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Sex-related differences in mortality, acute kidney injury, and respiratory failure among critically ill patients with COVID-19

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Abstract

Although the number of deaths due to coronavirus disease 2019 (COVID-19) is higher in men than women, prior studies have provided limited sex-stratified clinical data.

We evaluated sex-related differences in clinical outcomes among critically ill adults with COVID-19.

Multicenter cohort study of adults with laboratory-confirmed COVID-19 admitted to intensive care units at 67 U.S. hospitals from March 4 to May 9, 2020. Multilevel logistic regression was used to evaluate 28-day in-hospital mortality, severe acute kidney injury (AKI requiring kidney replacement therapy), and respiratory failure occurring within 14 days of intensive care unit admission.

A total of 4407 patients were included (median age, 62 years; 2793 [63.4%] men; 1159 [26.3%] non-Hispanic White; 1220 [27.7%] non-Hispanic Black; 994 [22.6%] Hispanic). Compared with women, men were younger (median age, 61 vs 64 years, less likely to be non-Hispanic Black (684 [24.5%] vs 536 [33.2%]), and more likely to smoke (877 [31.4%] vs 422 [26.2%]). During median follow-up of 14 days, 1072 men (38.4%) and 553 women (34.3%) died. Severe AKI occurred in 590 men (21.8%), and 239 women (15.5%), while respiratory failure occurred in 2255 men (80.7%) and 1234 women (76.5%). After adjusting for age, race/ethnicity and clinical variables, compared with women, men had a higher risk of death (OR, 1.50, 95% CI, 1.26–1.77), severe AKI (OR, 1.92; 95% CI 1.57–2.36), and respiratory failure (OR, 1.42; 95% CI, 1.11–1.80).

In this multicenter cohort of critically ill adults with COVID-19, men were more likely to have adverse outcomes compared with women.

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DEL, ACR, SMT-M and JC contributed equally to the work.

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Abbreviations: AKI = acute kidney injury, BMI = body mass index, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease 2019, ICU = intensive care unit, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, STOP-COVID = study of the treatment and outcomes in critically Ill patients with COVID-19.

Keywords: coronavirus disease 2019, mortality, sex

1. Introduction

The prevalence of coronavirus disease 2019 (COVID-19) appears to be similar in men and women, based on sex-disaggregated national statistical data reported by over 70 countries.[1,2] However, men have a higher risk of death and other adverse outcomes compared with women.[3–7] Reasons for these differences are unclear. Proposed mechanisms include higher prevalence of cigarette smoking among men, differential expression of angiotensin-converting enzyme 2 (the receptor for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) between men and women, and sex differences in immune response.[8–11] However, our understanding is limited because prior studies have not provided detailed clinical characteristics stratified by sex. Recognizing the importance of observed sex differences in COVID-19 outcomes, the European Association of Science Editors and other organizations urged all involved in collecting COVID-19 data to include sex data.[2,12,13] This is particularly important because sex, along with other key variables, can influence disease progression as well as access to health care services.[14] To examine factors that may play a role in sex differences in outcomes, we evaluated mortality, severe acute kidney injury (AKI), and respiratory failure in men versus women enrolled in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID).

2. Methods

2.1. Study design and patient population

Details regarding the design and methods of STOP-COVID have been previously published.[15] The study enrolled consecutive adults (≥18 years old) with laboratory-confirmed COVID-19 (detected by nasopharyngeal or oropharyngeal swab) admitted to an intensive care unit (ICU) at 67 participating hospitals in the US (Supplemental Digital Content Table 1, http://links.lww.com/MD/G621). The study was approved by the Institutional Review Board (IRB) of the STOP-COVID Coordinating Center (Mass General Brigham IRB), as well as the IRB of each of the 67 participating institutions with a waiver of informed consent. The current study included patients admitted to the ICU between March 4 and May 9, 2020, and followed patients until hospital discharge, death, or June 5, 2020, whichever came first.

2.2. Data collection

Study personnel at each site collected data by manual review of electronic medical records using a standardized case report form[15] to enter data into REDCap (Research Electronic Data Capture), a secure online data collection tool.[16] Patient-level data included baseline demographics (sex [men or women], race and ethnicity), coexisting medical conditions (including diabetes mellitus, hypertension, chronic obstructive pulmonary disease [COPD], asthma, chronic kidney disease), symptoms and medications prior to hospital admission, and vital signs on ICU admission. The definition of baseline characteristics, comorbidities, treatments and outcomes is presented in Supplemental Digital Content Table 2, http://links.lww.com/MD/G621. In addition, daily data for the 14 days following ICU admission were collected on physiologic and laboratory values, pharmacologic and non-pharmacologic treatments, and organ support.

2.3. Outcomes

The primary outcome was mortality within 28 days of ICU admission. Patients who were discharged from the hospital prior to 28 days were considered to be alive (we tested the validity of this assumption in a subset of patients, described elsewhere).[15] Secondary outcomes were severe AKI and respiratory failure occurring within 14 days of ICU admission. Respiratory failure was defined as requirement for invasive mechanical ventilation (delivered via endotracheal or tracheal tube). Severe AKI was defined as new requirement for kidney replacement therapy.[17]

2.4. Statistical analysis

Baseline characteristics stratified by sex (men and women) are summarized as mean or median (IQR) for continuous variables, and frequency (proportion) for categorical variables. Chi-squared test was used to compare categorical variables, and *t*-test or Wilcoxon rank sum test to compare continuous variables. To evaluate the association between sex (men vs women) and death, we performed a sequential modeling procedure using multilevel logistic regression with hospital as a random effect (to account for inter-hospital variation), and sex, as well as all other covariates as fixed effects. Covariates were chosen based on prior studies.[5–7,18] The base model contained only the exposure (sex, women or men). Model 2 additionally adjusted for age and race/ethnicity; model 3 added obesity (body mass index [BMI] ≥30 kg/m^2), smoking, hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, congestive heart failure, COPD, and duration of symptoms prior to ICU admission; model 4 added baseline (at the time of ICU admission) measurements of D-dimer, ratio of the partial pressure of arterial oxygen over the fraction of inspired oxygen, lymphocyte count, the renal component of the sequential organ failure assessment score, and number of pre-COVID-19 ICU beds; model 5 added angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, nonsteroidal anti-inflammatory drug, aspirin, and vitamin D use prior to hospital admission. We performed similar analyses for the secondary outcomes, severe AKI and respiratory failure. In analyses where AKI was the outcome, we excluded 156 patients (3.5%) with a history of end-stage kidney disease (85 men [3.0%] and 71 [4.4%] women). In addition, for the primary outcome, we conducted pre-specified stratified analyses by age (<60 or ≥ 60 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Other or unknown), hypertension, diabetes mellitus, and obesity. Formal test for interaction was performed by including an interaction term between sex and the potential effect modifier in the final regression model. As a sensitivity analysis, given that death is a competing risk for AKI, we examined the composite end point of severe AKI or death within 14 days following ICU admission.[19] Missing data were not imputed. Instead, we created a separate missing category for each covariate that had missing data (Table 1), since data may not have

Table 1

Characteristics of adults with coronavirus disease 2019 admitted to the intensive care unit.

Characteristic	Patients, No. (%) or median (IQR)		
	All (N = 4407)	Men (n = 2793)	Women (n = 1614)
Demographics			
Age, yr	62 (52–71)	61 (51–70)	64 (54–72)[a]
Race/ethnicity			
Non-hispanic White	1159 (26.3)	773 (27.7)	386 (23.9)[a]
Non-hispanic Black	1220 (27.7)	684 (24.5)	536 (33.2)
Hispanic	994 (22.6)	689 (24.7)	305 (18.9)
Asian/Other race/ethnicity	288 (6.5)	189 (6.8)	99 (6.1)
Unknown	746 (16.9)	458 (16.4)	288 (17.8)
Current or former smoker	1299 (29.5)	877 (31.4)	422 (26.2)
Body mass index, kg/m^2			
<30	1998 (45.3)	1391 (49.8)	607 (37.6)[a]
≥30	2199 (49.9)	1267 (45.4)	932 (57.7)
Missing	210 (4.8)	135 (4.8)	75 (4.7)
Symptoms			
Cough	3214 (72.9)	2048 (73.3)	1166 (72.2)
Sputum production	459 (10.4)	293 (10.5)	166 (10.3)
Sore throat	343 (7.8)	216 (7.7)	127 (7.9)
Nasal congestion	257 (5.8)	159 (5.7)	98 (6.1)
Headache	390 (8.9)	234 (8.4)	156 (9.7)
Fever	2958 (67.1)	1924 (68.9)	1034 (64.1)[a]
Chills	843 (19.1)	548 (19.6)	295 (18.3)
Fatigue or malaise	1406 (31.9)	877 (31.4)	529 (32.8)
Dyspnea	3290 (74.7)	2092 (74.9)	1198 (74.2)
Nausea or vomiting	698 (15.8)	386 (13.8)	312 (19.3)[a]
Diarrhea	898 (20.4)	549 (19.7)	349 (21.6)
Myalgia or arthralgia	954 (21.7)	622 (22.3)	332 (20.6)
Symptom duration prior to ICU admission	7.87 (5.8)	8.12 (5.9)	7.43 (5.70)
Comorbidities			
Diabetes	1822 (41.3)	1079 (38.6)	743 (46.0)[a]
Hypertension	2711 (61.5)	1660 (59.4)	1051 (65.1)[a]
Chronic obstructive pulmonary disease	373 (8.5)	214 (7.7)	159 (9.9)[a]
Asthma	466 (10.6)	196 (7.0)	270 (16.7)[a]
Coronary artery disease	589 (13.4)	400 (14.3)	189 (11.7)[a]
Congestive heart failure	433 (9.8)	247 (8.8)	186 (11.5)[a]
Chronic kidney disease	569 (12.9)	352 (12.6)	217 (13.4)
End-stage kidney disease	156 (3.5)	85 (3.0)	71 (4.4)[a]
Active malignancy	201 (4.6)	132 (4.7)	69 (4.3)
Home medications			
Angiotensin-converting enzyme inhibitor	804 (18.2)	537 (19.2)	267 (16.5)[a]
Angiotensin receptor blocker	671 (15.2)	394 (14.1)	277 (17.2)[a]
Non-steroidal anti-inflammatory drug	358 (8.1)	200 (7.2)	158 (9.8)[a]
Aspirin	984 (22.3)	656 (23.5)	328 (20.3)[a]
Vitamin D	474 (10.8)	248 (8.9)	226 (14.0)[a]
Vital signs on the day of ICU admission			
Temperature, °C	37.9 (37.2–38.8)	38.1 (37.2–38.9)	37.8 (37.2–38.6)
Systolic blood pressure, mm Hg	97 (85–110)	97 (85–111)	96 (85–110)
Heart rate, /min	105 (91–120)	105 (91–120)	103 (90–119)
Laboratory findings on the day of ICU admission[b]			
White blood cell count, k/μL	8.4 (6.0–11.8)	8.6 (6.0–11.9)	8.2 (5.9–11.6)
Lymphocyte count, /μL			
< 1000	2311 (52.4)	1547 (55.4)	764 (47.3)
≥ 1000	1263 (28.7)	728 (26.1)	535 (33.2)
Missing	833 (18.9)	518 (18.6)	315 (19.52)
Hemoglobin level, g/Dl	12.6 (11.1–14.0)	13.1 (11.6–14.4)	11.80 (10.3–13.0)
Serum Creatinine, mg/Dl	1.07 (0.80–1.66)	1.14 (0.88–1.74)	0.90 (0.70,1.43)
D-dimer, ng/Ml			
<1000	965 (21.9)	608 (21.8)	357 (22.1)
1000-2500	700 (15.9)	432 (15.5)	268 (16.6)
>2500	719 (16.3)	482 (17.3)	237 (14.7)
Missing	2023 (45.9)	1271 (45.5)	752 (46.6)
C-reactive protein, mg/L	152 (83–236)	157 (87–239)	144.0 (81–224)

(*continued*)

Table 1
(continued).

Characteristic	Patients, No. (%) or median (IQR)		
	All (N = 4407)	Men (n = 2793)	Women (n = 1614)
Medications and supportive treatment for COVID-19			
Remdesivir	278 (6.3)	160 (5.7)	118 (7.3)[a]
Corticosteroids	1666 (37.8)	1039 (37.2)	627 (38.9)
Tocilizumab	788 (17.9)	551 (19.7)	237 (14.7)[a]
Convalescent plasma	134 (3.0)	94 (3.4)	40 (2.5)
Anticoagulation	2011 (45.9)	1328 (47.8)	683 (42.6)[a]
Enrolled in a clinical trial	728 (16.6)	478 (17.2)	250 (15.6)
Severity of illness on the day of ICU admission			
Invasive mechanical ventilation	2757 (62.8)	1782 (64.1)	975 (60.7)
FiO_2	80 (60–100)	80 (60–100)	80 (60–100)
PEEP, cm H_2O	12 (10–15)	12 (10–15)	12 (10–15)
Non-invasive mechanical ventilation	106 (2.4)	62 (2.2)	44 (2.7)
High-flow nasal cannula or nonrebreather mask	978 (22.3)	589 (21.2)	389 (24.2)
PaO_2:FiO_2, mm Hg			
Not mechanically ventilated	1630 (37)	999 (36)	631 (39)
>200	528 (120)	339 (12.1)	189 (11.7)
100-199	938 (21.3)	608 (21.8)	330 (20.5)
<100	814 (18.5)	536 (19.2)	278 (17.2)
Missing	497 (11.3)	311 (11.1)	186 (11.5)
Vasopressor use	1803 (62.4)	1166 (63.5)	637 (60.6)
Hospital size (pre-COVID ICU beds)			
Small (<50)	1520 (34.5)	958 (34.3)	562 (34.8)
Medium (50–99)	1256 (28.5)	805 (28.8)	451 (27.9)
Large (≥100)	1631 (37.0)	1030 (36.9)	601 (37.2)

[a] $P < .05$.

[b] Data regarding hemoglobin level were missing for 251 patients (5.7%); serum creatinine for 216 (4.9%), C-reactive protein for 1650 (37.4%); anticoagulation, 29 (0.7%); and enrollment in a clinical trial, 26 (0.6%).

ICU = intensive care unit, IQR = interquartile range, 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.

been missing at random.[17,20] As a sensitivity analysis, we conducted Cox proportional hazards regression analysis to evaluate the association between ethnicity and the primary outcome. All tests were 2-sided, and $P < .05$ was considered statistically significant for hypothesis testing. Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics by sex

STOP-COVID enrolled 4407 participants (2793 [63%] men and 1614 [37%] women) from 67 US medical centers. Baseline characteristics, overall and stratified by sex, are shown in Table 1. The median [IQR] age was 62 [52–71] years, 1159 patients (26.3%) were non-Hispanic White, 1220 (27.7%) non-Hispanic Black, 994 (22.6%) Hispanic, and 288 (6.5%) were Asian or of another race/ethnicity. Compared with women, men were more likely to be younger (median [IQR] age 61 [51–70] vs 64 [54–72] years), Hispanic (689 [24.7%] vs 305 [18.9%]) or non-Hispanic White (773 [27.7%] vs 386 [23.9%]), and less likely to be non-Hispanic Black (684 [24.5%] vs 536 [33.2%]). Men were more likely to be current or former smokers than women (877 [31.4%] vs 422 [26.2%]). The presence of COVID-19 symptoms was similar in men and women except for fever, which was more common in men (1924 [69%] vs 1034 [64%]), and nausea or vomiting, which were less prevalent among men (386 [13.8%] vs 312 [19%]). Compared with women, men were less likely to have BMI ≥30 kg/m^2 (1267 [45.4%] vs. 932 [57.7%]). The prevalence of most major comorbid conditions was lower in men than women (Table 1). There were also sex differences in renin-angiotensin system blocker use prior to hospital admission: men were more likely to use angiotensin-converting enzyme inhibitor I (537 [19.2%] vs 267 [16.5%]), and were less likely to use angiotensin II receptor blocker (394 [14.1%] vs 277 [17.2%]). Laboratory findings, critical care parameters and treatment received are presented in Table 1.

3.2. Primary outcome

During a median (IQR) follow-up of 14 (7–24) days, 1072 men (38.4%) and 553 women (34.3%) died (Table 2). In both men and women, the most common causes of death were respiratory failure and septic shock. Death rates were higher in men than women across most subgroups based on age, race/ethnicity, comorbid conditions, BMI, and disease severity (ratio of PaO_2 over the fraction of inspired oxygen and number of vasopressor medications used) (Fig. 1). The sex difference in death rates was less pronounced among non-Hispanic Black patients (men, 37.3% vs women, 36.2%) due to higher death rates in non-Hispanic Black women (36.2%) compared with non-Hispanic white women (32.2%), and Hispanic women (28.9%) (Fig. 1). In models adjusted for age and race/ethnicity (Model 2), men had a 39% higher risk of death (odds ratio [OR], 1.39; 95% confidence

Table 2

Clinical outcomes by sex[a].

Outcome	Patients, No. (%)		
	All (N = 4407)	Men (n = 2793)	Women (n = 1614)
Died within 28 d	1625 (36.9)	1072 (38.4)	553 (34.3)
Causes of death[b]			
Respiratory failure	1605 (98.8)	1052 (98.1)	553 (100)
Heart failure	181 (11.1)	122 (11.5)	59 (10.7)
Septic shock	710 (43.7)	477 (44.5)	233 (42.1)
Kidney failure	619 (38.1)	436 (40.7)	183 (33.1)
Liver failure	83 (5.1)	51 (4.8)	32 (5.8)
Other	252 (15.5)	178 (16.6)	74 (13.4)
Severe acute kidney injury[c]	829 (19.5)	590 (21.8)	239 (15.5)
Length of kidney replacement therapy d, median (IQR)	6 (3–10)	6 (3–10)	7 (3–11)
Respiratory failure	3489 (79.2)	2255 (80.7)	1234 (76.5)
Length of mechanical ventilation d, median (IQR)	11 (6–14)	11 (6–14)	11 (6–14)

IQR = interquartile range.

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

[b] Defined as per medical record review. Patients could have had more than one cause of death.

[c] Patients with end-stage kidney disease (n = 156) were excluded from the denominator for analyses of acute kidney injury.

interval [CI], 1.21–1.61) compared with women (Fig. 2). This association remained significant and was actually strengthened after adjusting for comorbidities, laboratory values, severity of illness, hospital size and medications (Model 5, OR, 1.50; 95% CI, 1.26–1.77). Similar results were observed in analyses stratified by age, race/ethnicity, hypertension, diabetes, and obesity (Fig. 3). We found evidence of interaction between sex and race/ethnicity ($P = .004$). In stratified analysis, there was higher mortality risk among non-Hispanic Black males compared with non-Hispanic Black women, but it was attenuated compared with other racial/ethnic groups. The number of patients in other racial/ethnic groups was too small to conduct stratified analyses. Cox proportional regression analyses yielded similar results (multivariable-adjusted HR 1.20, 95% CI 1.07–1.36).

3.3. Secondary outcomes

During the initial 14 days after ICU admission, 829 patients (19.5%) developed severe AKI (590 men [21.8%] and 239 women [15.5%]), while 3489 patients (79.2%) developed respiratory failure (2255 men [80.7%] and 1234 women [76.5%]) (Table 2). In multivariable analyses, men were at higher risk of developing severe AKI (OR, 1.92; 95% CI 1.57–2.36) and respiratory failure (OR, 1.42; 95% CI, 1.11–1.80) (Fig. 2). Similar results were observed when the composite outcome of severe AKI or 14-day mortality was examined (OR, 1.65; 95% CI, 1.40–1.94).

4. Discussion

This study examined sex-related differences in sociodemographic characteristics and clinical outcomes in a large, multicenter US cohort of critically ill adult men women with COVID-19. Despite being younger and having a lower burden of comorbidities compared with women, men were at significantly higher risk of death, respiratory failure and severe acute kidney injury. These findings remained robust despite extensive adjustment for age, race/ethnicity and clinical variables. Notably, the higher risk of adverse outcomes observed in men compared with women was consistent among patients with and without diabetes, hypertension or obesity.

The underlying reasons for sex-related differences in COVID-19 outcomes observed in this study population are not well understood, but are likely due to multiple factors. Although the true prevalence of COVID-19 is not known, based on national statistical data, the number of cases among men and women appears to be similar.[1,2] Therefore, worse outcomes among men might reflect underlying sex differences in biological factors or exposures that might increase the risk of severe illness. In this cohort, compared with women, men were more likely to smoke cigarettes which is a risk factor for severe COVID-19.[21] In contrast, they were younger and less likely to have a diagnosis of major comorbidities such as obesity, diabetes, hypertension, COPD, asthma and heart failure. This is likely the reason for the negative confounding observed in regression analyses, given that older age and the presence of comorbid conditions have been associated with worse COVID-19 related outcomes.[22] In addition, it is possible that compared with women, men included in our study had less adequate control of hypertension, diabetes and other cardiovascular risk factors, as has been observed in general population studies;[23,24] unfortunately, data regarding the severity and control of these conditions was not available in our study. While we were unable to confirm occupational hazards, a prior study suggested that men are more likely to hold jobs associated with increased risk of viral load exposure such as food processing, transportation and delivery.[25] It is also possible that immune system differences may contribute to the sex-related discrepancies in COVID-19 outcomes.[26] A recent study focused on patients with moderate disease reported that men had higher plasma levels of innate immune cytokines such as IL-8 and IL-18, whereas women mounted a more robust T cell activation,[11] suggesting the need to evaluate sex-based treatment approaches to the management of COVID-19. Another study focused on patients with severe COVID-19 pneumonia found that men were more likely than women to have neutralizing auto-antibodies to type I interferons, which are known to impede the ability of type I interferons to block SARS-CoV-2 infection.[27] These findings

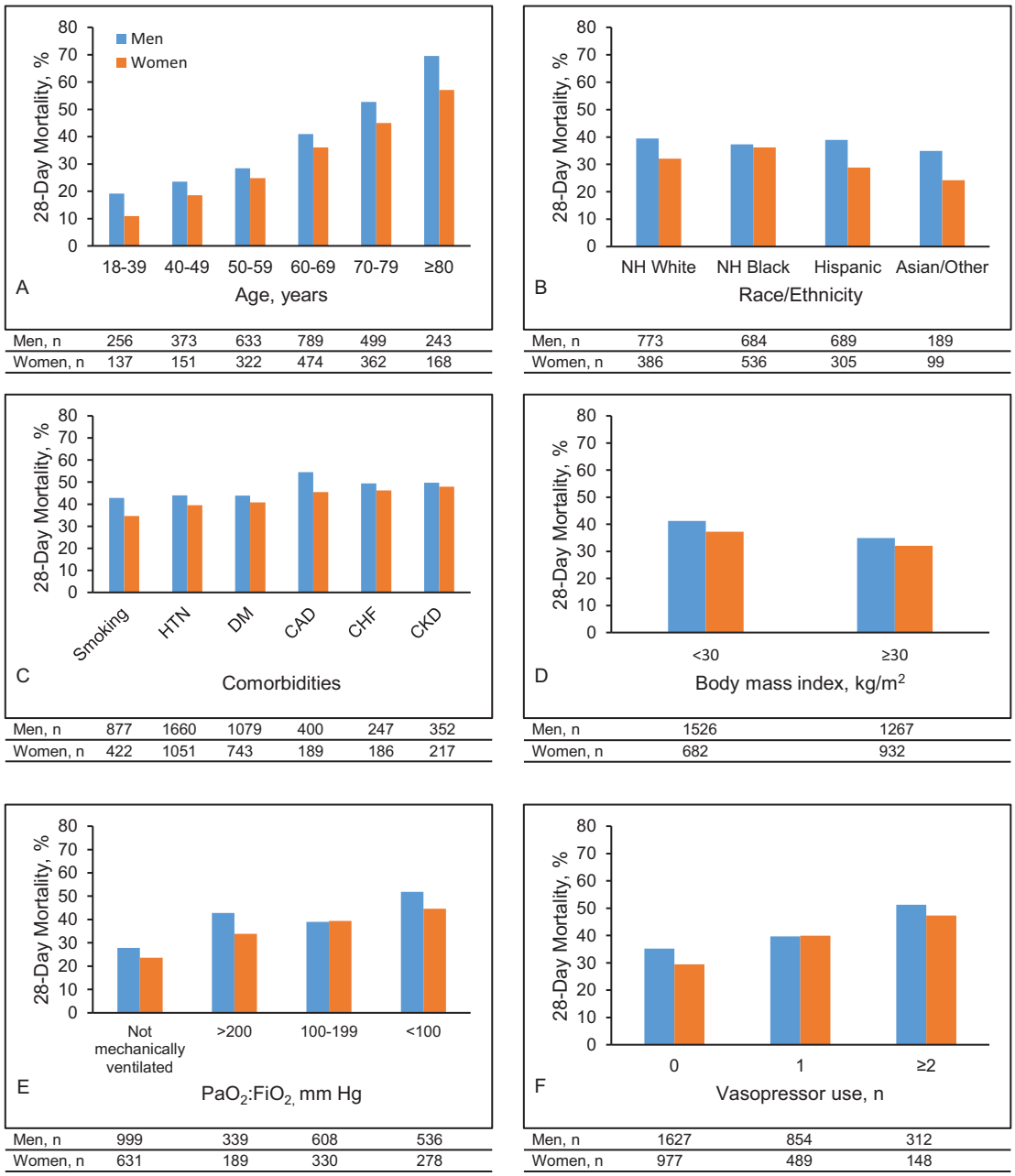
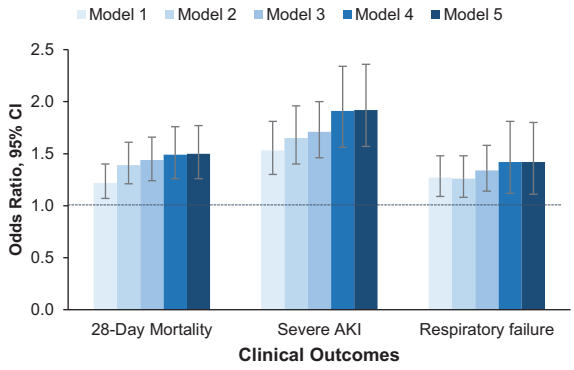


Figure 1. Mortality by sex and pre-specified subgroups. Twenty-eight-day mortality by sex and (A) age group, (B) race/ethnicity, (C) comorbities, (D) body mass index, (E) PaO_2:FIO_2, and (F) vasopressor use. CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, DM = diabetes, HTN = hypertension, PaO_2:FIO_2 = ratio of PaO_2 over the fraction of inspired oxygen (assessed only in patients receiving invasive mechanical ventilation).

support the notion that men and women have inherent differences in their immunologic response to COVID-19 infection that may increase their risk for severe disease in a sex-dependent manner.

Our findings are consistent with prior studies reporting higher risk of death among men.[3,5,6,28,29] In a cohort study of over 17 million individuals in England, the risk of death among men was 1.6 higher than women.[6] In contrast, in a US integrated-delivery health system study of over 1300 patients hospitalized for COVID-19, the difference in mortality risk between men and women was explained by indicators of baseline vital signs and laboratory measures.[7] These heterogeneous findings could be due to differences in the populations studied as well as the severity of COVID-19 illness, with our study focusing on patients admitted to intensive care units.

Although evidence suggest that Blacks are disproportionately affected by COVID-19,[7,30,31] there has been limited exploration of sex differences in outcomes among Blacks. In a recent study of 3481 patients with COVID-19, Black race was associated with increased risk for hospitalization but not mortality.[7] However, these analyses were not stratified by sex. We found that among Blacks, the risk of death was higher in men vs. women, but this difference is attenuated compared with other racial/ethnic groups. Furthermore, we found higher rates of death among



Model 1	1.22 (1.07-1.40)	1.53 (1.30-1.81)	1.27 (1.09-1.48)
Model 2	1.39 (1.21-1.61)	1.65 (1.40-1.96)	1.26 (1.08-1.48)
Model 3	1.44 (1.24-1.66)	1.71 (1.46-2.00)	1.34 (1.14-1.58)
Model 4	1.49 (1.26-1.76)	1.91 (1.56-2.34)	1.42 (1.12-1.81)
Model 5	1.50 (1.26-1.77)	1.92 (1.57-2.36)	1.42 (1.11-1.80)

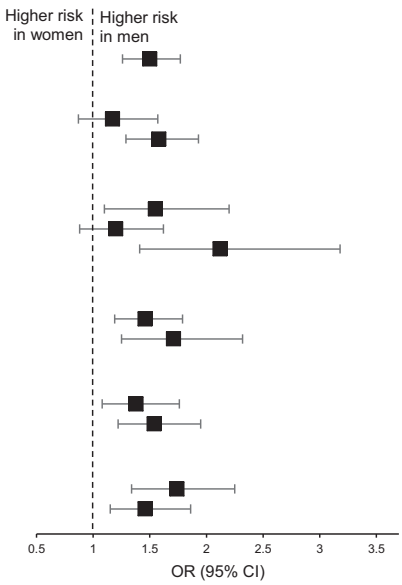
Model 1: Unadjusted
Model 2: Adjusted for age and race/ethnicity
Model 3: Model 2 + obesity, smoking, chronic kidney disease, hypertension, diabetes, coronary artery disease, heart failure, chronic obstructive pulmonary disease and duration of symptoms prior to ICU admission
Model 4: Model 3 + d-dimer, ratio of PaO_2 over the fraction of inspired oxygen, lymphocyte count, renal component of the sequential organ failure assessment score (SOFA) and number of intensive care unit beds
Model 5: Model 4 + medication use prior to hospital admission (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, nonsteroidal anti-inflammatory drug, aspirin and vitamin D)

Figure 2. Multivariable-adjusted risk models. Odds ratio with 95% confidence interval for 28-day mortality, severe acute kidney injury and respiratory failure.

Black women compared to other women, indicating that Black women are at particularly high risk. Future research is needed to better understand reasons for these findings.

In addition to differences in mortality, we observed increased risk of severe acute kidney injury and respiratory failure in men compared with women. Our findings are consistent with a study by Fisher et al, which compared AKI outcomes in patients with and without COVID-19 hospitalized in a large New York City health system. The investigators found that male sex was associated with a higher risk of kidney replacement therapy or death regardless of COVID-19 status.[32] Similarly, a recent meta-analysis of 28 non-COVID-19 population studies reported a two-fold higher risk of severe AKI among men.[33] Based on experimental data, Neugarten et al have proposed that this female reno-protection is mediated by effects of sex hormones on cellular processes which are important in the pathogenesis of AKI.[33–35] Women in our cohort were predominantly in the post-menopausal age range, therefore the protective role of sex hormones may be attenuated. Data regarding sex-differences in respiratory failure in the context of COVID-19 are more scarce. In a retrospective study of 130 adult patients in China, the rate of acute respiratory distress syndrome (ARDS) was similar in men and women.[36] However, in a large study of over 10 thousand patients who tested positive for SARS-CoV-2 in the Veterans Affairs health care system, male sex was associated with an almost 3-fold higher risk of requiring mechanical ventilation.[29] Traditionally, male sex has not been considered an independent risk factor for the development of ARDS in general populations. For example, the Lung Injury Prediction Score Study found no significant association.[37] However, multiple studies have reported higher number of male than female patients with

Source	No. of deaths / No. of patients (%) Men	Women	Adjusted OR (95% CI)	P value for interaction
All patients	1072/2793 (38.4)	553/1614 (34.3)	1.50 (1.26-1.77)	NA
Subgroups				
Age, y				
<60	317/1262 (25.1)	123/610 (20.2)	1.17 (0.87-1.57)	.08
≥60	755/1531 (49.3)	430/1004 (42.8)	1.58 (1.29-1.93)	
Race/ethnicity				
NH White	305/773 (39.5)	124/386 (32.1)	1.55 (1.10-2.20)	.004
NH Black	255/684 (37.3)	194/536 (36.2)	1.20 (0.88-1.62)	
Hispanic	268/689 (38.9)	88/305 (28.9)	2.12 (1.41-3.18)	
Hypertension				
Yes	730/1660 (44.0)	416/1051 (39.6)	1.46 (1.19-1.79)	.55
No	342/1133 (30.2)	137/563 (24.3)	1.71 (1.25-2.32)	
Diabetes				
Yes	473/1079 (43.8)	303/743 (40.8)	1.38 (1.08-1.76)	.09
No	599/1714 (35.0)	250/871 (28.7)	1.54 (1.22-1.95)	
Body mass index, kg/m²				
<30	629/1526 (41.2)	254/682 (37.2)	1.74 (1.34-2.25)	.71
≥30	443/1267 (35.0)	299/932 (32.1)	1.46 (1.15-1.86)	



Odds ratios (OR) greater than one indicate a higher risk of death in men vs. women and are adjusted for the following covariates: age, race/ethnicity, obesity, smoking, hypertension, diabetes, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, duration of symptoms prior to ICU admission, d-dimer, PaO2:FiO2, lymphocyte count, renal component of SOFA score, number of ICU beds, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, nonsteroidal anti-inflammatory drugs, aspirin and vitamin D use prior to hospital admission.

Abbreviations: ICU, intensive care unit; NH, non-Hispanic; PaO2:FIO2, ratio of PaO2 over the fraction of inspired oxygen; SOFA, sequential organ failure assessment.

Figure 3. Mortality in men vs women, overall and by subgroups. Mortality rates and multivariable-adjusted odds ratio with 95% confidence intervals by sex, overall and stratified by age, race/ethnicity, hypertension, diabetes, and body mass index.

ARDS, suggesting an association with other risk factors or comorbidities that are more prevalent in men.[38,39]

Findings from this study should be interpreted in light of its strengths and limitations. Some of its strengths include the comprehensive medical record data collection from a large number of critically ill patients with laboratory-confirmed COVID-19 treated at 67 centers across the US Although in-hospital mortality was ascertained over a period of 28 days, data regarding severe AKI and respiratory failure were only collected for the first 14 days of ICU admission; therefore, the true incidence of these outcomes might have been underestimated. In addition, the study did not include individuals from other countries. Thus, the findings may not be generalizable outside of the US. Lastly, as with all observational studies there may be residual confounding by unmeasured variables. For example, our analyses were not able to account for differences in immune system response or the role of sex hormones.

In this US multicenter cohort of critically ill adults with COVID-19, men were more likely to have adverse outcomes compared with women, even after accounting for the higher burden of chronic disease among women. Future therapeutic studies are needed to focus on sex differences in the immune system response to SARS-CoV-2 and the potential role of sex hormones in outcomes.

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