International Journal on Heart and Vascular System

Cardiovascular Morbidity and Mortality in COVID-19: A Multicenter Retrospective Analysis

Research Article

Volume 2 Issue 1- 2022

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Article History

Received: June 19,2022 Accepted: July 18, 2022 Published: July 19, 2022

Abstract

Background: Single-center data from COVID-19 studies suggest clinical risk factors for cardiovascular and prothrombotic complications. This study aims to identify clinical risk factors that increased the risk of pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular accident (CVA), mortality, and a composite of major adverse cardiovascular events (MACE) in an urban and diverse multicenter setting.

Methods: Between February and June, 2020, 4,547 patients were seen in the ER of 17 northeastern US hospitals and tested positive for COVID-19; of these, 1,171 patients were treated and released. We retrospectively analyzed the data on 3,376 patients who were admitted to these hospitals. A multivariable logistical regression analyzed patient characteristics and comorbidities in relation to said complications.

Results: COVID-19 infected patients with a history of any cancer were at 2.64 times greater risk (1.519, 4.533; p=.0005) of developing PE; however, increasing age decreased the risk for PE. Patients with a history of heart failure with preserved or reduced ejection fraction (HFpEF, HFrEF) (OR=1.918; 95% CI: 1.230, 2.990; p=.0041 and OR=3.205; 95% CI: 2.272, 4.520; p<.0001), ischemic heart disease (IHD) (OR=2.429; 95% CI: 1.836, 3.215; p<.0001), end stage renal disease (ESRD) (OR=1.566 95% CI: 1.002, 2.446; p=.0489) were at higher risk for MI. Women had decreased odds of CVA compared to men (OR=0.716; 95% CI: 0.529, 0.970; p=.0308). ESRD had a positive association with CVA (OR=2.465; 95% CI: 1.545, 3.934; p=.0002). HFrEF was highly associated with MACE while women had decreased odds of MACE (OR=2.020; 95% CI: 1.453, 2.810; p<.0001). Patients with HFrEF (OR=1.623; 95% CI: 1.191, 2.211; p=.0021), chronic kidney disease (OR=1.712; 95% CI: 1.227, 2.389; p=0.0016), and diabetes (OR=1.170; 95% CI: 0.973, 1.407; p=0.0960) had an increased risk of mortality from COVID-19.

Conclusion: Our analysis identified comorbidities that were strongly associated with major COVID-19 complications. Utilizing these findings may help guide clinicians with risk stratification and earlier clinical interventions.

Keywords: COVID-19; Mortality; Myocardial infarction; Pulmonary embolism; Cerebrovascular accident

Introduction

The global COVID-19 pandemic caused by SARS-CoV-2 has infected an estimated 186 million people with over 4 million confirmed deaths as of July 11, 2021 [1]. With over one year of collective case studies and retrospective data, multiple risk factors have been associated with increased morbidity and mortality. These risk factors include ethnicity (i.e Hispanic, African American, etc), age, smoking, diabetes, hypertension, heart failure, obesity, chronic kidney disease, and cancer [2-18]. Further, patients infected with COVID-19 can experience a wide gamut of sequalae ranging from transient loss of smell and taste to a life-threatening cytokine storm causing multiorgan failure [19].

Along the COVID-19 disease spectrum, prothrombotic coagulation abnormalities predispose patients to thromboembolic events including acute coronary syndrome (ACS) and pulmonary embolism (PE)5,20-24. A multicenter registry by Kite et al demonstrated COVID-19 positive ACS patients had increased in-hospital mortality compared with a pre-COVID-19 ACS population [21]. Cardiogenic shock was the leading contributor to worse outcomes in COVID-19 STEMI patients. Moreover, PE was a major contributor to worsening respiratory failure and mortality with COVID-19 [23,24]. Severely ill patients admitted to the ICU with COVID-19 saw a 31% incidence of thrombotic complications identified by Klok et al. [25] with PE being the predominant diagnosis [25].

Furthermore, cerebrovascular accident (CVA) is a life threatening sequalae of a prothrombotic state. In COVID-19 patients, acute ischemic stroke by thromboembolic phenomena is the prevailing pathogenesis with incidence rates ranging from 0.9% to 2.7% [29]. Large vessel thrombosis affecting major vascular cerebral territories was the predominant finding on neuroimaging. Patients with COVID-19 had a 1.2% greater risk of mortality from CVA than those uninfected [29].

Herein, we investigated the relationship between patient comorbidities and the cardiovascular, pulmonary, and neurological complications as well as mortality in patients admitted with COVID-19. Complications of interest were CVA, MI, PE, major adverse cardiovascular events (MACE) and death. Patients studied were admitted to one of 17 hospitals within a major northeastern United States healthcare system.

Design and Methods

Data Source

Deidentified patients were obtained from a manually entered patient registry who were admitted with COVID-19 between January 1, 2020 and June 30, 2020. Institutional review board (IRB) approval was obtained from the Hackensack Meridian Health IRB.

Study Design, Population, and Patient Involvement

This retrospective study was completed out of the Hackensack Meridian Health system, which consists of 17 hospitals, with the goal of analyzing patients admitted to the hospital for COVID-19. The original study included 4,547 patients; 1,171 patients were removed from the study due to being treated and discharged from an emergency department. The data for the remaining 3,376 patients was extracted from the COVID-19 registry. The study screened all qualifiable COVID-19 patients admitted to the hospital for the following variables: demographics, comorbidities of interest, and treatment modalities. Additionally, complications such as PE, MI, CVA, mortality, and a composite of MACE. Due to its retrospective design, patients were not involved in the design and conduct of this research study.

Statistical Methods

Descriptive statistics were reported for the sample and by each outcome to assess the distribution of patient demographics, clinical comorbidities, and COVID-19 treatments. Continuous variables were reported as median (IQR) and categorical variables by count (%). Rates were calculated separately for each cardiac complication, death, and the composite of MACE along with 95% confidence intervals. Further, associations between variables were tested with Fisher's exact test followed where appropriate with pairwise comparisons. Multiple p-values were corrected using Bonferroni's correction method. Analysis was done with rstatix package (R software).

Univariable and multivariable logistic regression were used to assess the association between potential risk factors and the outcomes of cardiopulmonary complications (PE, MI, CVA), death, and a composite MACE. Variables were included due to their clinical potential to be associated with the outcomes and consisted of patient demographics (age, sex, ethnicity) and comorbidities. A stepwise selection method was used to build the final multivariable model with entry criteria of $p<0.20$ and a significance level of $p<0.10$ to stay in the model. The Hosmer and Lemeshow test was used to assess goodness of fit. Odds ratios, 95% confidence intervals, and two-sided p-values were reported for all models. A $p<0.05$ was used to indicate statistical significance. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 4547 adult patients admitted with symptomatic COVID-19 diagnosis were extracted from the retrospective chart review and 3376 patients were included in analyses. 1,171 patients were removed from the study due to treatment and discharged from emergency trauma departments. 21.6% (n=729) of patients were ages 18-50, 29.4% (n=994) ages 51-64, 20.8% (n=703) ages 65-74, and 28.1% (n=950) had age greater than 75. The median age of patients was 64 (52, 76) years and 60.6% of the sample was male. Just over half (52.5%) were Caucasian, 20.7% were Hispanic, 10.5% African American, 4.7% Asian, and 11.6% as unidentified. One-third (n=1123) of patients were obese and 6.9% (n=234) were morbidly obese. Common comorbidities include hypertension (56.0%), HLD (50.0%), and diabetes (31.5%) (Table 1).

Table 1 Patient demographics and clinical characteristics. †HFrEF was defined as having an ejection fraction of less than 40% with clinical symptoms of heart failure. ‡HFpEF was defined as having an ejection fraction of greater than 50% with clinical symptoms of heart failure. Patients with a body mass index (BMI) of ≥30 and ≥40 were considered obese and morbidly obese. Anticoagulation was defined as full systemic anticoagulation using either unfractionated heparin, low molecular weight heparin, direct oral anticoagulants, or vitamin K antagonists.

PE

The PE rate was 2.4% (95% CI: 1.9%, 2.9%) in the sample. In multivariable analyses, age was identified as an independent risk factor for PE. Compared to patients 50 and below, patients 51-64 (OR=0.630; 95% CI: 0.369, 1.076; p=.0909), 65-74 (OR=0.366; 95% CI: 0.184, 0.727; p=.0041) and 75+ (OR=0.204; 95% CI: 0.096, 0.432; p<.0001) all had a decreased odds of PE in a linear fashion. The odds of PE for patients with a history of any cancer were 2.624 times that of patients without a history of cancer (95% CI: 1.519, 4.533; p=.0005) (Figure 1).

MI

In the sample, 321 (9.5%; 95% CI: 8.5%, 10.5%) COVID-19 patients had a MI. Multivariable logistic regression found that patients 51-64 (OR=3.884; 95% CI: 2.212, 6.819; p<.0001), 65-74 (OR=6.546; 95% CI: 3.742, 11.452; p<0.0001), and ages 75+ (OR=3.173; 95% CI: 1.757, 5.728; p=.0001) had an increasing odd of MI with progression of age. Patients with HFpEF and HFrEF both had increased odds of MI (OR=1.918; 95% CI: 1.230, 2.990; p=.0041 and OR=3.205; 95% CI:

2.272, 4.520; p<.0001, respectively). Other comorbidities independently associated with MI were ischemic heart disease (OR=2.429; 95% CI: 1.836, 3.215; p<.0001), HLD (OR=2.117; 95% CI: 1.523, 2.942; p<.0001), and ESRD (OR=1.566 95% CI: 1.002, 2.446; p=.0489) (Figure 2).

Table 1: Patient demographics and clinical characteristics

Characteristic	Total Sample (n=3,376)
Age, Median (IQR)	64.0 (52.0, 76.0)
18-50	729 (21.6%)
51-64	994 (29.4%)
65-74	703 (20.8%)
>75	950 (28.1%)
Gender	
Female	1331 (39.4%)
Male	2045 (60.6%)
Ethnicity	
African American	355 (10.5%)
Asian	159 (4.7%)
Caucasian	1773 (52.5%)
Hispanic	699 (20.7%)
Others	390 (11.6%)
BMI (kg/m2), Median (IQR)	28.5 (25.1, 32.7)
Not Obese	2019 (59.8%)
Obese	1123 (33.3%)
Morbidly Obese	234 (6.9%)
HFrEF†	227 (6.7%)
HFpEF‡	143 (4.2%)
Ischemic Heart Disease	607 (18.0%)
HLD	1687 (50.0%)
Diabetes	1063 (31.5%)
Cancer	466 (13.8%)
ESRD	142 (4.2%)
CKD	196 (5.8%)
Hypertension	1890 (56.0%)
Lung Disease (COPD, Emphysema)	259 (7.7%)
Ever Smoker	778 (23.0%)
Anticoagulation	207 (6.1%)
Hydroxychloroquine	2056 (60.9%)

CVA

The CVA rate was 6.5% (95% CI: 5.6%, 7.3%). Multivariable analysis found that women had decreased odds of CVA compared to men (OR=0.716; 95% CI: 0.529, 0.970; p=.0308). Patients aged 65-74 (OR=3.394; 95% CI: 1.597, 7.215; p=.0015) and 75+ (OR=5.873; 95% CI: 2.809, 12.276; p<.0001) both had increased odds of CVA in comparison to patients 50 or below. ESRD was the comorbidity with the strongest association with CVA (OR=2.465; 95% CI: 1.545, 3.934; p=.0002). Other comorbidities that independently increased odds of CVA were hypertension (OR=1.911; 95% CI: 1.295, 2.821; p=.0011), cancer (OR=1.511; 95% CI: 1.075, 2.125; p=.0176) and IHD (OR=1.682; 95% CI: 1.231, 2.298; p=.0011) (Figure 3).

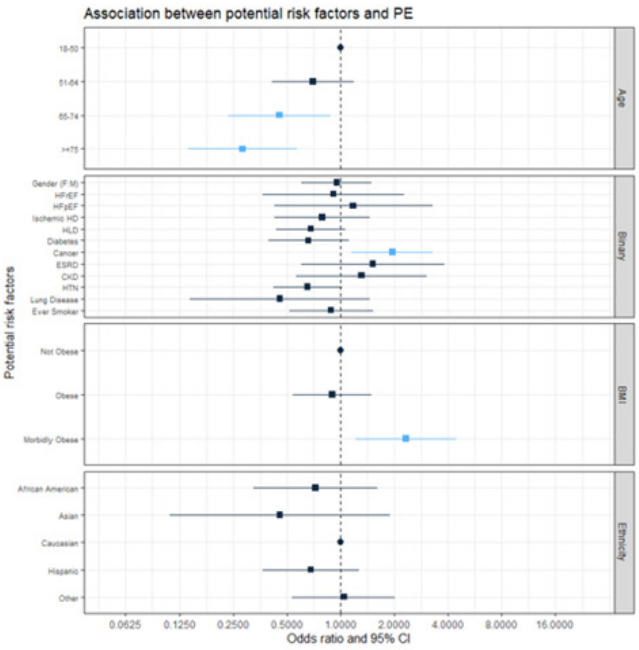

Figure 1: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for pulmonary embolism (PE). There is a statistically significant association of age and PE, with increasing age (65-74 and >75) being associated with lower odds of developing a PE. Patients with active malignancy have greater odds of developing a PE. Being classified as morbidly obese, described as a BMI ≥ 40, is also associated with greater odds of pulmonary embolism.

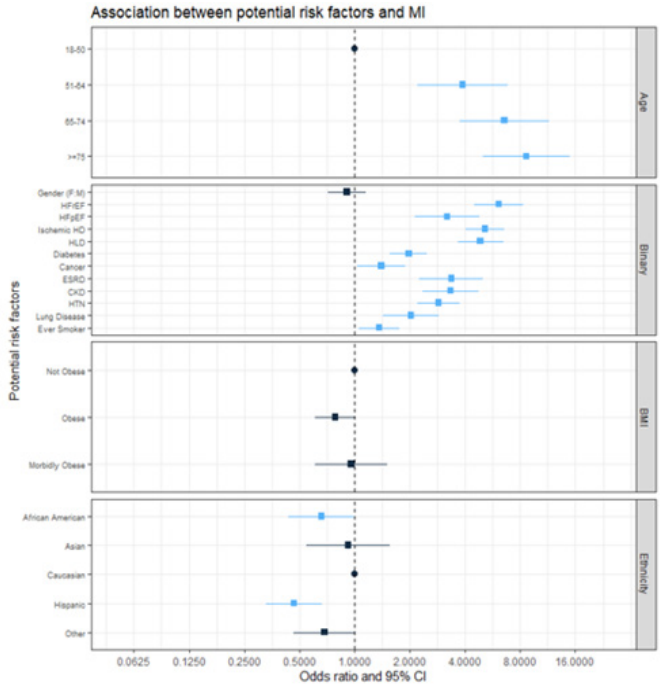

Figure 2: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for myocardial infarction (MI). There is a statistically significant association of age and PE, with increasing age (51-64, 65-74, >75) being associated with greater odds of developing a MI. Patients with risk factors including HFrEF, HFpEF, ischemic HD, HLD, diabetes, cancer, ESRD, CKD, HTN, lung disease and smoking history have greater odds of developing a MI.

Mortality

The mortality rate was 27.5% (95% CI: 26.0%, 29.0%). In the multivariable model, increasing age was found to increase odds of mortality (75 years old ≥ OR=13.009; 95% CI (8.986, 18.834; p= <.0001)

while female sex decreased odds of mortality by 33% (OR=0.670; 95% CI: 0.559, 0.802; p<.0001). HFrEF (OR=1.623; 95% CI: 1.191, 2.211; p=.0021) and ischemic heart disease (OR=1.342; 95% CI: 1.082, 1.665; p=.0075) were cardiac comorbidities associated with increased odds of death in COVID-19 patients. Additional comorbidities independently associated with odds of mortality were CKD (OR=1.712; 95% CI: 1.227, 2.389; p=0.0016), hypertension (OR=1.411; 95% CI: 1.151, 1.730; p=0.0009), cancer (OR=1.329; 95% CI: 1.056, 1.673; p=0.0155), and diabetes (OR=1.170; 95% CI: 0.973, 1.407; p=0.0960) which increased odds of mortality by 71%, 41%, 33%, and 17% (Figure 4).

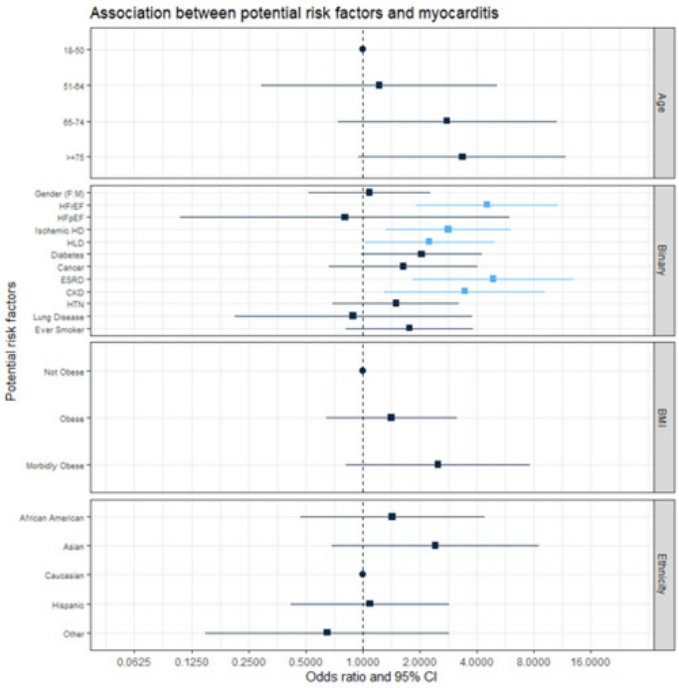

Figure 3: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for myocarditis. ESRD and HFrEF were both associated with increased odds of myocarditis.

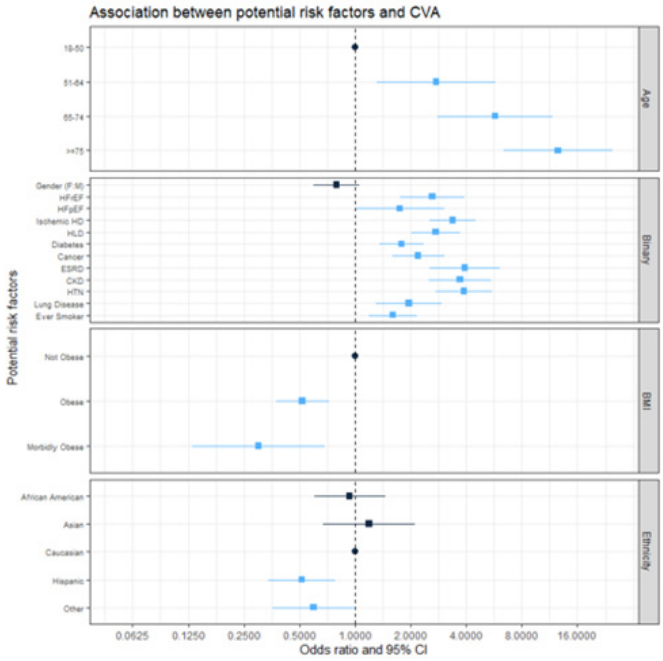

Figure 4: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for cerebrovascular event (CVA). There is a statistically significant association of age and CVA, with increasing age ((51-64, 65-74, >75) being associated with greater odds of developing CVA. Patients with risk factors including HFrEF, HFpEF, ischemic HD, HLD, diabetes, cancer, ESRD, CKD, HTN, lung disease and smoking history have greater odds of developing CVA.

Composite of Major Adverse Cardiovascular Events (MACE)

MACE was defined as the composite of total death, acute coronary syndrome, CVA, and PE along with a COVID-19 diagnosis. Overall, 35.2% (95% CI: 33.6%, 36.8%) of patients had either a cardiac complication or died. Multivariable logistic regression found that increasing age linearly increased odds of cardiovascular complications or mortality. Women were 30% less likely to have either outcome compared to men (OR=0.700; 95% CI: 0.590, 0.830; p<.0001). Patients who were morbidly obese had odds of the composite outcome 1.52 times that of non-obese patients (OR=1.519; 95% CI: 1.090, 2.116; p=.0136). Reduced EF heart failure was the comorbidity with the greatest association with cardiac complication or death (OR=2.020; 95% CI: 1.453, 2.810; p<.0001). Additional comorbidities that increased odds of cardiac complication or death were ESRD (OR=1.706; 95% CI: 1.016, 2.866; p=.0436), CKD (OR=1.686; 95% CI: 1.084, 2.623; p=.0204), ischemic heart disease (OR=1.591; 95% CI: 1.279, 1.980; p<.0001), cancer (OR=1.496; 95% CI: 1.193, 1.876; p=.0005), hypertension (OR=1.345; 95% CI: 1.109, 1.630; p=.0026), HLD (OR=1.250; 95% CI: 1.034, 1.511; p=.0212), and diabetes (OR=1.210; 95% CI: 1.011, 1.449; p=.0376) (Figure 5).

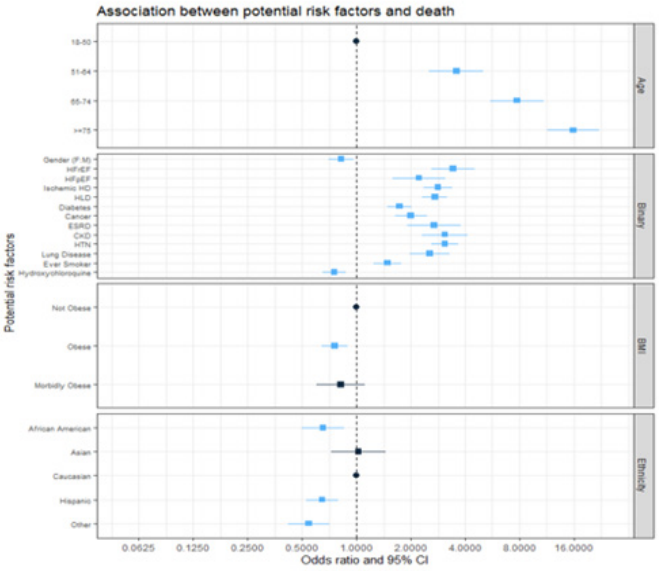

Figure 5: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for death. There is a statistically significant association of age and PE, with increasing age (51-64, 65-74, >75) being associated with greater odds of death. Patients with risk factors including HFrEF, HFpEF, ischemic HD, HLD, diabetes, cancer, ESRD, CKD, HTN, lung disease and smoking history have greater odds of death.

Discussion

This multicenter retrospective study provides important data regarding demographics, comorbidities, and complications associated with COVID-19 patients in an urban setting. Our cohort consisted of Caucasian (52.5%), Hispanic (20.7%), and Asian (4.7%) patients with the most prevalent comorbidities being obesity, hypertension, hyperlipidemia, and diabetes (Table 1). We found no statistical significance in race with outcomes studied. It reaffirms multiple single center COVID-19 studies that have investigated patient risk factors and their association with a single sequalae; however, this study was able to analyze multiple sequalae in an urban US population.

Pulmonary embolism has been a prothrombotic complication of interest in COVID-19 patients. Our cohort was found to have a low incidence of PE (2.4%) compared to a rate of 14.7% in a meta-analysis by Roncon et al. [23]. A low incidence of PE in our cohort was likely due to multiple factors including a low rate of screening during the first wave. Further, most of our patients were not admitted to the medical intensive care unit, which has been shown to be associated with a higher risk for PE in COVID-19 patients23,24. Our multivariable analysis

found age as an independent risk factor for PE. Interestingly, patients above the age of 50 had a linear decrease in the odds of PE when compared to patients below the age of 50. Cancer, whether being actively treated or in remission, was associated with a 2.64 times greater risk of developing PE when compared to noncancer patients (Figure 1). Morbidly obese (BMI ≥40) patients had a greater risk for PE as well. The prothrombotic attributes of cancer are likely potentiating COVID-19's innate upregulation of the coagulation cascade [9,19,22,25]. Moreover, only 207 patients received full systemic anticoagulation which may not provide sufficient statistical power to draw a statistical conclusion. Recent prospective trials have shown benefit for systemic anticoagulation in noncritically ill COVID-19 patients [30].

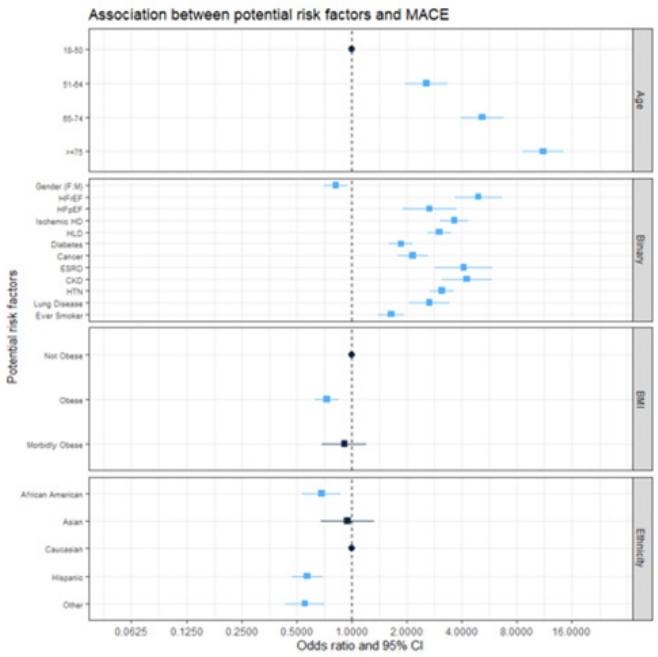

Figure 6: Forest plot depicting odds ratios on a logarithmic scale from logistic regression model for major adverse cardiac events (MACE). Major adverse cardiac events include a composite of total death, acute coronary syndrome, CVA, and hospitalization for heart failure along with a COVID-19 diagnosis. Risk factors such as HFrEF, ischemic heart disease, hyperlipidemia, ESRD and CKD are associated with greater odds of developing MACE.

Major adverse cardiovascular events (MACE) were defined as the composite of total death, acute coronary syndrome, CVA, and PE along with a COVID-19 diagnosis. The incidence of MACE was substantially high in our cohort with 35.2% of patients meeting criteria. Consistent with other studies, increasing age showed a linear increase in odds of MACE. Comorbidities such as increasing age, obesity (BMI ≥30), morbid obesity, diabetes, ESRD (requiring hemodialysis), CKD, ischemic heart disease, and hypertension were associated with greater odds of MACE (Figure 6). Patients with a history of heart failure with reduced ejection fraction (HFrEF) showed the highest odds of MACE consistent with Dalia et al's systematic review of COVID-19 patients with HFrEF. However, our analysis showed patient with both HFpEF and HFrEF were found to be at greater risk of MACE. Interestingly, women had a 30% reduction in risk of MACE. Similar clinical characteristics were associated with increased risk of MI (Figure 5). A high thrombus burden along with microcirculatory dysfunction have been the leading pathophysiological explanations for cardiovascular complications in COVID-19 patients [5]. Further, patients with a history of CKD, HFrEF, and/or ischemic heart disease had substantially greater risk of mortality (Figure 2).

A high incidence of cerebrovascular accident (CVA) was noted in our patient cohort when compared to a pooled incidence of 1.2% in a systematic review by Tan et al. Unique to our study, women were found to have decreased odds of CVA compared to men. Increasing age above 65 years old and comorbidities such as hypertension, ischemic heart disease, and history of cancer, were associated with a greater risk of CVA (Figure 4). Interestingly, patients with ESRD had the strongest association with CVA. ESRD patients typically have higher vascular disease burden and impaired platelet activity which may explain its association with a higher incidence of CVA.

Conclusion

From this multicenter study, we can conclude that COVID-19 patients with high-risk comorbidities in the US population are at risk of prothrombotic complications such as PE, MI, CVA , mortality, and a composite of MACE. Since these comorbidities were present in a diverse and urban cohort, the role of identifying said risk factors can aid in patient risk stratification, aggressive monitoring, and earlier treatment interventions.

Acknowledgments

The authors thank Angeline Sanders, MS and Simon Gelman for their expertise in statistical analysis and Jana Tancredi, BSN for project logistics at Hackensack Meridian Health.

This manuscript has not been published in whole or in part, nor has it been considered for publication elsewhere. The authors do not have any conflict of interests to declare and all authors had access to the case's data and equal contribution.

Limitations

This study has several limitations; due to its retrospective design, we cannot exclude unknown confounding factors with respect to patients in the registry. Further, our study did not subject patients to randomized and blinded medical interventions, thus warranting further investigation (i.e hydroxychloroquine, etc). The study did not segregate patients according to severity of illness which may play a role in outcomes including complications.

Contributorship and Funding

The authors do not have any conflict of interests to declare, and all authors had access to the case's data and equal contribution. The authors did not receive any funding for the creation of this manuscript.

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