The incidence of COVID-19 in patients with metabolic syndrome and non-alcoholic steatohepatitis: A population-based study ☆

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ABSTRACT

Background: The novel coronavirus disease (COVID-19) emerged from China in 2019 and rapidly spread worldwide. Patients with metabolic comorbid conditions are more susceptible to infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Metabolic syndrome is a constellation of interlinked metabolic risk factors that predispose patients to increased risk of complications. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and non-alcoholic steatohepatitis (NASH) is the aggressive form of NAFLD.
Objective: The aim of this study is to determine the relationship between metabolic syndrome components and the risk of COVID-19.
Methods: We reviewed data from a large commercial database (Explorys IBM) that aggregates electronic health records from 26 large nationwide healthcare systems. Using systemized nomenclature of clinical medical terms (SNOMED-CT), we identified adults with the diagnosis of metabolic syndrome and its individual components from 1999 to 2019. We included patients with the diagnosis of COVID-19 from December 2019 to May 2020. Comorbidities known to be associated with COVID-19 and metabolic syndrome such as obesity, diabetes mellitus, dyslipidemia, smoking, male gender, African American, and hypertension were collected. Univariable and multivariable analyses were performed to investigate whether metabolic syndrome or its individual components are independently associated with the risk of COVID-19.
Results: Out of 61.4 million active adult patients in the database, 8885 (0.01%) had documented COVID-19. The cumulative incidence of COVID-19 was higher if metabolic syndrome was the primary diagnosis (0.10% vs 0.01%, OR 7.00 [6.11–8.01]). The adjusted odds (aOR) of having COVID-19 was higher in patients if they were African Americans (aOR 7.45 [7.14–7.77]), hypertensive (aOR 2.53 [2.40–2.68]), obese (aOR 2.20 [2.10–2.32]), diabetic (aOR 1.41 [1.33–1.48]), hyperlipidemic (aOR 1.70 [1.56–1.74]), or diagnosed with NASH (aOR 4.93 [4.06–6.00]). There was a slight decrease in the adjusted odds of having COVID-19 in males as compared to females (aOR 0.88 [0.84–0.92]).
Conclusion: The incidence of COVID-19 in patients with metabolic syndrome is high. Among all comorbid metabolic conditions, NASH had the strongest association with COVID-19.

1. Introduction

In late December 2019, the People's Republic of China (Wuhan City of Hubei Province) observed an increased number of pneumonia cases of unknown etiology later confirmed by Chinese authorities to be caused by Coronavirus Disease 2019 (COVID-19). Subsequently, the virus was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2] This novel virus

took China by storm and transcended international borders in no time reaching the world tally of 4,731,458 confirmed cases and 316,169 deaths by mid-May [2]. To date this virus has been transmitted to 216 countries. Currently, the United States has the highest number of confirmed cases 5,119,711 and reported deaths 163,651 [2]. The SARS-CoV-2 belongs to a group of B-coronavirus which is an enveloped positive-sense RNA virus of subgenus sarbecovirus [3]. It can easily move across species through the spike glycoprotein S1 that binds to angiotensin converting enzyme 2 (ACE2) receptor present on host cells [4,5]. This receptor is highly expressed in respiratory and gastrointestinal epithelial cells [5]. The clinical manifestations of COVID-19 are highly variable. Up to 74% of patients initially present with atypical pneumonia [6,7]. Approximately 50% of patients develop hypoxia and 26% progress to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [7,8]. According to previous research, the presence of comorbidities increases the mortality risk with cardiac disease and diabetes being the most important components to predict adverse outcomes [9]. The US Centers for Disease Control (CDC) reported in their Morbidity and Mortality Weekly Report on April 17 that among those with comorbid conditions, the most common were hypertension (49.7%), obesity (48.3%) diabetes mellitus (28.3%) and cardiovascular disease (27.8%) [10]. Reported data by race/ethnicity indicate that African American individuals bear a disproportionate burden of COVID-19 related outcomes [11].

Metabolic syndrome (MetS) also known as syndrome X is a global problem. This syndrome feeds into the spread of diseases such as diabetes mellitus, hypertension and coronary disease. Non-alcoholic fatty liver disease is part of and victim of the global metabolic derangement seen with this condition [12]. Although a relationship between metabolic syndrome and COVID-19 severity might exist, It's currently unclear whether NASH is associated with a higher risk of SARS-CoV-2 infection. Our primary objective with this study was to identify whether metabolic syndrome or its individual components are independently associated with the diagnosis of COVID-19. Our secondary objective was to investigate whether a relationship exists between NASH and COVID-19.

2. Materials and methods

2.1. Study design

This is a retrospective analysis of a large electronic health record (EHR)-based commercial database called Explorys (IBM). Explorys platform assimilates patient information from 26 major healthcare systems spread over 50 states in the US. It stores over 60 million unique patient records [13]. Patient information is then de-identified, standardized and stored in a cloud database [13,14]. The Explorys platform uses SNOMED-CT for medical diagnoses and procedures. For diagnoses, International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes are mapped into the SNOMED-CT hierarchy [13]. Cohorts can further be refined demographically and comorbid diseases can be extracted [13,14]. The use of Explorys has been validated in multiple fields including Cardiology and Gastroenterology [13]. This platform is Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health Act (HITECH) compliant [13]. The Case Western Reserve University/Metrohealth Medical Center Institutional Review Board deemed studies using Explorys, as the dataset of record, to be exempt from approval because all patient information is de-identified. Explorys protects patient confidentiality by approximating each population count to 10. All counts between 0 and 10 are treated equally. For the purpose of this study, counts between 0 and 10 were approximated to be five [14].

2.2. Patient selection

Adult subjects (age above 18 years) with active electronic health records since 1999 were identified using the search tool in Explorys. Using the SNOMED-CT diagnosis "Non-alcoholic steatohepatitis", we identified patients who were diagnosed with NASH between 1999 and 2020. Patients with the diagnosis of "fatty liver disease", "alcoholic hepatitis" and "alcoholic fatty liver disease" were excluded. We searched for metabolic syndrome using the SNOMED-CT diagnosis "Metabolic Syndrome". Patients with COVID-19 were identified by the SNOMED-CT diagnosis for coronavirus infection for the period of December 2019 to May 2020. All sub-diagnoses of COVID-19 including "pneumonia and "severe acute respiratory syndrome" were included. Controls were classified as those patients without the diagnosis of COVID-19. For our analysis, we identified cohorts of patients with and without COVID-19. It was not possible to perform propensity-score matching because this database only provides population-level data and not individual cases.

2.3. Covariates

We collected cross-sectional information on patient demographics such as gender, race, and comorbidities known to be associated with metabolic syndrome such hypertension, diabetes, obesity and dyslipidemia by searching the database for their respective SNOMED-CT terms. Primary outcome of interest was COVID-19 cumulative incidence associated with different risk factors.

2.4. Statistical analysis

To assess the association between COVID-19 and patient demographics and metabolic characteristics, we divided the whole cohort of patients into COVID-19 infected and non-COVID infected patients.

The cumulative incidence of COVID-19 since the start of the pandemic (December 2020 to May 2020) was calculated by dividing the number of patients diagnosed with COVID-19 by total number of patients in each risk group. Categorical variables are presented as numbers and percentages and were compared using the Pearson $\chi 2$ test. Odds ratios are presented with 95% confidence intervals (CI). Univariate binary logistic model was constructed using COVID-19 as dependent variable and other variables as independent variables. To adjust for possible confounding, a multi-variable model adjusting for all covariates mentioned in univariate variables were added. Independence among covariate risk factors was assessed using the variance inflating factor (VIF) with cut-off of significant collinearity set at VIF > 1.5. "Goodness-of-fit" was assessed for all regression models using the Hosmer-Lemeshow test, with P > 0.05 indicating good fit. All statistical analysis was done using SAS version 9.4 (SAS Inst., Cary, NC). Significance was defined as the 2-tailed value of P < 0.05.

2.5. Regulatory approvals

This study was exempt from approval by the Case Western Reserve University at Metrohealth Medical Center Institutional Review Board as the dataset obtained from the Explorys platform is de-identified.

3. Results

Out of 61.4 million active adult patients in the database 8885 (0.01%) had documented COVID-19 infection. Baseline

characteristics are displayed in Table 1.

Using Univariate analysis, patients were found to have higher cumulative incidence of COVID-19 during the pandemic if they had an associated diagnosis of metabolic syndrome (0.10% vs 0.01%, OR 7.00 [6.11–8.01]). Looking at the individual components of metabolic syndrome, patients were at increased risk of COVID-19 if they had an underlying diagnosis of hypertension (0.04% vs 0.01%, OR 5.81 [5.57–6.07]), diabetes mellitus (0.05% vs 0.01%, OR 4.88 [4.67–5.10]), dyslipidemia (0.04% vs 0.01%, OR 4.22 [4.05–4.40]), or obesity (0.06% vs 0.01%, OR 6.13 [5.86–6.40]). African Americans had a higher risk of having COVID-19 than non-African Americans (0.07% vs 0.01%, OR 9.20 [8.82–9.59]), but the risk was lower if the patient was male (0.02% vs 0.01%, OR 0.85 [0.81–0.89]). NASH if present was the highest risk factor of all associated with COVID-19 (0.20% vs 0.01%, OR 14.10 [11.63–17.10]).

Multivariable binary logistic regression model was built using variables from univariate models (Table 2). Results showed adjusted odds of having COVID-19 was higher in patients if they were African Americans (aOR 7.45 [7.14–7.77]), hypertensive (aOR 2.53 [2.40–2.68]), obese (aOR 2.20 [2.10–2.32]), diabetic (aOR 1.41 [1.33–1.48]), hyperlipidemic (aOR 1.70 [1.56–1.74]), or diagnosed with NASH (aOR 4.93 [4.06–6.00]). There was a slight decrease in adjusted odds of having COVID-19 in males as compared to females (aOR 0.88 [0.84–0.92]) (Fig. 1).

4. Discussion

We report a strong positive association between metabolic syndrome and the risk of COVID-19. To date, this is the first US-based large database study that looked at the relationship between metabolic syndrome, its individual components and SARS-CoV-2 infection. Individuals with diabetes mellitus, hypertension, and obesity have been shown to have higher morbidity and mortality from infections with SARS-CoV-2.

The cumulative prevalence of hypertension among our study population was 21%. Similar to our findings, the prevalence of hypertension among US adults was recently estimated to be 29% [15]. Furthermore, in our COVID-19 cohort, approximately 60% had a diagnosis of essential hypertension. Prior studies have also

Table 2
The adjusted odds ratio for select variables and the incidence of COVID-19.

Variable	OR (95% CI) in Overall Study Population
African American	7.45 (7.14–7.77)
NASH	4.93 (4.06–6.00)
Hypertension	2.53 (2.40–2.68)
Obesity	2.20 (2.10–2.32)
Dyslipidemia	1.65 (1.56–1.74)
Diabetes mellitus	1.41 (1.33–1.48)
Male	0.88 (0.84–0.91)

confirmed a higher incidence rate of hypertension among patients with COVID-19 [16]. Of all the metabolic syndrome components adjusted for in our model, the incidence of COVID-19 was highest among the hypertensive group. The frequency with which COVID-19 patients are hypertensive may not be entirely surprising since older patients appear to be at a particularly higher risk of infection and are also the ones most likely to be hypertensive. It is also unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19 or whether controlled blood pressure among patients with hypertension is or is not a risk factor. Unfortunately, we are unable to distinguish between controlled and uncontrolled hypertension. But our observation raises the question about the susceptibility of hypertensive patients to SARS-CoV-2.

There was a strong association between dyslipidemia and COVID-19. Dyslipidemia was the second most common diagnosis in the COVID-19 cohort after hypertension with a reported incidence rate of 46.8%. Little data exists on whether dyslipidemia predisposes individuals to a higher risk of SARS-CoV-2. One proposed mechanism may involve the pro-inflammatory response induced by accumulated cholesterol in atherosclerotic plaques. ACE2 receptor is also highly expressed by activated macrophages [17]. The findings of our study therefore support the adverse association between dyslipidemia and infection by SARS-CoV-2.

Subjects with diabetes had an overall higher risk of COVID-19 than those without, possibly attributed to a dysfunctional innate immune system. Potential mechanisms suggested to increase the susceptibility of diabetic patients to SARS-CoV-2 include higher affinity cellular binding and entry, decreased viral clearance,

Table 1
Baseline characteristics of study population.

| Characteristics	Total Cohort	COVID-19	Non-COVID-19	P value
Sex				
Male	27,185,375 (44.21%)	3,585 (0.01%)	27,180,000 (99.99%)	<0.001
Female	34,308,025 (55.79%)	5,300 (0.02%)	34,300,000 (99.98%)	
Race				
African	6,263,210 (10.19%)	4,535 (0.07%)	6,258,675 (99.93%)	<0.001
Non-African	55,230,190 (89.81%)	4,350 (0.01%)	55,230,000 (99.99%)	
Metabolic Syndrome				
Yes	217,535 (0.35%)	215 (0.10%)	56,460 (89.63%)	<0.001
No	61,275,865 (99.65%)	8,670 (0.01%)	60,670,000 (99.52%)	
NASH				
Yes	52,230 (0.08%)	105 (0.20%)	52,125 (99.80%)	<0.001
No	61,441,170 (99.92%)	8,780 (0.01%)	61,430,000 (99.99%)	
Hypertension				
Yes	12,609,725 (20.51%)	5,330 (0.04%)	12,600,000 (99.96%)	<0.001
No	48,883,675 (79.49%)	3,555 (0.01%)	48,880,000 (99.99%)	
Diabetes mellitus				
Yes	5,301,230 (8.62%)	2,800 (0.05%)	5,298,430 (99.95%)	<0.001
No	56,192,170 (91.38%)	6,085 (0.01%)	56,190,000 (99.99%)	
Obesity				
Yes	4,792,675 (7.79%)	3,030 (0.06%)	4,789,645 (99.94%)	<0.001
No	56,700,725 (92.21%)	5,855 (0.01%)	56,690,000 (99.99%)	
Dyslipidemia				
Yes	10,616,650 (17.26%)	4,160 (0.04%)	50,870,000 (99.99%)	<0.001
No	50,876,750 (82.74%)	4,725 (0.01%)	10,610,000 (99.96%)	
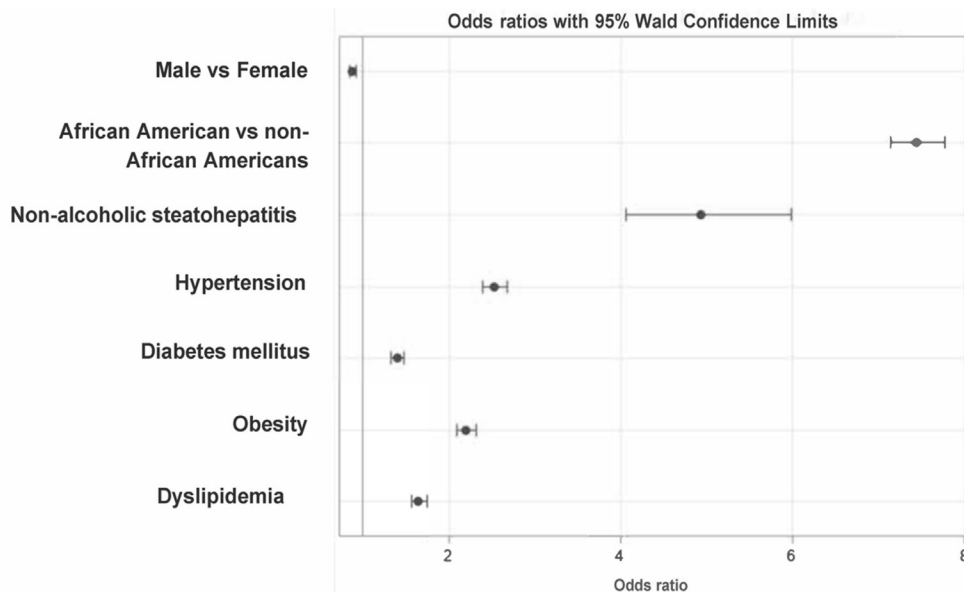
Fig. 1. Forest plot showing adjusted odds ratio of having COVID-19. The dots represent the odds ratio and the horizontal lines represents the 95% confidence interval.

diminished T cell function, increased susceptibility to hyper-inflammation and cytokine storm syndrome and the presence of cardiovascular disease. Augmented ACE2 expression has been demonstrated in the lungs, kidney, heart and pancreas in rodent models of diabetes [18,19]. Insulin administration attenuates ACE2 expression while antihypertensives such as ACE inhibitors, statins, and hypoglycemic agents such as glucagon-like peptide agonists upregulate ACE2 expression [19–23]. In our COVID-19 cohort 31.5% had a diagnosis of diabetes mellitus. Our findings are therefore in line with what was previously reported in literature implicating diabetes as an independent risk factor for COVID-19.

Obesity has been shown to be an independent risk factor for infection by this novel virus. In our cohort, obesity was strongly associated with COVID-19 and the third most prevalent metabolic risk factor after dyslipidemia and hypertension. A disproportionate number of obese patients with COVID-19 should be anticipated since it has been previously documented for different viral pathogens including influenza [24–27]. Although the exact mechanism by which obesity predisposes patients to COVID-19 is not yet defined, several parameters play a role. First patients with obesity have altered respiratory physiology including reduced functional residual capacity and expiratory reserve volume as well as hypoxemia and ventilation/perfusion abnormalities [25]. Second, obesity is associated with impaired immune response [28]. Third, ACE2 enzyme expression in adipose tissue shows high affinity for SARS-CoV-2 and may contribute to the significant association between this metabolic risk factor and COVID-19 [29].

There is limited data linking pre-existing liver disease with SARS-CoV-2 infection. NAFLD is unambiguously related to increased liver-related and all-cause mortality [30]. The progression of NAFLD to NASH is mirrored by increased activation of hepatic and systemic inflammatory cascades. Only recently has NASH been accepted as an inflammatory disorder [31]. Circulating inflammatory markers are more pronounced in patients with NASH compared to those with simple steatosis. Macrophages in hepatic parenchyma and adipose tissue release proinflammatory cytokines supporting liver injury and progression of NAFLD. Of all the metabolic risk factors investigated in this study, having NASH had the strongest association with the incidence of COVID-19. Whether the heightened inflammatory response seen in NASH increases the susceptibility to SARS-CoV-2 remains to be explored.

The cumulative incidence of COVID-19 was higher in women than in men (60% vs 40%). In Switzerland, early incidence reports documented higher cases of COVID-19 in women [32]. However, across all countries, prevalence studies have shown men with COVID-19 are at more risk of worse outcomes and death [32]. In our univariate analysis, males and females had comparable susceptibility to SARS-CoV-2. This is in line with what is currently reported by the CDC [10]. The mechanisms accounting for the sex imbalance currently seen in reported cases and case fatalities are currently unknown and it's unclear whether gender is a risk factor for COVID-19. More clinical and basic research investigating this association is needed in the future.

Preliminary prevalence reports have unmasked the racial disparities that exist in COVID-19 incidence and mortality [33]. Among all variables analyzed in our study, being African American had the strongest association with COVID-19. In Chicago alone, 70% of all COVID-19 deaths were seen in African Americans who only represent 29% of the city's population [33]. It is unclear if African Americans are infected more often, but social determinants of health appear to be powerful predictors of SARS-CoV-2 infectivity and mortality. African Americans are more likely to carry out high risk essential jobs, including low wage jobs that cannot be done remotely [33]. They are more likely to have co-morbid conditions such as hypertension, obesity, or diabetes. They are also more likely to be uninsured, more segregated and in concentrated poverty ultimately leading to higher COVID-19 susceptibility. Even after adjusting for serious co-morbid conditions, we observed the highest association among this race and COVID-19. In view of our findings, and as more data emerges, surveillance data on racial disparities in COVID-19 incidence and mortality will be critical to guide policy, health care and intervention efforts and mitigate the adverse consequences of this disease on the most vulnerable populations.

An important strength of our study is that we used a large national database and reported data on over 60 million active adult subjects. We also provided comprehensive epidemiological information on the risk of COVID-19 in patients with serious metabolic risk factors. Our results are therefore consistent with established data suggesting that metabolic syndrome and its individual

components might be significantly associated with SARS-CoV-2 infection. We also report a new association between NASH and the COVID-19 that is yet to be explored in literature.

There are several limitations to this study that should be addressed. Observational studies preclude us from addressing causality. Due to the design of Explorys, we could not establish temporal relationships between the duration of metabolic risk factors, their severity and impact of interventions on the associated risk of COVID-19. Second, being a retrospective database, patient-related information and data may be missing or incomplete. Moreover, the prevalence and natural disease progression of NAFLD is difficult to estimate as accurate diagnosis requires tissue analysis. The prevalence of NASH is estimated to be between 1.5% and 6.45% based on a few biopsy series [34]. The reported prevalence of NASH in our study was 0.09%. We excluded those with the diagnosis of fatty liver disease to increase the accuracy in our reporting; as the latter may be caused by drugs, viruses or alcohol. But even though the NASH population was underrepresented in the current study, we still saw a significant relationship with COVID-19 independent of other metabolic risk factors. Finally, as this is a retrospective study reliant on diagnosed SNOMED-CT codes, it is impossible to verify the accuracy of diagnoses and it is prone to coding errors. These limitations however are counterbalanced by a larger sample size and absence of reporting bias which usually results from selective publications from specialized centers.

In our large US-based cohort study, we found the cumulative incidence of COVID-19 to be the highest among patients with metabolic syndrome and its individual components. The findings of our study support the adverse association between this syndrome and SARS-CoV-2. NASH had the strongest relationship with COVID-19. Although the full pathogenic scenario is far to be elucidated, this association envisage the possibility of a complex bidirectional interface between SARS-CoV-2 and the distal inflammatory pathways perpetuated by NASH. A better understanding of the mechanisms underscoring the affinity of SARS-CoV-2 for patients with metabolic syndrome is needed and demonstrates the importance of care with this risk group in prophylaxis, monitoring and treatment.

CRediT authorship contribution statement

Sara Ghoneim: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Muhammad Umer Butt:** Data curation, Validation, Writing - review & editing. **Osama Hamid:** Data curation, Writing - original draft. **Aun Shah:** Visualization, Investigation, Writing - review & editing. **Imad Asaad:** Supervision, Writing - review & editing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2020.100057.

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