

ORIGINAL RESEARCH ARTICLE

Association of Body Mass Index and Age With Morbidity and Mortality in Patients Hospitalized With COVID-19

Results From the American Heart Association COVID-19 Cardiovascular Disease Registry

BACKGROUND: Obesity may contribute to adverse outcomes in coronavirus disease 2019 (COVID-19). However, studies of large, broadly generalizable patient populations are lacking, and the effect of body mass index (BMI) on COVID-19 outcomes—particularly in younger adults—remains uncertain.

METHODS: We analyzed data from patients hospitalized with COVID-19 at 88 US hospitals enrolled in the American Heart Association's COVID-19 Cardiovascular Disease Registry with data collection through July 22, 2020. BMI was stratified by World Health Organization obesity class, with normal weight prespecified as the reference group.

RESULTS: Obesity, and, in particular, class III obesity, was overrepresented in the registry in comparison with the US population, with the largest differences among adults ≤ 50 years. Among 7606 patients, in-hospital death or mechanical ventilation occurred in 2109 (27.7%), in-hospital death in 1302 (17.1%), and mechanical ventilation in 1602 (21.1%). After multivariable adjustment, classes I to III obesity were associated with higher risks of in-hospital death or mechanical ventilation (odds ratio, 1.28 [95% CI, 1.09–1.51], 1.57 [1.29–1.91], 1.80 [1.47–2.20], respectively), and class III obesity was associated with a higher risk of in-hospital death (hazard ratio, 1.26 [95% CI, 1.00–1.58]). Overweight and class I to III obese individuals were at higher risk for mechanical ventilation (odds ratio, 1.28 [95% CI, 1.09–1.51], 1.54 [1.29–1.84], 1.88 [1.52–2.32], and 2.08 [1.68–2.58], respectively). Significant BMI by age interactions were seen for all primary end points (P -interaction < 0.05 for each), such that the association of BMI with death or mechanical ventilation was strongest in adults ≤ 50 years, intermediate in adults 51 to 70 years, and weakest in adults > 70 years. Severe obesity (BMI ≥ 40 kg/m²) was associated with an increased risk of in-hospital death only in those ≤ 50 years (hazard ratio, 1.36 [1.01–1.84]). In adjusted analyses, higher BMI was associated with dialysis initiation and with venous thromboembolism but not with major adverse cardiac events.

CONCLUSIONS: Obese patients are more likely to be hospitalized with COVID-19, and are at higher risk of in-hospital death or mechanical ventilation, in particular, if young (age ≤ 50 years). Obese patients are also at higher risk for venous thromboembolism and dialysis. These observations support clear public health messaging and rigorous adherence to COVID-19 prevention strategies in all obese individuals regardless of age.

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Clinical Perspective

What Is New?

- In a large, diverse, and generalizable population, obese individuals were more likely to be hospitalized with coronavirus disease 2019 (COVID-19), and were at an increased risk of the composite of in-hospital death or mechanical ventilation. Severely obese individuals (body mass index ≥ 40 kg/m²) had an increased risk of in-hospital death.
- Significant age by body mass index interactions were observed, and the relative risks of death, and death or mechanical ventilation associated with obesity were accentuated in younger individuals (age ≤ 50 years old).
- Obesity was associated with a stepwise higher risk for in-hospital initiation of renal replacement therapy but not major adverse cardiovascular events.

What Are the Clinical Implications?

- Obese individuals are at higher risk for death or mechanical ventilation if hospitalized with COVID-19, even for young adults.
- These observations support clear public health messaging and rigorous adherence to COVID-19 prevention strategies in obese individuals of all ages.
- Severely obese individuals (body mass index ≥ 40 kg/m²) should be considered high risk for severe COVID-19 infection and may warrant prioritization for a COVID-19 vaccine.

Obesity affects >4 in 10 adults in the United States and contributes to diabetes, heart failure, and cardiovascular disease (CVD) morbidity and mortality.^{1,2} As the coronavirus disease 2019 (COVID-19) pandemic has progressed, preliminary observations, largely from single- or oligo-center studies, suggest that obesity may be an important driver of hospitalization and possibly death in patients with COVID-19.^{1,3-6} The association of obesity with increased risk has been seen with other respiratory viruses, such as influenza.⁷ Obese patients with influenza have a higher risk of hospitalization and death, and a longer length of stay and duration of mechanical ventilation than do patients who have normal weight.^{7,8} Studies of large, diverse, and broadly generalizable patient populations hospitalized with COVID-19 in the United States and Europe are still lacking; and the effect of body mass index (BMI) on cardiovascular, respiratory, and other clinical outcomes in patients with COVID-19 remains uncertain.

At the same time, younger age has been associated with a much lower risk of severe COVID-19 infection.⁹ However, it is not known whether the apparently

protective effect of younger age may extend to obese individuals. Although preliminary observations suggest that young, obese individuals hospitalized with COVID-19 may be at higher risk for adverse outcomes,⁴ the possibility of an interaction between obesity and age has not been fully elucidated. This knowledge gap may have important implications for younger obese individuals and for COVID-19 prevention strategies. We hypothesized that obesity would be associated with worse outcomes in COVID-19, in particular, among younger individuals. To address these questions, we evaluated the relationship between BMI and in-hospital death, mechanical ventilation, adverse cardiovascular, renal, and venous thromboembolic outcomes in patients admitted with COVID-19 in the American Heart Association's (AHA) COVID-19 CVD registry powered by Get With The Guidelines.

METHODS

All data and materials are available through the AHA Precision Medicine Platform (<https://precision.heart.org>) and are available to qualified researchers through a formal research proposal. We obtained patient data from 88 US hospitals in the first data release of the AHA COVID-19 CVD registry through July 22, 2020 (Table 1 and Figure 1 in the Data Supplement). The AHA COVID-19 CVD registry is voluntary, free of charge, and available to all health systems in the United States treating adult patients with active COVID-19. Recruitment of hospitals has been multifaceted and has used direct communications with potential sites, creation of a dedicated website, and outreach to hospitals participating in other Get With The Guidelines registries. Strategic outreach has been undertaken to recruit health systems from across the United States, including both rural and urban areas, to develop a diverse and representative registry. Existing AHA support staff and information technology experts from other Get With The Guidelines registries are used to train and support data abstractors and site principal investigators.

Personnel at participating hospitals are instructed to abstract data from all consecutive patients hospitalized with active COVID-19 infection, regardless of CVD status, and data are entered into an electronic case record form. The registry includes real-time validation rules, at the point of data entry, that flag and prevent saving of a record when the data entered are outside predefined ranges. Input outside these ranges generates an error attached to the specific field, until the data entry is corrected.¹⁰ Detailed demographic and clinical data are collected from the medical record for the duration of the hospital stay, but no outpatient follow-up is performed. Because the registry is designed as a quality improvement tool, with no intervention or participant contact, and collection of only a limited data set, informed consent is not obtained. IQVIA (Parsippany, NJ) serves as the data collection center and the Duke Clinical Research Institute is the data-coordinating center for the registry. The Duke University Institutional Review Board provided approval. Detailed methods of the registry have been previously described.¹⁰ All authors had access to the data and verified the integrity and data analysis.

The study cohort for the present analyses included all adults (≥ 18 years old) with available BMI data and completed field entries for age, sex, admission date, discharge date, discharge disposition, and a medical history (selected as either none or as applicable conditions). Patient records could not be closed until the patient had a discharge disposition, which prevents right censoring of events. The diagnosis of acute COVID-19 infection was defined by polymerase chain reaction testing evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, hospital-specific criteria, or the presence of immunoglobulin M antibodies to COVID-19. The primary exposure of interest was BMI, stratified by World Health Organization (WHO) obesity class, defined as: underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²), and class III obesity (≥ 40.0 kg/m²).² We prespecified the normal weight group (18.5–24.9 kg/m²) as the reference group for all outcomes analyses. We also performed analyses evaluating BMI as a continuous variable. The primary outcomes of interest were the composite of in-hospital death or mechanical ventilation, in-hospital death, and mechanical ventilation. Secondary outcomes included major adverse cardiovascular events (MACE, a composite of in-hospital stroke, heart failure, myocardial infarction, or all-cause death), venous thromboembolism (VTE, a composite of deep vein thrombosis or pulmonary embolism), and renal replacement therapy (RRT, in-hospital initiation of hemodialysis or continuous renal replacement).

Statistical Analysis

Continuous and categorical variables were presented as either median (interquartile range) or number (proportion), respectively. The AHA COVID-19 CVD Registry BMI distribution was compared with sample weight-adjusted aggregate normative data from the National Health and Nutrition Examination Survey sample from 2015 to 2016 and 2017 to 2018. Baseline characteristics and the incidence of clinical outcomes were compared across obesity classes with the Jonckheere-Terpstra trend test. Hazard ratios (HR) and 95% CIs were generated for in-hospital death, VTE, MACE, and initiation of RRT with stratified Cox proportional hazards models by hospital with the robust sandwich estimator for variances to account for the clustering of hospitals. Models evaluating nonfatal outcomes of the initiation of RRT and the composite of deep vein thrombosis or pulmonary embolism accounted for the competing risk of death. Odds ratios and 95% CIs were generated for mechanical ventilation, and the composite of in-hospital death or mechanical ventilation via generalized linear mixed models with a logit link function and binomial distribution with empirical estimates for the variances and random effects for patients clustered within hospitals. Multivariable Cox proportional hazards and logistic regression models were generated for the primary and secondary outcomes, with different baseline hazards and robust variance estimates for each center/site to account for patients clustered within hospitals. For the Cox models, the proportional hazards assumption was verified using Schoenfeld residuals. Covariates for the various models were chosen based on prior review of the literature and clinical judgment, focusing on variables that might be expected to confound the BMI-risk relationship. Models

were initially adjusted for age, sex, and race/ethnicity (model 1), and subsequently additionally adjusted for history of CVD (myocardial infarction, stroke, heart failure, or percutaneous coronary intervention), hypertension, diabetes, and chronic kidney disease (model 2).

To assess the possibility that the association of BMI with outcomes in individuals hospitalized with COVID-19 may differ across age strata, we tested for effect modification between age and BMI on primary outcomes, using multiplicative interaction terms of age \times BMI in all multivariable models. Next, the adjusted association between BMI and primary outcomes was compared across 3 age strata (≤ 50 , 51–70, and > 70 years old). Restricted cubic splines with a reference point at BMI of 25 mg/kg² were generated to visually represent the continuous association of BMI with the primary outcomes of a composite of in-hospital death or mechanical ventilation, in-hospital death, and mechanical ventilation across the 3 age strata. These analyses were adjusted for the variables in model 2. Two-sided *P* values of ≤ 0.05 were considered statistically significant. All analyses were performed with SAS version 9.4 using a deidentified data set housed on the AHA Precision Medicine Platform (<https://precision.heart.org>).¹¹ No imputation was performed for missing data because rates of missingness for all covariates included in the models was $< 1\%$.

RESULTS

Hospital and Patient Characteristics

Characteristics and locations of hospitals contributing data to the first data release of the AHA COVID-19 CVD registry are shown in Table 1 and Figure 1 in the [Data Supplement](#). The hospitals represent 28 US states and are weighted toward larger teaching hospitals in urban locations. Of the 8519 unique patients hospitalized with COVID-19 from the first data release of the AHA COVID-19 CVD Registry, 7606 (89%) had BMI data available for analysis. Patients with missing BMI data were slightly older, more likely to be Hispanic, and less likely to have a history of smoking, or have had a prior percutaneous coronary intervention. However, there were no differences by sex or remaining medical comorbidities ($P > 0.05$ for all; Table II in the [Data Supplement](#)). The study cohort had a median age of 63 years (interquartile range, 49–75) with slight male predominance (55%), and was racially and ethnically diverse with a high prevalence of diabetes and hypertension (Table 1). The proportions of each BMI category in the AHA COVID-19 CVD Registry were: underweight (3%), normal weight (24%), overweight (30%), class I obesity (21%), class II obesity (11%), and class III obesity (11%). In comparison with a weighted population sample from the National Health and Nutrition Examination Survey, hospitalized patients with COVID-19 were more likely to be overweight or obese. Differences were particularly notable among individuals ≤ 50 years old, with class III obesity twice as common among patients hospitalized with COVID-19 than

Table 1. Baseline Characteristics, by Obesity Classes

Characteristics	Obesity class						P value
	Underweight (n=194)	Normal (n=1793)	Overweight (n=2308)	Class I (n=1623)	Class II (n=846)	Class III (n=842)	
COVID-19 polymerase chain reaction positive	188 (97)	1667 (93)	2099 (91)	1491 (92)	768 (91)	778 (93)	0.10
Weight, kg	48 (41–52)	64 (57–70)	78 (71–85)	91 (83–100)	103 (95–113)	127 (113–146)	<0.01
Age, y	77 (62–86)	71 (59–82)	63 (51–75)	59 (47–71)	56 (45–66)	53 (41–63)	<0.01
Male	104 (53.6)	1021 (56.9)	1472 (63.8)	865 (53.3)	394 (46.6)	351 (41.7)	<0.01
Race							
White	81 (41.8)	655 (36.5)	747 (32.4)	477 (29.4)	269 (31.8)	260 (30.9)	<0.01
Black	43 (22.2)	364 (20.3)	453 (19.6)	400 (24.7)	263 (31.1)	328 (40.0)	<0.01
Hispanic	34 (17.5)	462 (25.8)	772 (33.5)	547 (33.7)	243 (28.7)	189 (22.5)	0.36
Asian	22 (11.3)	177 (9.9)	152 (6.6)	48 (3.0)	11 (1.3)	11 (1.3)	<0.01
Comorbidities							
Hypertension	116 (59.8)	1084 (60.5)	1316 (57.0)	961 (59.2)	527 (62.3)	521 (62.9)	0.23
Diabetes	53 (27.3)	609 (34.0)	770 (33.4)	656 (40.4)	357 (42.2)	354 (42.0)	<0.01
Smoking	18 (9.3)	140 (7.8)	153 (6.6)	105 (6.5)	45 (5.3)	49 (5.8)	<0.01
Prior cardiovascular disease*	63 (32.5)	459 (25.6)	440 (19.1)	285 (17.6)	158 (18.7)	160 (19.0)	<0.01
Prior coronary artery bypass surgery	5 (2.6)	71 (4.0)	83 (3.6)	45 (2.8)	24 (2.8)	9 (1.1)	<0.01
History of deep vein thrombosis	9 (4.6)	73 (4.1)	58 (2.5)	44 (2.7)	23 (2.7)	33 (3.9)	0.19
Prior pulmonary embolism	3 (1.6)	37 (2.1)	38 (1.7)	27 (1.7)	13 (1.5)	25 (3.0)	0.52
Dialysis	11 (5.7)	126 (7.0)	88 (3.8)	44 (2.7)	18 (2.1)	18 (2.1)	<0.01
Chronic kidney disease	25 (12.9)	316 (17.6)	281 (12.2)	178 (11.0)	94 (11.1)	78 (9.3)	<0.01
Cancer	27 (13.9)	268 (15.0)	264 (11.4)	151 (9.3)	58 (6.9)	65 (7.7)	<0.01
Asthma	11 (5.7)	123 (6.9)	183 (7.9)	163 (10.0)	112 (13.2)	149 (17.7)	<0.01
Chronic obstructive pulmonary disease	37 (19.1)	177 (9.9)	165 (7.2)	100 (6.2)	76 (9.0)	75 (8.9)	<0.01
Symptomst							
Confusion	43 (22.4)	290 (16.6)	239 (10.6)	134 (8.4)	48 (5.8)	36 (4.4)	<0.01
Fever/chills	85 (44.3)	983 (56.3)	1496 (66.3)	1034 (65.1)	605 (73.1)	556 (68.5)	<0.01
Headache	4 (2.1)	101 (5.8)	223 (9.9)	172 (10.8)	94 (11.4)	102 (12.6)	<0.01
Nausea or vomiting	25 (13.0)	412 (23.6)	614 (27.2)	496 (31.2)	257 (31.0)	277 (34.1)	<0.01
Shortness of breath	85 (44.3)	887 (50.8)	1357 (60.1)	996 (62.7)	574 (69.3)	589 (72.5)	<0.01
Pulmonary infiltrate	131 (67.9)	1258 (71.1)	1669 (73.1)	1223 (76.2)	631 (74.9)	645 (76.9)	<0.01
Admission vital signs							
Oxygenation saturation <94%	50 (27.3)	488 (29.6)	678 (32.0)	506 (34.3)	270 (34.6)	311 (39.8)	<0.01
Temperature	37.0 (36.7–37.8)	37.0 (36.8–37.8)	37.2 (36.8–38.0)	37.2 (36.8–38.0)	37.2 (36.9–38.2)	37.3 (36.9–38.3)	<0.01
Heart rate, beats/min	92 (79–109)	90 (77–104)	93 (80–106)	95 (82–108)	97 (85–110)	98 (86–110)	<0.01
Systolic blood pressure, mmHg	126 (109–148)	127 (113–145)	128 (115–142)	130 (116–144)	130 (115–145)	134 (121–148)	<0.01
Diastolic blood pressure, mmHg	74 (63–83)	73 (65–82)	75 (66–84)	76 (68–85)	78 (68–86)	79 (69–88)	<0.01
Therapies							
Glucocorticoids	32 (17.1)	344 (19.9)	479 (22.2)	347 (22.2)	198 (24.1)	245 (29.7)	<0.01
Remdesivir	7 (3.6)	97 (5.4)	188 (8.2)	175 (10.8)	82 (9.7)	87 (10.4)	<0.01

Baseline values are presented as median (25th–75th percentile) for continuous variables and n (%) for categorical variables. World Health Organization body mass index classes: underweight, <18.5 kg/m²; normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; class I obesity, 30.0–34.9 kg/m²; class II obesity, 35.0–39.9 kg/m²; and class III, obesity ≥40.0 kg/m².

*Cardiovascular disease defined by prior myocardial infarction, stroke, heart failure, or percutaneous coronary intervention.

tn=7424 with reported symptoms available.

individuals from the National Health and Nutrition Examination Survey (Figure 1).

Among patients included in the registry, higher BMI categories were associated with younger age, female sex, and a higher prevalence of Black race and diabetes. Class II and III obese patients in the registry were ≈ 16 and 18 years younger, respectively, than those with normal weight. Conversely, patients in the lower BMI classes had a higher prevalence of chronic kidney disease, current hemodialysis, and CVD (P -trend <0.001 for all). There were no differences in the prevalence of hypertension or prior VTE by obesity class. On presentation to the hospital, patients in higher BMI classes had a higher prevalence of headache, nausea/vomiting, and shortness of breath, and had a higher systolic and diastolic blood pressure (P -trend <0.01 for all). Obese patients were more likely to have pulmonary infiltrates and a low oxygen saturation at admission (P -trend <0.01 for each; Table 1). Remdesivir and glucocorticoids were used more often in obese patients (P -trend <0.01 for each; Table 1).

Primary Outcomes

In-hospital death or mechanical ventilation occurred in 2109 (27.7%) patients, in-hospital death in 1302 (17.1%), and mechanical ventilation in 1602 (21.1%) (Table 2). In the unadjusted model, there was no association of BMI class with the composite of in-hospital death

or mechanical ventilation. However, after adjustment for age, sex, and race/ethnicity in model 1, class I, II, and III obesity were associated with progressively higher risks of in-hospital death or mechanical ventilation in comparison with individuals who had a normal weight ($P<0.01$ for all). After subsequent adjustment for the variables in model 2, class I (odds ratio, 1.28 [95% CI, 1.09–1.51]), class II (1.57 [1.29–1.91]), and class III (1.80 [1.47–2.20]) obesity remained associated with progressively higher risks of in-hospital death or mechanical ventilation in comparison with individuals with a normal weight (Figure 2A).

For the individual components of the composite primary outcome, overweight and class I, II, and III obesity were associated with a lower incidence of in-hospital death in comparison with individuals with normal weight in unadjusted analyses ($P<0.01$ for each). After multivariable adjustment for the variables in model 1, these associations changed, such that class III obesity became significantly associated with a higher risk of in-hospital death (HR, 1.30 [95% CI, 1.03–1.63]). After further adjustment for the variables in model 2, class III obesity remained associated with a higher risk of in-hospital death (HR, 1.26 [95% CI 1.00–1.58]) (Figure 2A). Overweight and obese individuals were at increasingly higher risk for mechanical ventilation with higher obesity class in both unadjusted and adjusted analysis in comparison with individuals who have normal weight (model 2, odds ratio, 1.28 [95% CI, 1.09–1.51] for overweight; 1.54 [1.29–1.84] for class I obesity; 1.88

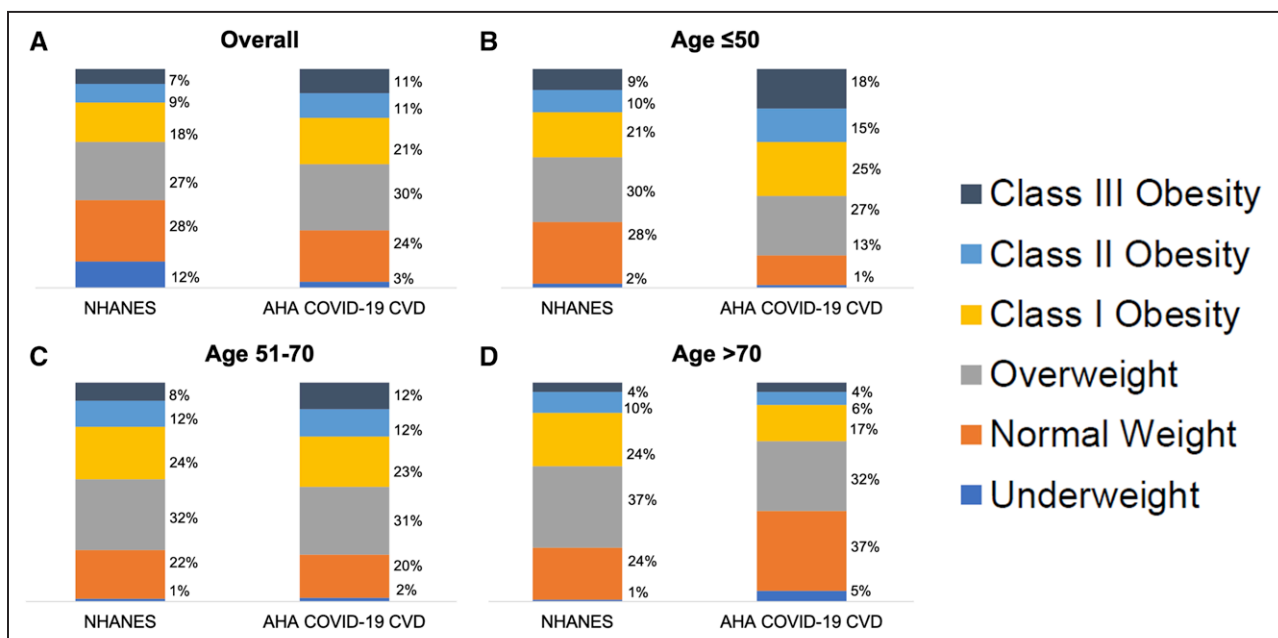


Figure 1. Proportion of individuals hospitalized by COVID-19 by BMI in comparison with NHANES.

A. NHANES sample weighted proportion of US adults 2015 to 2016 and 2017 to 2018 (≥ 18 years old) by BMI in comparison with US adults in the AHA COVID-19 CVD Registry. **B.** Proportion of US adults 18 to 50 years old by BMI from NHANES and the AHA COVID-19 CVD Registry. **C.** Proportion of US adults 51 to 70 years old by BMI from NHANES and the AHA COVID-19 CVD Registry. **D.** Proportion of US adults >70 years old by BMI from NHANES and the AHA COVID-19 CVD Registry. World Health Organization BMI classes: underweight <18.5 kg/m²; normal weight 18.5 to 24.9 kg/m²; overweight 25.0 to 29.9 kg/m²; class I obesity 30.0 to 34.9 kg/m²; class II obesity 35.0 to 39.9 kg/m²; and class III obesity ≥ 40.0 kg/m². AHA COVID-19 CVD indicates American Heart Association COVID-19 Cardiovascular Disease Registry; BMI, body mass index; COVID-19, coronavirus disease 2019; and NHANES, National Health and Nutrition Examination Survey.

Table 2. Unadjusted Clinical Outcomes, by Obesity Classes

Outcomes	Obesity class						P value
	Underweight (n=194)	Normal (n=1793)	Overweight (n=2308)	Class I (n=1623)	Class II (n=846)	Class III (n=842)	
Primary							
Hospital death	53 (27.3)	368 (20.6)	391 (17.0)	237 (14.6)	132 (15.6)	121 (14.4)	<0.01
Mechanical ventilation	30 (15.5)	303 (16.9)	468 (20.3)	364 (22.5)	214 (25.3)	223 (26.5)	<0.01
Death or mechanical ventilation	66 (34.2)	497 (27.8)	618 (26.9)	437 (27.0)	244 (28.8)	247 (29.5)	0.79
Secondary							
Major adverse cardiovascular events*	57 (29.5)	396 (22.2)	418 (18.2)	263 (16.2)	145 (17.2)	133 (15.9)	<0.01
New hemodialysis/continuous renal replacement therapy	3 (1.6)	47 (2.6)	75 (3.3)	67 (4.1)	50 (5.9)	67 (8.0)	<0.01
Deep vein thrombosis	5 (2.6)	32 (1.8)	47 (2.0)	36 (2.2)	28 (3.3)	26 (3.1)	0.01
Pulmonary embolism	1 (0.5)	14 (0.8)	32 (1.4)	28 (1.7)	22 (2.6)	11 (1.3)	<0.01
Deep vein thrombosis/pulmonary embolism	6 (3.1)	44 (2.5)	74 (3.2)	54 (3.3)	46 (5.4)	32 (3.8)	<0.01
Cardiac arrest	10 (5.2)	95 (5.3)	130 (5.7)	92 (5.7)	42 (5.0)	56 (6.7)	0.42
Shock	25 (13.6)	205 (12.0)	279 (12.8)	218 (14.2)	121 (15.0)	118 (14.4)	0.02
Length of stay	6.7 (3.8–11.5)	6.3 (3.6–11.6)	5.8 (3.6–10.8)	5.8 (3.6–10.8)	5.8 (3.7–10.7)	6.6 (3.7–11.8)	0.75
Hospital day of intubation	0 (0–2)	0 (0–3)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	0.52
Duration of mechanical ventilation	6 (1–13)	6 (2–12)	8 (4–15)	8 (4–14)	9 (5–16)	9 (4–13)	<0.01

Values are reported as a number (%) or median (25th–75th percentile). World Health Organization body mass index classes: underweight, <18.5 kg/m²; normal weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; class I obesity, 30.0–34.9 kg/m²; class II obesity, 35.0–39.9 kg/m²; and class III obesity, ≥40.0 kg/m².

*Defined by myocardial infarction, stroke, heart failure, and all-cause death.

[1.52–2.32] for class II obesity; 2.08 [1.68–2.58] for class III obesity) (Figure 2A).

There were no BMI by sex interactions for the composite of in-hospital mortality and mechanical ventilation or the individual components of death and mechanical ventilation (P -interaction>0.05 for each), with similar risk relationships seen across higher BMI classes for women and men. (Tables III through V in the [Data Supplement](#)).

Secondary Outcomes

In the unadjusted models, overweight and obese individuals were at lower risk of MACE (P <0.01 for all); however, in the adjusted models there was no association between obesity classes and MACE (P >0.05 for all) (Figure 2B). Class II obesity was associated with a higher risk of VTE in comparison with individuals who have normal weight in unadjusted analyses (HR, 2.28 [95% CI, 1.48–3.51]), and in model 1 (2.01 [1.30–3.12]) and model 2 (1.91 [1.22–2.98]), as well. Last, obesity was associated with a stepwise higher risk for in-hospital initiation of RRT both in unadjusted analyses and after multivariable adjustment in comparison with individuals who have normal weight (model 2: HR, 1.87 [95% CI, 1.26–2.78] for class I obesity; 2.86 [1.86–4.40] for class II obesity; and 3.86 [2.55–5.85] for class III obesity).

Effect Modification of the Association of BMI with Primary Outcomes by Age

We observed effect modification by age on the associations between BMI and the outcomes of in-hospital death or mechanical ventilation, death, and mechanical ventilation (P -interaction <0.05 for all). We then evaluated the associations between continuous BMI and the primary outcomes by age strata of ≤50 (n =2094), 51 to 70 (n =3012), and >70 years (n =2487) using adjusted cubic splines (Figure 3). Although higher BMI was associated with greater odds for in-hospital death or mechanical ventilation across all age strata, the slope of the odds ratio spline for the composite end point was steeper in those ≤50 years than in the older groups (Figure 3). Moreover, BMI ≥40 was associated with a significantly greater odds of death or mechanical ventilation in those ≤50 years old (odds ratio, 1.64 [95% CI, 1.23–2.21]), and a moderately increased risk in those 51 to 70 years old (1.40 [1.10–1.80]), but no significant increase in risk for those >70 years old (1.28 [0.83–1.95]). The absolute risk for death or mechanical ventilation among patients ≤50 years old with class III obesity was 23.1% in comparison with 12.5% for individuals who have normal weight.

When the individual outcome of in-hospital death was assessed in this manner, the slope of the HR spline

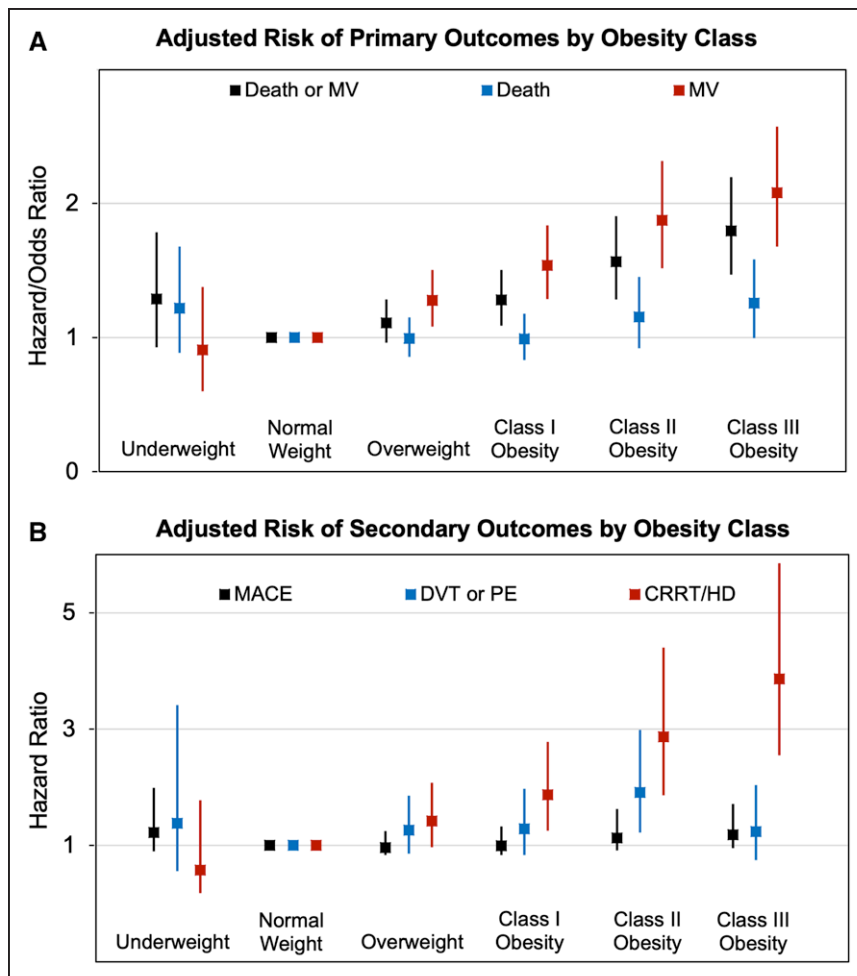


Figure 2. Primary and secondary outcomes by BMI class.

A, Adjusted risk of primary and secondary outcomes by BMI classes with 95% CIs. **B**, Adjusted odds ratio for mechanical ventilation, and death or mechanical ventilation with remainder of outcomes represented as adjusted hazard ratios. Outcomes were adjusted for age, sex, race, hypertension, diabetes, prior stroke, prior myocardial infarction, prior heart failure, chronic kidney disease, and current hemodialysis. Secondary outcomes considered the competing risk of death. BMI indicates body mass index; CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; HD, hemodialysis; MACE, composite of in-hospital myocardial infarction, stroke, all-cause death, and heart failure; MV, mechanical ventilation; and PE, pulmonary embolism.

in the age ≤ 50 group increased sharply after BMI ≥ 40 kg/m², whereas the slope of the hazard among older groups remained relatively flat (Figure 3). BMI ≥ 40 kg/m² was associated with significantly increased risk of in-hospital death in those ≤ 50 years old (HR, 1.36 [1.01–1.84]), but not those 51 to 70 years old (HR, 1.10 [0.82–1.46]) or >70 years old (HR, 1.16 [0.79–1.73]). The crude mortality rate for patients with age ≤ 50 and BMI ≥ 40 kg/m² was 8.3%, versus 3.3% and 5.0% for class I and II obesity (P -trend <0.05 ; Table VI in the [Data Supplement](#)). The odds of mechanical ventilation increased linearly across higher BMIs in all age groups, with similar appearances of the splines (Figure 3).

DISCUSSION

This analysis highlights several key observations regarding the influence of obesity on clinical outcomes for patients hospitalized with COVID-19. First, obesity was overrepresented in this population of hospitalized individuals with COVID-19 in comparison with a contemporary ambulatory population in the United States, in particular, among individuals ≤ 50 years old. Furthermore, patients with more severe obesity hospitalized

with COVID-19 were much younger, and more likely were Black and female than their lower BMI counterparts. Obese patients had higher rates of diabetes and similar rates of hypertension, which is notable given the much younger age of those who were obese. Second, obesity was associated with a higher risk of the composite of in-hospital death or mechanical ventilation and the individual components of this end point, observations that were independent of demographic characteristics and comorbid conditions associated with adverse COVID-19 outcomes. Third, we observed a significant interaction between age and BMI, with the association between higher BMI and death or mechanical ventilation accentuated in younger individuals. Fourth, obese patients also had a higher risk of VTE and a dose-dependent increase in risk for RRT initiation with increasing obesity class. Last, we did not observe higher rates of MACE among more obese individuals.

Obesity has become a well-recognized risk factor for hospitalization and adverse outcomes with COVID-19.^{3,4} Several mechanisms may explain, in part, the overrepresentation of obesity in the AHA COVID-19 CVD Registry and its association with adverse outcomes among those hospitalized with COVID-19. First, obesity

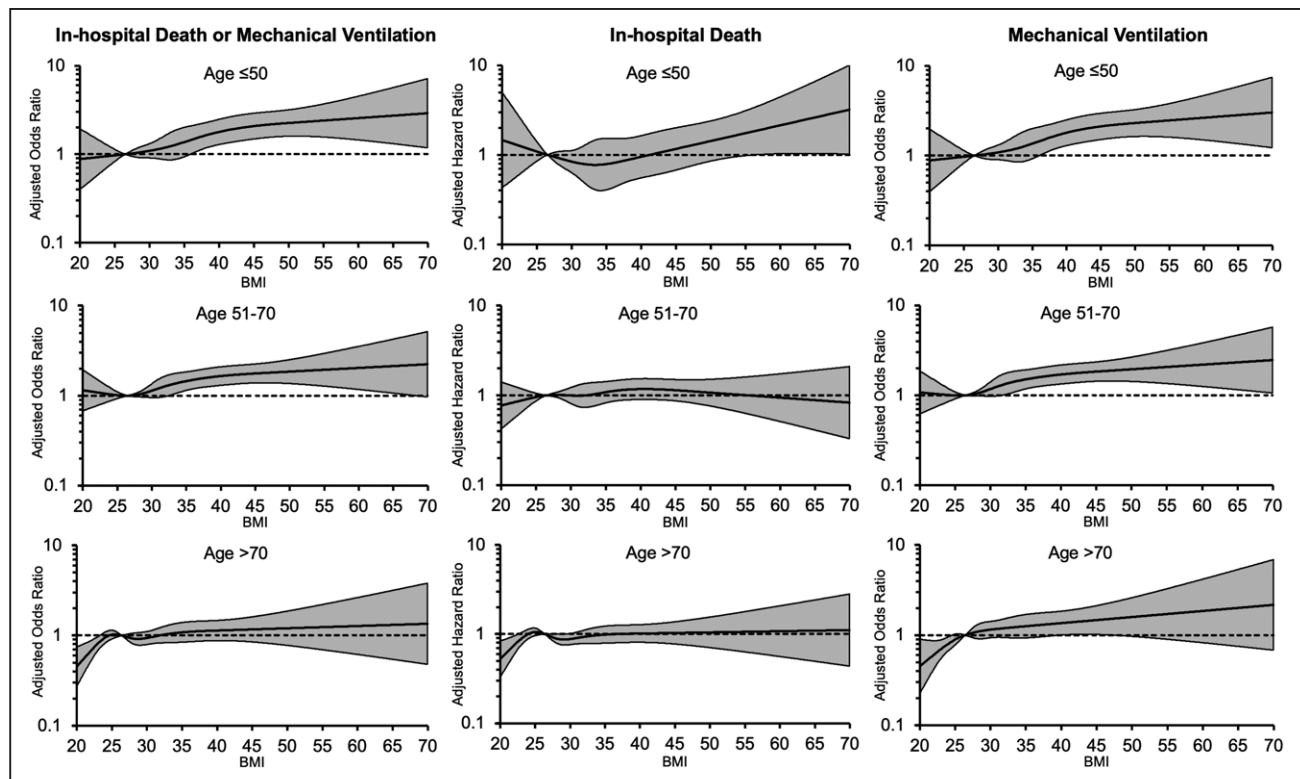


Figure 3. Risk of in-hospital death or mechanical ventilation by age and BMI.

Adjusted odds ratio for in-hospital death or mechanical ventilation (**Left**), adjusted hazard ratio for in-hospital death (**Center**), and adjusted odds ratio for mechanical ventilation (**Right**) by continuous BMI and ages ≤ 50 , 51 to 70, and >70 years. BMI of 25.0 kg/m² serves as the reference. Adjustment variables include age, sex, and race/ethnicity, history of cardiovascular disease (myocardial infarction, stroke, heart failure, or percutaneous coronary intervention), hypertension, diabetes, and chronic kidney disease. BMI indicates body mass index.

is associated with higher prevalence of cardiometabolic diseases such as hypertension and diabetes, which are linked with worse outcomes in COVID-19.^{4,12,13} Although associations of obesity with adverse outcomes remained robust after accounting for these factors, residual contributions related to the duration and severity of these risk factors is possible. Second, SARS-CoV-2, which results in COVID-19, has a high affinity for host cell angiotensin-converting enzyme 2, which is essential for host cell infection.¹⁴ Angiotensin-converting enzyme 2 is highly expressed in adipose tissue, and therefore the presence of excess adipose tissue may exacerbate the severity of infection.^{15,16} Third, obesity may contribute to the severity of COVID-19 disease because of adverse respiratory mechanical factors including decreased pulmonary expiratory reserve volume, functional capacity, and respiratory system compliance. For example, increased thoracic mass may contribute to the need for higher positive end-expiratory and peak pressures to maintain adequate oxygenation in obese versus patients with normal weight.¹⁷ We observed more hypoxemia and higher prevalence of radiographic abnormalities on chest x-ray among obese patients in the registry, and higher rates of remdesivir and corticosteroid use, as well, highlighting greater respiratory disease severity with obesity.

Past studies have observed associations between obesity and death and mechanical ventilation with COVID-19; however, most of these studies used administrative data, which lack granularity, or were limited to one or a few health systems. Cunningham et al¹⁸ recently reported an increased risk of in-hospital death or mechanical ventilation for adults <35 years old with morbid obesity in a claims-based cross-sectional study. Tartof et al⁴ reported stronger associations of BMI with death in COVID-19 among individuals ≤ 60 years old than in older individuals, but their analysis included both outpatients and inpatients and had only 206 total deaths. Our findings, in a large, multicenter, ethnically diverse inpatient cohort, with >1300 death events, has greater power to evaluate age interactions, and extends past observations by demonstrating that excess risk from higher BMI on death is limited mostly to individuals ≤ 50 years old with class III obesity. In contrast, the association of obesity with the use of mechanical ventilation is linear, with a slope that is steeper in younger versus older patients. The reasons why obesity associates more strongly with death and the need for ventilation among younger versus older individuals is not clear. It is plausible that weaker associations of high BMI with mortality in older individuals may reflect

competing risks for death among older nonobese individuals from multimorbidity, frailty, or other factors.

Higher obesity class was associated with a progressively higher risk for the initiation of RRT. This finding may relate to a more severe SARS-CoV-2 infection among obese patients. Although acute kidney injury is common in critically ill patients and often related to shock,¹⁹ the rates of shock did not markedly increase across obesity classes in our study. One potential explanation may be related to the reduced expression of renal angiotensin-converting enzyme 2 in higher-risk obese individuals.^{20,21} However, it is possible that factors aside from adiposity may explain these observations. For instance, unequal allocation of limited resources by age may have biased hemodialysis use preferentially to younger ages.

Several limitations merit comment. First, hospitals that participate in the registry are weighted toward larger urban hospitals affiliated with medical schools and thus may not be fully generalizable to small rural hospitals. Second, clinical events were recorded by study personnel at the local sites and there was no formal adjudication of nonfatal outcomes. Rates of VTE were lower than previously reported in COVID-19, likely reflecting low rates of systematic surveillance for these outcomes in clinical practice.^{22,23} Third, the initial registry data collection form did not include information on advanced directives or code status, and we were not able to discern which patients may have died with a do-not-resuscitate order in place. Although this may have created a differential bias underestimating event rates in the lower BMI classes, the number of these patients may be low given that most patients who died also had mechanical ventilation. Furthermore, the small number of patients in the underweight class may have limited power to detect important observations in this BMI class. Fifth, we are unable to account for temporal trends in the pandemic because of the deidentified nature of our data, which lack date and time designation. However, variation by date or region would, in part, still be addressed by our analysis because it accounts for site-specific clustering of outcomes. Despite these limitations, our study is a robust, large, and diverse multicenter registry with large numbers of documented adverse outcomes.

Our findings have important clinical and public health implications. Although the severity of COVID-19 and probability of hospitalization and death are, in general, manyfold lower in younger than in older individuals,⁹ our findings confirm that the protection from younger age does not extend to class III obese individuals. Moreover, the similar in-hospital rates of cardiac arrest, shock, and MACE, despite the much younger age of obese patients hospitalized with COVID-19, highlights that young age does not protect against the cardiovascular complications of obesity. Current data from the

National Health and Nutrition Examination Survey highlights that >40% of American adults ≤50 years old are obese and 8% have class III obesity.² Such individuals are more likely to be hospitalized, and when hospitalized they are more likely to die, require mechanical ventilation, or require RRT, in comparison with individuals who have normal weight.

In conclusion, patients with high BMI hospitalized with COVID-19, in particular, those with class III obesity, are at significantly higher risk of in-hospital death or mechanical ventilation, VTE, and initiation of RRT. They are at similar adjusted risk for major cardiac events. These obese patients are overrepresented in the hospital in comparison with the general population and are substantially younger than patients with normal weight who are hospitalized with COVID-19. These observations support rigorous adherence to COVID-19 prevention strategies in obese individuals of all ages. Clear public health messaging is needed for younger obese individuals who may underestimate their risk of severe COVID-19.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Figure 1

Data Supplement Tables I–VI

REFERENCES

- Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006;368:666–678. doi: 10.1016/S0140-6736(06)69251-9
- Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief*. 2020;1–8.
- Kalligeros M, Shehadeh F, Mylona EK, Benitez G, Beckwith CG, Chan PA, Mylonakis E. Association of obesity with disease severity among patients with coronavirus disease 2019. *Obesity (Silver Spring)*. 2020;28:1200–1204. doi: 10.1002/oby.22859
- Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, Li Z, Shaw SF, Caparosa SL, Nau CL, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization [published online August 12, 2020]. *Ann Intern Med*. doi: 10.7326/M20-3742. <https://www.acpjournals.org/doi/10.7326/M20-3742>
- Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med*. 2020;382:2372–2374. doi: 10.1056/NEJMc2010419
- Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis*. 2020;71:896–897. doi: 10.1093/cid/ciaa415
- Jain S, Chaves SS. Obesity and influenza. *Clin Infect Dis*. 2011;53:422–424. doi: 10.1093/cid/cir448
- Kwong JC, Campitelli MA, Rosella LC. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada: a cohort study. *Clin Infect Dis*. 2011;53:413–421. doi: 10.1093/cid/cir442
- Centers for Disease Control and Prevention. COVIDView: A Weekly Surveillance Summary of U.S. COVID-19 Activity. 2020. Accessed October 16, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>
- Alger HM, Rutan C, Williams JH 4th, Walchok JG, Bolles M, Hall JL, Bradley SM, Elkind MSV, Rodriguez F, Wang TY, et al. American Heart Association COVID-19 CVD Registry powered by Get With The Guidelines. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006967. doi: 10.1161/CIRCOUTCOMES.120.006967
- Kass-Hout TA, Stevens LM, Hall JL. American Heart Association Precision Medicine Platform. *Circulation*. 2018;137:647–649. doi: 10.1161/CIRCULATIONAHA.117.032041
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
- Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–79. doi: 10.1001/jama.289.1.76
- Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation*. 2020;141:1903–1914. doi: 10.1161/CIRCULATIONAHA.120.047349
- Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev*. 2020;21:e13034. doi: 10.1111/obr.13034
- Al-Benna S. Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. *Obes Med*. 2020;19:100283. doi:10.1016/j.obmed.2020.100283
- Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax*. 2010;65:44–50. doi: 10.1136/thx.2009.117572
- Cunningham JW, Vaduganathan M, Claggett BL, Jering KS, Bhatt AS, Rosenthal N, Solomon SD. Clinical outcomes in young US adults hospitalized with COVID-19 [published online September 9, 2020]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2020.5313. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770542>
- Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015;41:1411–1423. doi: 10.1007/s00134-015-3934-7
- Reich HN, Oudit GY, Penninger JM, Scholey JW, Herzenberg AM. Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease. *Kidney Int*. 2008;74:1610–1616. doi: 10.1038/ki.2008.497
- Lely AT, Hamming I, van Goor H, Navis GJ. Renal ACE2 expression in human kidney disease. *J Pathol*. 2004;204:587–593. doi: 10.1002/path.1670
- Ren B, Yan F, Deng Z, Zhang S, Xiao L, Wu M, Cai L. extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. *Circulation*. 2020;142:181–183. doi: 10.1161/CIRCULATIONAHA.120.047407
- Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. *Circulation*. 2020;142:114–128. doi: 10.1161/CIRCULATIONAHA.120.046702