COVID-19 severity and risk of subsequent cardiovascular events

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Running Title: COVID-19 severity and cardiovascular events
ABSTRACT

Background

Little is known about the relationship between COVID-19 severity and subsequent risk of experiencing a cardiovascular event (CVE) after COVID-19 recovery. We evaluated this relationship in a large cohort of US adults.

Methods

Using a claims database, we performed a retrospective cohort study of adults diagnosed with COVID-19 between April 1, 2020 and May 31, 2021. We evaluated the association between COVID-19 severity and risk of CVE >30 days after COVID-19 diagnosis using inverse probability of treatment weighted competing risks regression. Severity was based on level of care required for COVID-19 treatment: intensive care unit (ICU) admission, non-ICU hospitalization, or outpatient care only.

Results

1,357,518 COVID-19 patients were included (2% ICU, 3% non-ICU hospitalization, and 95% outpatient only). Compared to outpatients, there was an increased risk of any CVE for patients requiring ICU admission (adjusted hazard ratio [HR]: 1.80 [95%CI: 1.71–1.89]) or non-ICU hospitalization (HR: 1.28 [1.24–1.33]). Risk of subsequent hospitalization for CVE was even higher (HR: 3.47 [3.20–3.76] for ICU and HR: 1.96 [1.85–2.09] for non-ICU hospitalized vs. outpatient only).
Conclusions

COVID-19 patients hospitalized or requiring critical care had a significantly higher risk of experiencing and being hospitalized for post-COVID-19 CVE than patients with milder COVID-19 who were managed solely in the outpatient setting even after adjusting for differences between these groups. These findings underscore the continued importance of preventing SARS-CoV-2 infection from progressing to severe illness to reduce potential long-term cardiovascular complications.

Key Words: PASC, post-acute COVID-19 syndrome; SARS-CoV-2; long-covid; post-covid syndrome
Introduction

An estimated 30% of COVID-19 survivors continue to experience an array of symptoms for weeks to months after initial diagnosis [1], suggesting many individuals have incomplete recovery from acute illness [2-5]. The constellation of post-acute COVID-19 syndromes, persistent symptoms, and new ailments are termed Post-Acute Sequelae of SARS-CoV-2 infection (PASC), informally known as “long COVID” [6]. Although the most widely recognized PASC syndrome is multisystem inflammatory syndrome in both adults and children (Multisystem Inflammatory Syndrome in Adults (MIS-A) and children (MIS-C)) [7], a multitude of other post-COVID outcomes have been documented, spanning from persistent fatigue [8] and sleep difficulties [4] to type 1 diabetes [9] and neurological manifestations [10]. The incidence of these syndromes varies significantly and appears to be driven by the demographic and clinical characteristics of the patient [11].

The pathophysiology of SARS-CoV-2 infection suggests the ability to produce cardiac damage after infection. Several investigations and reviews suggest that multiple cardiovascular complications such as hypertension, arrhythmia, thromboembolism, acute myocardial infarction, cerebrovascular accident, and others may be more frequent after recovery from COVID-19 [12-24]. Limited data have suggested that more severe disease may lead to a higher probability of cardiovascular complications. However, this has not been widely investigated in the general population and was assessed only as a secondary outcome in one study conducted among US Veterans [12]. Thus, we evaluated the association between COVID-19 severity and the risk of subsequent cardiovascular events (CVE) among adults in a large, generalizable US population.
Methods

Study Design and Population

We performed a retrospective cohort study of adults (≥18 years) using nationwide health insurance claims data from the US HealthVerity Real-Time Insights and Evidence database, including both open- and closed-source claims.

Study eligibility required medical and pharmacy coverage and a diagnosis for COVID-19 (ICD-10-CM: U07.1) between April 1, 2020, and May 31, 2021, with at least 365 days of continuous medical and pharmacy enrollment before index. The patient’s date of first COVID-19 diagnosis served as the index date. We excluded patients with a documented history of any cardiovascular outcome under analysis or with anti-thrombotic use 365 days before index, as well as patients who experienced any cardiovascular outcome or died within 30 days after index.

Outcomes and Follow-up

Pre-specified outcomes were selected to replicate major CVE groups as outlined in Xie et al. [12]. The primary outcome was the first occurrence of dysrhythmia, ischemic heart disease, thrombotic disorders, cerebrovascular accident (i.e., stroke or TIA), or other cardiac disorders (e.g., heart failure, myocarditis, etc.). Secondarily, we considered each CVE group separately and for atherosclerotic, inflammatory, and acute and chronic CVEs. We also repeated all analyses where only CVEs requiring inpatient care were included as an outcome to reduce potential detection biases whereby patients with more severe COVID-19 might have been followed more closely for sequelae thereafter. For persons who remained hospitalized ≥30 days after COVID diagnosis, any cardiovascular event that occurred in the inpatient setting, regardless of whether it occurred during the continuation of the initial hospitalization or as a new admission, was counted. All outcomes were identified using ICD-10-CM codes (Table S1) [25].
Code lists used the COVID-19 Natural History Master Protocol from the US Food and Drug Administration’s Sentinel Initiative [26], and were augmented by expert medical review. Patients were followed starting >30 days after the index until the event of interest. Patients were censored if they disenrolled from the data source or at the end of the study period (December 31, 2021).

**Exposure**

COVID-19 site of care was defined as the highest level of care experienced over the 30-day window after index as a proxy for COVID-19 disease severity: intensive care unit (ICU) admission, non-ICU hospitalization, or outpatient care only. To classify hospitalizations as “for” COVID-19 rather than “with” COVID-19, the COVID-19 diagnosis was required to be present on admission or the principal admitting diagnosis. ICU status was identified using revenue codes, Healthcare Common Procedure Coding System (HCPCS) codes, or Current Procedural Terminology Fourth Edition (CPT-4) codes as used in a previously defined algorithm [27].

**Covariates**

Unless otherwise noted, all pre-defined covariates were assessed 365 days before the index. Demographics included age, sex, region of residence (US Census region categories: Northeast, Midwest, South, West), and insurance provider. The month of COVID-19 diagnosis was used to account for any pandemic-related time trends, including circulating variants. Clinical characteristics were identified using ICD-10-CM diagnosis codes, HCPCS codes, and CPT-4 procedure codes. These included individual variables of the Charlson Comorbidity Index; other measures of poor health, including immunosuppressive conditions, smoking status, obesity, hypertension (defined based on diagnosis or medication usage), prior hospitalization, prior or
current residence in a nursing home or skilled nursing facility, impaired functional status (i.e.,
required nursing facility services, at-home medical visit services, supplemental oxygen, or
wheelchair use), and measures of preventive health (history of influenza and pneumococcal
vaccination and history of at least one wellness visit in the year before index). Prior COVID-19
vaccination was assessed using National Drug Codes (NDC) and CPT-4 vaccine administration
codes. Indicator variables were used in propensity score estimation for missing sex or region
variables. The absence of a code for all other covariates, such as comorbid conditions, was
considered to be the absence of the condition rather than missing data.[28]

Statistical Analysis

Baseline characteristics were summarized with counts and percentages for categorical
variables and means with standard deviations for continuous variables. Multinomial propensity
score models were used to calculate stabilized inverse probability of treatment weights (IPTW)
for patients across care settings to account for imbalances in baseline characteristics between
patients in different care settings. Covariate balance before and after weighting was assessed
using standardized mean differences (SMD) as ICU admission or non-ICU hospitalization vs.
outpatient care only. Variables with residual imbalance (>10% SMD) were included in the final
model for further adjustment.

Weighted cumulative incidence curves were calculated to describe the occurrence of each
outcome separately over the entire follow-up period. Proportional sub-distribution hazards
models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI), accounting
for the competing risk of death. Finally, we quantified the amount of independent unmeasured
confounding that would have had to be present to change the interpretation of the results using E-
values. All analyses were performed in SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA) and R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

We also performed subgroup analyses replicating the primary analyses separately for each of the following age groups: 18–49, 50–64, and ≥65 years. Standard Cox proportional hazards models were used for the 18–49 subgroup due to the low number of deaths experienced in this subgroup. Propensity scores were re-estimated in each analysis, and a doubly robust set of covariates was re-assessed.

Conduct and ethics statements

The study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [29]. This study was deemed exempt from Institutional Review Board (IRB) review pursuant to the terms of the US Department of Health and Human Service’s Policy for Protection of Human Research Subjects at 45C.F.R. 46.104(d); category four exemption (Sterling IRB, Atlanta, GA, waived ethical approval for this work).

Results

There were 4,898,787 eligible adults (≥18 years of age) with COVID-19 in the database, of which 1,357,518/4,898,787 (27.7%) met the selection criteria for final analysis (Figure 1). Most were treated in the outpatient setting only (1,292,064; 95.2%), 44,385 (3.3%) required hospitalization without ICU admission, and 21,069 (1.6%) were admitted to ICU (Table 1). Outpatients tended to be younger than patients requiring ICU admission and non-ICU hospitalized patients (mean age 41 years vs. 54 and 50 years, respectively) and had a lower prevalence of obesity (20% vs. 33% and 30%, respectively), diabetes without complications (13% vs. 35% and 27%, respectively), chronic kidney disease or end-stage renal disease (5% vs. 8% and 12%, respectively).
16% and 13%, respectively), and hospitalization in the prior year (7% vs. 16% and 18%, respectively) (Table 1). Trends were similar when stratified by age group (Tables S2-S4).

Weighted cohorts were well balanced, with no remaining imbalances in the non-ICU hospitalized vs. outpatient comparisons. Only a single variable (age) was included in the doubly robust outcome model for the ICU admission group comparison (Table S5).

For each group, the median was one inpatient visit in the first 6 months of follow-up (Supplementary Table S6). For outpatient visits, there was an increasing number of outpatient visits with increasing acute COVID severity. We observed a dose-response between the severity of COVID-19 and the incidence of any CVE (Figure 2A). This relationship was observed early on and was maintained through the end of the follow-up. At nine months after COVID-19 diagnosis, the weighted cumulative incidences of any CVE event were 14% among patients requiring ICU care, 10% among non-ICU hospitalized patients, and 8% among outpatients (Figure 2A and Table S7) and continued to increase throughout follow-up for all three groups. Similar trends were observed for each CVE outcome, with dysrhythmia the most commonly occurring outcome and thrombotic disorders the least common (Figure S1).

We also observed a dose-response between the severity of COVID-19 and the incidence of any CVE requiring hospitalization (Figure 2B). Weighted cumulative incidence of CVEs requiring hospitalization at 9 months after COVID-19 diagnosis were 4%, 2%, and 1% among these three groups, respectively (Figure 2B and Table S8).

In adjusted competing risk regression models, COVID-19 patients requiring ICU admission (adjusted HR: 1.80 [1.71–1.89]) and non-ICU hospitalized patients (HR: 1.28 [95%CI: 1.24–1.33]) had significantly higher risk of CVE compared to COVID-19 patients treated only in the outpatient setting (Figure 3A and Table S7). E-values for the composite
outcome were 1.88 for non-ICU hospitalized and 3.00 for ICU patients (Table S9). This effect was even more pronounced when restricting the outcome to CVEs requiring hospitalization (HR: 3.47 [3.20–3.76] for ICU patients and HR: 1.96 [1.85–2.09] for non-ICU hospitalized patients vs. outpatients (Figure 3B and Table S8). We observed similar trends when categorizing CVEs into atherosclerotic and inflammatory events, and acute and chronic events (Table S10).

The risk of individual CVEs was also elevated for both groups of hospitalized COVID-19 patients (i.e., with or without ICU admission) compared to outpatients, with a larger risk for each CVE among those requiring ICU care. Compared to outpatients, risks of individual cardiac conditions were increased by 59–166% for COVID-19 patients admitted to ICU and 22–76% for non-ICU hospitalized patients (Figure 3A and Table S7). The largest effect sizes were found among patients admitted to the ICU for the risk of other cardiovascular disorders (HR: 2.66 [2.42–2.94]) and thrombotic disorders (HR: 2.51 [2.21–2.84]).

When stratified by age group, among adults requiring ICU admission for COVID-19, the risk of any CVE was higher among patients 18–49 years of age (HR: 1.92 [1.79–2.05]) compared to those 50-64 (HR: 1.64 [1.55–1.75]) and ≥65 years (HR: 1.36 [1.26–1.48]). These trends were consistent across individual CVEs except for dysrhythmia, where middle-aged adults had the higher risk (Tables S11-S13).

Similarly, when stratified by age group, among adults requiring ICU admission for COVID-19, the risk of any CVE requiring a subsequent hospitalization was higher among patients 18–49 years of age (HR: 4.04 [3.56–4.59]) compared to those 50-64 (HR: 2.87 [2.58–3.20]) and ≥65 years (HR: 2.23 [1.95–2.55]) (Tables S14-S16). These trends were generally consistent across individual CVEs and among non-ICU hospitalized adults, except for thrombotic disorders and cerebrovascular accidents, where middle-aged adults had a higher risk.
Discussion

Despite broad public health efforts, the large and growing number of individuals infected with SARS-CoV-2 [30, 31] is concerning in terms of how many may experience long-term sequelae, such as CVEs, in the months and years ahead. Our study suggests that increasing the severity of COVID-19 illness increases the risk of developing a subsequent, non-acute, CVE among individuals without a history of cardiac illness in the prior year, independent of the many factors included in the IPTW weighted analysis. Specifically, compared to patients who had COVID-19 that required outpatient care only, those who required ICU admission were 80% more likely, and those who required non-ICU hospitalization were 28% more likely to experience a CVE >30 days after the initial COVID-19 episode. Compared to outpatients, these same two groups were 247% and 96% more likely, respectively, to be hospitalized for a CVE after COVID-19 illness. This dose-response relationship persisted after adjustment for many potentially confounding patient demographic and clinical characteristics (e.g., age, month of COVID-19 diagnosis, obesity, smoking, immunocompromising status, and other relevant comorbidities). Standardized mean differences and E-values provided quantitative evidence of the risk of bias from residual confounding, and suggested our results are unlikely to be entirely explained by patient characteristics rather than solely COVID-19 severity.

While the incidence of cardiovascular sequelae is lower in younger adults than older adults, we saw larger relative hazards for the youngest age group (18–49 years). Older adults are a well-described group at higher risk of severe COVID-19, yet these results also underscore the importance of mitigation measures among younger adults. Similarly, the more severe outcomes, such as thrombotic events and cerebrovascular accidents, while rare overall, occur substantially more often among the more severe COVID-19 cases than those managed in the outpatient
setting. These findings reiterate the importance of vaccination for preventing SARS-CoV-2 infection and reducing its severity—as results from our study suggest that subsequent CVEs appear to be linked to more severe COVID-19 illness. Likewise, these results support the prompt treatment of acute COVID-19 illness with antivirals to minimize severe disease from developing to help reduce the risk of potentially life-threatening post-COVID-19 cardiovascular events.

Our results are consistent with Xie et al., who reported approximately 1.5 to 2.0 times higher risk of various CVEs after SARS-CoV-2 infection in a US Veterans Affairs population. These results also showed a dose-response with increasing severity of disease [12]. Similarly, Jovanoski and colleagues reported a higher risk of CVEs after COVID-19, which increased with increasing disease severity in a patient cohort from the Optum electronic health record database [32]. Recently, myocarditis and pericarditis have been found to be substantially higher in patients who have recovered from COVID-19 [33], which is also consistent with our secondary analyses.

Interestingly, increased cardiovascular risk after acute infection may not be unique to COVID-19. Although few studies have evaluated long-term cardiovascular risks, several have linked other severe infections such as bacteremia, influenza, and pneumonia with acute CVEs [34-43]. For example, Ou and colleagues reported a 22–65% increased risk of CVEs in sepsis survivors persisting for up to 5 years after hospital discharge. However, this was not statistically significant after multivariable modeling [44]. Corrales-Medina et al. suggested there could be a 50–60% higher risk of cardiovascular disease after hospitalization due to pneumonia five to ten years after discharge [45]. Yende and colleagues identified a 10% increased risk in CVEs in sepsis survivors compared with matched hospitalized or intensive care control subjects [46].

There is uncertainty about the biological mechanisms behind the apparent increased risk of CVEs following SARS-CoV-2 infection. SARS-CoV-2 infects cardiac myocytes through the
ACE-2 receptor and may remain persistent, invoking chronic inflammatory responses and subsequent tissue damage or fibrosis [47]. Another mechanism is thought to be an autoimmune response to cardiac antigens resulting in delayed damage to cardiac tissues [48, 49]. These autoantibodies may target various systems, including platelets, phospholipids, and endothelial cells, and may activate neutrophils or promote thrombosis [23]. Further, anti-heart antibodies have been shown to correlate with cardiovascular manifestation in COVID-19 patients and, importantly, correlate with the severity of illness [50]. Other potential mechanisms of cardiovascular damage include direct viral toxicity leading to long-term cardiac damage or thrombosis in vasculitis, either of which may result in immediate or delayed risk to cardiac health [47]. Future studies should attempt to elucidate the mechanisms of cardiac damage due to COVID-19.

This study has limitations. First, in the absence of a COVID-19 negative control group, it was not possible to quantify an increased risk in CVEs precisely due to COVID-19. Second, these results cannot be generalized to reflect the risk of CVEs exacerbation for patients with a pre-existing cardiovascular condition or patients who died within 30 days of COVID-19 diagnosis as these individuals were excluded from our analyses. Further, exclusion of these individuals, and those with CVEs in the prior year, may not fully prevent carryover and may underestimate the number of CVEs, potentially biasing our results toward the null. Despite this limitation, these methods have been used in prior studies to report the risk of cardiovascular-associated mortality after bacterial pneumonia.[45] Third, it is possible that residual or unmeasured confounding remains beyond the balance we were able to demonstrate with the stabilized propensity scores. Specifically, as is common in claims-based analyses in the United States, COVID-19 vaccination status was underreported compared to publicly available vaccine
uptake estimates. Thus, we were unable to account for vaccination in our analyses beyond
including an indicator in the propensity score for whether or not a patient had received at least
one COVID vaccine dose based on administrative claims. Additionally, it is possible that
confounding by COVID-19 treatment status may have biased our results, particularly in the
outpatient setting. However, COVID-19 treatment was rare in our study (<5% for
dexamethasone; <1% each for monoclonal antibodies and remdesivir; Supplemental Table S17),
and likely had minimal impact on the results. Our use of a composite endpoint encompassing a
broad range of CVEs may make it difficult to tease apart the distinct events or organ impacts of
COVID-19. Lastly, the HealthVerity dataset has limited capture of in-hospital deaths and does
not capture out-of-hospital deaths.

In conclusion, we found that patients diagnosed with COVID-19 who were hospitalized
or required ICU care had a significantly higher risk of experiencing and being hospitalized for
post-COVID-19 cardiac events than those treated in the outpatient setting only. This finding
showed dose-response and persisted after controlling for demographic and clinical characteristics
differences. These findings underscore the continued importance of preventing SARS-CoV-2
infection from progressing to severe illness to reduce potential long-term cardiovascular
complications.

NOTES

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Author Contributions:

Drs. Wiemken and McGrath, and Mr. Khan had full access to all the data in the study and took responsibility for the data's integrity and the accuracy of the data analysis.

Concept and design: Drs. Wiemken, McLaughlin, McGrath, and Andersen and Mr. Khan

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors. Drs. Wiemken, McGrath, Andersen, and McLaughlin wrote the first draft.

Critical revision of the manuscript for important intellectual content: All Authors

Obtained funding: N/A.

Administrative, technical, or material support: All Authors

Supervision: Dr. McLaughlin.

Funding/Support: Pfizer, Inc

Role of the Funder/Sponsor: This study was sponsored by Pfizer.

Conflict of Interest Disclosures: All authors are employees and shareholders of Pfizer Inc.
1 References


26. United States Food and Drug Administration Sentinel Initiative. COVID-19 Natural History Codelist. Available at:


**Table 1**: Characteristics of COVID-19 patients meeting inclusion criteria for analysis

(n=1,357,518)

<table>
<thead>
<tr>
<th></th>
<th>Outpatient (n=1,292,064)</th>
<th>Non-ICU Hospitalization (n=44,385)</th>
<th>ICU Admission (n=21,069)</th>
<th>Weighted SMD: Non-ICU Hospitalization vs outpatient</th>
<th>Weighted SMD: ICU Admission vs outpatient</th>
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<td><strong>Mean age</strong></td>
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<td>50 (18)</td>
<td>54 (16)</td>
<td>0.058</td>
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<td><strong>Sex</strong></td>
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<td>26,793 (60)</td>
<td>10,911 (52)</td>
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<td>0.012</td>
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<td>Male</td>
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<td>17,258 (39)</td>
<td>10,050 (48)</td>
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<td>108 (&lt; 1)</td>
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<td>10,088 (23)</td>
<td>3,968 (19)</td>
<td>0.021</td>
<td>0.057</td>
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<td>9,623 (22)</td>
<td>4,130 (20)</td>
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<td>South</td>
<td>583,955 (45)</td>
<td>19,357 (44)</td>
<td>9,873 (47)</td>
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<td>West</td>
<td>155,522 (12)</td>
<td>5,195 (12)</td>
<td>3,071 (15)</td>
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<td>Other</td>
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<td>119 (&lt; 1)</td>
<td>24 (&lt; 1)</td>
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<td>Missing</td>
<td>95 (&lt; 1)</td>
<td>3 (&lt; 1)</td>
<td>3 (&lt; 1)</td>
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<td><strong>≥1 COVID-19 vaccine dose</strong></td>
<td>13,533 (1)</td>
<td>350 (1)</td>
<td>171 (1)</td>
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<td>-0.044</td>
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<td><strong>Indicators of poor health</strong></td>
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<tr>
<td>Smoking</td>
<td>118,289 (9)</td>
<td>6,369 (14)</td>
<td>2,789 (13)</td>
<td>0.024</td>
<td>0.018</td>
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<td>Obesity</td>
<td>264,017 (20)</td>
<td>13,404 (30)</td>
<td>7,033 (33)</td>
<td>0.073</td>
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<td>Nursing home residence</td>
<td>13,946 (1)</td>
<td>909 (2)</td>
<td>466 (2)</td>
<td>0.019</td>
<td>0.032</td>
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<td>Skilled nursing facility</td>
<td>17,235 (1)</td>
<td>1,139 (3)</td>
<td>537 (3)</td>
<td>0.025</td>
<td>0.037</td>
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<td>Prior hospitalization</td>
<td>84,842 (7)</td>
<td>7,949 (18)</td>
<td>3,345 (16)</td>
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<td>0.018</td>
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<td>Impaired functional status</td>
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<td>3,415 (8)</td>
<td>1,697 (8)</td>
<td>0.026</td>
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<td><strong>Indicator of health-seeking behavior</strong></td>
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<td>Pneumococcal vaccine</td>
<td>32,714 (3)</td>
<td>2,168 (5)</td>
<td>1,299 (6)</td>
<td>0.015</td>
<td>0.026</td>
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<td>Influenza vaccine</td>
<td>433,282 (34)</td>
<td>15,298 (34)</td>
<td>7,556 (36)</td>
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<td>0.018</td>
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<td>Wellness visit</td>
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<td>25,088 (57)</td>
<td>11,884 (56)</td>
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<td>-0.010</td>
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<td>Hypertension</td>
<td>352,584 (27)</td>
<td>19,934 (45)</td>
<td>11,411 (54)</td>
<td>0.045</td>
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<td><strong>Comorbid conditions</strong></td>
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<tr>
<td>Myocardial infaration</td>
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<td>249 (1)</td>
<td>133 (1)</td>
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<td>5,589 (&lt; 1)</td>
<td>511 (1)</td>
<td>287 (1)</td>
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<td>1,939 (9)</td>
<td>0.025</td>
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<td>Cerebrovascular disease</td>
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<td>666 (3)</td>
<td>0.013</td>
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<td>Dementia</td>
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<td>1,552 (3)</td>
<td>734 (3)</td>
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<td>Chronic pulmonary disease</td>
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<td>9,486 (21)</td>
<td>4,778 (23)</td>
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<td>Rheumatic disease</td>
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<td>1,502 (3)</td>
<td>807 (4)</td>
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<td>0.023</td>
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<td>Peptic ulcer disease</td>
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<td>729 (2)</td>
<td>353 (2)</td>
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<tr>
<td>Mild liver disease</td>
<td>77,435 (6)</td>
<td>4,409 (10)</td>
<td>2,532 (12)</td>
<td>0.029</td>
<td>0.051</td>
</tr>
<tr>
<td>Diabetes without complications</td>
<td>168,215 (13)</td>
<td>11,856 (27)</td>
<td>7,373 (35)</td>
<td>0.046</td>
<td>0.098</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>54,980 (4)</td>
<td>5,156 (12)</td>
<td>3,448 (16)</td>
<td>0.027</td>
<td>0.048</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>5,304 (&lt; 1)</td>
<td>492 (1)</td>
<td>300 (1)</td>
<td>0.009</td>
<td>0.028</td>
</tr>
<tr>
<td>Any malignancy</td>
<td>36,265 (3)</td>
<td>2,352 (5)</td>
<td>1,255 (6)</td>
<td>0.014</td>
<td>0.024</td>
</tr>
<tr>
<td>Condition</td>
<td>Count (Obs)</td>
<td>Count (1)</td>
<td>Count (13)</td>
<td>SMD</td>
<td>P-value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Moderate/severe liver disease</td>
<td>2,567 (&lt; 1)</td>
<td>321 (1)</td>
<td>211 (1)</td>
<td>0.008</td>
<td>0.014</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>4,776 (&lt; 1)</td>
<td>431 (1)</td>
<td>220 (1)</td>
<td>0.006</td>
<td>0.012</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>7,016 (1)</td>
<td>470 (1)</td>
<td>210 (1)</td>
<td>0.004</td>
<td>0.006</td>
</tr>
<tr>
<td>CKD/ESRD</td>
<td>70,571 (5)</td>
<td>5,898 (13)</td>
<td>3,447 (16)</td>
<td>0.024</td>
<td>0.043</td>
</tr>
<tr>
<td>High-risk immunocompromised conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid malignancy</td>
<td>167,019 (13)</td>
<td>6,526 (15)</td>
<td>3,341 (16)</td>
<td>0.008</td>
<td>0.020</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>3,227 (&lt; 1)</td>
<td>313 (1)</td>
<td>184 (1)</td>
<td>0.004</td>
<td>0.010</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>192 (&lt; 1)</td>
<td>19 (&lt; 1)</td>
<td>12 (&lt; 1)</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>2,533 (&lt; 1)</td>
<td>399 (1)</td>
<td>202 (1)</td>
<td>0.005</td>
<td>0.013</td>
</tr>
<tr>
<td>Rheumatologic or other inflammatory condition</td>
<td>105,910 (8)</td>
<td>5,065 (11)</td>
<td>2,691 (13)</td>
<td>0.017</td>
<td>0.034</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td>20,480 (2)</td>
<td>1,589 (4)</td>
<td>909 (4)</td>
<td>0.009</td>
<td>0.019</td>
</tr>
<tr>
<td>Other immune condition</td>
<td>30,450 (2)</td>
<td>1,823 (4)</td>
<td>905 (4)</td>
<td>0.011</td>
<td>0.006</td>
</tr>
<tr>
<td>Immunosuppressive medication &gt;= 14 days</td>
<td>78,312 (6)</td>
<td>3,616 (8)</td>
<td>2,067 (10)</td>
<td>0.021</td>
<td>0.026</td>
</tr>
<tr>
<td>Antimetabolite medication &gt;= 14 days</td>
<td>8,952 (1)</td>
<td>599 (1)</td>
<td>330 (2)</td>
<td>0.011</td>
<td>0.016</td>
</tr>
</tbody>
</table>

1  *Measured using all-available history before the index date*

2  SMD: Standardized Mean difference
**FIGURE LEGENDS**

**Figure 1:** Study Flowchart

**Figure 2:** Weighted cumulative incidence of cardiovascular events by level of care required among patients with COVID-19. Panel A: any post-acute cardiovascular event. Panel B: post-acute cardiovascular event requiring hospital admission

**Figure 3:** Forest plot of adjusted hazard ratios and 95% confidence intervals from competing risks survival analysis evaluating the association between site of care and incident cardiovascular events among patients with COVID-19. Panel A: any post-acute cardiovascular event. Panel B: post-acute cardiovascular event requiring hospital admission. See supplementary appendix tables S7 and S8 for raw values as well as weighted and unweighted Hazard Ratios with 95% Confidence Intervals.
Patients ≥18 years at index, diagnosed with confirmed COVID-19 (ICD10 U07.1) with medical or pharmacy benefit coverage in HealthVerity RTIE between April 1, 2020 - May 31, 2021

n=4,898,787

Patients had ≥365 days continuous medical and pharmacy enrollment prior to the index date with <30-day gap
n = 2,168,902 (44.3%)

Patients had >30 days continuous medical and pharmacy enrollment post index with no gap
n = 1,841,695 (37.6%)

Patients are alive 30 days following index date
n = 1,839,163 (37.6%)

Patients do not have any outcome specific exclusion
n = 1,357,518 (27.7%)

Final sample, n = 1,357,518
Figure 2
CVE: Cardiovascular Event; ICU: Intensive Care Unit
### A

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Cardiovascular Event</td>
<td>1.38 (1.34-1.40)</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1.13 (1.17-1.19)</td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>1.24 (1.16-1.32)</td>
<td></td>
</tr>
<tr>
<td>Other Cardiac Disorders and Myocarditis/Pericarditis</td>
<td>1.64 (1.62-1.77)</td>
<td></td>
</tr>
<tr>
<td>Thrombotic Disorders</td>
<td>1.75 (1.66-1.84)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>1.36 (1.27-1.45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.90 (1.74-2.08)</td>
<td></td>
</tr>
</tbody>
</table>

### B

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Cardiovascular Event</td>
<td>1.96 (1.84-2.09)</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.92 (0.86-0.98)</td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>1.57 (1.48-1.67)</td>
<td></td>
</tr>
<tr>
<td>Other Cardiac Disorders and Myocarditis/Pericarditis</td>
<td>1.82 (1.71-1.92)</td>
<td></td>
</tr>
<tr>
<td>Thrombotic Disorders</td>
<td>2.04 (1.77-2.33)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Accident</td>
<td>1.94 (1.84-2.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.75 (2.41-3.19)</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 3**

165x110 mm (x DPI)