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Metabolic syndrome and clinical outcomes in patients infected with COVID-19: Does age, sex, and race of the patient with metabolic syndrome matter?

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Abstract

Background: Metabolic syndrome (MetS) is highly prevalent worldwide, and its individual components obesity, diabetes, and hypertension have been identified as risk factors to develop severe coronavirus disease 2019 (COVID-19); however, data on MetS and clinical outcomes in COVID-19 are scarce. This study aims to determine association between MetS and severe disease outcomes, that is, mortality, need for mechanical ventilation, and intensive care unit (ICU) requirement among patients with COVID-19.

Methods: This is a retrospective multihospital cohort study on 1871 patients with confirmed COVID-19 diagnosis. Patient data including demographics, comorbidities, body mass index (BMI), smoking, laboratory data, and the clinical course of hospitalization were collected. Multivariable regression was performed adjusting for age, sex, race, insurance, smoking, and comorbidities.

Results: A total of 1871 patients (median age 66 [interquartile range, IQR 54-75]; 965 (51.6%) males; 1494 (80%) African Americans; median BMI 29.4 kg/m^2 [IQR 25-35.8]; 573 (30.6%) patients with MetS) were included. Patients with MetS had increased mortality (odds ratio [OR], 1.40; 95% CI, 1.11-1.75; $P = .004$), higher ICU admission (OR, 1.68; 95% CI, 1.36-2.08; $P < .001$), and increased need for mechanical ventilation (OR, 1.90; 95% CI, 1.52-2.37; $P < .001$). Among individual comorbidities, diabetes had significant association with mortality (OR, 1.30; 95% CI, 1.05-1.63; $P = 0.02$), ICU admission (OR, 1.56; 95% CI, 1.27-1.93; $P < .001$), and need for mechanical ventilation (OR, 1.63; 95% CI, 1.30-2.03; $P < .001$).

Conclusions: MetS is a better prognostic indicator for severe disease outcomes in patients with COVID-19 than its individual components. Patients with MetS had significantly higher mortality, increased ICU admissions, and need for mechanical ventilation.

KEYWORDS

COVID-19, critical care, diabetes mellitus, metabolic syndrome, mortality

Highlights

- Metabolic syndrome (MetS) is a vital prognostic indicator of outcomes in coronavirus disease 2019.
- Patients with MetS had worse clinical outcomes compared with the ones without MetS.
- Patients with MetS had a higher need for intensive care unit irrespective of their age, sex, or race.
- Need for mechanical ventilation was higher for all patients with MetS except Caucasians.
- Females, younger patients (<65), and African Americans with MetS had higher mortality.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly spread worldwide and has now become a global pandemic. As of early November, in the USA alone more than 11.6 million people have been infected, with 250 000 fatalities. Severe cases of COVID-19 can lead to development of acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure.[1] In some critically ill patients with COVID-19, cytokine storm has been reported to increase mortality. This storm results from the release of pro-inflammatory cytokines and chemokines.[2-4]

Metabolic syndrome (MetS), which is manifested with obesity, hypertension, hyperglycemia, and dyslipidemia, is characterized by a prothrombotic and pro-inflammatory state with elevated C-reactive protein and interleukin-6.[5] These systemic inflammatory markers are the main risk factors for the development of macrovascular complications that lead to significant increase in morbidity and mortality.

The prevalence of MetS in the USA, according to the National Health and Nutrition Examination Survey (NHANES) for 1988 through 2012, has been found to be more than 30% of the population.[6] The individual components of MetS obesity, diabetes, and hypertension have been identified as risk factors to develop severe COVID-19.[7-10] The pro-inflammatory state in MetS along with associated risk factors may contribute to worse outcomes in COVID-19; however, literature looking at the association between MetS and clinical outcomes in COVID-19 is scarce.

The main objective of this study is to determine the association between MetS and outcomes of severe COVID-19 infection, focusing on its mortality, the need for mechanical ventilation, and intensive care unit (ICU) admissions. We have also explored the association of the individual components of MetS, namely hypertension, diabetes, obesity, and hyperlipidemia, to the clinical outcomes of COVID-19 infection. Moreover, we have looked into the effects of race, age, and sex of the patient on the association between MetS and clinical outcomes. In addition, we explored if presence of the abnormal liver enzymes and inflammatory markers in patients with COVID-19 has any association with clinical outcomes.

2 | METHODS

2.1 | Research design

We conducted a retrospective cohort study on 1871 adult (≥18 years of age) patients with laboratory confirmed COVID-19 diagnosis (either via nasopharyngeal or oropharyngeal swab) from 10 March to 30 June 2020 at an academic medical center located in metropolitan Detroit. This study was approved by the Detroit Medical Center (DMC) and the Wayne State University Institutional Review Board (IRB application number 20-06-2429). The data were collected from patients with COVID-19 admitted into the four DMC hospitals located in the metropolitan area of Detroit which serve predominantly African American patients. Any patient under the age of 18, readmission, ambulatory surgery patients, and pregnant patients were excluded. Additionally, patients who were transferred to an outside facility for other services such as extracorporeal membrane oxygenation (ECMO) therapy were also excluded.

Electronic medical records for all patients meeting the inclusion criteria were collected and thoroughly reviewed. Data points were manually collected and coded for each patient. To ensure data integrity, randomly selected patient charts were additionally verified by the principal investigator.

Data collected included demographic information (age, sex, race, and insurance status); prior comorbidities, namely hypertension, coronary artery disease (CAD), congestive heart failure (CHF), diabetes, hyperlipidemia, chronic obstructive pulmonary disease (COPD), asthma, any malignancy, liver disease, chronic kidney disease (CKD), end-stage renal disease (ESRD) on hemodialysis, and any prior history of stroke; body mass index (BMI); and smoking status. Laboratory values collected included the last recorded triglyceride (TG) levels and high-density lipoprotein (HDL) levels prior to admission and other laboratory values (lymphocyte and neutrophil counts, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, d-dimer, and ferritin) within 24 hours of admission. The cutoff values for the laboratory data were taken as three times the upper normal limit for AST and ALT, twice the upper normal limit for total bilirubin, d-dimer >2 mg/L, and ferritin >300 ng/mL based on previous studies.[8,11-13] Absolute lymphocyte counts less than 1000 per microliter were defined as lymphopenia and an absolute neutrophil count less than 1500 per microliter as neutropenia. To determine the clinical course, we collected the disposition of each patient from the emergency department (ED) and if the patient had ever needed ICU admission. Smoking status was assigned based on any documentation of prior or current smoking.

Study outcomes were defined as mortality, need for mechanical ventilation, and ICU admission, and every patient had a documented outcome (discharged status or mortality) at the time of data collection. Patients were considered to have MetS when they met three of the following five criteria: (a) history of diabetes or use of diabetic medication, (b) obesity (BMI >30), (c) history of hypertension or use of antihypertensive medications, (d) TG >150, and (e) HDL <40 in males/HDL <50 in females, or history of hypercholesterolemia and use of cholesterol-lowering medication. Recent literature looking at the association between MetS and COVID-19 mortality have used similar criteria for identifying patients with MetS.[14]

2.2 | Statistical analysis

Baseline characteristics of the two groups—MetS and non-MetS—were compared using the Mann-Whitney *U* test for continuous variables and chi-square test for categorical variables. Continuous variables such as age and BMI did not have a normal distribution and are described as median and IQR, while categorical variables are described as frequency and percentages. Multivariable logistic regression was done to compare outcomes of MetS and non-MetS patients after adjusting for covariates such as age, sex, race, insurance, smoking status, and comorbidities including CAD, CHF, COPD, asthma, any malignancy, any liver disease, CKD, ESRD on hemodialysis, and any prior history of stroke. Stratified analysis based on sex, race, and age groups (18-64 years, and 65 and older) was also conducted to ascertain if any of these variables affected the association of MetS with the clinical outcomes. Multivariable logistic regression was also conducted separately on the individual components of MetS diagnostic criteria (diabetes, hypertension, obesity, and hyperlipidemia). A *P* value of less than .05 was determined to be significant. Subgroup analysis based on race was limited to the African American and Caucasian race due to the limited sample size of the remaining races. Statistical analyses were performed using IBM SPSS software (version 26; IBM Corp, New York, New York).

3 | RESULTS

3.1 | Baseline characteristics

A total of 1871 patients with confirmed COVID-19 diagnosis were included in the study. A total of 573 (30.6%) patients met the criteria for MetS. The median age (interquartile range, IQR) of the cohort was 66 years (54-75), and 965 (51.6%) were males. Close to 80% (n = 1494) of the patients were African Americans, and the median BMI (IQR) was 29.4 kg/m^2 (25-35.8). Hypertension (n = 1485; 79.4%), diabetes (n = 792; 42.3%), and hyperlipidemia (n = 513; 27.4%) were the three most common comorbidities. In this cohort 1334 (71.3%) patients had Medicare or private insurance. The distribution of age ($P = .73$), sex ($P = .06$), race (.38), and insurance status ($P = .25$) was similar across the MetS and non-MetS groups. However, as expected, the two groups differed in the distribution of BMI ($P < .001$), where 81.3% of the patients in the MetS group were obese compared with only 31.8% of patients in the non-MetS group. Comorbidities such as CHF, hypertension, diabetes, CAD, COPD, hyperlipidemia, and CKD were also not equally distributed in the MetS and non-MetS groups. Given these differences in the two groups of comparison, it was vital to adjust for these possible confounders during the analysis, as done in this study, to ensure reliability of the results. Comparison of baseline laboratory values, when available, within 24 hours of admission showed no significant difference in the two groups for ALT, AST, bilirubin, lymphopenia, neutropenia, or elevated d-dimer and ferritin. The baseline characteristics of the cohort and

TABLE 1 Baseline characteristic of patients

Characteristic	Cohort (N = 1871)	MetS (n = 573)	Non-MetS (n = 1298)	*P* value
Age, (y) n (%)				
Median (IQR)	66 (54-75)	65 (57-73)	66 (53-76)	.73
Less than 65	874 (46.7)	279 (48.7)	595 (45.8)	
≥65	997 (53.3)	294 (51.3)	703 (54.2)	
Sex, n (%)				
Male	965 (51.6)	277 (48.3)	688 (53)	.06
Female	906 (48.4)	296 (51.7)	610 (47)	
Race/ethnicity, n (%)				
African American	1494 (79.9)	469 (81.8)	1025 (79)	.38
Caucasian	340 (18.2)	97 (16.9)	243 (18.7)	
Asian	21 (1.1)	5 (0.9)	16 (1.2)	
Middle Eastern	14 (0.7)	2 (0.3)	12 (0.9)	
Latino/Hispanic	2 (0.1)	0	2 (0.2)	
BMI				
Median (IQR)	29.4 (25-35.8)	34.7 (30.8-40.45)	27.2 (24-32.1)	<.001
<18.5 (underweight)	46 (2.5)	2 (0.3)	44 (3.4)	
18.5-24.9 (normal)	411 (22)	41 (7.2)	370 (28.5)	
25-29.9 (overweight)	512 (27.4)	64 (11.2)	448 (34.5)	
≥30 (obese)	879 (47)	466 (81.3)	413 (31.8)	
BMI missing	23 (1.2)		23 (1.8)	
Comorbidities, n (%)				
Coronary artery disease	392 (21)	170 (29.7)	222 (17.1)	<.001
Hypertension	1485 (79.4)	567 (99)	918 (70.7)	<.001
Diabetes	792 (42.3)	480 (83.8)	312 (24)	<.001
Congestive heart failure	253 (13.5)	106 (18.5)	147 (11.3)	<.001
COPD	317 (16.9)	117 (20.4)	200 (15.4)	.008
Asthma	134 (7.2)	41 (7.2)	93 (7.2)	.99
Hyperlipidemia	513 (27.4)	327 (57.1)	186 (14.3)	<.001
Stroke	194 (10.4)	64 (11.2)	130 (10)	.45
Any cancer	173 (9.2)	44 (7.7)	129 (9.9)	.12
Any liver disease	69 (3.7)	15 (2.6)	54 (4.2)	.1
CKD	201 (10.7)	84 (14.7)	117 (9)	<.001
ESRD on dialysis	174 (9.3)	61 (10.6)	113 (8.7)	.18
Insurance status				
Medicaid/uninsured	537 (28.7)	154 (26.9)	383 (29.5)	.25
Medicare/private	1334 (71.3)	419 (73.1)	915 (70.5)	
Laboratory values				
Median ALT (IQR)	22 (14-36)	22 (13-36)	22 (14-37)	.71
ALT >3 UNL	37/1420 (2.6)	10/443 (2.3)	27/977(2.8)	.58
Median AST (IQR)	37 (24-61)	36.5 (23.25-60)	37 (24-61)	.59
AST >3 UNL	80/1421 (5.6)	25/444 (5.6)	55/977 (5.6)	.99
Median bilirubin (IQR)	0.53 (0.4-0.76)	0.54 (0.4-0.74)	0.53 (0.41-0.77)	.48
Bilirubin >2 UNL	16/1247 (1.3)	5/384 (1.3)	11/863 (1.3)	.97

(Continues)

TABLE 1 (Continued)

Characteristic	Cohort (N = 1871)	MetS (n = 573)	Non-MetS (n = 1298)	*P* value
Lymphopenia	761/1572 (48.4)	240/494 (48.6)	521/1078 (48.3)	.93
Neutropenia	10/1842 (0.5)	5/569 (0.8)	5/1273 (0.4)	.19
Ferritin >300	870/1257 (69.2)	272/397 (68.5)	598/860 (69.5)	.72
D-dimer >2	527/1055 (50.0)	157/327 (48.0)	370/728 (50.8)	.4

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; IQR, interquartile range; MetS, metabolic syndrome; UNL, upper normal limit.

TABLE 2 Clinical course of patients

Characteristic	Cohort (N = 1871)	MetS (n = 573)	Non-MetS (n = 1298)
Mortality	613 (32.8)	214 (37.3)	399 (30.7)
Mechanical ventilation	489 (26.1)	204 (35.6)	285 (22)
ICU admission	592 (31.6)	229 (40)	363 (28)
Admission disposition			
ER visit only (discharged from ED)	165 (8.8)	30 (5.2)	135 (10.4)
Inpatient admission	1379 (73.7)	422 (73.6)	957 (73.7)
Direct ER to ICU admission	327 (17.5)	121 (21.1)	206 (15.9)

Abbreviations: ED, emergency department; ER, emergency room; ICU, intensive care unit; MetS, metabolic syndrome.

TABLE 3 Association between MetS and severe disease outcomes (total cohort and stratified for age, sex, and race). Mortality, mechanical ventilation, and ICU admission adjusted for age, sex, race, smoking, insurance, and comorbidities[a]

	Mortality		ICU admission		Mechanical ventilation	
Characteristic	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Total cohort	1.40 (1.11-1.75)	.004	1.68 (1.36-2.08)	<.001	1.90 (1.52-2.37)	<.001
Less than 65	2.14 (1.46-3.13)	<.001	1.71 (1.23-2.39)	.002	1.86 (1.30-2.65)	.001
65 or older	0.99 (0.75-1.31)	.94	1.59 (1.19-2.11)	.002	1.95 (1.45-2.61)	<.001
Male	1.35 (0.98-1.84)	.06	1.56 (1.16-2.09)	.003	1.65 (1.21-2.25)	.001
Females	1.46 (1.04-2.04)	.03	1.85 (1.35-2.53)	<.001	2.30 (1.66-3.20)	<.001
African Americans	1.54 (1.20-1.98)	.001	1.63 (1.28-2.06)	<.001	1.99 (1.55-2.54)	<.001
Caucasian	0.83 (0.47-1.49)	.54	1.84 (1.10-3.07)	.02	1.62 (0.93-2.82)	.09

Abbreviations: COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ICU, intensive care unit; MetS, metabolic syndrome; OR, odds ratio.

[a]Comorbidities include coronary artery disease, congestive heart failure, COPD, asthma, chronic kidney disease, ESRD on dialysis, any cancer, any liver disease, and history of previous stroke.

their distribution across the two groups has been outlined in Table 1.

3.2 | Clinical course

Mortality in the total cohort was 32.8% (n = 613), and 31.6% (n = 592) patients required ICU services during their hospitalization. About 26.1% (n = 489) of all patients needed mechanical ventilation, and about 8.8% of the patients (n = 165) presenting to the hospital were discharged home from the ED. The clinical course of the total cohort, MetS, and non-MetS groups is further described in Table 2.

3.3 | MetS and severe disease outcomes

In the multivariable models that looked at association between MetS and severe disease outcomes, MetS was

significantly associated with mortality (odds ratio [OR], 1.40; 95% CI, 1.11-1.75; $P = .004$), ICU admission (OR, 1.68; 95% CI, 1.36-2.08; $P < .001$), and need for mechanical ventilation (OR, 1.90; 95% CI, 1.52-2.37; $P < .001$). Stratified analysis based on age showed MetS was associated with increased mortality in patients less than 65 years old (OR, 2.14; 95% CI, 1.46-3.13; $P < .001$), but not in the patients 65 years and older (OR, 0.99; 95% CI, 0.75-1.31; $P = .94$). In addition, the association of MetS with mortality was noted to be significant in females (OR, 1.46; 95% CI, 1.04-2.04; $P = .03$) and in the African American race (OR, 1.54; 95% CI, 1.20-1.98; $P = .001$). The need for ICU admission was significantly higher in the MetS group compared with the non-MetS group across all age groups, both sexes, and races. Similarly, the need for mechanical ventilation was significantly higher in people with MetS across all the stratified groups except for the Caucasian race (OR, 1.62; 95% CI, 0.93-2.82; $P = .09$). Further details about the association between MetS and the clinical outcomes in the total cohort and different subgroups have been summarized in Table 3.

3.4 | Individual components of MetS and severe disease outcomes

Upon comparing individual comorbidities that form the definition criteria of MetS separately, instead of clubbing them together as MetS, only diabetes was significantly associated with mortality (OR, 1.30; 95% CI, 1.05-1.63; $P = .02$), ICU admission (OR, 1.56; 95% CI, 1.27-1.93; $P < .001$), and need for mechanical ventilation (OR, 1.63; 95% CI, 1.30-2.03; $P < .001$). In addition, obesity (BMI >30) was associated with an increased need for mechanical ventilation (OR, 1.37; 95% CI, 1.09-1.72; $P = .007$), but not for mortality (OR, 1.23; 95% CI, 0.98-1.54; $P = .08$) or ICU admission (OR, 1.17; 95% CI, 0.94-1.45; $P = .16$). Hypertension and hyperlipidemia were not associated with any of the severe disease outcomes of COVID-19 explored by this study. The results of the association of individual MetS components with the clinical outcomes have been outlined in Table 4.

3.5 | Diabetic patients with MetS and severe disease outcomes

Since diabetes was found to be associated with worse clinical outcomes among patients with COVID-19 in this cohort, we further explored if the presence of MetS in diabetic patients had any association with the severe disease outcomes. Diabetic patients with MetS had a significantly increased need for mechanical ventilation (OR, 1.58; 95% CI, 1.15-2.18; $P = .005$) and a higher need for ICU admission (OR, 1.42; 95% CI, 1.04-1.93; $P = .03$) compared with the diabetic patients without MetS. However, the mortality was not significantly different in these two groups of diabetic patients (OR, 1.23; 95% CI, 0.89-1.69; $P = .2$). Table 5 summarizes the results of the association of MetS with severe disease outcomes in COVID-19 patients with diabetes.

3.6 | Liver enzymes/inflammatory markers and severe disease outcomes

Additional analysis of liver enzymes (ALT, AST, and total bilirubin), inflammatory markers (elevated d-dimer and ferritin), and the presence of lymphopenia and neutropenia at

TABLE 4 Association between MetS/individual MetS components and severe disease outcomes (mortality, mechanical ventilation, and ICU admission)

	Mortality		ICU admission		Mechanical ventilation	
Characteristic	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
MetS	1.40 (1.11-1.75)	.004	1.68 (1.36-2.08)	<.001	1.90 (1.52-2.37)	<.001
Hypertension[a]	1.23 (0.88-1.73)	.23	1.27 (0.93-1.73)	.13	1.29 (0.92-1.81)	.14
Diabetes[a]	1.30 (1.05-1.63)	.02	1.56 (1.27-1.93)	<.001	1.63 (1.30-2.03)	<.001
Obesity (BMI >30)[b]	1.23 (0.98-1.54)	.08	1.17 (0.94-1.45)	.16	1.37 (1.09-1.72)	.007
Hyperlipidemia[a]	0.97 (0.76-1.23)	.79	1.04 (0.83-1.31)	.74	1.00 (0.79-1.28)	.98

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ICU, intensive care unit; MetS, metabolic syndrome; OR, odds ratio.

[a]Adjusted for age, sex, race, smoking, BMI, insurance, and comorbidities which include coronary artery disease, congestive heart failure, COPD, asthma, chronic kidney disease, ESRD on dialysis, any malignancy, any liver disease, history of previous stroke, hypertension, diabetes, and hyperlipidemia.

[b]Adjusted for age, sex, race, smoking, insurance, and comorbidities which include coronary artery disease, congestive heart failure, COPD, asthma, chronic kidney disease, ESRD on dialysis, any malignancy, any liver disease, history of previous stroke, hypertension, diabetes, and hyperlipidemia.

Mortality		ICU admission		Mechanical ventilation	
OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
1.23 (0.89-1.69)	.2	1.42 (1.04-1.93)	.03	1.58 (1.15-2.18)	.005

Abbreviations: COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ICU, intensive care unit; MetS, metabolic syndrome; OR, odds ratio.
[a]Comorbidities include coronary artery disease, congestive heart failure, COPD, asthma, chronic kidney disease, ESRD on dialysis, any cancer, any liver disease, and history of previous stroke.

TABLE 5 Association between MetS and severe disease outcomes among diabetic patients. Mortality, mechanical ventilation, and ICU admission adjusted for age, sex, race, smoking, insurance, and comorbidities[a]

TABLE 6 Association between laboratory values and severe disease outcomes (mortality, mechanical ventilation, and ICU admission)[a]

	Mortality		ICU admission		Mechanical ventilation	
Characteristic	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Total cohort						
ALT >3 UNL	1.25 (0.60-2.60)	.55	0.98 (0.48-1.99)	.96	0.99 (0.47-2.09)	.97
AST >3 UNL	0.95 (0.57-1.58)	.84	0.89 (0.55-1.46)	.65	0.87 (0.51-1.47)	.6
Bilirubin >2 UNL	1.31 (0.43-3.95)	.64	0.64 (0.20-2.03)	.45	1.21 (0.41-3.57)	.73
Lymphopenia	1.18 (0.94-1.49)	.15	1.20 (0.97-1.49)	.1	1.10 (0.87-1.38)	.42
Neutropenia	8.13 (1.79-36.94)	.007	3.44 (0.95-12.37)	.06	3.21 (0.91-11.30)	.07
Ferritin >300	1.00 (0.76-1.32)	.1	0.97 (0.75-1.26)	.82	0.94 (0.72-1.24)	.66
D-dimer >2	0.84 (0.63-1.10)	.2	0.87 (0.67-1.14)	.32	0.82 (0.62-1.08)	.16
MetS						
ALT >3 UNL	0.44 (0.08-2.29)	.33	0.34 (0.07-1.68)	.18	0.45 (0.09-2.27)	.33
AST >3 UNL	0.78 (0.32-1.91)	.59	0.41 (0.15-1.07)	.07	0.47 (0.18-1.24)	.13
Bilirubin >2 UNL	1.18 (0.18-7.92)	.87	0.95 (0.15-6.00)	.96	0.54 (0.06-5.00)	.58
Lymphopenia	1.27 (0.87-1.87)	.22	1.10 (0.76-1.60)	.61	1.23 (0.84-1.79)	.29
Neutropenia	8.82 (0.91-85.47)	.06	6.14 (0.65-57.72)	.11	7.27 (0.79-67.27)	.08
Ferritin >300	1.23 (0.76-1.99)	.39	1.26 (0.79-2.00)	.33	1.47 (0.91-2.37)	.11
D-dimer>2	0.97 (0.59-1.58)	.89	0.98 (0.60-1.60)	.93	0.81 (0.50-1.32)	.4
Non-MetS						
ALT >3 UNL	1.83 (0.77-4.34)	.17	1.38 (0.61-3.11)	.44	1.37 (0.57-3.26)	.48
AST >3 UNL	0.94 (0.50-1.78)	.86	1.27 (0.71-2.27)	.43	1.15 (0.61-2.19)	.67
Bilirubin >2 UNL	1.35 (0.33-5.56)	.68	0.45 (0.09-2.13)	.31	1.74 (0.48-6.30)	.4
Lymphopenia	1.10 (0.83-1.47)	.51	1.25 (0.95-1.63)	.11	1.02 (0.76-1.37)	.89
Neutropenia	5.4 (0.55-53.23)	.15	1.85 (0.30-11.26)	.51	1.04 (0.11-9.47)	.97
Ferritin >300	0.88 (0.62-1.25)	.48	0.84 (0.61-1.16)	.29	0.73 (0.52-1.04)	.08
D-dimer >2	0.78 (0.55-1.10)	.16	0.82 (0.59-1.14)	.24	0.80 (0.56-1.15)	.23

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ICU, intensive care unit; MetS, metabolic syndrome; OR, odds ratio; UNL, upper normal limit.
[a]Adjusted for age, sex, race, smoking, insurance, and comorbidities which include coronary artery disease, congestive heart failure, COPD, asthma, chronic kidney disease, ESRD on dialysis, any malignancy, any liver disease, and history of previous stroke.

admission showed no association with any of the severe disease outcomes in MetS or non-MetS patients. Neutropenia within 24 hours of hospital admission was associated with higher mortality in the total cohort (OR, 8.13; 95% CI, 1.79-36.94; $P = .007$). The results are further summarized in Table 6.

4 | DISCUSSION

This multihospital cohort study conducted on 1871 patients with confirmed COVID-19 diagnosis reports that MetS had a significant association with worse clinical outcomes in patients with COVID-19. Patients with

MetS had a 40% increase in all-cause mortality, 68% increase in the need for critical care services, and a 90% increase in the need for mechanical ventilation compared with the hospitalized patients without MetS. To our knowledge, this is the first study which conducted stratified analysis to ascertain if the age, sex, or race of a patient had any effect on this association of MetS with the severe disease outcomes in COVID-19, and we report some novel findings. The association of MetS with increased mortality in COVID-19 was noted to be significant in females, but not in males, and in patients younger than 65 years of age, but not in older patients. Several previous studies have reported that although MetS is more prevalent in elderly patients, its association with all-cause mortality decreases with age,[15-18] similar to what is seen in patients with COVID-19 in our study. The absence of association between obesity and mortality among patients with COVID-19 more than 65 years old reported by Anderson et al[19] may partly explain these findings. Other plausible explanations for these age-related differences could be survival bias and better management of the individual components of MetS in the elderly.[15] However, further studies are warranted to better understand the underlying mechanisms responsible for this lack of association between MetS and mortality among elderly patients with COVID-19. According to the NHANES data from 2011 to 2016, the prevalence of MetS among women has increased significantly,[20] and literature reviewing several prospective studies suggests increased cardiovascular risk from MetS in women compared with men.[21] This may account for, at least in part, the increased all-cause mortality among females with MetS seen in our study.

African Americans have been disproportionately affected by COVID-19.[22,23] Recent data released from the Centers for Disease Control and Prevention (CDC) show 32.9% above average deaths due to COVID-19 among African Americans.[24] Given the results of our study, race might be playing a role in the clinical outcomes in COVID-19, especially in patients with underlying comorbidities since the association of MetS with high mortality and with increased need for mechanical ventilation was found to be significant in African Americans, but not in Caucasians. Thereby, further studies with larger sample size exploring the effect of race and its interaction with various comorbidities are warranted.

Hypertension and diabetes have been reported frequently among hospitalized patients with COVID-19.[25-27] According to the CDC, the current studies exploring hypertension and clinical outcomes among patients with COVID-19 offer mixed evidence.[28] This study reports no significant association between hypertension and mortality or other severe disease outcomes, and several recent studies have reported similar results.[29-31] In our study, obesity was associated with increased need for mechanical ventilation, but not with increased mortality, and similar results were outlined in another cohort study done in New York.[32] This might be explained by the obesity paradox wherein prior studies have demonstrated that obesity is associated with decreased mortality in critically ill patients with pneumonia and ARDS.[33,34] In our study, we found no association of hyperlipidemia with any of the severe disease outcomes, and a possible explanation can be the immunomodulating properties of statin and decreased cytokine production.[35,36] Among individual comorbidities clubbed together as MetS, only diabetes was associated with significant worse outcomes in this cohort, and many other cohort studies have noted similar findings.[10,26,27] Our study also reports that among the diabetic patients presenting with COVID-19, those with MetS had a significantly increased need for mechanical ventilation and a higher need for ICU admission. This study highlights that the presence of MetS is a better predictor of severe disease outcomes in COVID-19 compared with individual comorbidities since it takes into the account the complex interaction of these comorbidities which might be responsible for the variations in the severity of clinical outcomes seen in COVID-19.

Numerous studies in the past have also noted association of MetS with abnormal liver enzymes,[37,38] and it has been noted that 14% to 53% of patients with COVID-19 can develop hepatic dysfunction particularly in severe disease.[39] In our study of patients with COVID-19, elevated liver enzymes within 24 hours of admission were not different in the MetS and non-MetS group, neither did they have any association with mortality or other clinical outcomes. Though MetS is characterized by a pro-inflammatory state, and elevated d-dimer and ferritin have been reported to be associated with severe disease outcomes,[40,41] we noted no association between these inflammatory markers and severe disease outcomes among patients with COVID-19, irrespective of whether they had MetS or not. The mechanisms by which MetS contributes to worse disease outcomes thereby need to be further explored.

Our study has several limitations which must be acknowledged. This study only included patients from the greater metropolitan Detroit area, and the majority of them were African Americans, which may limit generalization of the results. Data collection relied on clinical notes to gather information about comorbidities, and collection of laboratory data were limited to within 24 hours of admission. Additionally, a small number of patients (n = 15) transferred for ECMO to an outside facility were excluded, and differential exclusion of critical patients

might introduce some bias. Furthermore, since waist circumference and impaired fasting glucose information was not available, thereby to characterize patients into MetS and non-MetS categories, we relied on BMI and history of diabetes, thus a subset of patients might be unaccounted for. Finally, this is a retrospective cohort study, and hence the results can only imply association, but not causation.

5 | CONCLUSION

MetS is a better prognostic indicator for severe disease outcomes in patients with COVID-19 than its individual components. Patients with MetS had a significantly higher need for ICU admission irrespective of their age, sex, or race. The need for mechanical ventilation was also higher across all patients with MetS except the Caucasians. The association of MetS with higher mortality was significant for females, patients younger than 65 years of age, and for the African American race. Future studies and development of a clinical risk score for mortality/severe outcomes in COVID-19 should consider incorporating MetS.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The de-identified data that support the findings of this study are available from the corresponding author upon reasonable request and appropriate permission from the IRB.

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