COVID-19 Associated Mortality and Cardiovascular Disease Outcomes Among U.S. Women Veterans

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Research Article

Abstract

Background

The burden of COVID-19 has been noted to be disproportionately greater in minority women, a population that is nevertheless still understudied in COVID-19 research.

Methods

We conducted a case-control cohort study to examine COVID-19-associated mortality and cardiovascular disease outcomes after testing (henceforth index) among a racially diverse adult women veteran population. We drew data from a Veterans Affairs (VA) national COVID-19 shared data repository, collected between February and August 2020. Kaplan-Meier curves and the Cox proportional hazards model were employed to examine the distribution of time to death and the effects of baseline predictors on mortality risk. Generalized linear models were used to examine 60-day cardiovascular disease outcomes. Covariates studied included age, body mass index (BMI), and active smoking status at index, and pre-existing conditions of diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and a history of treatment with antiplatelet or anti-thrombotic drug at any time in the 2 years prior to the index date.

Results

Women veterans who tested positive for SARS-CoV-2 had 4 times higher mortality risk than women veterans who tested negative (Hazard Ratio 3.8, 95% Confidence Interval CI 2.92 to 4.89) but had lower risk of cardiovascular events (Odds Ratio OR 0.78, 95% CI 0.66 to 0.92) and developing new heart disease conditions within 60 days (OR 0.67, 95% CI 0.58 to 0.77). Older age, obesity (BMI > 30), and prior CVD and COPD conditions were positively associated with increased mortality in 60 days. Despite a higher infection rate among minority women veterans, there was no significant race difference in mortality, cardiovascular events, or onset of heart disease.

Conclusions and Relevance

SARS-CoV-2 infection increased short-term mortality risk among women veterans similarly across race groups. However, there was no evidence of increased cardiovascular disease incidence in 60 days. A longer follow-up of women veterans who tested positive is warranted.

Key Points

Question: What is the impact of COVID-19 on mortality and cardiovascular disease outcomes in women and particularly in women of different racial and ethnic background?

Findings: In a case-control observational study using data from racially diverse women veterans collected between February 24 and November 25, 2020, this study found that SARS-CoV-2 infection increased 60-

day mortality risk among women veterans similarly across race groups. Within this 60 day study period, those who tested positive were at lower risk of cardiovascular events and developing new heart disease conditions.

Meaning

The study fills a current gap in the COVID-19 studies and literature that underrepresent women, in particular, racial and ethnic minority women. While the findings from the current study are specific to women veterans, the ethnic and racial diversity of our study cohort suggests that our findings may apply to women in the general population, thus providing a better understanding of the impact of COVID-19 in women.

Introduction

The short-term outcomes of Coronavirus disease 2019 (COVID-19), the disease resulting from infection by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, on women, especially minority women, is an area in need of heightened focus and investigation. While the socio-economic effects of COVID-19 on women have been publicized in the mainstream media,[1,2] the extent of the health burden, in terms of mortality and cardiovascular morbidity, remains understudied and poorly understood. While earlier studies showed that men were at higher risk of mortality after contracting COVID-19 than women,[3-6] older women and minority women are also at increased risk of mortality.[7-10] In addition to mortality, COVID-19 patients are at elevated risk of cardiovascular complications.[11,12] Furthermore, pre-existing cardiovascular disease and chronic disease, such as diabetes and COPD,[13,14] have been linked to worse prognosis in COVID-19.[12,15]

The United States (U.S.) Veteran Health Administration (VHA) is the largest integrated healthcare system in the U.S. Although the VHA data is focused on Veteran health, results of large studies based on Veterans Affairs (VA) data have been extrapolated to the general population and now constitute the bases of clinical practice guidelines and standards of care.[16-18] The VHA electronic health record (EHR) provides a rich longitudinal database for the analysis of short term and longer term outcomes. The U.S. VA COVID-19 shared repository is a part of VA Infrastructure and Computing Infrastructure (VINCI) Corporate Data Warehouse (CDW) and available to VA researchers. The VA COVID-19 shared repository includes patient level data on COVID testing, diagnoses, drug utilization from COVID-19 National Bio-Surveillance team and a comprehensive data set of patient's demographic and clinical characteristics, treatment, laboratory results, pharmacological therapy, and any adverse events such as death and cardiovascular disease events from VHA EHR.

The purpose of this study was to examine the effect of COVID-19 on Veteran women, and specifically minority women, since previous studies have demonstrated that COVID-19 has affected veterans of racial and ethnic minorities disproportionately.[3] The women veteran population has a greater number of cardiovascular disease risk factors than the general population,[19] and their aging trajectory of increased

cardiovascular disease (CVD) risk starts as young as age 30.[20] In light of these findings, the women veteran population may be at higher risk of COVID-19-associated mortality and cardiovascular complications than the general population.

This study capitalized on a large number of women representing racial and ethnic minorities in the women veteran population. With a study cohort comprised of 33% African Americans and 8% Hispanics, the current study examined the effect of COVID-19 on mortality and cardiovascular risk in women veterans within 60 days of testing positive using data from the U.S. VA COVID-19 shared data repository, collected between February 24 and November 25, 2020. Notably, most previous studies reporting a lower risk among females rely on data collected up to June 2020. The study findings from data including the second and the third waves of COVID-19 pandemic data between July 2020 and November 2020 therefore provide more insight on the effect of COVID-19 on short-term mortality and cardiovascular disease outcomes among women.

Results

Data

We conducted a case-control cohort study using a VA COVID-19 shared data resource collected between February and November 2020. VA COVID-19 shared data included data on patient demographic characteristics, smoking status, and BMI at index date, laboratory testing results, including troponin within 7 days from the date of COVID-19 screen testing (henceforth, the index date), disease conditions and pharmacological therapy up to 2 years prior to and 60-days after the index date, and 60-day adverse events after the index date.

The index date was determined hierarchically. If a patient ever tested positive (presumed positive) for SARS-CoV-2 then the date of first positive (presumed positive) was selected. If a patient tested negative on all occasions, then the date of first negative test was designated the index date. COVID-19 associated outcomes considered in the current study are all-cause mortality with actual date of death, cardiovascular events, and new onset of cardiovascular disease within 60 days from index date. Cardiovascular events included non-fatal ischemic and hemorrhagic stroke, myocardial injury defined by troponin level > 0.4 ng/mL within 7 days from index,[11] and non-fatal heart failure. Heart disease included cardiovascular disease, hypertension, coronary artery atherosclerotic heart disease, cerebrovascular disease, cardiomyopathy and other ill-defined heart disease. A new onset of heart disease was defined as any heart disease diagnosed 60 days post index without a prior heart disease condition in the preceding 2 years. Cardiovascular outcome variables were constructed from International Statistical Classification of Disease (ICD) 9 and 10 diagnostic codes from VA Electronic Health Records (eTable 1 in Supplement).

Baseline characteristics

Patient age, body mass index (BMI), and active smoking status on the index date were collected. Other baseline characteristics included presence of diabetes, chronic kidney disease (CKD), chronic obstructive

pulmonary disease (COPD), and a history of treatment with either an antiplatelet drug or antithrombotic drug at any time in the 2 years prior to the index date. Antithrombotic medications included heparin and warfarin (eTable 1 in Supplement).

The study analyzed effects of medications administered pre and post index date. The classes of medications considered, in addition to those mentioned above, were Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB), hydroxychloroquine, and Corticosteroid. All but a history of antiplatelet or antithrombotic drugs were excluded from the final model due to lack of variance and lack of statistical significance. Exclusion of these variables from the final model was guided by Akaike Information Criteria (AIC), multicollinearity tests, and statistical significance.

Statistical methods

We compared baseline variables and 60-day outcomes between the SARS-CoV-2 positive (+) and negative (−) groups by computing descriptive statistics and t and chi-squared tests.

We assessed differences in event-time outcomes between the SARS-CoV-2 positive and negative groups using Kaplan-Meier curves and the Cox proportional hazards model, with adjustment for baseline confounders. We censored all event times at 60 days. We assessed differences in binary CVD outcomes between the SARS-CoV-2 positive and negative groups using logistic regression, again with adjustment for baseline confounders. We displayed odds ratios (ORs) from the logistic regressions using forest plots with 95% confidence intervals (CIs).

We conducted all analyses in SAS version 9.4 (SAS Institute, Cary, NC) or R version 3.6.1 (cran.r-project.org).

Findings

We analyzed data from 77,364 women veterans who were tested for SARS-CoV-2 infection at VA hospitals and clinics between February 24, 2020 and November 25, 2020. The mean age of the women veterans was 50.69 ± 12.80 years. Approximately 50% (49.44%) of the women veterans were Caucasian; 32% were African American and 9% were Hispanic (Table 1). In terms of co-morbidities, 19% had diabetes, 19% had a previous diagnosis of cardiovascular disease, and 11% had been diagnosed with COPD. Approximately 11% of the women (n = 8,308) tested positive (confirmed and presumptively positive) for SARS-CoV-2.

Table 1. Baseline characteristics and 60 day outcomes of veteran women stratified by COVID-19 testing result, positive (+) and negative (-)

Baseline characteristics at index			All (n= 77.364)	Positive (+) (n= 8.308)	Negative (-) (n= 69.056)	P-value[a]
Age at index		mean±SD	50.69±12.80	48.62±12.66	50.94±12.80	<.001
BMI at index		mean±SD	30.72±6.88	31.67±6.84	30.61 ±6.88	<.001
Race	Black	n (%)	24,703 (31.93)	3,086 (37.14)	21,617 (31.30)	
	Hispanics	n (%)	6,611 (8.55)	882 (10.62)	5,729 (8.30)	<.001
	White	n (%)	39,507 (51.07)	3,688 (44.39)	35,819 (51.87)	
	Other	n (%)	6,543 (8.46)	652 (7.85)	5,891 (8.53)	
DM	Yes	n (%)	14,667 (19.0)	1,591 (19.1)	13,076 (18.9)	.64
Current smoker	Yes	n (%)	12.259 (15.85)	698 (8.40)	11,561 (14.94)	<.001
CVD	Yes	n (%)	14,908 (19.27)	1,351 (16.26)	13,557 (19.63)	<.001
COPD	Yes	n (%)	8,501 (10.99)	624 (7.51)	7,877 (11.41)	<.001
CKD	Yes	n (%)	3,915 (5.06)	347 (4.18)	3,568 (5.17)	<.001
Anticoagulant	Yes	n (%)	10,133 (13.10)	907 (10.91)	9,226 (13.36)	<.001
60 day outcomes						
Death	Yes	n (%)	321 (0.41)	79 (0.95)	242 (0.35)	<.001
CVD	Yes	n (%)	2,232 (2.89)	166 (2.00)	2,066 (2.67)	<.001
Ischemic stroke	Yes	n (%)	703 (0.90)	48 (0.58)	655 (0.95)	<.001
Hemorrhagic stroke	Yes	n (%)	44 (0.06)	4 (0.05)	40 (0.06)	0.72
Troponin>0.4mg/dL	Yes	n (%)	87 (0.11)	15 (0.18)	72 (0.10)	0.06
Heart Failure	Yes	n (%)	1,606 (2.08)	117 (1.41)	1,489 (2.16)	<.001
New diagnosis in 60 days from index						
New CVD	Yes	n (%)	2,161 (2.79)	151 (1.82)	2,010 (2.60)	<.001
New CAHD	Yes	n (%)	790 (1.02)	46 (0.55)	744 (1.081)	<.001
New cardiomyopathy	Yes	n (%)	164 (0.21)	13 (0.16)	151 (0.20)	0.24
New Cerebrovascular disease	Yes	n (%)	183 (0.24)	10 (0.12)	173 (0.25)	0.02
New Hypertension	Yes	n (%)	1,169 (1.51)	109 (1.31)	1,060 (1.53)	0.12
New Other ill-defined heart disease	Yes	n (%)	296 (0.38)	28 (0.34)	268 (0.35)	0.48

Abbreviations. BMI = Body Mass Index; CAHD = coronary artery heart disease; CVD = cardiovascular disease; DM = Diabetes; CKD = Chronic Kidney Disease; COPD = Chronic Obstructive Pulmonary Disease; HR= Hazard Ratios; CI = Confidence Intervals

a. T and chi-squared tests were used for continuous and categorical characteristics, respectively.

eFigure 1 in Supplement depicts the proportions of test-positive women veterans by state. While the total number of women veterans who were tested are highest from VA facilities located in California and New York, the proportion of SARS-CoV-2-positive patients was disproportionately higher in southern states including Texas, Louisiana, Alabama, Georgia, and South Carolina, as well as in New Jersey and Nevada. The number of test-positive women veterans at VA reached an initial peak during July 2020, at which time the number of tests in women veterans was the highest, but the number of test-positive women veterans continued to rise in November 2020 to surpass the number of test-positive women veterans in July 2020 (**eFigure 2 in Supplement**). There were 79 COVID-19 associated deaths among women veterans. Women

veterans living in Texas had the highest numbers of COVID-19-associated death within 60 days of a positive test (**eFigure 3 in Supplement**).

Women veterans who were SARS-CoV-2-positive were significantly younger but had a higher BMI than those who tested negative (Table 1). Significantly higher numbers of women veterans with minority ethnicity tested positive. While similar to SARS-CoV-2-negative women veterans in terms of prevalence of diabetes, the SARS-CoV-2-positive women veterans were less likely to be current smokers, less likely to have been diagnosed with CVD, CKD, or COPD prior to the index date, and less likely to have been prescribed an antiplatelet or antithrombotic medication in the 2 years prior to the index date (Table 1). Overall, women veterans who tested positive for SARS-CoV-2 were healthier than their test-negative counterparts at the index date.

SARS-CoV-2-positive women veterans were at nearly 4 times (Hazard Ratio HR 3.8, 95% Confidence Interval CI 2.92 to 4.89) higher risk of death within 60 days than SARS-CoV-2-negative women veterans (Fig. 1).

We tested whether age and BMI at index were linearly associated with 60-day mortality risk by fitting generalized additive models[21] with splines with two degrees of freedom. The test results confirmed that the effect of age on mortality risk was linear ($\chi 2 = 1.87$; $p = 0.17$), while the effect of BMI was non-linear with a change in the rate occurring at a BMI value of 30 ($\chi 2 = 42.22$; $p < 0.001$; **eFigure 4 in Supplement**). Thus, the BMI covariates included both the BMI level and an indicator of BMI > 30 additionally to capture this nonlinearity.

Older age (HR 1.07, 95% CI 1.06 to1.09) and BMI in excess of 30 (HR 1.20, 95% CI 1.15 to1.25) were independently associated with increased 60-day mortality risk among all women veterans and also the SARS-CoV-2-positive group (Older age HR 1.10, 95% CI 1.07 to 1.13; BMI > 30 HR 1.15, 95% CI 1.05 to 1.25). The pre-existing conditions of CVD (HR 1.50, 95% CI 1.15 to 1.96), COPD (HR 1.38, 95% CI 1.06 to 1.78), CKD (HR 1.55, 95% CI 1.16 to 2.88), and prior antiplatelet or antithrombotic therapy (HR 2.21, 95% CI 1.69 to 2.88) significantly increased the risk of death at 60 days after the index date for all women veterans who underwent testing, while only CVD (HR 2.04, 95% CI 1.18 to 3.52) and ??? (HR 1.81, 95% CI 1.08 to 3.06) remained significantly associated with increased risk of 60-day mortality among the SARS-CoV-2-positive group. The pre-existing CKD condition was positively associated with 60-day mortality among the SARS-CoV-2-positive group but with attenuated statistical significance (HR 1.65, 95% CI 0.92 to 2.93. p = 0.09). Prior antiplatelet or antithrombotic therapy was no longer associated with mortality risk among the SARS-CoV-2-positive group.

Women veterans who tested positive were at a significantly elevated risk of early myocardial ischemia (OR 2.23, 95% CI 1.27 to 3.94; Fig. 2), as defined by an elevation in troponin at 7 days after index. However, testing positive for SARS-CoV-2 was associated with a reduced risk of experiencing the combined endpoint of any CVD event (including ischemic or hemorrhagic stroke, early MI, and heart

failure) within 60 days of the index date (OR 0.78, 95% CI 0.66 to 0.92; Fig. 2). Moreover, there was no significant impact on the risk of new onset heart disease at 60 days (Fig. 2).

There was no significant difference between race groups in the rate of CVD events or new onset of heart disease at 60 days post-test.

Within the SARS-CoV-2-positive group, older age, obesity, the pre-existing conditions of CVD, CKD, and COPD, and prior antiplatelet or antithrombotic therapy were associated with increased risk of CVD events within 60 days (Fig. 3). Older age and pre-existing diabetes and COPD increased the risk of developing new heart disease after the positive test (Fig. 4).

Discussion

In this case-control cohort study in a racially diverse population of women military veterans, we found that a positive SARS-CoV-2 test was associated with a 4 times increased risk of mortality, but also a lower risk of experiencing cardiovascular events and developing new heart disease within 60 days.

The current study confirmed older age,[4,7,22–24] obesity,[25–27] and prior CVD[4,14] and COPD[4,14] conditions as risk factors for mortality in COVID-19 disease. We observed only weak associations of prior CKD[4,14] with COVID-19 mortality risk. While SARS-CoV-2 positive women veterans were at lower risk of CVD events at 60 days than those who were negative, positive subjects showed strong associations between older age, obesity, and prior diagnoses of CVD, COPD, and CKD with increased risk of CVD events. Unlike previous studies,[14,23,28] the current study found that having diabetes prior to testing positive was not a significant risk factor for 60-day mortality,[3] but might increase risk of a new onset of heart disease in SARS-CoV-2-positive women.[29]

The U.S. veteran population differs from the general population in the prevalence of pre-existing conditions. Moreover, women veterans differ from the general population of women in terms of socio-demographic characteristics. The women veteran population is slightly older (median age 50) than the general population of women (median age 45), and Black women comprise a greater portion of the veteran population (19% vs. 12%). Additionally, Veteran women have a lower rate of being uninsured (4% vs. 9%) and a higher rate of being college educated (35% vs. 28%) and employed (72% vs. 70%).[30] Overall, minority women veterans may have better access to care than women of minority background in the general population.[31] Nevertheless, the current study, using VA national data, was able to confirm several previously reported risk factors of COVID-19-associated mortality and cardiovascular complications.

Racial and ethnic minority women are understudied in COVID-19 research due to their under-representation in available data sets,[10,32] despite the fact that these groups are disproportionately affected by COVID-19.[33] By focusing on a racially diverse cohort of women veterans, our study can disentangle the effects of race, sex, and access to care on risk factors for COVID-associated mortality and

cardiovascular outcomes. Demographic and health data on women veterans are readily available from VA national COVID-19 shared resources built from VA national electronic health records (EHR). The current study provides a better understanding of this understudied population.[10,32] A further advantage of VA EHR data is that there is no confounding effect of access to care on disease outcomes. Despite the elevated rate of SARS-CoV-2 positivity observed among minority women veterans, there was no accompanying elevated mortality rate. This is in stark contrast to other studies that have suggested that racial and socioeconomic disparities in access to care contribute to the higher mortality rates in minority women diagnosed with COVID.[34–38] Although the cohort of women veterans may not exactly mirror the general population, our study does provide important insight into the effect of COVID on a racially diverse group of women in the absence of confounders such as access to care.

We found that SARS-CoV-2 infection itself does not increase a short-term CVD disease risk in women veterans, which may be explained by the observation women veterans who tested positive were overall younger and healthier than those who tested negative prior to index date. Although there was an association with early troponin elevation, it is unknown whether this was associated with any cardiac symptoms or EKG changes. Furthermore, as depicted in Fig. 2, there were no increases in new-onset heart disease after 60 days. However, longer-term ramifications of SARS-CoV-2 infection on cardiovascular disease are still unknown. The clinical presentation of COVID-19 associated cardiovascular disease in women may be delayed beyond 60 days. Thus, longer follow-up is warranted.

A history of treatment with either an antiplatelet or antithrombotic medication was consolidated into a single field in the VA COVID-19 shared data repository. Although the current analysis found that there is a significant association between prior antiplatelet or antithrombotic therapy and a cardiovascular event within 60 days of being diagnosed with COVID19, the lack of granularity in the data collection does pose significant challenge with interpreting the result. A history of treatment with an antithrombotic may reflect a patient's pre-existing risk of deep vein thrombosis or venous thromboembolism, Arterial Fibrillation (A-Fib), or stroke, or a hypercoagulable state prior to COVID-19 infection, which may be associated with worse outcomes.[39–41] Similarly, prior treatment with antiplatelet medications may reflect underlying coronary artery disease or peripheral artery disease. While some clinicians and investigators have proposed anticoagulants as a successful treatment of COVID-19 infected patients with a complication of coagulopathy,[42,43] their effectiveness in improving survival and CVD outcomes is yet to be proven.[44,45] Separate analyses of the role of antiplatelets and antithrombotics in CVD outcomes and mortality after diagnosis with COVID-19, though not feasible with this current data set, would improve our understanding of risk factors driving adverse outcomes in patients with COVID-19. Finally, we did not include post-index pharmacotherapy in a final model to examine factors associated with COVID-19−related mortality or cardiovascular outcomes, since at the time of this writing, there is no single known medication proven to be effective to treat severely ill COVID-19 patients.[44]

Our study has some limitations: First, we used CVD event occurrence and new onset of CVD at 60 days as binary outcomes due to data availability; a time-to-event analysis would provide a more detailed picture

of the natural history of COVID. Second, the study did not include post-index medications such as antithrombotics, antiplatelets, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), hydroxychloroquine, losartan, and corticosteroids, to examine COVID-associated mortality and cardiovascular complications with respect to pharmacologic interventions, due to limited data availability on timing of drug administration and concomitant drugs. Additional future studies investigating the long term consequences of COVID-19 on women's cardiovascular health are necessary to understand the full societal impact of the COVID-19 pandemic.

Methods

This study is approved by VA North Texas Institutional Research Board (IRB) and the VA North Texas Research and Development Committee, and supported using data from the VA COVID-19 Shared Data Resource. VA North Texas IRB waived the study from obtaining informed consents from study subjects.

Because of the sensitive nature of the data collected for this study, requests to access the dataset are limited to qualified VA-affiliated researchers trained in human subject confidentiality. Protocols may be sent to the VA North Texas Health Care System Institutional Review Board (IRB) at NTXIRBAdmin@va.gov. SQL, SAS and R programming code used in the analysis of this study are available from the corresponding author upon reasonable request. All methods were performed in accordance with the relevant guidelines and regulations

Declarations

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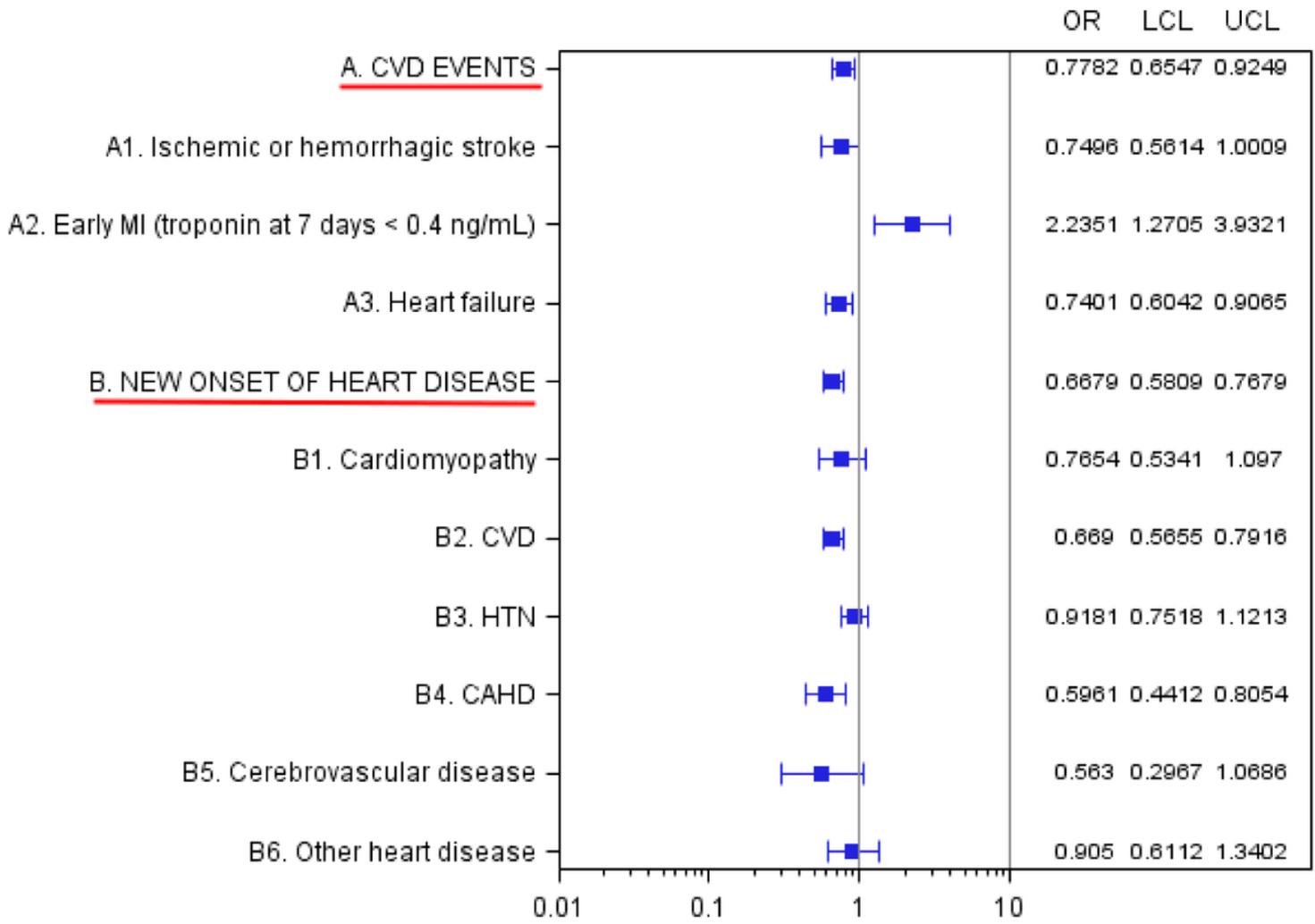
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Figures

Odds Ratio and 95% CL

	OR	LCL	UCL
A. CVD EVENTS	0.7782	0.6547	0.9249
A1. Ischemic or hemorrhagic stroke	0.7496	0.5614	1.0009
A2. Early MI (troponin at 7 days < 0.4 ng/mL)	2.2351	1.2705	3.9321
A3. Heart failure	0.7401	0.6042	0.9065
B. NEW ONSET OF HEART DISEASE	0.6679	0.5809	0.7679
B1. Cardiomyopathy	0.7654	0.5341	1.097
B2. CVD	0.669	0.5655	0.7916
B3. HTN	0.9181	0.7518	1.1213
B4. CAHD	0.5961	0.4412	0.8054
B5. Cerebrovascular disease	0.563	0.2967	1.0686
B6. Other heart disease	0.905	0.6112	1.3402

Figure 2

Estimated odds ratios of 60 day cardiovascular outcomes after SARS-CoV-2 exposure. Abbreviations. CAHD = Coronary artery Atherosclerosis Disease; CKD = Chronic Kidney disease; CVD = cardiovascular disease; MI = Myocardial Ischemia; HTN = Hypertension; OR= Odds Ratios; CI = Confidence Intervals Notes. a. Adjusted for age at index, race, diabetes, current smoking status, CVD, COPD, CKD, and anticoagulant medication. b. Adjusted for age at index, race, diabetes, current smoking status, COPD, CKD, and anticoagulant medication. c. CVD events included subcategories of events such as Ischemic or hemorrhagic stroke at 60 days, early MI at 7 days, and Heart failure at 60 days. All CVD events are withing 60 days from the index date except early MI which is within 7 days. d. New onset of heart disease included subcategories of heart disease such as Cardiomyopathy, CVD, HTN, CAHD, Cerebrovascular disease, and Other heart disease. e. A 95% CI excluding 1 indicates statistical significance at α = 0.05.

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