Research Article ISSN 2639-9326

Diabetes & its Complications

Presence of Metabolic Syndrome as a Risk Factor for COVID-19 Mortality: A Retrospective Analysis

Shannon S. Wu[1], James F. Bena[2], Keren Zhou MD[3], Anita D. Misra-Hebert MD MPH[4] and Sangeeta R. Kashyap MD[3]

[1]*Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio.*

[2]*Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio.*

[3]*Department of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, Ohio.*

[4]*Department of Internal Medicine, Cleveland Clinic Community Care, Cleveland, Ohio.*

***Correspondence:**
Sangeeta R. Kashyap, MD, Cleveland Clinic Foundation, Department of Endocrinology and Metabolism, 9500 Euclid Avenue/A53, Cleveland, OH 44195, USA, Tel: +1-216-445-2679.

Received: 11 July 2021; **Accepted:** 04 August 2021

Citation: Shannon S. Wu, Bena JF, Zhou K, et al. Presence of Metabolic Syndrome as a Risk Factor for COVID-19 Mortality: A Retrospective Analysis. Diabetes Complications. 2021; 5(2); 1-10.

ABSTRACT

Background: *Mortality due to COVID-19 is higher in patients with hypertension, diabetes, and obesity. These comorbidities are collectively present in metabolic syndrome. The aim of this study is to characterize the association between metabolic syndrome and its surrogate biomarkers with severity of COVID-19 disease course.*

Methods: *This retrospective study included patients over age 18 who tested for COVID-19 at Cleveland Clinic between March 8 and May 17, 2020. Demographics, labs, hospitalization, intensive care unit (ICU) admission, and death were analyzed.*

Results: *Of 23282 patients, 3679 (15.8%) tested positive for COVID-19. Metabolic syndrome as defined by modified WHO Criteria was present in 834 (39%) of 2146 with available data. Patients with metabolic syndrome were older, male, African-American, heavier, and had more comorbidities. Metabolic syndrome was associated with higher rates of hospital admission and death ($p<0.001$). On multivariable analysis, patients with metabolic syndrome had an increase in risk of 77% for hospitalization, 57% for ICU admission, and 81% for death ($p<0.001$). High AST: ALT and TG: HDL were associated with hospitalization and ICU admission, but not mortality.*

Conclusion: *Metabolic syndrome is associated with hospitalization and mortality due to COVID-19, even after adjusting for other factors. Obesity, hyperglycemia, dyslipidemia, and hypertension are modifiable risk factors that would reduce mortality from COVID-19.*

Keywords

Coronavirus, COVID-19, dyslipidemia, diabetes, hyperglycemia, hypertension, metabolic syndrome, obesity.

Introduction

Common medical comorbidities stemming from insulin resistance, visceral obesity, and adipogenic inflammation are linked to more severe SARS-CoV-2 infection and higher mortality, suggesting a pathophysiologic link between these disease processes and course of viral illness. Of 44,672 confirmed coronavirus disease 2019 (COVID-19) cases, the case-fatality rate was elevated among those with preexisting medical conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, and 6.0% for hypertension, compared to the overall rate of 2.3% [1]. In New York, leading comorbidities among COVID-19 deaths were hypertension (55.4%), diabetes (37.3%), and hyperlipidemia (18.5%) [2]. Meta-analyses show that patients with obesity had worse outcomes than those without obesity (odds ratio, OR, 2.31) [3]. Patients with dyslipidemia

had more severe COVID-19 (relative risk (RR), 1.39) [4]. The prevalence of diabetes (OR, 3.52) and hypertension (OR, 2.69) in severely ill patients were higher than that in non-severe patients [5]. Moreover, a recent report suggests that individuals who have undergone bariatric surgery for their obesity and diabetes have better COVID-19 outcomes than non-surgical controls [6].

To date, the vast majority of published studies on COVID-19 have reported effects of obesity, diabetes, dyslipidemia, and hypertension on COVID-19 outcomes separately. A comprehensive analysis of metabolic syndrome, the common denominator to these conditions, may provide insight into the pathophysiology of worse outcomes in these patient populations [7,8]. Metabolic syndrome is a multiplexed risk factor constituting increased visceral fat, elevated blood pressure, atherogenic dyslipidemia (high triglycerides and low HDL), and hyperglycemia [9]. In metabolic syndrome, risk of heart attack, stroke, heart failure, and diabetes is increased due to a multifactorial etiology. Systemic metabolic disruption may permit maintenance of a pro-inflammatory state that dysregulates the immune response, contributes to activation of the "cytokine storm" after COVID-19 infection, and exacerbates risk of death from thromboembolic consequences. Due to compromised immune response, both susceptibility to SARS-CoV-2 infection and worse prognosis after infection is likely potentiated by metabolic disease. Ghoneim et al. reported that the cumulative incidence of COVID-19 was higher in patients with metabolic syndrome (OR, 7.00) [10]. In a cohort of 157 COVID-positive patients, metabolic syndrome was associated with more severe hospital course and mortality [11]. The prevalence of metabolic syndrome is higher in North America and Europe than in Asia, perhaps explaining in part the more severe COVID-19 course observed in Western continents. Establishing the clinical and biochemical parameters of metabolic dysfunction is key to better understanding the disease course of COVID-19.

This study analyzed patients in the Cleveland Clinic health system for classical and non-classical components of metabolic syndrome. The primary endpoint was the association between metabolic syndrome, as defined by the NCEP/ATP criteria, and outcomes including rate of hospitalization, rate of ICU admission, and all-cause mortality. Secondary outcomes include underlying associations between surrogate laboratory markers of metabolic syndrome (i.e. AST/ALT ratio, uric acid, TG/HDL ratio) and these outcomes. We hypothesized that metabolic syndrome and its surrogate biomarkers are associated with more severe COVID-19 disease course. This study aims to inform the mechanistic link between metabolic disorder, inflammation, and immune dysfunction and increased susceptibility to severe COVID-19 disease course.

Materials and Methods

Study Design

This retrospective, cross-sectional study consisted of patients over 18 years old who were tested for COVID-19 at all Cleveland Clinic locations in Ohio and Florida between March 8, 2020 and May 17, 2020. Patients were included in the Cleveland Clinic Health System COVID-19 registry (IRB#20-283). This study received Institutional Review Board approval (IRB#20-483). Written informed consent was waived as no direct risk to patients was present.

Metabolic syndrome was defined using modified World Health Organization (WHO) criteria [12]. Patients were defined as having metabolic syndrome if at least three of the following five criteria were met: (1) body mass index (BMI) > 30 kg/m^2, (2) fasting glucose ≥ 100 mg/dl (or treatment), (3) serum triglycerides ≥ 150 mg/dl (or treatment), (4) HDL cholesterol < 40mg/dl in males or <50 mg/dl in females (or treatment), (5) systolic blood pressure >130 mmHg or diastolic >85 mmHg. When fasting plasma glucose level was not available, random glucose > 200 mg/dL, diagnosis of type 1 or type 2 diabetes mellitus or treatment met this criterion. Treatments included any oral antihyperglycemic (metformin, sulfonylurea, acarbose inhibitor, SGLT2 inhibitor, GLP1 agonist, or DPP4 inhibitor) or insulin use. When serum triglycerides were not available, random triglyceride >200 mg/dL or any cholesterol-lowering agent (statin, fibrate, ezetimibe, PCSK9 inhibitor, or bile acid resin) met the third criteria [13]. The fifth criteria could be met by antihypertensive treatment including angiotensin-converting enzyme (ACE) inhibitor, aldosterone receptor blocker, calcium channel blocker, or beta blocker. All lab values obtained within one year prior to date of COVID-19 test were included; otherwise, the lab value was considered missing. Lab values obtained on the date of or after the COVID-19 test were excluded. Patients had to meet at least three criteria to be considered positive for metabolic syndrome. Those with missing data on three or more criteria were excluded. Patient characteristics were described by presence or absence of metabolic syndrome.

Lab measurements were collected for the following variables: HDL, triglycerides, AST, ALT, uric acid, and fasting or random glucose. Outcomes of interest were rate of hospitalization, rate of ICU admission, and mortality. A modification of the WHO seven-point ordinal scale analyzed in previous studies was analyzed as an outcome measure [14,15]. In this study, the modified scale is defined as follows: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5, hospitalized, requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or both; and 6, death. Covariates of interest included age, sex, race, and comorbidities such as hypertension, obstructive sleep apnea (OSA), non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), asthma, heart failure, and coronary artery disease (CAD). These comorbidities were selected for their common associations with metabolic syndrome.

Statistical Methods

For each analysis, the results were restricted to those with valid responses to the primary variables and covariates of interest. AST:

ALT ratio was categorized as a binary variable. Ratios above 1 were considered elevated, whereas levels less than or equal to 1 were treated as normal [16–19]. TG: HDL was analyzed as a continuous variable. Uric acid was categorized as a binary variable, with hyperuricemia defined as greater than 6.8 mg/dL[20]. Categorical factors were described with frequencies and percentages, while continuous measures were described with means and standard deviations, if normally distributed, and medians and quartiles otherwise. Factors of interest were compared on these measures using Pearson chi-square tests for unordered factors, Wilcoxon rank sum tests or Kruskal-Wallis tests for ordered factors and non-normal continuous measures, and two-sample t-tests for continuous measures. Spearman correlations were used to measure the association between TG: HDL ratio and continuous demographic variables. Logistic regression models were fit for each outcome and primary predictor, with adjustment for key covariates that were associated with the primary predictor or were believed to be associated with outcome. Adjusted odds ratios with 95% confidence limits were presented for each outcome. All analyses were performed using SAS software (version 9.4; Cary, NC), with p-value <0.05 considered statistically significant.

Results

Between March 8, 2020 and May 17, 2020, 23282 patients were tested for COVID-19 in the Cleveland Clinic health system in Ohio and Florida locations. Of these, 3679 (15.8%) patients had a positive test result and were subsequently analyzed. In total, 3679 patients with a positive test result were analyzed. Subgroup analysis included 2146 patients in the metabolic syndrome subgroup, 2475 patients in the AST/ALT ratio subgroup, and 1806 patients in the TG/HDL ratio subgroup.

Metabolic Syndrome

Metabolic syndrome characterization was available in 2146 (58.3%) patients with positive COVID-19 test results. Of these, 834 (38.9%) patients met criteria for metabolic syndrome. Among those with metabolic syndrome data, mean age was 56.5 years and 56% were female. Those with metabolic syndrome were more likely to be older, male, African-American, have higher BMI, have hypertension, OSA, NAFLD, asthma, heart failure, and CAD (p<0.05) (Table 1). Patients with metabolic syndrome had higher glucose, triglycerides, AST, and ALT and lower HDL (p<0.001). On endpoint analysis, patients with metabolic syndrome had higher rates of hospitalization, ICU admission, and death (p<0.01). Increased requirement for invasive respiratory support was observed in patients with metabolic syndrome (p<0.001). On multivariable analysis, patients with metabolic syndrome had a 77% increase in the odds of hospitalization relative to those without metabolic syndrome after adjustment for age, sex, race, asthma, coronary artery disease, and heart failure (Table 2). Odds of ICU admission were higher by 56% per Table 2 and odds of death were higher by 81% in patients with metabolic syndrome. In the same model, patients of white race had 57% lower odds of hospitalization relative to those of African-American race. Age was positively associated with all three outcomes, while sex and heart failure were associated with hospitalization and ICU admission only, and asthma and race were associated with hospitalization only.

AST/ALT Ratio

There were 2475 (67.3%) patients who tested positive with COVID-19 and had AST: ALT ratios. There were 1655 (66.9%) patients with AST: ALT>1 were older, male, Black or African-American and had higher BMI and more comorbidities (Table 3). Lab values for glucose, triglycerides, AST, and ALT were all higher in the AST: ALT>1 group. Higher hospitalization rates and higher respiratory requirements were observed in the AST: ALT>1 group. On multivariable analysis, significant odds ratios indicating greater risk for those with high AST: ALT ratios were observed for both hospitalization and ICU admission, but not mortality (Table 4). As a sensitivity analysis, NAFLD was also included as an adjustment factor, but the results were similar and are not presented. After adjusting for age, sex, race, asthma, coronary artery disease, and heart failure, AST: ALT remained a significant predictor of hospitalization and ICU admission. Age and race were associated with all three outcomes, sex and heart failure were associated with hospitalization and ICU admission only, and asthma was associated with hospitalization only.

Triglyceride/HDL Ratio

TG: HDL ratios were analyzed continuously using the 1806 (49.1%) patients with positive test results, who had complete data in both lab values. Median TG: HDL ratio was higher among males, white and other races, those with OSA, heart failure, and CAD (Supplementary Table 1). Median TG: HDL ratios were higher in patients that were hospitalized, admitted to the ICU, died, or had increased need for respiratory support (Supplementary Table 1). The correlation between TG: HDL ratio and BMI was weakly positive. TG: HDL was non-significant on multivariable analysis (Supplementary Table 2).

Discussion

This is the largest study to date analyzing the association between metabolic syndrome and surrogate biomarkers with COVID-19 disease. Our results demonstrate that patients with metabolic syndrome were 77% more likely to be hospitalized, 56% more likely to be admitted to the ICU, and 81% more likely to die from COVID-19. While the patients in this study were from a single institution, compared to prior studies of metabolic syndrome which were limited by sample size and population [7,8,16,21–23], the present study analyzed outcomes of patients more representative of the United States populace in terms of body mass index, comorbid conditions, and race and ethnicities included. Furthermore, this study analyzed a large patient population presenting to a multi-center healthcare system across two different geographic regions within the United States (Ohio and Florida). Outcomes were stratified by severity including risk of hospitalization, risk of ICU admission, and risk of death.

Elevated liver transaminase levels indicate hepatic steatosis and inflammation, which lead to increased hepatic glucose production,

Table 1: Metabolic Syndrome Results.

Factor	Total (N=2,146)	No Metabolic Syndrome (N=1,312)		Metabolic Syndrome (N=834)		p-value
		N	Statistics	N	Statistics	
Covariates						
Age	56.5 ± 19.6	1,312	53.2 ± 20.9	831	61.8 ± 15.9	***<0.001***[a2]
Gender		1,312		831		***<0.001***[c]
Male	944 (44.1)		517 (39.4)		427 (51.4)	
Female	1,199 (55.9)		795 (60.6)		404 (48.6)	
Race		1,263		804		***<0.001***[c]
Other	87 (4.2)		60 (4.8)		27 (3.4)	
Black or African-American	660 (31.9)		363 (28.7)		297 (36.9)	
White	1,320 (63.9)		840 (66.5)		480 (59.7)	
Ethnicity		1,250		802		***0.021***[c]
Non-Hispanic	1,926 (93.9)		1,161 (92.9)		765 (95.4)	
Hispanic	126 (6.1)		89 (7.1)		37 (4.6)	
BMI	30.7 ± 8.1	1,287	27.8 ± 7.0	826	35.1 ± 7.6	***<0.001***[a2]
Hypertension	1,184 (56.8)	1,265	452 (35.7)	821	732 (89.2)	***<0.001***[c]
OSA	401 (18.7)	1,312	152 (11.6)	834	249 (29.9)	***<0.001***[c]
NAFLD	65 (3.0)	1,312	27 (2.1)	834	38 (4.6)	***<0.001***[c]
PCOS	31 (1.4)	1,312	20 (1.5)	834	11 (1.3)	0.70[c]
Asthma	368 (18.3)	1,244	208 (16.7)	772	160 (20.7)	***0.024***[c]
Heart failure	272 (13.5)	1,234	99 (8.0)	783	173 (22.1)	***<0.001***[c]
Coronary artery disease	334 (16.5)	1,248	138 (11.1)	782	196 (25.1)	***<0.001***[c]
Labs						
Glucose	103.0 [91.0, 128.0]	895	94.0 [86.0, 106.0]	744	119.0 [103.5, 151.0]	***<0.001***[b]
Triglycerides	97.0 [67.0, 141.0]	1,064	85.0 [60.0, 116.0]	722	124.0 [84.0, 192.0]	***<0.001***[b]
HDL	48.0 [38.0, 61.0]	1,062	55.0 [45.0, 66.0]	718	39.0 [32.0, 48.0]	***<0.001***[b]
AST	23.0 [18.0, 32.0]	1,149	22.0 [18.0, 30.0]	807	25.0 [18.0, 37.0]	***<0.001***[b]
ALT	19.0 [14.0, 29.0]	1,159	18.0 [13.0, 26.0]	811	22.0 [15.0, 32.0]	***<0.001***[b]
Outcomes						
Hospitalized	692 (33.0)	1,278	331 (25.9)	818	361 (44.1)	***<0.001***[c]
Admitted to ICU	231 (11.0)	1,278	105 (8.2)	817	126 (15.4)	***<0.001***[c]
Death	85 (6.9)	720	36 (5.0)	504	49 (9.7)	***0.001***[c]
WHO Outcome		1,312		834		***<0.001***[b]
1.Not Hospitalized	1,450 (67.6)		981 (74.8)		469 (56.2)	
2.Hospitalized	199 (9.3)		102 (7.8)		97 (11.6)	
3.Hosp., Supplemental Oxygen	215 (10.0)		98 (7.5)		117 (14.0)	
4. Hosp. Hi-flow, Non-Inv. Mech. Vent.	104 (4.8)		53 (4.0)		51 (6.1)	
5. Hosp. ECMO, Inv. Mech. Vent.	93 (4.3)		42 (3.2)		51 (6.1)	
6.Death	85 (4.0)		36 (2.7)		49 (5.9)	

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).
P-values: a1=t-test, a2=Satterthwaite t-test, b=Wilcoxon Rank Sum test, c=Pearson's chi-square test, d=Fisher's Exact test

Table 2: Multivariable Models of Metabolic Syndrome.

Outcome	Predictor	Odds Ratio (95% CI)	p-value
Hospitalization	Metabolic Syndrome	1.77 (1.42,2.20)	***< 0.001***
	Male Gender	1.81 (1.46,2.25)	***< 0.001***
	Other vs. Black Race	0.88 (0.51,1.51)	0.64
	White vs. Black Race	0.43 (0.34,0.55)	***< 0.001***
	Asthma	1.62 (1.23,2.12)	***< 0.001***
	Heart Failure	1.67 (1.21,2.32)	***0.002***
	Coronary Artery Disease	1.12 (0.83,1.51)	0.46
	Age (per decade)	1.44 (1.35,1.54)	***< 0.001***
ICU Admission	Metabolic Syndrome	1.56 (1.15,2.12)	***0.004***
	Male Gender	1.66 (1.22,2.25)	***0.001***
	Other vs. Black Race	0.69 (0.28,1.69)	0.42
	White vs. Black Race	0.74 (0.53,1.02)	0.068
	Asthma	1.12 (0.76,1.66)	0.57
	Heart Failure	1.86 (1.26,2.74)	***0.002***

Outcome	Predictor	Odds Ratio (95% CI)	p-value
	Coronary Artery Disease	1.02 (0.69,1.49)	0.93
	Age (per decade)	1.39 (1.26,1.53)	***< 0.001***
Mortality	Metabolic Syndrome	1.81 (1.05,3.12)	***0.034***
	Male Gender	0.72 (0.42,1.24)	0.24
	Other vs. Black Race	0.35 (0.04,3.05)	0.34
	White vs. Black Race	1.76 (0.97,3.18)	0.062
	Asthma	0.65 (0.31,1.37)	0.26
	Heart Failure	1.58 (0.85,2.96)	0.15
	Coronary Artery Disease	1.50 (0.82,2.75)	0.19
	Age (per decade)	2.88 (2.26,3.68)	***< 0.001***
Odds Ratios are from logistic regression models			

Table 3: AST/ALT Results.

Factor	Total (N=2,475)	AST/ALT≤1 (N=820)		AST/ALT>1 (N=1,655)		*p*-value
		N	Statistics	N	Statistics	
Covariates						
Age	57.1 ± 19.3	815	51.2 ± 16.1	1,644	60.1 ± 20.1	***<0.001***[a2]
Gender		813		1,641		***<0.001***[c]
Male	1,082 (44.1)		434 (53.4)		648 (39.5)	
Female	1,372 (55.9)		379 (46.6)		993 (60.5)	
Race		780		1,581		***<0.001***[c]
Other	107 (4.5)		48 (6.2)		59 (3.7)	
Black/African-American	789 (33.4)		215 (27.6)		574 (36.3)	
White	1,465 (62.0)		517 (66.3)		948 (60.0)	
Ethnicity		754		1,550		***<0.001***[c]
Non-Hispanic	2,167 (94.1)		683 (90.6)		1,484 (95.7)	
Hispanic	137 (5.9)		71 (9.4)		66 (4.3)	
BMI	31.1 ± 8.0	767	32.7 ± 7.7	1,581	30.3 ± 8.1	***<0.001***[a1]
Hypertension	1,339 (57.3)	764	420 (55.0)	1,571	919 (58.5)	0.11[c]
OSA	418 (16.9)	820	154 (18.8)	1,655	264 (16.0)	0.077[c]
NAFLD	71 (2.9)	820	41 (5.0)	1,655	30 (1.8)	***<0.001***[c]
PCOS	34 (1.4)	820	12 (1.5)	1,655	22 (1.3)	0.79[c]
Asthma	420 (18.6)	745	137 (18.4)	1,511	283 (18.7)	0.85[c]
Heart failure	296 (13.2)	743	52 (7.0)	1,505	244 (16.2)	***<0.001***[c]
Coronary artery disease	362 (16.0)	743	74 (10.0)	1,522	288 (18.9)	***<0.001***[c]
Labs						
Glucose	103.0 [90.0, 126.0]	632	104.5 [93.0, 130.0]	1,264	102.0 [89.0, 125.0]	***0.002***[b]
Triglycerides	98.0 [68.0, 141.0]	581	108.0 [72.0, 155.0]	1,189	95.0 [66.0, 132.0]	***<0.001***[b]
HDL	48.0 [38.0, 61.0]	581	46.0 [38.0, 57.0]	1,182	49.0 [39.0, 63.0]	***<0.001***[b]
AST	23.0 [18.0, 34.0]	820	23.0 [17.0, 30.5]	1,655	24.0 [19.0, 35.0]	***<0.001***[b]
ALT	20.0 [14.0, 30.0]	820	29.0 [21.0, 43.0]	1,655	16.0 [12.0, 23.0]	***<0.001***[b]
Outcomes						
Hospitalized	870 (36.0)	798	204 (25.6)	1,622	666 (41.1)	***<0.001***[c]
Admitted to ICU	294 (12.2)	798	60 (7.5)	1,621	234 (14.4)	***<0.001***[c]
Death	102 (7.0)	501	12 (2.4)	956	90 (9.4)	***<0.001***[c]
WHO Outcome		820		1,655		***<0.001***[b]
1.Not Hospitalized	1,600 (64.6)		615 (75.0)		985 (59.5)	
2.Hospitalized	254 (10.3)		74 (9.0)		180 (10.9)	
3.Hosp., Supplemental Oxygen	273 (11.0)		73 (8.9)		200 (12.1)	
4. Hosp. Hi-flow, Non-Inv. Mech. Vent.	121 (4.9)		24 (2.9)		97 (5.9)	
5. Hosp. ECMO, Inv. Mech. Vent.	125 (5.1)		22 (2.7)		103 (6.2)	
6.Death	102 (4.1)		12 (1.5)		90 (5.4)	

Statistics presented as Mean ± SD, Median [P25, P75], N (column %).
p-values: a1=t-test, a2=Satterthwaite t-test, b=Wilcoxon Rank Sum test, c=Pearson's chi-square test, d=Fisher's Exact test.

Table 4: Multivariable Models for AST: ALT.

Outcome	Predictor	Odds Ratio (95% CI)	p-value
Hospitalization	AST:ALT>1	1.52 (1.22,1.90)	***< 0.001***
	Male Gender	2.10 (1.72,2.56)	***< 0.001***
	Other vs. Black Race	1.00 (0.61,1.62)	0.99
	White vs. Black Race	0.44 (0.36,0.55)	***< 0.001***
	Asthma	1.48 (1.15,1.91)	***0.003***
	Heart Failure	1.56 (1.14,2.13)	***0.005***
	Coronary Artery Disease	1.04 (0.78,1.39)	0.80
	Age (per decade)	1.42 (1.33,1.51)	***< 0.001***
ICU Admission	AST:ALT>1	1.60 (1.14,2.26)	***0.007***
	Male Gender	2.02 (1.53,2.68)	***< 0.001***
	Other vs. Black Race	0.75 (0.34,1.64)	0.47
	White vs. Black Race	0.74 (0.55,0.99)	***0.046***
	Asthma	1.04 (0.72,1.50)	0.82
	Heart Failure	1.83 (1.27,2.64)	***0.001***
	Coronary Artery Disease	1.02 (0.71,1.47)	0.91
	Age (per decade)	1.32 (1.21,1.44)	***< 0.001***
Mortality	AST:ALT>1	1.55 (0.75,3.19)	0.23
	Male Gender	0.83 (0.50,1.37)	0.46
	Other vs. Black Race	0.31 (0.04,2.69)	0.29
	White vs. Black Race	1.77 (1.03,3.05)	***0.040***
	Asthma	0.60 (0.30,1.23)	0.16
	Heart Failure	1.77 (0.99,3.19)	0.055
	Coronary Artery Disease	1.32 (0.74,2.35)	0.35
	Age (per decade)	2.73 (2.19,3.41)	***< 0.001***
	Odds Ratios are from logistic regression models		

fasting hyperglycemia, and dyslipidemia [24]. Elevated AST/ALT ratio may be an important indicator of COVID-19 severity due to direct viral effects of SARS-CoV-2 on the liver, systemic inflammation, or drug-induced effects. The ACE2 receptor has not been detected on hepatocytes; thus, direct viral entry into hepatocytes is unlikely to be the main mechanism of liver damage [25]. Rather, the compensatory reaction to systemic pro-inflammation and cytokine release induced by SARS-CoV-2 may underlie the elevation in liver transaminases. Hepatic steatosis and inflammation may be a common mechanism that hallmarks metabolic syndrome and exacerbates COVID-19 response leading to hospitalization. Prior studies have demonstrated the correlation between transaminase levels and severity of COVID-19 [23,26,27]. In this study, patients with pre-admission serum AST: ALT>1 were more likely to be hospitalized compared to patients with AST: ALT<1. Our results support the findings highlighted by Cai et al in which the hepatocellular pattern of liver injury is a strong predictor of severe COVID-19 [16].

Our results support the findings by Lohia et al. and Xie et al. that metabolic syndrome is a significant predictor of mortality and hospitalization [7,8]. We sought to further explore the predictive role of surrogate lab markers of metabolic syndrome, and demonstrate that the serum values AST/ALT ratio >1 independently predicts hospitalization but not mortality. Interestingly, while our results showed that escalating need for supplemental oxygen, non-invasive oxygenation, and extracorporeal membrane oxygenation (ECMO) was significantly higher in the metabolic syndrome group, this contrasted with the study by van Zelst et al in their smaller cohort of 82 patients that metabolic syndrome was not associated with increasing respiratory requirements [28].

The increasing prevalence of metabolic syndrome is concerning for worsening morbidity and mortality with COVID-19 infection. In 2016, over 1.9 billion adults were overweight, constituting 39% of the world population [29]. Moreover, countries with higher rates of obesity tend also to have more severe COVID-19 infection [30]. Unlike the variables of age and sex, metabolic syndrome and its components are modifiable risk factors. Lifestyle and dietary changes to achieve weight loss, low salt diet, decreased alcohol intake, as well as medical treatment of dyslipidemia, hyperglycemia, and hypertension target the individual components of metabolic syndrome [30]. The effects of improved glucose, blood pressure, and weight control may modulate the systemic inflammatory response and mitigate COVID-19 disease severity, particularly for preventing thrombosis formation [31]. The protective role of statins and renin-angiotensin-aldosterone system (RAAS) modulators in management of COVID-19 and other pro-inflammatory viral illnesses are still unclear [32–35]. Efforts to improve biochemical and anthropometric parameters that define metabolic syndrome would reduce morbidity and mortality for not only COVID-19, but future pandemics.

Limitations

This retrospective, cross-sectional study could not explain causal relationships between surrogate markers of metabolic syndrome and outcomes. Underlying molecular factors such as cytokines, interleukin, and apolipoprotein levels that were not routinely

performed in a clinical, non-investigational setting were unable to be captured. Many patients tested for COVID-19 at the Cleveland Clinic did not have prior medical records in the Cleveland Clinic health system, leading to a high rate of missing data. Lab values within one year were not available or could not be retrieved for a sizable percentage of the patient cohort. We cannot exclude the influence of potential confounders due to missing laboratory measurements. Besides AST and ALT, other markers of liver function (e.g. albumin, alkaline phosphatase, gamma-glutamyl transferase, C-reactive protein, LDH) were unable to measured. Most patients in this cohort were residents of Ohio or Florida, and results may not be generalizable to all populations.

Conclusion

Metabolic syndrome is significantly associated with increased hospitalization, ICU admission, and mortality due to COVID-19, even after adjusting for sex, age, race, and comorbidities. Elevations in the surrogate biomarker ratios AST/ALT and TG/HDL were significantly associated with hospitalization but not mortality. Obesity, hyperglycemia, dyslipidemia, and hypertension are modifiable components of metabolic syndrome that would reduce morbidity and mortality of COVID-19.

Funding Sources

Cleveland Clinic internal funding. None of the authors has a financial interest, commercial association, or disclosure regarding any of the companies, organizations, products, services, devices, or drugs that may be mentioned in this manuscript. There are no funding sources to disclose, including NIH, Wellcome Trust, or HHMI. Dr. Misra-Hebert receives funding from the Agency for Healthcare Research and Quality grant # K08HS024128 and reports grants from NHLBI, grants from Novo Nordisk Inc, grants from Merck Inc, grants from Boehringer Ingelheim Pharmaceuticals Inc, outside the submitted work.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323: 1239-1242.
2. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020:1-8.
3. Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: A systematic review and meta-analysis. J Med Virol. 2021; 93: 257-261.
4. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020; 14: 1463-1465.
5. Yanai H. Adiposity is the Crucial Enhancer of COVID-19. Cardiol Res. 2020; 11: 353-354.
6. Aminian A, Fathalizadeh A, Tu C, et al. Association of prior metabolic and bariatric surgery with severity of coronavirus disease 2019 (COVID-19) in patients with obesity. Surg Obes Relat Dis Off J Am Soc Bariatr Surg. 2021; 17: 208-214.
7. Lohia P, Kapur S, Benjaram S, et al. Metabolic syndrome and clinical outcomes in patients infected with COVID-19: Does age, sex, and race of the patient with metabolic syndrome matter? J Diabetes. 2021; 13: 420-429.
8. Xie J, Zu Y, Alkhatib A, et al. Metabolic Syndrome and COVID-19 Mortality Among Adult Black Patients in New Orleans. Diabetes Care. 2020; 44:188-193.
9. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486-2497.
10. Ghoneim S, Butt MU, Hamid O, et al. The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study. Metab open. 2020; 8:100057.
11. Alamdari NM, Rahimi FS, Afaghi S, et al. The impact of metabolic syndrome on morbidity and mortality among intensive care unit admitted COVID-19 patients. Diabetes Metab Syndr. 2020;14:1979-1986.
12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15: 539-553.
13. Wannamethee SG, Shaper AG, Lennon L, et al. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med. 2005;165: 2644-2650.
14. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020; 382:1787-1799.
15. International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC).
16. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020; 73: 566-574.
17. Giannini E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. Arch Intern Med. 2003;163: 218-224.
18. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology. 1988; 95: 734-739.
19. Nyblom H, Berggren U, Balldin J, et al. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol. 2004; 39: 336-339.
20. Grassi D, Ferri L, Desideri G, et al. Chronic hyperuricemia, uric acid deposit and cardiovascular risk. Curr Pharm Des. 2013; 19: 2432-2438.
21. Quispe R, Martin SS, Jones SR. Triglycerides to high-density lipoprotein-cholesterol ratio, glycemic control and cardiovascular risk in obese patients with type 2 diabetes. Curr Opin Endocrinol Diabetes Obes. 2016; 23:150-156.

22. Zhang B, Dong C, Li S, et al. Triglyceride to High-Density Lipoprotein Cholesterol Ratio is an Important Determinant of Cardiovascular Risk and Poor Prognosis in Coronavirus Disease-19: A Retrospective Case Series Study. Diabetes Metab Syndr Obes. 2020; 13: 3925-3936.

23. Qin C, Wei Y, Lyu X, et al. High aspartate aminotransferase to alanine aminotransferase ratio on admission as risk factor for poor prognosis in COVID-19 patients. Sci Rep. 2020;10:16496.

24. Yang KC, Hung H-F, Lu C-W, et al. Association of Non-alcoholic Fatty Liver Disease with Metabolic Syndrome Independently of Central Obesity and Insulin Resistance. Sci Rep. 2016; 6: 27034.

25. Bansal R, Gubbi S, Muniyappa R. Metabolic Syndrome and COVID 19: Endocrine-Immune-Vascular Interactions Shapes Clinical Course. Endocrinology. 2020; 161: 1-15.

26. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382:1708-1720.

27. Lu H, Ai J, Shen Y, et al. A descriptive study of the impact of diseases control and prevention on the epidemics dynamics and clinical features of SARS-CoV-2 outbreak in Shanghai, lessons learned for metropolis epidemics prevention. medRxiv. 2020.

28. van Zelst CM, Janssen ML, Pouw N, et al. Analyses of abdominal adiposity and metabolic syndrome as risk factors for respiratory distress in COVID-19. BMJ open Respir Res. 2020; 7: e000792.

29. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

30. Mechanick JI, Rosenson RS, Pinney SP, et al. Coronavirus and Cardiometabolic Syndrome: JACC Focus Seminar. J Am Coll Cardiol. 2020; 76: 2024-2035.

31. Yanai H. Metabolic Syndrome and COVID-19. Cardiol Res. 2020;11: 360-365.

32. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. Hypertens Res. 2020; 43: 648-654.

33. Kow CS, Hasan SS. Meta-analysis of Effect of Statins in Patients with COVID-19. Am J Cardiol. 2020;134:153-155.

34. Grover A, Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Eur Hear journal Cardiovasc Pharmacother. 2021; 7: 148-157.

35. Lo KB, Bhargav R, Salacup G, et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers and outcomes in patients with COVID-19: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther. 2020;18: 919-930.

Supplementary

Supplementary Table 1: Univariable Analysis for TG: HDL.

Factor	N	Statistics	p-value
Covariates			
Gender	.		***<0.001***
. Male	785	2.4 [1.4, 4.3]	
. Female	1019	1.8 [1.1, 3.0]	
Race	.		***<0.001***
. Other	74	2.2 [1.3, 4.1]	
. Black/African-American	550	1.7 [1.1, 2.9]	
. White	1119	2.1 [1.3, 3.8]	
Ethnicity	.		0.69
. Non-Hispanic	1626	2.0 [1.2, 3.5]	
. Hispanic	96	2.1 [1.3, 3.7]	
OSA	.		***0.001***
. No	1416	2.0 [1.2, 3.5]	
. Yes	390	2.3 [1.4, 3.9]	
NAFLD	.		0.062
. No	1744	2.0 [1.2, 3.6]	
. Yes	62	2.2 [1.7, 3.8]	
PCOS	.		0.43
. No	1774	2.0 [1.2, 3.6]	
. Yes	32	1.7 [1.2, 2.9]	
Asthma	.		0.85
. No	1357	2.0 [1.2, 3.6]	
. Yes	313	2.1 [1.2, 3.4]	
Heart failure	.		***<0.001***
. No	1411	2.0 [1.2, 3.4]	
. Yes	255	2.3 [1.4, 4.1]	
Coronary artery disease	.		***<0.001***
. No	1359	2.0 [1.1, 3.3]	
. Yes	320	2.5 [1.5, 4.5]	
Age	1804	0.04 (-0.00, 0.09)	0.076
BMI	1760	0.22 (0.17, 0.26)	***<0.001***
Outcomes			
Hospitalized	.		***<0.001***
. No	1164	1.9 [1.1, 3.4]	
. Yes	597	2.3 [1.3, 3.8]	
Admitted to ICU	.		***<0.001***
. No	1561	2.0 [1.2, 3.5]	
. Yes	199	2.5 [1.4, 4.2]	
Death	.		***0.035***
. No	944	2.1 [1.2, 3.5]	
. Yes	76	2.6 [1.4, 4.5]	
WHO Outcome	.		***0.006***
. 1. Not Hospitalized	1206	1.9 [1.1, 3.4]	
. 2. Hospitalized	160	2.2 [1.3, 3.3]	
. 3. Hosp., Supplemental Oxygen	198	2.2 [1.4, 3.9]	
. 4. Hosp. Hi-flow, Non-Inv. Mech. Vent.	89	2.3 [1.2, 4.0]	
. 5. Hosp. ECMO, Inv. Mech. Vent.	77	2.2 [1.3, 3.8]	
. 6.Death	76	2.6 [1.4, 4.5]	

Statistics presented as Median [25th, 75th percentiles] with Kruskal Wallis test or Spearman's correlation (95% CI).

Supplemental Table 2: Multivariable Models for TG: HDL.

Outcome	Predictor	Odds Ratio (95% CI)	p-value
Hospitalization	TG:HDL	1.01 (1.00,1.03)	0.16
	Male Gender	1.84 (1.45,2.32)	***< 0.001***
	Other vs. Black Race	0.85 (0.47,1.53)	0.59
	White vs. Black Race	0.41 (0.32,0.52)	***< 0.001***
	Asthma	1.78 (1.32,2.39)	***< 0.001***
	Heart Failure	1.92 (1.37,2.69)	***< 0.001***
	Coronary Artery Disease	1.27 (0.93,1.74)	0.13
	Age (per decade)	1.43 (1.33,1.54)	***< 0.001***
ICU Admission	TG:HDL	1.01 (0.99,1.03)	0.33
	Male Gender	1.82 (1.31,2.52)	***< 0.001***
	Other vs. Black Race	0.77 (0.31,1.91)	0.57
	White vs. Black Race	0.66 (0.46,0.93)	***0.018***
	Asthma	1.22 (0.80,1.84)	0.35
	Heart Failure	2.01 (1.34,3.01)	***< 0.001***
	Coronary Artery Disease	1.22 (0.82,1.82)	0.32
	Age (per decade)	1.35 (1.21,1.50)	***< 0.001***
Mortality	TG:HDL	1.01 (0.99,1.04)	0.36
	Male Gender	0.81 (0.46,1.45)	0.48
	Other vs. Black Race	0.38 (0.04,3.58)	0.40
	White vs. Black Race	1.38 (0.75,2.55)	0.30
	Asthma	0.65 (0.30,1.43)	0.29
	Heart Failure	1.81 (0.94,3.47)	0.076
	Coronary Artery Disease	1.86 (0.99,3.49)	0.054
	Age (per decade)	2.60 (2.03,3.33)	***< 0.001***

Odds Ratios are from logistic regression models.