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Original Article

Increased Body Mass Index and Metabolic Syndrome Are Associated with Poor Outcomes in SARS-CoV-2-Positive Emergency Department Patients

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Background: Increased body mass index (BMI) and metabolic syndrome (MetS) have been associated with adverse outcomes in viral syndromes. We sought to examine associations of increased BMI and MetS on several clinical outcomes in patients tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: The registry of suspected COVID-19 in emergency care (RECOVER) is an observational study of SARS-CoV-2-tested patients (n=27,051) across 155 United States emergency departments (EDs). We used multivariable logistic regression to test for associations of several predictor variables with various clinical outcomes.

Results: We found that a BMI ≥30 kg/m^2 increased odds of SARS-CoV-2 test positivity (odds ratio [OR], 1.30; 95% confidence interval [CI], 1.23–1.38), while MetS reduced odds of testing positive for SARS-CoV-2 (OR, 0.76; 95% CI, 0.71–0.82). Adjusted multivariable analysis found that MetS was significantly associated with the need for admission (OR, 2.11; 95% CI, 1.89–2.37), intensive care unit (ICU) care (OR, 1.58; 95% CI, 1.40–1.78), intubation (OR, 1.46; 95% CI, 1.28–1.66), mortality (OR, 1.29; 95% CI, 1.13–1.48), and venous thromboembolism (OR, 1.51; 95% CI, 1.07–2.13) in SARS-CoV-2-positive patients. Similarly, BMI ≥40 kg/m^2 was significantly associated with ICU care (OR, 1.97; 95% CI, 1.65–2.35), intubation (OR, 2.69; 95% CI, 2.22–3.26), and mortality (OR, 1.50; 95% CI, 1.22–1.84).

Conclusion: In this large nationwide sample of ED patients, we report a significant association of both high BMI and composite MetS with poor outcomes in SARS-CoV-2-positive patients. Findings suggest that composite MetS profile may be a more universal predictor of adverse disease outcomes, while the impact of BMI is more heavily modulated by SARS-CoV-2 status.

Key words: Obesity, Body mass index, Metabolic syndrome, COVID-19, SARS-CoV-2

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an international public health crisis, yet uncertainty remains regarding its evolving epidemiology. Identifying demographic and clinical factors that impart a higher risk of adverse disease outcomes is particularly difficult. Prior literature supports an association between increasing body mass index (BMI) and worsening prognosis of viral infections.[1] For instance, higher mortality rates and more severe clinical course have been observed in different forms of influenza, such as the 2009 H1N1 influenza pandemic.[1] The unfavorable effects of obesity in the course of viral infections

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have previously been attributed to metabolic derangements and chronic inflammation resulting in a blunting of the immune response to viral pathogens.[2] Furthermore, impaired respiratory mechanics, increased airway resistance, and impaired gas exchange in obese patients are presumed to be associated with an increased need for intubation and, resultantly, increased mortality.[1] Anecdotally, early studies on SARS-CoV-2 in China fit into this assessment; an association was noted between increased BMI and the need for mechanical ventilation.[1] Similarly, among SARS-CoV-2-positive patients treated at an academic health center in New York City, BMI ≥ 40 kg/m^2 was a strong predictor of hospitalization with an odds ratio (OR) of 6.2.[1] Reports from a small cohort of SARS-CoV-2-positive patients in France also reported BMI > 35 kg/m^2 to be associated with the need for mechanical ventilation.[1] Additional single-center studies of SARS-CoV-2-positive patients demonstrated that BMI ≥ 35 kg/m^2 was associated with significant risk of invasive mechanical ventilation and hospitalization.[3,4] However, somewhat paradoxically, SARS-CoV-2-positive patients with an elevated BMI have also been noted to have an increased survival rate compared to their normal-weight counterparts.[5] This apparent survival benefit in obese patients has been previously noted in several disease processes, in what has been termed "the obesity paradox." Although this finding remains controversial and in need of higher quality evidence, the proposed protective mechanism of obesity on mortality may represent a distinction between BMI and overall metabolic health.[6-11]

Metabolic syndrome (MetS) is defined as the clustering of the following clinical components: abdominal obesity, impaired glucose metabolism, dyslipidemia, and hypertension. The prevalence of MetS continues to increase, with cross-sectional data from the U.S. National Health and Nutrition Examination Survey 2007–2012 demonstrating a national prevalence of MetS of approximately 34%, an increase from 28% in 1988–1994.[12,13] MetS has been previously hypothesized to play a significant role in determining the severity of respiratory disease and these comorbid conditions likely also play an important role in coronavirus disease 2019 (COVID-19) disease course.[14] SARS-CoV-2 targets organs and tissues that are relevant to metabolic health, and thus associations with certain metabolic diseases have been observed. For example, diabetes or impaired glycemic control is associated with severe COVID-19 and has become an important determinant of COVID-19 severity.[2] Pandemic data have demonstrated that the highest SARS-CoV-2 fatality rates occurred in patients with cardiovascular disease (10.5%) and diabetes mellitus (7.3%), followed by chronic respiratory diseases (6.3%), hypertension (6.0%), and cancer (5.6%).[5] However, as BMI and MetS are often comorbid factors the extent to which increased BMI in the presence or absence of these accompanying comorbid MetS risk factors predisposes individuals to severe disease in SARS-CoV-2 has yet to be determined. The purpose of this study was to examine the association of increased BMI versus a composite MetS profile on several adverse clinical outcomes in a large nationwide sample of emergency department (ED) patients tested for SARS-CoV-2.

METHODS

The registry of suspected COVID-19 in emergency care (RECOVER) is a large observational clinical study of patients from 155 United States EDs across 27 states.[15] Eligible patients included any ED patient with a SARS-COV-2 test at index visit or 14 days prior from March to September 2020. The index visit from which data were abstracted came from the first ED visit that occurred within 14 days of SARS-COV-2 testing, unless meeting specific exclusions.[15] Exclusion criteria included predefined circumstances where the index ED visit lacked a reasonable probability of being related to possible COVID-19 symptoms (e.g., trauma, drug intoxication, poisoning, psychiatric reasons, suspected rape or other domestic violence, involuntary commitment, other isolated chief complaints clearly not related to COVID-19, and testing done purely for policy).[15] SARS-CoV-2-positive disease status required a positive molecular reverse transcription polymerase chain reaction test performed on a nasopharyngeal swab, or positive serum antibody titers for SARS-CoV-2 within 30 days; all others were considered SARS-CoV-2-negative.[15]

Data were collected in REDCap. REDCap is a secure web application for organizing databases that is compliant with 21 CFR Part 11, FISMA, HIPAA and GDPR. It was specifically developed to support data capture for research studies. Outcomes were recorded up to 30 days after index visit. Data abstractors and their site investigators all attended a training session via Zoom to introduce the

manual of operations which described patient eligibility and the goals of the registry with specific instructions on data abstraction and the data dictionary. Trained abstractors used the written manual of operations as they transferred data from the local electronic medical record and directly entered data into REDCap using handheld tablets. Sites were encouraged to contact the overall primary investigator for any questions about patient eligibility or data entry. Additionally, in April 2020 at Indiana University, using a convenience sample of 50 charts, two abstractors, each of whom had experience using REDCap and with 1 hour of training from the site principal investigator, double-coded two REDCap forms for each of the 50 patients and compared results, which indicated 98% concordance in answer with 100% agreement on the venous thromboembolism (VTE) questions. The final RECOVER database is devoid of any protected health information. Funding was derived from unrestricted internal monies from the Department of Emergency Medicine at Indiana University School of Medicine under the direction of the senior principal investigator (JAK).

The protocol for the registry was reviewed by the Indiana University School of Medicine Institutional Review Board (IRB No. 2003886956) who approved the protocol under waiver of authorization for participation in research as well as a waiver for informed consent. All participating sites were also required to and therefore obtained approval from their respective IRBs for waiver of authorization for participation in research as well as a waiver of informed consent. For more information on the development and methodology of the registry please refer to Kline et al.[15] We recorded pertinent demographic and comorbidity data including the following: BMI, age, sex, race, ethnicity, smoking status, and the presence or absence of several medical comorbidities. We then determined whether or not patients met criteria for a composite MetS diagnosis. The presence of MetS was defined as having three or more defining characteristics per the electronic medical record at the time of the index visit; these included an elevated BMI (≥ 30 kg/m^2), hyperlipidemia, diabetes, and hypertension.[16] We also recorded several clinical outcomes of interest including hospital admission, intensive care unit (ICU) care, intubation, mortality, and 30-day new or recurrent VTE.

In the whole sample of patients tested for SARS-Cov-2, we tested the effects of BMI and MetS on the odds of SARS-CoV-2 test positivity, first utilizing an unadjusted model and then adjusted for potential confounders including age, sex, race, ethnicity and smoking. BMI was examined as a categorical variable based on obesity classification—i.e., BMI 18.5 to <25 kg/m^2 (normal), 25 to <30 kg/m^2 (overweight), 30 to <35 kg/m^2 (class I obesity), 35 to <40 kg/m^2 (class II obesity), and ≥ 40 kg/m^2 (class III obesity).[17] BMI analyses included all patients regardless of MetS status. Age was categorized as <25 years, 25 to <40 years, 40 to <65 years, and ≥ 65 years. To better understand which specific components of MetS were primarily driving the association with SARS-CoV-2 test positivity, we then repeated this unadjusted model for each of the following: hypertension, hyperlipidemia, and diabetes mellitus. Next, we utilized multivariable logistic regression to test the independent effect of several predefined predictor variables, including BMI, MetS, age, sex, race, ethnicity, and smoking on the following clinical outcomes of interest: hospital admission, ICU care, intubation, mortality, and 30 day new or recurrent VTE . Adjusted ORs with 95% confidence interval (CI) were calculated for all included variables. Frequencies, unadjusted and adjusted multivariable logistic regression analyses were performed using IBM SPSS version 26 (IBM Corp., Armonk, NY, USA) and independently verified using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

The registry included a total of 27,051 patients of which 14,056 patients (52%) were SARS-CoV-2-positive and 12,995 patients (48%) were SARS-CoV-2 negative. Pertinent demographic data for all patients are included in Table 1. Patients in the SARS-CoV-2-positive group tended to be slightly older (56.4 ± 19.5 years vs. 48.6 ± 20.9 years) with a higher predominance of men (53% vs. 46%) than those in the SARS-CoV-2-negative cohort. SARS-CoV-2-positive patients had a higher prevalence of obesity (BMI ≥ 30 kg/m^2) than SARS-CoV-2-negative patients (42% vs. 39%) but a slightly lower prevalence of composite MetS diagnosis (18% vs. 19%).

In an unadjusted model examining the association between BMI ≥ 30 kg/m^2 and SARS-CoV-2 test positivity in all SARS-CoV-2-tested ED patients, BMI ≥ 30 kg/m^2 was significantly associated with increased odds of a positive test result (OR, 1.13; 95% CI, 1.08–1.20). In contrast, MetS had a trended toward a "protective" association

Table 1. Study characteristics of patients enrolled in the RECOVER registry

Characteristic	SARS-CoV-2 positive	SARS-CoV-2 negative
Total	14,056	12,995
Age (yr)	56.4 ± 19.5	48.6 ± 20.9
< 25	921	1,752
25–40	2,293	2,813
40–65	5,963	5,252
> 65	4,879	3,178
Sex		
Male	7,423 (53)	6,002 (46)
Female	6,633 (47)	6,993 (54)
BMI (kg/m^2)		
< 25	4,108 (29)	4,651 (36)
25 to < 30	3,990 (28)	3,265 (25)
30 to < 35	2,866 (20)	2,315 (18)
35 to < 40	1,571 (11)	1,379 (11)
≥ 40	1,521 (11)	1,385 (11)
Metabolic syndrome		
Yes	2,497 (18)	2,407 (19)
No	11,559 (82)	10,588 (81)

Values are presented as mean ± standard deviation or number (%).
RECOVER, registry of suspected COVID-19 in emergency care; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index.

against SARS-CoV-2 test positivity but this did not reach significance (OR, 0.95; 95% CI, 0.89–1.01). In a multivariable model that included both BMI ≥ 30 kg/m^2 and MetS, BMI was again significantly associated with increased odds of SARS-CoV-2 test positivity (OR, 1.17; 95% CI, 1.11–1.23), while MetS was found to confer significantly reduced odds of test positivity (OR, 0.89; 95% CI, 0.83–0.95). These associations remained after further adjustment with potential confounders, including age, sex, race, ethnicity, and smoking. We then performed similar analyses looking at unadjusted outcomes with the individual MetS components of hyperlipidemia, diabetes mellitus and hypertension. Diabetes mellitus was found to be significantly associated with SARS-CoV-2 test positivity (OR, 1.37; 95% CI, 1.28–1.46). In contrast, hyperlipidemia was associated with significantly reduced odds of test positivity (OR, 0.73; 95% CI, 0.69–0.78), while hypertension trended towards reduced positivity but did not reach significance (OR, 0.95; 95% CI, 0.90–1.01). These associations were also seen with the subsequent adjusted analysis (Table 2).

In a separate unadjusted model, we further examined the association of BMI with SARS-CoV-2 positivity in all ED SARS-CoV-2-tested patients as a categorical variable based on CDC classification.

Table 2. Association of BMI ≥ 30 kg/m^2 and metabolic syndrome with SARS-CoV-2 positivity in emergency department patients tested for SARS-CoV-2

Variable	Unadjusted	Model 1*	Model 2†
BMI ≥ 30 kg/m^2	1.13 (1.08–1.20) (P ≤ 0.001)	1.17 (1.11–1.23) (P ≤ 0.001)	1.30 (1.23–1.38) (P ≤ 0.001)
MetS	0.95 (0.89–1.01) (P = 0.106)	0.89 (0.83–0.95) (P = 0.001)	0.76 (0.71–0.82) (P ≤ 0.001)
HLD	0.73 (0.69–0.78) (P ≤ 0.001)	0.73 (0.69–0.78) (P ≤ 0.001)	0.69 (0.65–0.74) (P ≤ 0.001)
DM	1.37 (1.28–1.46) (P ≤ 0.001)	1.35 (1.26–1.44) (P ≤ 0.001)	1.26 (1.17–1.35) (P ≤ 0.001)
HTN	0.95 (0.90–1.01) (P = 0.103)	0.95 (0.89–1.00) (P = 0.05)	0.99 (0.93–1.06) (P = 0.81)

Values are presented as odds raio (95% confidence interval).
*Model 1 includes BMI ≥ 30 kg/m^2 and MetS or BMI ≥ 30 kg/m^2 and HLD, DM and HTN; †Model 2 includes BMI ≥ 30 kg/m^2, MetS, and five potential confounders (age, biological sex, race, ethnicity, and smoking) or BMI ≥ 30 kg/m^2 and HLD, DM and HTN and the five above-mentioned potential confounders.
BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MetS, metabolic syndrome; HLD, hyperlipedemia; DM, diabetes mellitus; HTN, hypertension.

Table 3. Unadjusted associations of BMI categories with SARS-CoV-2 positivity in emergency department patients tested for SARS-CoV-2

Categorical variable	SARS-COV-2	P
BMI (kg/m^2)		
< 25	1.00 (ref)	
25 to < 30	1.38 (1.20–1.47)	≤ 0.001
30 to < 35	1.40 (1.31–1.50)	≤ 0.001
35 to < 40	1.29 (1.19–1.40)	≤ 0.001
≥ 40	1.24 (1.14–1.35)	≤ 0.001

Values are presented as odds raio (95% confidence interval).
BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Again, elevated BMI was associated with increased odds of SARS-CoV-2 test positivity (Table 3). In subgroup analysis including only SARS-CoV-2-positive patients, increasing BMI was significantly associated with increased odds of ICU care and intubation, again with the magnitude of the association increasing with each subsequent BMI category. Similar to the results in the overall cohort of SARS-CoV-2-tested patients, BMI ≥ 40 kg/m^2 was significantly associated with all major outcomes. Similarly, when examining the association of MetS with adverse outcomes in SARS-CoV-2-positive patients, composite MetS diagnosis was also associated with significantly increased odds of all measured outcomes (Table 4).

Table 5 displays results from a multivariable regression model including both BMI and MetS in three distinct cohorts: all SARS-CoV-2-tested patients, SARS-CoV-2-positive patients, and SARS-

Table 4. Multivariable analysis of BMI* and MetS† on major outcomes in emergency department patients who tested positive for SARS-CoV-2

Variable	Admission (n = 12,604)	ICU (n = 12,602)	Intubation (n = 12,607)	Mortality (n = 12,594)	VTE (n = 12,607)
BMI (kg/m^2)					
< 25	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25 to < 30	1.02 (0.91–1.13)	1.15 (1.00–1.32)	1.27 (1.09–1.49)	0.98 (0.86–1.13)	0.98 (0.66–1.48)
30 to < 35	0.99 (0.88–1.12)	1.35 (1.16–1.56)	1.56 (1.32–1.83)	0.95 (0.81–1.11)	1.05 (0.67–1.62)
35 to < 40	1.09 (0.95–1.25)	1.76 (1.48–2.09)	2.02 (1.67–2.45)	1.08 (0.88–1.32)	1.61 (1.00–2.58)
≥ 40	1.44 (1.25–1.66)	2.35 (1.99–2.79)	3.13 (2.60–3.77)	1.67 (1.38–2.03)	1.90 (1.19–3.03)
MetS	2.07 (1.86–2.31)	1.82 (1.63–2.03)	1.79 (1.59–2.02)	1.32 (1.17–1.49)	1.67 (1.22–2.30)

Values are presented as odds raio (95% confidence interval).
Multivariable models include *BMI (kg/m^2), age, biological sex, race, ethnicity, and smoking or †MetS, age, biological sex, race, ethnicity, and smoking.
BMI, body mass index; MetS, metabolic syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; VTE, venous thromboembolism.

Table 5. Multivariable analysis of BMI and MetS on major outcomes in emergency department patients tested for SARS-CoV-2

Variable	Admission (n = 25,347)	ICU (n = 25,328)	Intubation (n = 25,353)	Mortality (n = 25,335)	VTE (n = 25,353)
All tested patients					
BMI < 25	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25 to < 30	0.86 (0.80–0.93)	1.00 (0.90–1.11)	1.14 (1.00–1.29)	0.89 (0.79–0.99)	1.11 (0.84–1.47)
BMI 30 to < 35	0.76 (0.70–0.83)	0.98 (0.88–1.11)	1.22 (1.06–1.40)	0.78 (0.68–0.89)	0.94 (0.68–1.31)
BMI 35 to < 40	0.78 (0.70–0.86)	1.15 (1.00–1.31)	1.40 (1.19–1.65)	0.73 (0.61–0.87)	1.09 (0.74–1.61)
BMI ≥ 40	0.94 (0.85–1.04)	1.39 (1.21–1.60)	1.92 (1.64–2.25)	1.04 (0.87–1.23)	1.88 (1.34–2.64)
MetS	1.81 (1.68–1.96)	1.45 (1.32–1.59)	1.33 (1.19–1.48)	1.18 (1.06–1.32)	1.23 (0.95–1.60)
SARS-CoV-2 positive	(n = 12,604)	(n = 12,602)	(n = 12,607)	(n = 12,594)	(n = 12,607)
BMI < 25	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25 to < 30	1.00 (0.90–1.12)	1.13 (0.99–1.30)	1.26 (1.08–1.47)	0.98 (0.85–1.12)	0.97 (0.65–1.46)
BMI 30 to < 35	0.84 (0.74–0.94)	1.17 (1.00–1.36)	1.38 (1.16–1.63)	0.87 (0.73–1.02)	0.92 (0.59–1.45)
BMI 35 to < 40	0.90 (0.78–1.04)	1.51 (1.27–1.80)	1.78 (1.46–2.17)	0.98 (0.80–1.20)	1.40 (0.86–2.29)
BMI ≥ 40	1.15 (0.99–1.33)	1.97 (1.65–2.35)	2.69 (2.22–3.26)	1.50 (1.22–1.84)	1.61 (0.99–2.63)
MetS	2.11 (1.89–2.37)	1.58 (1.40–1.78)	1.46 (1.28–1.66)	1.29 (1.13–1.48)	1.51 (1.07–2.13)
SARS-CoV-2 negative	(n = 12,743)	(n = 12,726)	(n = 12,746)	(n = 12,761)	(n = 12,746)
BMI < 25	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI 25 to < 30	0.75 (0.68–0.83)	0.83 (0.71–0.98)	0.88 (0.71–1.10)	0.71 (0.58–0.86)	1.24 (0.84–1.83)
BMI 30 to < 35	0.68 (0.61–0.77)	0.72 (0.60–0.87)	0.80 (0.62–1.04)	0.56 (0.44–0.72)	0.94 (0.58–1.52)
BMI 35 to < 40	0.67 (0.58–0.77)	0.73 (0.58–0.92)	0.75 (0.54–1.04)	0.35 (0.24–0.50)	0.67 (0.34–1.32)
BMI ≥ 40	0.78 (0.68–0.89)	0.80 (0.63–1.00)	0.80 (0.58–1.11)	0.45 (0.32–0.63)	2.16 (1.34–3.49)
MetS	1.71 (1.53–1.90)	1.41 (1.20–1.66)	1.39 (1.12–1.74)	1.23 (1.00–1.52)	0.97 (0.66–1.44)

Values are presented as odds raio (95% confidence interval). Multivariable models include BMI (kg/m^2), MetS, age, biological sex, race, ethnicity, and smoking.
BMI, body mass index; MetS, metabolic syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; VTE, venous thromboembolism.

CoV-2-negative patients. In SARS-CoV-2-positive patients, similar trends were seen for both BMI and MetS when both exposures were included in the multivariable regression model. Increasing BMI was consistently associated with increased need for critical care (ICU and intubation), while patients with BMI ≥ 40 kg/m^2 had increased mortality. MetS was associated with increased odds of all major outcomes. When adjusting for both exposures, the absolute ORs were generally lower compared to the unadjusted individual analyses (Tables 4 and 5). This suggests that BMI and MetS may overlap in their association with major outcomes. This is likely due to BMI being a component of MetS. In SARS-CoV-2-negative patients, increasing BMI had a non-linear "protective" association with admission, ICU, and mortality; patients with a BMI < 25 kg/m^2 were at higher risk of these outcomes than all other BMI categories. In contrast, BMI ≥ 40 kg/m^2 was associated with VTE, as seen in the SARS-CoV-2-positive patients. The presence of MetS was still

associated with universally worse outcomes in SARS-CoV-2-negative patients. These findings suggest that the association between BMI and major outcomes may be modified by SARS-CoV-2 status. Conversely, MetS was associated with worse outcomes independent of SARS-CoV-2 status, although the odds of poor outcomes were higher among SARS-CoV-2-positive patients.

DISCUSSION

Our study revealed that obesity is significantly associated with SARS-CoV-2 test positivity, while MetS is associated with decreased odds of a positive test, with and without adjustment for BMI. The presence of MetS was found to be significantly associated with increased odds of all adverse outcomes of interest, including an increased need for hospital admission, ICU care, intubation, mortality, and development of VTE. This was true regardless of SARS-CoV-2 status, although the association appeared somewhat more severe in the SARS-CoV-2-positive cohort of patients. The role of BMI, however, was more complex, as this relationship appeared to be heavily modulated by SARS-CoV-2 status. In SARS-CoV-2-positive patients, a higher BMI was generally found to be associated with worse outcomes, increasing in a stepwise pattern with each subsequent BMI category. Interestingly, this was not the case in SARS-CoV-2-negative patients, where increasing BMI demonstrated a significant protective association against poor outcomes until BMI ≥ 40 kg/m^2, where this protection only remained for admission and mortality. This suggests a synergistic interaction between obesity and SARS-CoV-2 status. Although MetS may be more universally predictive of poor outcomes than BMI alone in the whole cohort, as it conferred a negative effect on all measured outcomes regardless of SARS-CoV-2 status, the negative impact of obesity appears to be more important when limited to those positive for SARS-CoV-2 infection.

The immune system and metabolic pathways are intrinsically related for homeostasis.[18] MetS is characterized as a cluster of metabolic disorders resulting in disruptions of homeostasis leading to impaired regulation and overall control of the immune response.[18,19] MetS and obesity are both associated with chronic low-grade inflammation and immune dysregulation, which may be in part related to dysregulated secretion of adipokines.[19] However, it is not entirely clear the role that these inflammatory pathways are affected in other disease processes or how they influence comorbidity. In the case of SARS-CoV-2, it appears that patients with metabolic disease are at risk of more severe disease course and associated complications.[20] Hypertension (56.6%) and diabetes (33.8%) are the most prevalent comorbidities among individuals with COVID-19 who require hospitalization.[21] In a study originating from Wuhan, China, patients with newly diagnosed diabetes mellitus had the highest risk of ICU admission (11.7%) and were most likely to require invasive mechanical ventilation (11.7%), followed by patients with known diabetes mellitus (4.1% ICU; 9.2% mechanical ventilation) and patients with hyperglycemia (6.2% ICU; 4.7% mechanical ventilation), compared with patients with normal glycemic levels (1.5% ICU; 2.3% mechanical ventilation).[22] Also, in a separate single-center retrospective study originating from Wuhan, China, hypertensive patients had more severe SARS-CoV-2 infection and a higher death rate, 10.3% vs. 6.4%, when compared with the non-hypertensive group. Also, hypertensive patients with COVID-19 were found to have higher concentrations of C-reactive protein, procalcitonin, and interleukin-6 when compared to controls, indicating that hypertension may enhance inflammation in SARS-CoV-2 infection.[23] Similarly, epidemiologic data from China demonstrated a higher case fatality rate in patients with established cardiovascular disease.[20]

Our study provides further evidence that increasing BMI and composite MetS are associated with several adverse outcomes including increased risk of hospitalization, ICU admission, intubation and disease mortality in SARS-CoV-2-positive patients. Interestingly, in SARS-CoV-2-negative patients, we found composite MetS to be associated with several of the associated adverse outcomes, whereas elevated BMI demonstrated a negative (or "protective") association with measured outcomes. A similar cohort study performed in Italy during the early days of the pandemic found that while obese patients with COVID-19 infection were more likely to be admitted to ICU than non-obese patients, there were no significant differences in mortality between the two groups.[24] This may be reflective the oft debated and incompletely understood "obesity paradox". The "obesity paradox" posits that in hospitalized and ICU patients, as well as in patients with various chronic illnesses, a J-shaped relationship between BMI and mortality has been dem-

onstrated, with overweight and moderate obesity being protective compared with a normal BMI or more severe obesity.[25] While the Italian study mentioned above is reflective of a paradoxical relationship with BMI, our study differs in that, although we did see a paradoxical relationship with BMI in SARS-CoV-2-negative patients, in SARS-Co-V-2-positive patients we found a clear association with adverse outcomes as BMI increased. This may be partially explained by the simple stratification of obesity to a BMI >30 kg/m^2 in the Italian study, whereas our study further stratified BMI into five groups. Therefore, our data demonstrate that concomitant metabolic disease is associated with worse outcomes in all patients regardless of SARS-CoV-2 status, while obesity confers adverse outcomes for those patients positive for SARS-CoV-2 infection.

Our findings are consistent with early systematic reviews that identified obesity as a predictor for a worse prognosis in SARS-CoV-2.[2] In addition to obesity, prior studies have also demonstrated the negative impact of the other components that comprise MetS. For instance, in separate meta-analyses, dyslipidemia and hyperglycemia were associated with increased disease severity and mortality.[3,5] A meta-analysis of SARS-CoV-2-positive patients showed that diabetes mellitus and hypertension were associated with composite poor outcomes i.e., mortality, severe SARS-CoV-2 infection and acute respiratory distress syndrome development.[26] Multiple additional studies have also reported that diabetes, as well as hyperglycemia alone, is associated with severe SARS-CoV-2.[27] Taken together, we believe that the available evidence suggests that the risk of increased BMI in SARS-CoV-2 infection is likely multifactorial, and may more accurately represent both a higher association with comorbid metabolic disease and impaired respiratory mechanics. It has been reported that the majority of obese patients can be characterized as having comorbid metabolic disease, with only approximately 30% of patients having metabolic health comparable to that of a normal weight individual.[6] Therefore, when attempting to determine a patient's risk of a more severe disease course, it may be more beneficial to consider obese individuals as belonging to one of two distinct subgroups: metabolically healthy or metabolically abnormal.

Although composite MetS diagnosis appeared to be more universally associated with adverse outcomes than increasing BMI alone, our findings were consistent with previous meta-analyses indicating that SARS-CoV-2-positive patients with a higher BMI were at greater risk of certain medical complications including ICU admission, intubation, and VTE development.[4,5] This may be a representation of the impaired baseline respiratory mechanics in obese patients.[2] In other infectious viral pathogens, such as influenza in the 1918 "Spanish" influenza pandemic, the 1957 pandemic, the 1968 pandemic, and the 2009 Influenza A virus H1N1 pandemic, obesity was associated with a more severe course of disease.[28] However, the worsened disease severity in those studies was attributed to obese patients having poor respiratory mechanics and baseline respiratory dysfunction.[2,28]

Limitations

The RECOVER registry was restricted to ED patients who underwent SARS-CoV-2 diagnostic testing and had a disease prevalence approximating 50%. This could bias toward reporting characteristics of patients with typical symptoms, therefore missing patients with atypical or no symptoms. There was also heterogeneity in sampling nationwide, and by hospital site over time, driven in part by the availability of testing and changing recommendations and guidelines. Another limitation is the potentially limited diagnostic sensitivity of molecular testing.[29] Electronic surveillance methodology utilized by RECOVER may also miss important outcomes such as death at home or presentation to another hospital system. Furthermore, in this particular analysis, we defined MetS based on a surrogate collection of hypertension, hyperlipidemia, diabetes and obesity as recorded in the electronic medical record. This differs from the more stringent guidelines traditionally used to define MetS such as specific cut-offs for triglycerides, high-density lipoprotein, systolic and diastolic blood pressure, fasting blood glucose, and waist circumference. The lack of these discrete data points may limit the overall interpretation of our findings. Finally, in an attempt to determine the effect of obesity on outcomes of interest, we separated patients into categories based on calculated BMI. Elevated BMI was not isolated from additional comorbidities and therefore patients may have had multiple diagnoses including components of MetS that could result in some degree of collinearity.

Conclusions

In this large nationwide sample of ED patients undergoing SARS-

CoV-2 testing, we report a significant association between MetS and increased need for admission, ICU care, intubation, and mortality across all patients regardless of SARS-CoV-2 status. However, the role of increased BMI was more complex and appeared to be heavily modulated by SARS-CoV-2 status; while an elevated BMI demonstrated a somewhat paradoxical relationship with the outcomes of interest in SARS-CoV-2-negative patients, it was significantly associated with adverse ICU care, intubation, and mortality outcomes in SARS-CoV-2-positive patients. Our study findings suggest that increasing BMI and composite MetS are both predictive of more severe disease and worse outcomes in SARS-CoV-2-positive patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study conception and design: JK, JJT, and LKS; acquisition of data: JK, DMC, KEN, and CAC; analysis and interpretation of data: JJT and LKS; drafting of the manuscript: JJT, LKS, and LP; critical revision of the manuscript: JK, DMC, KN, and CAC; statistical analysis: JJT and LKS; administrative, technical, or material support: JK; and study supervision: JK.

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