One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID

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Abstract

The cardiovascular complications of acute COVID-19 are well described; however, a comprehensive characterization of the post-acute cardiovascular manifestations of COVID-19 at one year has not been undertaken. Here we use the US Department of Veterans Affairs national healthcare databases to build a cohort of 151,195 people with COVID-19, 3,670,087 contemporary and 3,656,337 historical controls to estimate risks and 1-year burdens of a set of pre-specified incident cardiovascular outcomes. We show that beyond the first 30 days of infection, people with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease. The risks and burdens were evident among those who were non-hospitalized during the acute phase of the infection and increased in a graded fashion according to care setting of the acute infection (non-hospitalized, hospitalized, and admitted to intensive care). Taken together, our results provide evidence that risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial. Care pathways of people who survived the acute episode of COVID-19 should include attention to cardiovascular health and disease.

Introduction

Post-acute sequelae of SARS-CoV-2 — the virus that causes COVID-19 — can involve the pulmonary and several extrapulmonary organs including the cardiovascular system[1]. Few studies investigated cardiovascular outcomes in the post-acute phase of the COVID-19; however, most were limited to hospitalized individuals (who represent the minority of people with COVID-19), and all had short duration of follow up, and a narrow selection of cardiovascular outcomes[2–5]. A comprehensive assessment of post-acute COVID-19 sequelae of the cardiovascular system at 12 months is not yet available. And studies of post-acute COVID-19 sequelae across the spectrum of care settings of the acute infection (non-hospitalized, hospitalized, and admitted to intensive care) are also lacking. Addressing this knowledge gap will inform post-acute COVID care strategies.

In this work, we use the US Department of Veterans Affairs national health care databases to build a cohort of 151,195 US Veterans who survived the first 30 days of COVID-19 infection and two control groups — a contemporary cohort consisting of 3,670,087 non-COVID-19 infected users of the US Department of Veterans Health Care System (VHA), and a historical cohort consisting of 3,656,337 non-COVID-19 infected VHA users during 2017. These cohorts were followed longitudinally to estimate the risks and 12-month burdens of pre-specified incident cardiovascular outcomes in the overall cohort and according to care setting of the acute infection (non-hospitalized, hospitalized, and admitted to intensive care).

Results

There were 151,195, 3,670,087, and 3,656,337 participants in the COVID-19, the contemporary control, and the historical control groups, respectively. Median follow-up time in the COVID-19, contemporary control, and historical control groups was 286 (interquartile range: 256-382), 286 (256-381), and 286 (256-379) days respectively. The COVID-19, contemporary control, and historical control groups had 131,295, 3,194,889 and 3,178,862 person-years of follow up, respectively. Altogether corresponding to 6,633,341 person years of follow up. The demographic and health characteristics of the COVID-19, the contemporary control, and historical control groups before and after weighting are presented in supplementary tables 1 and 2, respectively.

Risks and 12-month burdens of incident cardiovascular disease in people with COVID-19 vs non-infected contemporary controls

Assessment of covariate balance after application of inverse probability weighting suggested that covariates were well balanced (supplementary figure 1).

We estimated the risks of a set of pre-specified cardiovascular outcomes in COVID-19 vs contemporary control; we also estimated the adjusted excess burden of cardiovascular outcomes due to COVID-19 per 1,000 persons at 12 months on the basis of the difference between the estimated incidence rate in individuals with COVID-19 and the contemporary control group. Risks and burdens of individual cardiovascular outcomes are provided in figure 1 and supplementary table 3 and are discussed below. Risks and burdens of the composite end points are provided in figure 2 and supplementary table 3.

Cerebrovascular disorders: People who survived the first 30 days of COVID-19 exhibited increased risk of stroke (HR 1.48 (1.38, 1.58); burden 3.69 (3.59, 3.78) per 1000 persons at 12 months; for all hazard ratios and burdens, parenthetical ranges refer to 95% confidence intervals) and transient ischemic attacks (HR 1.40 (1.27, 1.53); burden 1.48 (1.41, 1.54)). The risk and burden of a composite of these cerebrovascular outcomes were 1.48 (1.40, 1.57), and 4.95 (4.84, 5.07).

Dysrhythmias: There was increased risks of atrial fibrillation (HR 1.79 (1.69, 1.90); burden 7.99 (7.87, 8.10)), sinus tachycardia (HR 1.82 (1.72, 1.93); burden 6.46 (6.36, 6.56)), sinus bradycardia (HR 1.49 (1.42, 1.57); burden 5.48 (5.36, 5.60)), ventricular arrhythmias (HR 1.56 (1.47, 1.66); burden 4.61 (4.51, 4.71)); and atrial flutter (HR 1.57 (1.45, 1.70); burden 4.49 (4.40, 4.59)). The risk and burden of a composite of these dysrhythmia outcomes were 1.66 (1.60, 1.72), and 19.31 (19.12, 19.51).

Inflammatory disease of the heart or pericardium: included pericarditis (HR 1.62 (1.43, 1.83); burden 0.89 (0.85, 0.93)) and myocarditis (HR 5.22 (3.71, 7.35); burden 0.29 (0.28, 0.29)). The risk and burden of a composite of these inflammatory diseases of the heart or pericardium were 1.77 (1.57, 1.99), and 1.15 (1.10, 1.19).

Ischemic heart disease: included acute coronary disease (HR 1.48 (1.38, 1.58); burden 4.99 (4.87, 5.10)), myocardial infarction (HR 1.61 (1.49, 1.73); burden 3.19 (3.11, 3.27)), ischemic cardiomyopathy (HR 1.41 (1.28, 1.55); burden 2.69 (2.60, 2.78)), and angina (HR 1.48 (1.37, 1.60); burden 2.33 (2.25, 2.41)). The risk

and burden of a composite of these ischemic heart disease outcomes were 1.47 (1.40, 1.56), and 6.67 (6.54, 6.80).

Other cardiovascular disorders: included heart failure (HR 1.73 (1.65, 1.81); burden 11.57 (11.43, 11.72)), non-ischemic cardiomyopathy (HR 1.35 (1.28, 1.41); burden 4.26 (4.14, 4.38)), cardiac arrest (HR 2.15 (1.75, 2.65); burden 0.55 (0.53, 0.58)), and cardiogenic shock (HR 2.17 (1.70, 2.77); burden 0.44 (0.42, 0.46)). The risk and burden of a composite of these other cardiovascular disorders were 1.64 (1.58, 1.71), and 13.28 (13.11, 13.44).

Thromboembolic disorders: included pulmonary embolism (HR 3.06 (2.83, 3.31); burden 5.21 (5.15, 5.26)); deep vein thrombosis (HR 1.62 (1.53, 1.71); burden 4.69 (4.59, 4.78)); and superficial vein thrombosis (HR 1.73 (1.61, 1.87); burden 2.84 (2.77, 2.91)). The risk and burden of a composite of these thromboembolic disorders were 1.92 (1.84, 2.01), and 10.36 (10.25, 10.48).

Additional composite endpoints: We then examined the risks and burdens of 2 composite endpoints including major adverse cardiovascular event (MACE) — a composite of myocardial infarction, stroke, or all-cause mortality — and any cardiovascular outcome (defined as the occurrence of any incident prespecified cardiovascular outcome included in this study). Compared to the contemporary control group, there was increased risks and burdens of MACE (HR 1.55 (1.50, 1.60); burden 24.39 (24.15, 24.62)), and any cardiovascular outcome (HR 1.64 (1.60, 1.68); burden (48.32 (48.00, 48.64)).

Risks and 12-month burdens of incident cardiovascular diseases in people with COVID-19 vs non-infected contemporary controls by care setting of the acute infection.

We further examined the risks and burdens of cardiovascular diseases by the care setting of the acute infection (that is whether people were non-hospitalized, hospitalized, or admitted to intensive care during the acute phase of COVID-19); demographic and health characteristics of these groups before weighting can be found in supplementary table 4 and after weighting in supplementary table 5. Assessment of covariate balance after application of weights suggested covariates were well balanced (supplementary figure 2). Compared to the contemporary control group, the risks and 12-month burdens of the prespecified cardiovascular outcomes increased according to the severity of the acute infection (figure 3 and supplementary table 6); results for the composite outcomes are shown in figure 4 and supplementary table 6.

Risks and 12-month burdens of incident cardiovascular diseases in people with COVID-19 vs non-infected historical controls

We then examined the associations between COVID-19 and the prespecified outcomes in analyses considering a historical control group as the referent category; the characteristics of the exposure groups were balanced after weighting (supplementary figure 3). The results were consistent with analyses using the contemporary control as the referent category and showed increased risks and associated burdens of the prespecified outcomes in comparisons of COVID-19 vs. the overall historical control group

(supplementary figures 4, 5 and supplementary table 7). Associations between COVID-19 and our prespecified outcomes based on care setting of the acute infection were also assessed using the historical control group as the referent category; demographic and clinical characteristics are presented before weighting in supplementary table 8 and after weighting in supplementary table 9. Characteristics of the exposure groups were balanced after weighting (supplementary figure 6). The risks and 12-month burdens of the prespecified outcomes by care setting of the acute infection were also consistent with those shown in analyses considering COVID-19 vs contemporary control (supplementary figures 7, 8 and supplementary table 10).

Sensitivity analyses:

We tested robustness of results in several sensitivity analyses involving the outcomes of MACE, and any cardiovascular outcome (supplementary table 11 and 12). The sensitivity analyses were performed in comparisons involving COVID-19 vs the contemporary control and COVID-19 vs the historical control, and additionally COVID-19 by care setting vs both controls. 1) To test whether the inclusion of additional algorithmically selected covariates would challenge robustness of study results, we selected and utilized 300 high dimensional variables (instead of the 100 used in the primary analyses) to construct the inverse probability weighting; 2) we then also tested the results in models specified to only include predefined covariates (i.e. without inclusion of algorithmically selected covariates) to build the inverse probability weighting; and 3) we changed the analytic approach by using the doubly robust method (instead of the inverse weighting method used in primary analyses) to estimate the magnitude of the associations between COVID-19 exposure and the prespecified outcomes. All sensitivity analyses yielded results consistent with those produced using the primary approach (supplementary tables 11 and 12).

Positive and negative outcome controls:

To assess whether our data and analytic approach would reproduce known associations, we examined the association between COVID-19 and the risk of fatigue (known to be a signature sequela of post-acute COVID-19) as a positive outcome control. The results suggested that COVID-19 was associated with higher risk of fatigue (supplementary table 13).

We then examined the association between COVID-19 and a battery of 4 negative outcome controls where no prior knowledge suggests an association is expected. The results yielded no significant association between COVID-19 and any of the negative outcome controls — results were consistent with a priori expectations (supplementary table 13).

Discussion

In this work involving 151,195 people with COVID-19, 3,670,087 contemporary controls, and 3,656,337 historical controls — which altogether correspond to 6,633,341 person years of follow up, we provide evidence that beyond the first 30 days of infection, people with COVID-19 exhibited increased risks and 12-month burdens of incident cardiovascular disease including cerebrovascular disorders, dysrhythmias,

inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease, and other cardiac disorders. Our analyses of the risks and burdens of cardiovascular outcomes across care settings of the acute infection reveal two key findings: (1) that the risks and associated burdens were evident among those who were not hospitalized during the acute phase of the disease — this group represents the majority of people with COVID-19 and (2) that the risks and associated burdens exhibited a graded increase across the severity spectrum of the acute COVID-19 infection (from non-hospitalized to hospitalized individuals, to those admitted to intensive care). The risks and associated burdens were consistent in analyses considering the contemporary control group and — separately — the historical control group as the referent category. The results were robust to challenge in multiple sensitivity analyses. Application of a positive outcome control yielded results consistent with established knowledge; and testing of a battery of negative outcome controls yielded results consistent with a priori expectations. Taken together, our results suggest that one-year risk and burden of cardiovascular disease among those who survive the acute phase of COVID-19 are substantial and span several cardiovascular disorders. Care strategies of people who survived the acute episode of COVID-19 should include attention to cardiovascular health and disease.

The broader implications of the findings are clear. Cardiovascular complications have been described in the acute phase of COVID-19[6–8]. Our studies suggest that the risk of incident cardiovascular disease extends well beyond the acute phase of COVID-19. Given the large and growing number of people infected with COVID-19 (more than 43 million people in the US, nearly 8 million people in the UK, and more than 231 million people globally), the risks and 12-month burdens cardiovascular disease reported here may translate in large number of potentially affected people around the world. Governments and health systems around the world should be prepared to deal with the likely significant contribution of the COVID-19 pandemic to a rise in the burden of cardiovascular diseases.

The mechanism or mechanisms that underlie the association between COVID-19 and development of cardiovascular diseases in the post-acute phase of the disease are not entirely clear[9,10]. Putative mechanisms include lingering damage from direct viral invasion of cardiomyocytes and/or endothelial cells and subsequent cell death, transcriptional alteration of multiple cell types in heart tissue, downregulation of ACE2 and dysregulation of the renin–angiotensin–aldosterone system, autonomic dysfunction, pro-coagulant state, elevated levels of pro-inflammatory cytokines, and subsequent fibrosis and scarring of cardiac tissue[9,11–13]. An aberrant persistent hyperactivated immune response, autoimmunity, or persistence of the virus in immune privileged sites has also been cited as putative explanations of extrapulmonary (including cardiovascular) post-acute sequelae of COVID-19[9,11,12,14]. Insight developed from prior natural disasters and previous pandemics also suggest the putative presence of indirect effects including changes in the broader contextual environment, social (e.g. isolation, quarantine, reduced social contact and loneliness), economic (e.g. financial distress due to complete loss or reduced income), and behavioral conditions (e.g. changes in dietary habits and physical activity), lived experiences of trauma and grief (from pandemic related happenings) that may be differentially experienced by people with COVID-19 may also shape their cardiovascular outcomes[15–20].

These putative direct and indirect mechanistic pathways may accelerate the progression pre-existing subclinical disease and/or lead to development of de novo disease. A deeper understanding of the direct biologic mechanisms and the putative contribution of indirect contextual drivers will be needed to inform development of prevention and treatment strategies of the cardiovascular manifestations among people with COVID-19.

This study has several strengths. We used the vast and rich national healthcare databases of the US Department of Veterans Affairs to build a large cohort of people with COVID-19. We designed the study cohort to investigate incident cardiovascular disease in the post-acute phase of the disease. We pre-specified a comprehensive list of cardiovascular outcomes. We examined the associations using two large control groups – a contemporary and a historical control; this approach allowed us to deduce that the associations between COVID-19 and risks of cardiovascular outcomes are not related to the broader temporal changes between the pre-pandemic and the pandemic eras, but rather related (possibly through both a direct and indirect pathway) to exposure to COVID-19 itself. Our modeling approach included specification of 19 predefined variables selected based on established knowledge and 100 algorithmically selected variables from VA high dimensional data domains including diagnostic codes, prescription records, and laboratory test results. We evaluated the associations across care settings of the acute infection. We challenged robustness of results in multiple sensitivity analyses, and successfully tested positive and negative outcome controls. We provided estimates of risk on both the ratio scale (hazard ratios) and the absolute scale (burden per 1000 persons at 12 months); the latter also reflects the contribution of baseline risk and provides an estimate of potential harm that is more easily explainable to the general public than risk reported on the ratio scale (e.g., hazard ratio).

This study has several limitations. The demographic composition of our cohort (majority White and male) may limit generalizability of study findings. We used the electronic healthcare databases of the US Department of Veterans Affairs to conduct this study, and although we used validated outcome definitions, and took care to adjust the analyses for a large set of predefined and algorithmically selected variables, we cannot completely rule out misclassification bias and residual confounding. The associations should not be interpreted as causal effects of COVID-19 exposure; our approach does not allow us to disentangle the direct effects of the viral infection and the immune response to it from the putative contribution of indirect contextual exposure (differentially experienced by people with COVID-19) to cardiovascular outcomes; however, regardless of relative contribution of a direct and indirect pathway, the excess burden experienced by people with COVID-19 represents the additional burden of disease that health systems will encounter as a result of this pandemic. Finally, as the pandemic with all its dynamic features continues to progress, as the virus continues to mutate and as new variants emerge, as treatment strategies of the acute and post-acute COVID-19 evolve, as vaccine uptake improves, it is possible that the epidemiology of cardiovascular manifestations in COVID-19 may also change over time[21].

In sum, using a national cohort of people with COVID-19, we show that at risk and 12-month burden of incident cardiovascular disease are substantial and span several cardiovascular disease categories

(ischemic and non-ischemic heart disease, dysrhythmias, and others). The risk and burden of cardiovascular disease were evident even among those whose acute COVID-19 did not necessitate hospitalization. Care pathways of people who survived the acute episode of COVID-19 should include attention to cardiovascular health and disease.

Methods

Setting:

We used the electronic healthcare databases of the US Department of Veterans Affairs to conduct this study. The Veterans Health Administration (VHA) — within the US Department of Veterans Affairs — provides healthcare to discharged veterans of the US armed forces. It operates the largest nationally integrated healthcare system in the USA, with 1,255 healthcare facilities (including 170 VA Medical Centers and 1,074 outpatient sites) located across the USA. All Veterans who are enrolled with the VHA have access to the comprehensive medical benefits package of the VA (which includes preventative and health maintenance, outpatient care, inpatient hospital care, prescriptions, mental healthcare, home healthcare, primary care, specialty care, geriatric and extended care, medical equipment, and prosthetics). The VA electronic healthcare databases are updated daily.

Cohort:

A flowchart of cohort construction is provided in supplementary figure 9. Within 6,239,465 participants who encountered the VHA in 2019, 162,363 participants who had a positive COVID-19 test between March 1, 2020 and January 15, 2021 were selected into the COVID-19 group. To examine post-acute outcomes, we then selected participants from the COVID-19 group who were alive 30 days after the date of the positive COVID-19 test (n=151,195). The date of the COVID-19 positive test served as T_0 for the COVID-19 group.

A non-infected contemporary control group was constructed from those who had encountered the VHA in 2019 (n=6,239,465). Within those who were still alive by March 1, 2020 (n=5,959,033), 5,759,997 participants were not in the COVID-19 group and were selected into the non-infected contemporary control group. To ensure this contemporary control group had a similar follow up time as the COVID-19 group, we assigned a T_0 from each participant in the COVID-19 group to 25 participants in the contemporary control group (n in the contemporary control at this stage=3,779,875). Following the assigned T_0, 3,670,087 participants in the contemporary control group were alive 30 days after T_0. In the COVID-19 and contemporary control groups, August 31, 2021 was the end of follow up.

To examine the associations between COVID-19 and cardiovascular outcomes compared to those who did not experience the pandemic, a historical control group was constructed from 7,684,758 participants who used the VHA in 2017. Within the 6,459,578 participants who were alive on March 1, 2018, 5,965,557 participants did not enroll into the COVID-19 group were further selected into the historical control group. To ensure this historical control group had a similar follow up time as the COVID-19 group, we assigned

25 historical control participants to a T_0 set two years prior to the T_0 of each participant in the COVID-19 cohort (n in the historical control at this stage=3,779,875). Of these historical control participants with assigned T_0, 3,656,337 were alive 30 days after T_0. In the historical control group, end of follow up was set as August 31, 2019 (supplementary figure 9).

Data Sources:

Electronic health records from the VA Corporate Data Warehouse (CDW) were used in this study. Demographic information was collected from the CDW Patient domain. The CDW Outpatient Encounters domain provided clinical information pertaining to outpatient encounters while the CDW Inpatient Encounters domains provided clinical information during hospitalization. Medication information was obtained from the CDW Outpatient Pharmacy and CDW Bar Code Medication Administration domains. The CDW Laboratory Results domain provided laboratory test information, and the COVID-19 Shared Data Resource provided information on COVID-19. Additionally, the Area Deprivation index (ADI) — which is a composite measure of income, education, employment, and housing — was used as summary measure of contextual disadvantage at participants' residential locations[22].

Pre-specified Outcomes:

The pre-specified outcomes were selected based on the 2022 American College of Cardiology and American Heart Association Key Data Elements and Definitions for Cardiovascular Complications of COVID-19[23] and our prior work on the systematic characterization of long covid[1]. Incident cardiovascular outcomes in the post-acute phase of COVID-19 infection were assessed in the follow-up period between 30 days after T_0 until the end of follow-up in those without history of the outcome in the year prior to T_0. Each cardiovascular outcome was defined based on validated diagnostic codes. We also aggregated individual outcomes in a related category of composite outcome (e.g., stroke and TIA were aggregated to cerebrovascular disease). We also specified 2 composite outcomes: 1) MACE was a composite outcome of all-cause mortality, myocardial infarction, and stroke and 2) the composite of any cardiovascular outcome was defined as the first incident occurrence of any of the cardiovascular outcomes investigated in this study.

Covariates:

To adjust for the difference in baseline characteristics between groups, we considered both predefined and algorithmically selected high-dimensional covariates assessed within one year before T_0. Predefined variables were selected based on prior knowledge[1,7,24,25]. This included demographic information such as age, race (White, Black, and Other), sex; contextual factors such as ADI; health characteristics such as body mass index (BMI), smoking status (current, former, and never); and healthcare utilization parameters including use number of outpatient and inpatient encounters and use of long-term care. We additionally specified several comorbidities as pre-defined variables including cancer, chronic kidney disease, chronic lung disease, dementia, diabetes, dysautonomia, hyperlipidemia, and hypertension. Additionally, we

adjusted for laboratory and vital measurements including estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure. Missing values were accounted for by mean imputation and continuous variables were transformed into restricted cubic spline functions to account for potential non-linear relationships.

In addition to predefined covariates, we further algorithmically selected additional potential confounders from data domains including diagnoses, medications, and laboratory tests[26]. To accomplish this, we gathered all patient encounter, prescription, and laboratory data and classified the information into 540 diagnostic categories, 543 medication classes, and 62 laboratory test abnormalities. For the diagnoses, medications and laboratory abnormalities which occurred in at least 100 participants within each group, univariate relative risk between the variable and exposure was calculated and the top 100 variables with the strongest relative risk were selected[27]. The process of algorithmically selecting high dimensional covariates was independently conducted for the COVID-19 vs contemporary control analyses, and the COVID-19 vs historical control analyses and used along with predefined variables as covariates in the models.

Statistical Analyses:

Baseline characteristics of the COVID-19 and contemporary and historical non-infected control groups, along with standardized mean difference between groups were described.

We then estimated the risks, burdens, and excess burdens of incident cardiovascular outcomes for COVID-19 compared to the contemporary control group and — separately — compared to the historical control group, after adjusting for differences in baseline characteristics through inverse probability weighting. To estimate the risk of each incident cardiovascular outcome, we built a sub-cohort of participants without a history of the outcome being examined (i.e., the risk of incident heart failure was estimated within a sub-cohort of participants without history of heart failure in the year prior to enrollment). In each sub-cohort, a propensity score for each individual was estimated as the probability of belonging to the VHA users group in 2019 (target population) based on both predefined and algorithmically selected high dimensional variables. This propensity score was then used to calculate the inverse probability weight as the probability of belonging in the target population divided by 1 – (the probability of being in the target population). Covariate balance after application of weights were assessed by standardized mean differences.

Hazard ratios of incident cardiovascular outcomes between the COVID-19 and contemporary cohorts and the COVID-19 and historical cohorts were estimated from cause-specific hazard models where death was considered as a competing risk and the inverse probability weights were applied. Burden per 1000 participants at 12 months (1-year) of follow up and the excess burden based on the differences between COVID-19 and control groups were estimated.

We also evaluated the associations between COVID-19 and risks of post-acute cardiovascular sequelae according to care setting of the acute phase of the disease (that is whether people were non-hospitalized,

hospitalized, and admitted into the intensive care unit during the first 30 days of infection). Inverse probability weights were estimated for each care setting group using the approach outlined in the previous paragraph. Cause specific hazard models with inverse probability weighting were then applied and hazard ratios, burdens, and excess burdens were reported.

We conducted multiple sensitivity analyses to test the robustness of our study results. 1) To capture additional potential confounders, we expanded our inclusion of high dimensional variables from top 100 to top 300 when constructing the inverse probability weight. 2) We then modified our adjustment strategy by using only predefined variables when constructing the inverse probability weight (not including the 100 high dimensional covariates used in the primary analyses) 3) We alternatively applied a doubly robust approach, where both covariates and the inverse probability weights were applied to the survival models, to estimate the associations[28].

To test whether our approach would reproduce known associations, we examined the association between COVID-19 and fatigue as a positive outcome control.

We also subjected our approach to the application of a battery of negative outcome controls where no prior knowledge supports the existence of an association[29]. The negative outcome controls included hypertrichosis, melanoma in situ, perforation of the tympanic membrane, and sickle cell disorder. The successful application of negative outcome controls may reduce concern about presence of spurious biases related to cohort building, study design, covariates selection, analytic approaches, outcome ascertainment, residual confounding, and other sources of latent biases.

Estimation of variance when weightings were applied was accomplished by using robust sandwich variance estimators. In all analyses, a 95% confidence interval that excluded unity was considered evidence of statistical significance. This study was approved by the Department of Veterans Affairs St. Louis Health Care System Institutional Review Board. Analyses were conducted using SAS Enterprise Guide version 8.2 (SAS Institute, Cary, NC), and results were visualized using R version 4.04.

Declarations

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Author Contributions: ZAA, EX, and YX contributed to the development of the study concept and design. ZAA, EX, and YX contributed to data analysis and interpretation of results. ZAA, EX, and YX drafted the manuscript. ZAA, EX, YX, and BB contributed to critical revision of the manuscript. ZAA provided

administrative, technical, and material support, as well as supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the report. The corresponding author attests that all the listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Data availability: The data that support the findings of this study are available from the US Department of Veterans Affairs.

Code Availability: SAS programing codes will be made available upon request.

Ethical approval: This research project was reviewed and approved by the Institutional Review Board of the Department of Veterans Affairs Saint Louis Health Care System.

Competing interests: The authors declare no conflict of interest.

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Figures

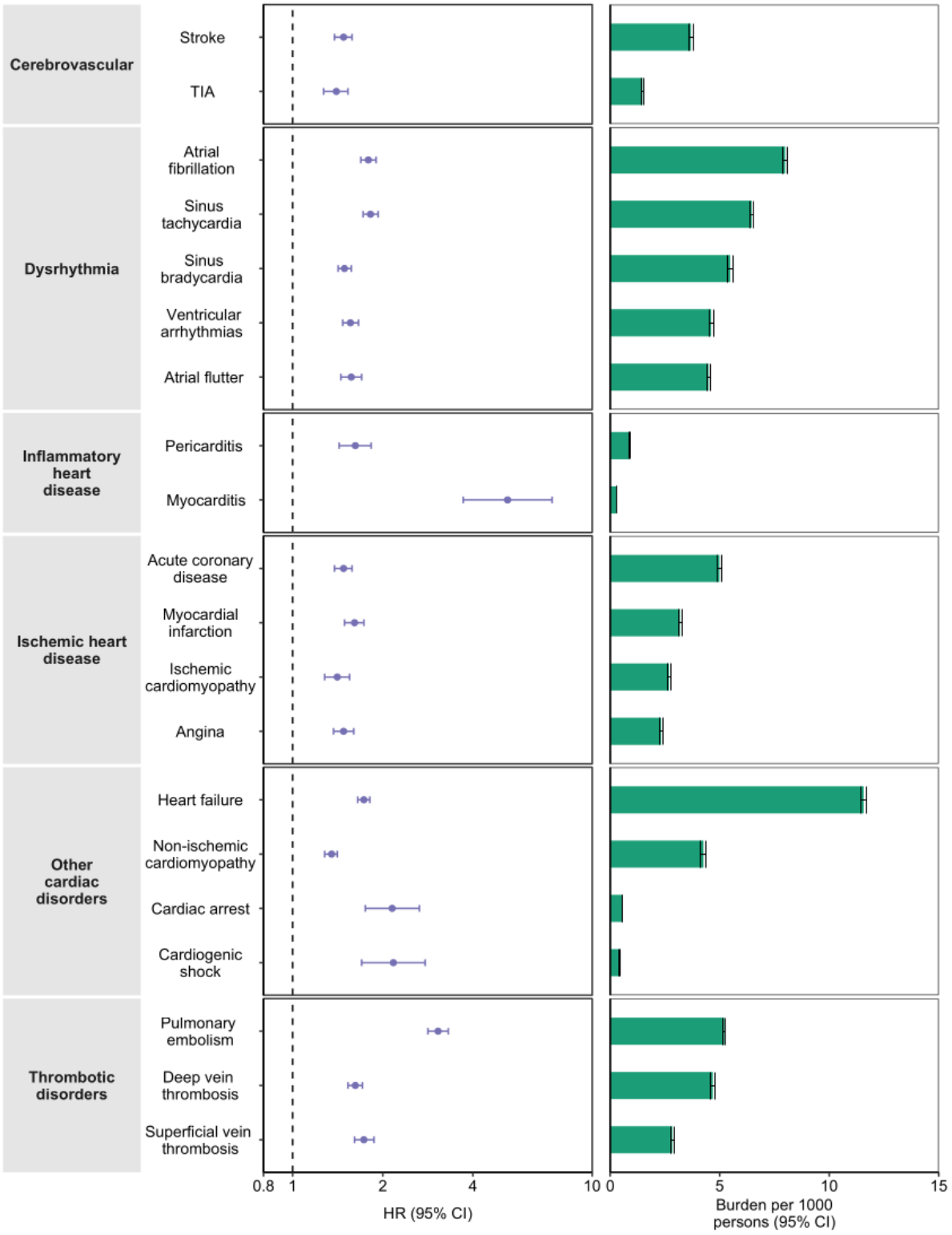

Figure 1

Risks and 12-month burdens of post-acute COVID-19 cardiovascular outcomes compared to the contemporary control. Outcomes were ascertained 30 days after the initial COVID-19 infection until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. TIA, transient ischemic attack.

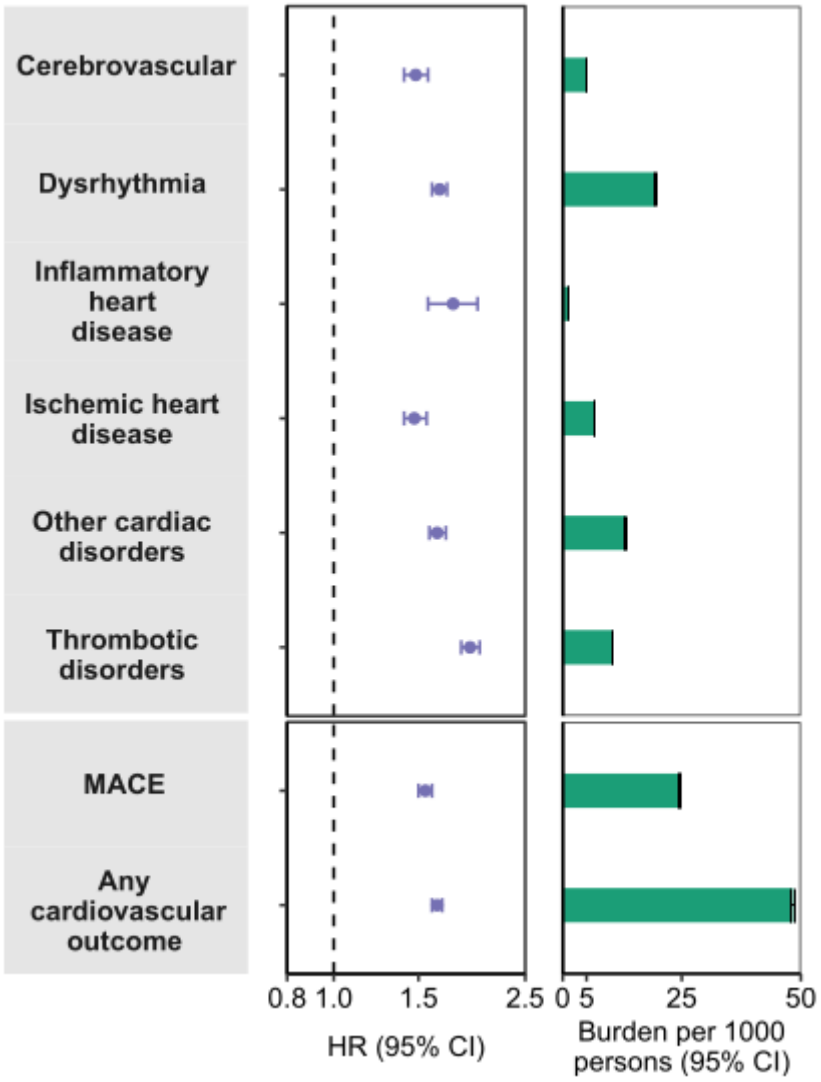

Figure 2

Risks and 12-month burdens of post-acute COVID-19 composite cardiovascular outcomes compared to the contemporary control. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied). Outcomes were ascertained 30 days after the initial COVID-19 infection until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The excess burden per 1000 persons at 12 months and associated 95% confidence intervals are also shown. MACE, major adverse cardiac events.

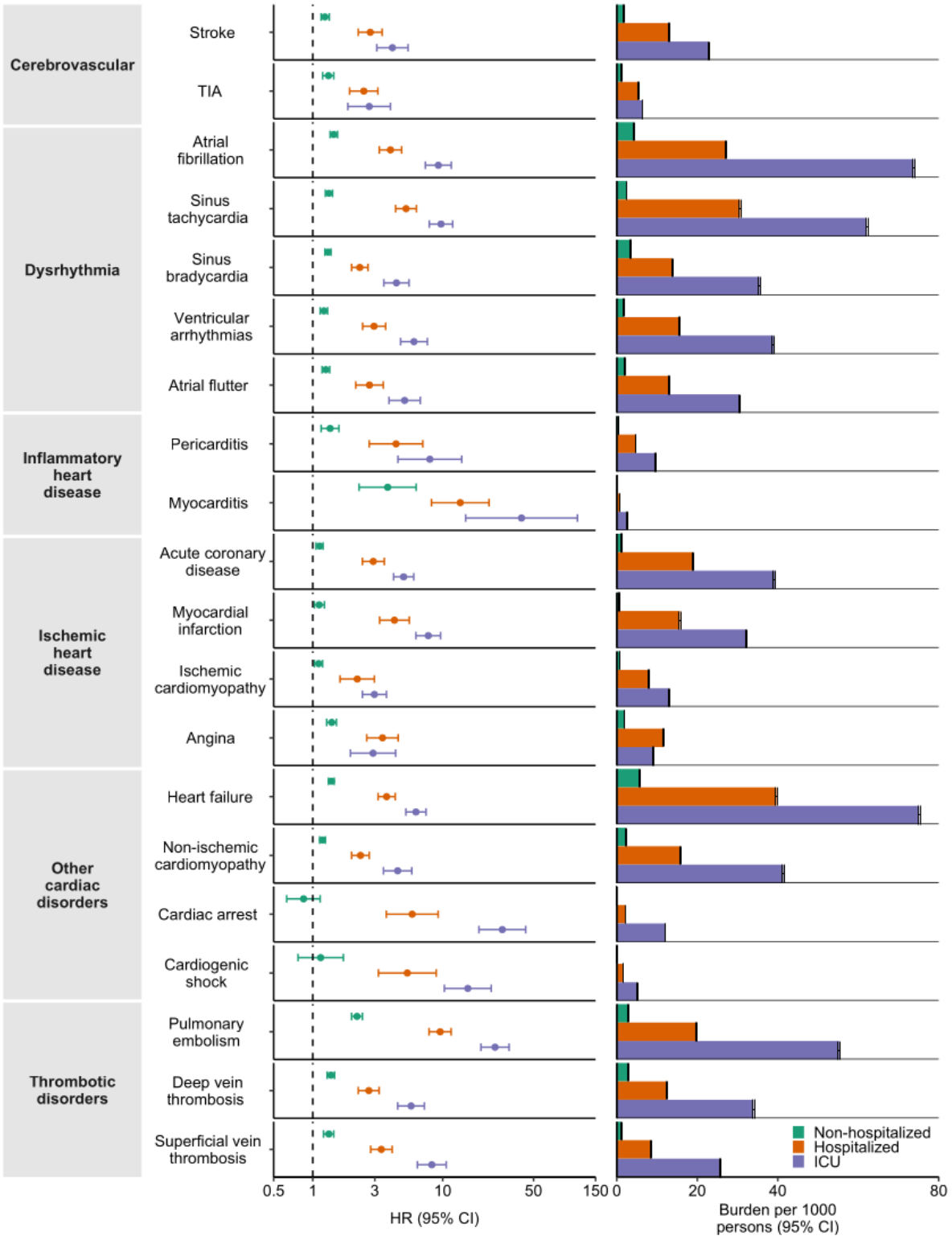

Figure 3

Risks and 12-month burdens of post-acute COVID-19 cardiovascular outcomes compared to the contemporary control by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange), and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 days) of COVID-19 (blue). The contemporary control group served as the

referent category. Outcomes were ascertained 30 days after the initial COVID-19 infection until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The excess burden per 1000 persons at 12 months and related 95% confidence intervals were also presented.

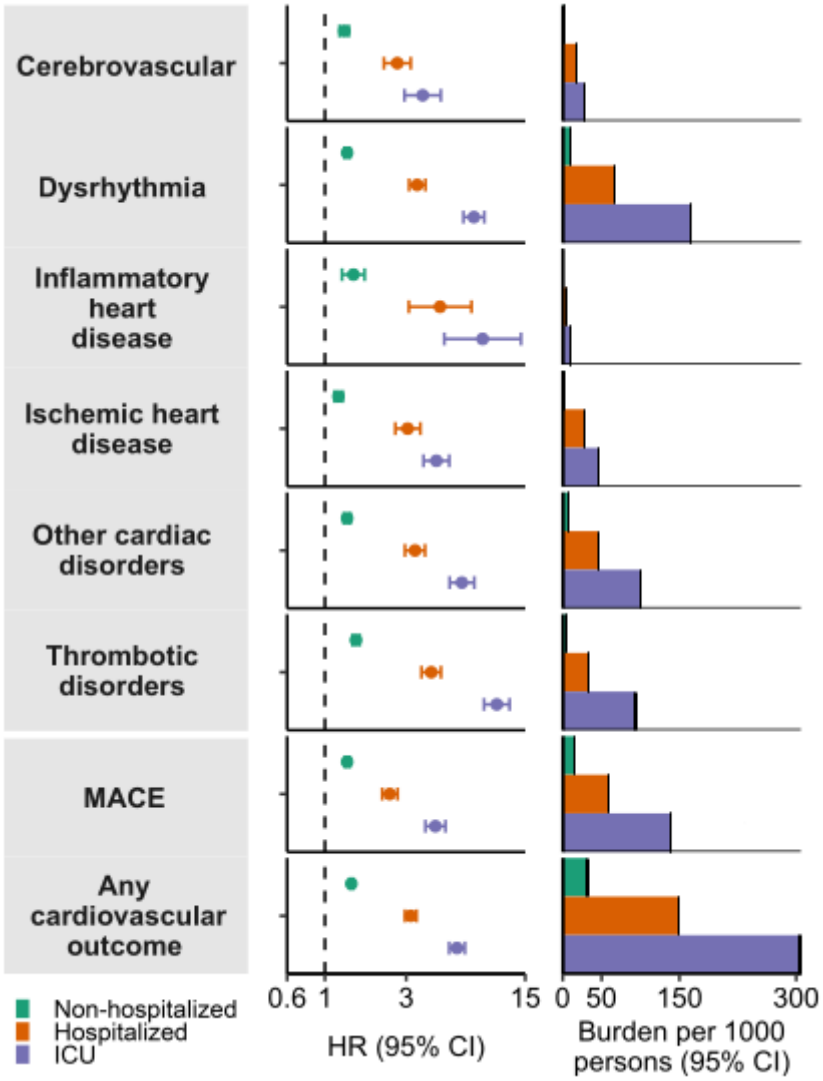

Figure 4

Risks and 12-month burdens of post-acute COVID-19 composite cardiovascular outcomes compared to the contemporary control by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange), and individuals admitted to intensive care for COVID-19 during the acute phase (first 30 days) of COVID-19 (blue). The contemporary control group served as the referent category. Outcomes were ascertained 30 days after the initial COVID-19 infection until the end of follow-up. Adjusted hazard ratios and 95% confidence intervals are presented. The excess burden per 1000 persons at 12 months and related 95% confidence intervals were also presented. Composite outcomes consisted of cerebrovascular (stroke and TIA), dysrhythmias (atrial fibrillation, sinus tachycardia, sinus bradycardia, ventricular arrhythmias, and atrial flutter), inflammatory heart disease (pericarditis, myocarditis), ischemic heart disease (acute coronary disease, myocardial infarction,

ischemic cardiomyopathy, and angina), other cardiac disorders (heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock), thrombotic disorders (pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis), MACE (all-cause mortality, stroke, and myocardial infarction), and any cardiovascular outcome (incident occurrence of any cardiovascular outcome studied).

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