Cardiac arrhythmia 50 (1.2%), HIV or immune suppression 36 (0.9%), solid tumor without metastasis 28 (0.6%), paralysis 26 (0.6%), coagulopathy 55 (1.3%), history of tumor or bone marrow transplant 55 (1.3%), coronary artery disease 36 (0.9%), hepatitis C 46 (1.1%), rheumatoid arthritis/collagen vascular disease 19 (0.4%), blood loss anemia 43 (1.0%), valvular heart disease 25 (0.6%), peptic ulcer disease 12 (0.3%), malnutrition 20 (0.5%), hepatitis B 12 (0.3%), metastatic cancer 10 (0.3%), pulmonary circulation disorders 7 (0.2%), dementia 2 (0.05%), and other 820 (20.4%).

oxygen by nasal cannula, face mask, HFNC, therapeutic proning, or ECMO). Provision of oxygen via nasal cannula was the most common respiratory support mode (31.0%; *n* = 1,242). Noninvasive and invasive ventilation were used in 7.3% patients (*n* = 292) and 12.5% patients (*n* = 500), respectively. Only 1.3% patients (*n* = 54) required ECMO, for which the cannulation strategy was most commonly venovenous (*n* = 48). The median ECMO duration among survivors was 12.0 days (IQR, 7.9–20.9 d). Mortality in those who received ECMO was 24% (*n* = 13). Overall hospital mortality rate was 3.2% (*n* = 129/4,005), and ICU mortality rate was 8.3% (*n* = 109/1,313) (missing data on 63 patients). The mortality rate among patients from the United States was 3.0% (99/3,260), and for international patients, it was 4.03% (30/745) ($p = 0.16$). Most patients were discharged home without assistance (2,599/3,349 survivors; 77.6%). Among survivors who required invasive and noninvasive ventilation, the median duration of support was 8 days (IQR, 3.3–15.5 d) and 4.0 days (IQR, 1.9–7.0 d), respectively. The median hospital and ICU length of stay among survivors were 5.0 days (IQR, 2.3–8.5 d) and 4.9 days (IQR, 2.0–9.1 d), respectively (**Table 3**).

Comparison of Patients With Critical Versus Noncritical Illness

The median age of patients with critical illness was 34 years (IQR, 28–37 yr) compared with 32 years (IQR, 26–36 yr) for noncritical illness ($p < 0.001$; Cohen's D = 0.18). The median BMI of patients with critical illness was also higher (33.3 vs 29.4; $p < 0.001$; Cohen's D = 0.40). There was a higher proportion of patients from the United States in the critical illness cohort than the noncritical illness cohort (84.2% vs 80.4%; $p = 0.007$). A significantly higher proportion of patients with critical illness were obese (58.4% vs 37.9%; $p < 0.001$) and male (58.6% vs 45.8%; $p < 0.001$). There was a significant difference in the racial/ethnic distribution with slightly more Hispanic patients in the critical illness cohort and more non-Hispanic Asians in the noncritical illness cohort. There was a significant difference in the proportion of patients with any comorbidity (69.9% vs 60.9%; $p < 0.001$) and the proportion of patients with greater than or equal to two comorbidities (37.2% vs 25.1%; $p < 0.001$) with more comorbidities in the critical illness cohort. Hypertension, asthma, and diabetes were significantly more common among patients with critical illness. Patients with critical illness reported more signs and symptoms at presentation, with a significant difference in the proportion of patients having sign symptoms of cough, diarrhea, dyspnea, fever, and nausea/vomiting in the critical illness cohort. There was no difference in the proportion of patients presenting with myalgia/fatigue in the two groups (**SDC 4**, http://links.lww.com/CCX/A752).

On multivariable analysis after adjusting for age, sex, race and ethnicity, presence of obesity, any comorbidity, and comorbidities of hypertension, asthma, diabetes mellitus, smoking exposure, and depression, age (adjusted OR [aOR], 1.01 yr [1.004–1.03 yr]; $p = 0.007$), patients with obesity (aOR, 2.13 [1.81–2.50]; $p < 0.001$), male sex (aOR, 1.80 [1.54–2.09]; $p < 0.001$), patients with any comorbidity (aOR, 1.32 [1.10–1.59]; $p = 0.002$) had higher odds of critical illness. Independent association of age, obesity, male sex, and presence of any comorbidity with critical illness was seen in most sensitivity analyses. The non-Hispanic White race was associated with a lower OR of critical illness compared with Hispanics (aOR, 0.70 [0.55–0.88]; $p = 0.03$) when only high-volume centers were included in the sensitivity analysis (**Fig. 2*A***) (**SDCs 6–10**, http://links.lww.com/CCX/A752).

Comparison of Survivors Versus Nonsurvivors

Nonsurvivors had significantly higher median age (34 [29–37.6] vs 32 [27–36.7]; $p = 0.001$; Cohen's D = 0.30) and BMI (33.4 [IQR, 26.3–47.3) vs 30.4 [IQR, 25.6–37.7]; $p = 0.002$; Cohen's D = 0.39) compared with survivors. There was a significant difference in the BMI categories between survivors and nonsurvivors, with a higher proportion of patients within the obese category among nonsurvivors (65.0% vs 52.3%; $p = 0.01$). There were a higher proportion of male patients among nonsurvivors (63.6% vs 48.5%; $p < 0.001$) and patients with two or more comorbidities (44.2% vs 27.6%; $p < 0.001$). Among the six most common comorbidities, only hypertension and diabetes were more common among nonsurvivors. A higher proportion of nonsurvivors also presented with symptoms of dyspnea and diarrhea. However, the effect size of the differences between the two groups was weak for all the variables (**SDC 5**, http://links.lww.com/CCX/A752).

TABLE 3.
Hospital Therapeutic Interventions and Outcomes

Category	Subcategory		*N*	Values
Categorical variables, *n* (%)				
Therapeutic interventions	Respiratory support[a]	Nasal cannula	4,005	1,242 (31.0)
		Face mask		442 (11.0)
		High-flow nasal cannula		444 (11.1)
		Noninvasive ventilation		292 (7.3)
		Invasive ventilation		500 (12.5)
		Nitric oxide		58 (1.4)
	Proning[b]			385 (9.6)
	ECMO[c]		4,005	54 (1.3)
	Continuous renal replacement therapy/hemodialysis			19 (0.4)
	Inotropes			72 (1.8)
	Vasopressors			214 (5.3)
	Neuromuscular blocker			190 (4.7)
	Tracheostomy			45 (1.1)
Mortality	ICU[d]		1,313	109 (8.3)
	Hospital[e,f,g,h]		4,005	129 (3.2)
Hospital discharge location[i,j]	Home without assistance		3,349	2,599 (77.6)
	Home with home health			469 (14.0)
	Hospice			3 (0.09)
	Long-term care facility			54 (1.6)
	Other hospital (overflow)			56 (1.6)
	Subacute rehabilitation			62 (1.8)
	Other			106 (3.1)
Continuous variables, median (interquartile range)[j,k]				
Hospital length of stay (d)			3,876	5 (2.3–8.5)
ICU length of stay (d)			1,231	4.9 (2.0–9.1)
Ventilator duration (d)			355	8 (3.3–15.5)
Noninvasive ventilator duration (d)			208	4 (1.9–7.0)
High-flow nasal cannula duration (d)			324	3 (1.8–6.0)
ECMO duration (d)			42	12 (7.9–20.9)

ECMO = extracorporeal membrane oxygenation.

[a]Total number of patients requiring respiratory support either by nasal cannula, face mask, high-flow nasal cannula, noninvasive or invasive ventilation, proning, or ECMO 64.7% (2,590/4,005).

[b]Includes "self-proning" while not on ventilator" as well as "prone ventilation."

[c]Venoarterial (2), venovenous (48), missing type (4); mortality of all on ECMO 13 (24.0%).

[d]ICU mortality for patients admitted to the ICU. Missing ICU mortality status 63 (4.6%).

[e]Of the 3,876 patients discharged alive, 28-d outcome available on 2,619 patients (missing 1,257/3,876; 32.4%), and seven (0.3%) patients deceased within 28 d of discharge.

[f]Mortality rate of patients with critical illness 12.1% (119/986), 10 patients with mortality did not meet criteria of critical illness (mortality rate 0.3%; 10/3,019), although cumulative category of critical illness included all patients with mortality.

[g]Mortality among U.S. centers 3.04% (99/3,260) and international centers 4.03% (30/745), $p = 0.16$.

[h]Mortality rates for invasive mechanical ventilation 22.6% (113/500), noninvasive ventilator 9.9% (29/292), high-flow nasal cannula 5.2% (23/444), and low-flow nasal cannula 2.1% (26/1,242).

[i]Missing hospital discharge location in 527 survived patients (527/3,876; 13.5%).

[j]Survived patients only.

[k]Missing data among survivors: ICU length of stay 1.7% (22/1,253), invasive ventilator duration 8.2% (32/387), noninvasive ventilator duration 21% (55/263), high-flow nasal cannula duration 23% (97/421), and ECMO duration 0% (0).

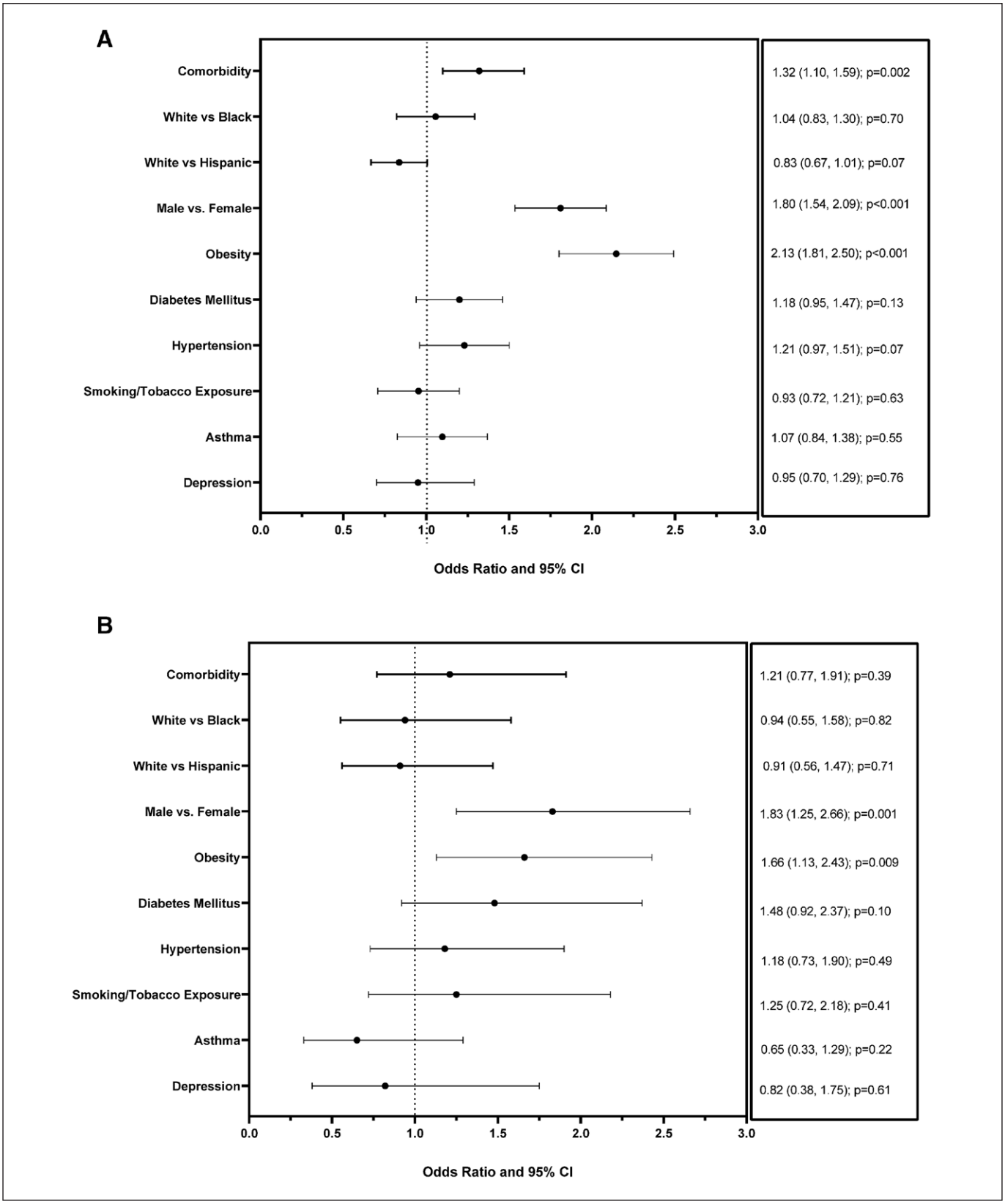

Figure 2. Forest plot for the adjusted odds ratio (aOR) of critical coronavirus disease 2019 (**A**) and mortality (**B**) in hospitalized young adults. Results are from separate regression models for each outcome and contain all the categorical variables listed in the figures. Five levels of race and ethnicity entered in the model. Of a total of 20 comparative groups, only two are shown. Age was entered in the respective models as a continuous variable and not shown in the figure. aOR for critical illness per unit increase in age 1.01 (95% CI, 1.004–1.03; $p = 0.007$). aOR for mortality per unit increase in age 1.03 (95% CI, 1.002–1.06; $p = 0.03$). Obesity is not included as a comorbidity in the composite category of any comorbidity. Variance inflation factor less than 5 for all variables included in the model.

On multivariable analysis after controlling for age, sex, race, presence of obesity, presence of comorbidities, and individual comorbidity of hypertension, diabetes mellitus asthma, depression, and smoking history, only older age (aOR, 1.03 yr [1.002–1.06 yr]; $p = 0.03$), male sex (aOR, 1.83 [1.25–2.66]; $p = 0.001$), and presence of obesity (aOR, 1.66 [1.13–2.43]; $p = 0.009$) were associated with mortality. Male sex and obesity were associated with mortality in most sensitivity analyses, including the analysis of patients from U.S. sites and high-volume sites. Among patients admitted to high-volume sites only, non-Hispanic Whites had a lower OR of mortality compared with non-Hispanic Black and Hispanic patients (**Fig. 2***B*) (SDCs 6–9, http://links.lww.com/CCX/A752).

DISCUSSION

In this international multicenter study from 152 hospitals on young adults (18–40 yr) who required hospitalization with laboratory-confirmed COVID-19–related illnesses, nearly 25% of the patients had a critical illness, 12.5% required invasive ventilation, and 3.2% died during hospitalization. We identified specific demographics and comorbidities independently associated with critical COVID-19 and mortality, including the presence of any comorbidity, male sex, and obesity. To the best of our knowledge, this is the largest and most comprehensive evaluation of risk factors for critical illness/mortality in this age group.

We used a composite outcome of critical illness instead of ICU admission as a marker of severe COVID-19 (21). This is relevant because ICU admission is subject to the bias of geographic cohorting and hospital-specific ICU admission criteria. Our composite outcome may be a better indicator of morbidity than ICU admission alone. This is supported by our data, where nearly 44% of patients (615/1,376) admitted to the ICU did not have a critical illness. Our characterization of critical illness is adapted from the NIH definition of critical illness (16), using objective procedures and complications for identification. It is also similar but more liberal in inclusion than Cunningham et al (10). It is still possible that our definition included some patients who were not critically ill, while also missing some critical patients with COVID-19. However, we expect the number of patients with critical illness missed by our definition to be small, as evident by very low mortality among patients not meeting critical illness criteria (0.3%). Sensitivity analysis using a more conservative definition of critical illness had similar findings. Furthermore, our simultaneous analysis of patients with mortality is not subject to such limitations.

In this study, we have classified patients between 18 and 40 years as young adults. This is based on the CDC data tracker age categorization (combined category of 18–25 and 25–40 yr) (22). Prior studies have used a varied age cutoff for young adults (18–22 yr [23], 18–25 yr [24, 25], 18–44 yr [26], and 18–34 yr [10]). The differences in age cutoffs for young adult definition may limit direct comparison between different studies.

Our study design is similar to that by Cunningham et al (10), with some notable differences: 1) use of a database specially designed for COVID-19–associated illness as compared to administrative data using *International Classification of Diseases*, 10th revision, codes for patient selection and identification of comorbidities, 2) age categorization differences, 3) definition of critical illness using a composite outcome that is broader than a composite outcome by Cunningham et al (10) of "mortality + need of mechanical ventilation," and 4) multinational as compared to data from the United States only. Overall, our patients had higher mortality (3.2% vs 2.7%) and higher ICU resource utilization (ICU admission, 34.4% vs 21% and mechanical ventilation, 12.5% vs 10%). However, our reported mortality among U.S. patients (3.04%) is closer to the mortality reported in the study by Cunningham et al (10).

The patient characteristics associated with critical illness in our study were older males who were obese and had other comorbidities. Our finding indicating the association of comorbidity with critical illness is similar to prior reports (27). As noted by Katz (28), the comorbidities most commonly associated with critical illness and mortality are also the ones that are potentially modifiable (hypertension, obesity, and diabetes). Male sex has been previously described as an independent risk factor for mortality in all age groups (29), including younger adults (10). A meta-analysis from 34 studies including 5,057 patients of all age adults, Nasiri et al (30), showed a significantly higher mortality rate for males than females (OR, 3.4; 95% CI, 1.2–9.1). Our reported OR of mortality for males (aOR, 1.8) was lower, which might reflect the overall lower mortality rate in a younger population. The

association of obesity with critical illness and mortality also deserves special mention. Obesity was associated with critical illness and mortality irrespective of the model choice in our analysis. Our findings concur with the prior reports on the adverse impact of obesity on outcomes from COVID-19 (31), including reports suggesting that the younger adults might be more susceptible to the obesity-related risk from COVID-19 than elderly adults (32). The impact of older age on susceptibility to COVID-19 is well established (33). Even though we had selected patients between the age group of 18 and 40, age was independently associated with critical illness and mortality after adjusting for confounders. This suggests that even within the young age group, people toward the older end of the spectrum are at higher risk.

Our study did not find any independent association of race/ethnicity with critical illness or mortality. The impact of racial disparities on outcomes from COVID-19 has been variably reported in the literature (1, 24, 34, 35). In a large urban study, Price-Haywood et al (34) reported a higher disease burden for Blacks but no significant difference in mortality. Although the proportion of Hispanics and Black populations in our study was high, it was not possible to conclude admission risk in the absence of population distribution for the included sites. Analysis of high-volume sites showed a lower risk for critical illness in patients of the White race (compared with Hispanics) and mortality (compared with Hispanics and non-Hispanic Blacks). This finding was not observed in other models (including the main model with all patients and the model with the U.S. patients only), raising the possibility of a selection bias. Our analysis was also not adjusted for economic status, which has been shown to have a significant impact on COVID-19 outcomes (36).

Our study has limitations inherent to large observational registries. First, a significant proportion of patients had missing data. Data MNAR can introduce bias. Although physician-diagnosed obesity acted as a good surrogate for missing BMI, chances of uncertainty remain. Sensitivity analysis, including patients with missing ICU admission status variable, concurred with the conclusions of the main model. Certain essential confounding variables like geographic location and socioeconomic status were not available to us, and thus, their impact on outcomes could not be evaluated. Missing data analysis was limited to essential data variables, and the missingness of other variables such as ICU length of stay/duration of respiratory support/comorbidities, etc., may still introduce errors. We have provided the exact number and percentages of missing values wherever possible. Second, the composite category of critical illness gives equal weightage to every variable. We, therefore, separately analyzed risk factors for patients with mortality. This classification also does not differentiate if the event happened early or late during hospitalization. Third, to avoid model overfitting, interaction effects were not evaluated. Fourth, only comorbidities and signs/symptoms entered as discrete variables in the REDCap data collection form were assessed. Thus, patients with comorbidities and sign symptoms listed as "others" were not counted in the absolute numbers. However, since most comorbidities and signs/symptoms were already included in the data collection forms, we expect this number to be small and unlikely to influence the conclusions. Fifth, patients with an incidental diagnosis of SARS-CoV-2 were excluded from the registry; however, occasionally, this distinction is ambiguous. It is possible that site investigators may have entered borderline cases in the registry (and vice versa). Finally, the occurrence rate of mortality, ICU admission, and critical illness only reflects the population of the participating hospitals and entered in the VIRUS registry. The risk of mortality and the risk of critical illness is only reflective of the already sick hospitalized cohort of patients. For the general population, results should be interpreted within the limitations of the retrospective registry studies.

CONCLUSIONS

In conclusion, contrary to general belief, young adults are susceptible to SARS-CoV-2 infection, and hospitalized young adults may develop a critical illness with poor outcomes, including death. Among hospitalized young patients between 18 and 40 years old, obese males with other comorbidities are a demographic category most at risk of critical illness and mortality due to COVID-19. Even between the 18- and 40-year age cohort, patients at the older end of the age spectrum are at higher risk of adverse outcomes. Across the world, people within these high-risk categories should be strongly encouraged to get vaccinated.

ACKNOWLEDGMENTS

We want to acknowledge Donna L. Armaignac, PhD (Baptist Health South Florida, FL), Michael Baram, MD (Thomas Jefferson University Hospital, Philadelphia, PA), Juan Pablo Domecq Garces, MD (Mayo Clinic, Rochester, MN), Surapaneni Krishna Mohan, PhD, MHPE (Panimalar Medical College Hospital and Research Institute, Chennai, India), and Amy B. Christie, MD (Medical Center Navicent Health, Macon, GA) for their contribution to the Viral Infection and Respiratory Illness Universal Study registry.

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Supported, in part, by the Gordon and Betty Moore Foundation and Janssen Research & Development, LLC.

Dr. Kumar is currently funded by funding the Gordon and Betty Moore Foundation, Centers for Disease Control and Prevention Foundation through the University of Washington, and Janssen Research & Development, LLC. Dr. Khanna is currently funded by a Clinical and Translational Science Institute National Institutes of Health (NIH)/National Center for Advancing Translational Science KL2 TR001421 award for a trial on continuous postoperative hemodynamic and saturation monitoring and is a site principal investigator (PI) (institutional funding) for a randomized trial of cytokine filtration in severe coronavirus disease 2019 (COVID-19) and a prospective observational trial of blood volume assessment and capillary permeability in COVID-19. He is funded for his position on the steering committee for the SILtuximab in Viral Acute Respiratory distress syndrome study. His institution also received funding for the Society of Critical Care Medicine (SCCM) Viral Infection and Respiratory Illness Universal Study (VIRUS) Electronic Medical Records (EMR) automation pilot. Dr. Bhalala is currently funded by the NIH (Site-PI for Stress Hydrocortisone in Pediatric Septic Shock–R01HD096901), The Children's Hospital of Philadelphia (Site PI for Pediatric Resuscitation Quality Collaborative), Voelcker Pilot Grant (PI for the project on Prearrest Electrocardiographic Changes), The Children's Hospital of San Antonio Endowed Chair Funds for ancillary projects related to SCCM VIRUS (COVID-19) Registry, and SCCM VIRUS EMR automation pilot. Dr. Kashyap receives funding from the NIH/National Heart, Lung and Blood Institute: R01HL 130881, UG3/UH3HL 141722; Gordon and Betty Moore Foundation and Janssen Research & Development, LLC; and royalties from Ambient Clinical Analytics. Inc. Dr. Gajic receives funding from the Agency of Healthcare Research and Quality R18HS 26609-2, NIH/National Heart, Lung and Blood Institute: R01HL 130881, UG3/UH3HL 141722; Department of Defense DOD W81XWH; American Heart Association Rapid Response Grant–COVID-19; and royalties from Ambient Clinical Analytics. Inc. Dr. Walkey currently receives funding from the NIH/National Heart, Lung and Blood Institute grants R01HL151607, R01HL139751, R01HL136660, Agency of Healthcare Research and Quality, R01HS026485, Boston Biomedical Innovation Center/NIH/NHLBI 5U54HL119145-07, and royalties from UpToDate. The remaining authors have disclosed that they do not have any conflicts of interest.

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Collaborative coauthors of the initiative are listed in the **Appendix** *(http://links.lww.com/CCX/A753).*

ClinicalTrials.gov identifier: NCT04323787.

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