Associations of COVID-19 Status with Risk for Death and Hospitalization Among Prevalent and Incident Cardiovascular Medication Users

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Abstract

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Abstract:

The relationship between cardiovascular disease/injury and COVID-19 has been well described, but the use of cardiovascular medication as a proxy for cardiovascular disease and injury has not been explored. Our study used electronic health record (EHR) data in a large prospective cohort of 17,003 patients from University of Washington, Seattle, WA, to assess the risk of hospitalization and death by COVID-19 status for individuals taking cardiovascular medications. Use of cardiovascular medication was separated into prevalent and incident use based on COVID-19 diagnosis date. Information on demographics and comorbidities including age, race, gender, primary language spoken, chronic respiratory illnesses, diabetes, hypertension, heart disease, stroke/transient ischemic attach, chronic kidney disease, liver disease, cancer, vascular disease, and auto-immune disorders were extracted from EHR and used as covariates in the analysis. We analyzed data using Cox Proportional Hazard models to ascertain Hazard Ratios, 95% Confidence Intervals and p-values. We found that individuals who were using cardiovascular medications prior to a COVID-19 diagnosis (prevalent use) were at a higher risk of death but not hospitalization after becoming COVID-19 positive (HR: 1.88, 95% CI: 1.48-2.38) in fully adjusted models. This relationship remained when stratifying patients by type of medication used, either antihyperlipidemics, antihypertensives, or beta blockers. There were no associations between COVID-19 and increased risk of hospitalization or death in patients that were prescribed new CVD medications after becoming COVID-19 positive (incident use). However, non-significant hazard ratios below 1.00 (reduced risk) of death were found. Those with prevalent use of cardiovascular medication should take preventative measures to avoid COVID-19 infection and clinicians should be aware of increased risk of death in these patients. Use of cardiovascular medications when indicated for new COVID-19 diagnoses should be further explored.

Introduction:

As of May of 2023, there have been over 766 million documented cases of COVID-19 (SARS-CoV-2) infections worldwide.[1] Symptoms of COVID-19 vary greatly, with some people experiencing only mild-respiratory illness, while others suffer with long-term symptoms including fatigue, anosmia/ageusia, and cardiovascular injury.[2–4] As the COVID-19 pandemic has progressed, it has become clear that the long-term health effects of COVID-19 are relatively unknown, and more information is needed to adequately care for individuals who have experienced a SARS-CoV-2 infection.[3,5–8]

Cardiovascular injury and disease have already been identified as one potential acute and long-term effect that can be caused by a COVID-19 infection.[5] Additionally, prevalent cardiovascular disease has been shown to increase vulnerability to COVID-19 and severe outcomes such as death and hospitalization.[5,9,10] Cardiovascular disease (CVD) is the leading cause of death and one of the major contributors of disability for adults in the United States. It is estimated that close to half of all adults in the United States have some type of cardiovascular disease.[11] There is mounting evidence that demonstrates increased risk of death for individuals with prevalent CVD that experience a COVID-19 infection.[5,10,12] However, of the research that has been done, none have used medications as a proxy for looking at CVD. Of the reviewed literature, most use diagnosis codes, which has been shown to be unreliable on ascertaining true prevalence of disease.[13,14] In the studies that have been done, cardiovascular medications have been shown to either have a null or protective quality in COVID-19 positive patients against death.[12] Using medications as a proxy for disease increases our ability to examine currently treated cardiovascular disease and measure its impact on outcomes such as hospitalization and death. Ascertaining new use of cardiovascular medications also allows the ability to evaluate the impact of these treatments following a COVID-19 event. With the large burden of CVD and COVID-19 currently occurring in patients, more information is needed regarding adverse outcomes and risk factors. This study aims to add to the literature focusing on the relationships between treated CVD, COVID-19, and outcomes related to prevalent and incident use of these medications in association with COVID-19 onset.

Methods:

These analyses utilized a prospective cohort study design of patients enrolled into the COVID-RELIEF Study from March 1, 2020 through December 31, 2021 using extracted electronic health records (EHR) at University of Washington Medicine, Seattle, WA. Patients were included if they had a minimum of one COVID-19 test during the study period, demographic data populated within the UW IT system, were 18 years of age or older, resided in a zip code within Washington State, had a minimum of one encounter (inpatient, outpatient, telemedicine or phone call with a diagnosis code) following testing or a diagnosis of COVID-19 if a positive PCR test was not found. All patients had at least one out-patient cardiovascular medication prescribed (antianginal agents, antiarrhythmic, anticoagulants, antihyperlipidemic, antihypertensive, beta blockers, calcium blockers, calcium blockers, cardiotonics, cardiovascular and pressors) between January 1, 2019, through December 31, 2021. Outpatient medications were defined as having a refill supply listed in the EHR for the medication. Inpatient medication was included if patients had refills listed in their EHR. Patients were divided into either prevalent or incident cardiovascular medication use. Prevalent use was defined as patients who began a cardiovascular medication prior to their COVID-19 diagnosis. Incident use was defined as patients who began cardiovascular medication either on the day of

or any day after their COVID-19 diagnosis. Medication use, including type of cardiovascular medication, was ascertained by using pharmaceutical classes of medication listed in EHR.

The exposure of interest between our two groups was a positive PCR test or clinician diagnosis indicating presence of COVID-19. Cases were defined as individuals who had a record of a positive result of SARS-CoV-2 via a laboratory run polymerase chain reaction (PCR) test and/or an ICD-10 code indicating a positive COVID-19 diagnosis in their EHR. The ICD-10 codes used to indicate a COVID-19 diagnosis were: U07.1- COVID-19, virus identified; U09.0 - Post COVID-19 condition; J12.82 - Pneumonia due to coronavirus disease 2019; B97.29 - Other coronavirus as the cause of diseases classified elsewhere; B34.2 - Coronavirus infection, unspecified; M35.81- Coronavirus infection, unspecified. Cases entered the cohort on the date of their first positive PCR test or 5 days prior to a healthcare encounter with a COVID-19 ICD-10 code if they did not have a positive PCR test recorded in their EHR. Negative control patients were individuals with only negative laboratory run PCR tests and no ICD-10 codes indicating COVID-19 diagnosis for the duration of the study period recorded in their EHR. Patients entered the cohort (index date) on the date of their first PCR test, regardless of diagnosis status.

The outcomes included in the study were hospitalization and death. Death was defined as having a date of death populated within the EHR while hospitalization was defined as having a patient encounter type listed as “Inpatient” in the EHR.

In addition to the main exposure (COVID-19 status) and outcome (death/hospitalization), this study examined covariates that may serve as confounders in the associations between exposure and outcome. Demographic covariates extracted from the EHR include age (in years), self-reported gender (female, male), self-reported race (American Indian/Alaskan Native, Asian, Black/African American, Multi-Racial, Native Hawaiian/Other Pacific Islander, White/Caucasian), Insurance status (commercial, Medicaid, self-pay, worker’s compensation, and other), primary language spoken (English, Spanish, Other). Comorbidities were identified from ICD-10 codes in medical records dated prior to the beginning of the study or before the positive PCR test or COVID-19 diagnosis for the patient; these included chronic respiratory illnesses, diabetes, hypertension, heart disease, stroke/transient ischemic attach, chronic kidney disease, liver disease, cancer, vascular disease, and auto-immune disorders). Comorbidities were defined using ICD-10 codes for the specific disease/condition found prior to the date of onset of COVID-19 (Appendix 1). Analyses were also stratified by the three most common cardiovascular medications found to be used by patients, antihyperlipidemic, antihypertensives and beta blockers.

We utilized descriptive statistics for COVID-19 positive and negative patients to examine covariates as well as medications of interest presented as count, percentage (%) and mean/Standard Deviation (SD) for categorical or continuous variables, respectively. These data included patients using cardiovascular medications at any time within the study period, e.g. both prevalent and incident use. Results are presented for patients by COVID-19 status as well as use of prevalent or incident cardiovascular medications.

Cox Proportional Hazard Regressions were used to determine Hazard Ratios for death and hospitalization for COVID positive patients. Patients entered the analysis on the date of their first PCR test (positive or negative). We utilized a time dependent variable within the Cox model, in which patients who began as COVID negative were updated into the COVID positive group if/when they received a positive COVID-19 PCR result or a corresponding ICD-10 code

indicating a COVID-19 diagnosis (minus 5 days to indicate start of the infection). Four separate models were run with differing levels of adjustment for covariates. The first model was unadjusted and examined only the crude relationships between death or hospitalization and COVID-19 status. The second model adjusted for demographics, which included age, race, gender, insurance status and primary language spoken. The next model adjusted for comorbidities, which included heart disease, autoimmune disorders, diabetes, respiratory disease, non-autoimmune liver disease, hypertension, kidney disease and stroke. The final model adjusted for both demographics and comorbidities. Models that included race had small numbers and therefore race was collapsed into White and Non-White to ensure models converged. Hazard ratios, 95% Confidence Intervals and p-values were presented for each model. Models for the three most common medication type were also run, each of them having a crude model, demographic adjusted model, comorbidities adjusted model and a fully adjusted model for both demographics and comorbidities. Hazard ratios, 95% Confidence Intervals and p-values were presented for each of these models.

Results:

During the study period, 17,003 patients were identified as meeting study criteria. Of the patients, 1,979 or 11.6% had a positive COVID-19 PCR result or corresponding ICD-10 code indicating a COVID-19 diagnosis (positive patients) while 15,024 or 88.4% never experienced a COVID-19 diagnosis (negative patients) (Table 1). There were 7,581 or 44.6% patients who had prevalent use of cardiovascular medication and 9,422 or 55.4% who had incident use of cardiovascular medication at the time of their index date. Patients were most commonly white, had self-pay insurance, and spoke English as their primary language. The mean age for patients with prevalent use of cardiovascular medication was 62.6 (SD 14.9) while incident use of cardiovascular medications had a mean age of 59 (SD 15.7). Within patients with prevalent use of cardiovascular medication, hypertension was the most common comorbidity with 5,461 or 72.0% of patients having a documented hypertension diagnosis within their EHR. Similarly, hypertension was the most common comorbidity for patients with incident cardiovascular medication use with 4708 or 50.0% of patients having a documented hypertension diagnosis within their EHR.

Of the different medication types, the most common was antihyperlipidemic with 51.9% of study participants taking this type of medication (Table 2). The least common medication was cardiotonics, with only 1.1% of participants taking a cardiotonic. For individuals with prevalent cardiovascular medication, antihyperlipidemic was also the most common medication, with 60.1% of these patients using this medication. Similar for patients with incident medication use, hyperlipidemic was the most common medication with 45.3% of patients taking this medication, followed closely by antihypertensives at 43.3%.

Prevalent Use

Cox Proportional Hazard analyses were used for patients with prevalent and incident use of cardiovascular medications to determine risk of death/hospitalization based on COVID-19 status. Results of unadjusted models and those adjusted for demographics, comorbidities, and both demographics and comorbidities (fully adjusted model) can be found in Table 3. Patients with a positive COVID-19 diagnosis taking any CVD medication during the study period had a fully adjusted Hazard Ratio (HR) of 1.17 (95% CI: 0.60-2.29, $p=0.64$) for hospitalization and 1.88 (95% CI: 1.48-2.38, $p<0.001$) for death. COVID-19 positive patients taking

antihyperlipidemics had a fully adjusted HR of 1.26 (95% CI: 0.62-2.55, p=0.52) for hospitalization and 2.29 (95%CI: 1.63-3.23, p <0.001) for death. Those taking anithypertensives and were COVID-19 positive had a fully adjusted HR of 1.65 (95% CI: 0.93-2.95, p=0.09) for hospitalization and 2.11 (95% CI: 1.44-3.11, p<0.001) for death. Finally, COVID-19 positive patients taking Beta Blockers had a fully adjusted HR of 1.48 (95% CI: 0.84-2.62, p=0.18) for hospitalization and 2.18 (95% CI: 1.51-3.13, p <0.001) for death.

Incident Use

For patients who were prescribed new cardiovascular medications after their COVID-19 diagnosis (incident use), COVID-19 positive patients had a fully adjusted HR of 1.30 (95% CI: 0.90-1.90, p=0.17) for hospitalization and 0.80 (95% CI: 0.57-1.13, p=0.20) for death. For medication types, COVID-19 positive patients that were taking antihyperlipidemics had a fully adjusted HR of 1.12 (95% CI: 0.62-2.00, p=0.71) for hospitalization and 0.91 (95% CI: 0.54-1.53, p = 0.72) for death. Antihypertensive users with a positive COVID-19 diagnosis had a fully adjusted HR of 0.92 (95% CI: 0.50-1.70, p =0.80) for hospitalization and 0.91 (95% CI: 0.54-1.54, p = 0.72) for death. Finally, patients using beta blockers with a positive COVID-19 diagnosis had a fully adjusted HR of 1.29 (95% CI: 0.75-2.23, p=0.36) for hospitalization and 0.80 (95% CI: 0.47-1.33, p=0.39) for death.

Discussion:

By using cardiovascular medication use, our study demonstrated a unique way to examine the associations between treated cardiovascular disease and COVID-19. We found that COVID-19 status was not associated with hospitalization or death for patients using cardiovascular medication for the first time after their COVID-19 diagnosis although non-significant hazard ratios above 1.0 (increased risk) and below 1.0 (protective) resulted for hospitalization and death, respectively. Results were similar when examining patients using the three most common cardiovascular medications; antihyperlipidemics, antihypertensives and beta blockers. However, we did find that COVID-19 status was significantly associated with increased risk of death among prevalent cardiovascular medication users. We also saw that COVID-19 status was significantly associated with increased risk of death within patients' use of the three most common medications

Our findings suggest that for patients with prevalent use of cardiovascular medication, COVID-19 is associated with higher risk of death. These findings are also true when looking only at patients using the three most common cardiovascular medications. Individuals with prevalent use of cardiovascular medication indicate that these patients had pre-existing cardiovascular conditions that were severe enough to need medication to manage their condition. Our results are supported by other studies and meta-analyses that have shown higher risk of death for individuals with a pre-existing cardiovascular disease.[5,9,12,19–21] These results may have implications for clinical decision making and policy recommendations for people with pre-existing cardiovascular disease or medication use. For people with prevalent use of cardiovascular medication, clinicians should understand these patients have higher risk of death and therefore should be closely monitored after receiving a positive COVID-19 diagnosis. Further, patients that use a cardiovascular medication should take extra preventative measures, such as masking, social distancing, and handwashing to avoid contracting COVID-19.

However, for patients with incident use of cardiovascular medications, COVID-19 does not increase the risk for hospitalization or death after adjusting for relevant covariates and when

examining only specific medications. Previous studies have shown that people with COVID-19 are at higher risk for cardiovascular complications post-COVID-19 diagnosis.[9,15–17] It is possible that while patients may have higher risk of developing cardiovascular complications, these complications can be well managed at home and do not result in hospitalization or death. Further, there is a possibility that cardiovascular medication was prescribed and successfully treated either previously undiagnosed or new onset of cardiovascular disease potentially due to complications from COVID-19. This may result in a protective effect of cardiovascular medication. This relationship was seen in our results, but was not statistically significant. Similarly, the non-significant increased risk of hospitalization for patients subsequently treated with new cardiovascular medications may suggest that undiagnosed CVD (e.g. hypertension, hyperlipidemia) results in a more severe acute case of COVID-19.

A major strength of this study is our unique use of medication data to measure cardiovascular disease. This approach allowed us to avoid some reliability issues related to use of ICD-10 codes that have been seen in previous studies.[13,14] Other strengths include the inclusion of negative patients to be used as a comparison to positive COVID-19 cases, use of both PCR testing and diagnosis of COVID-19 to designate cases status, and collection of several important socioeconomic factors including insurance status. Our study also had several limitations. These included the selection of patients being limited to patients who accessed healthcare services in the UW Medicine system at least once after their initial PCR test. This could have unintentionally caused selection bias by ruling out patients who did not receive PCR testing at UW Medicine or healthier patients who did not return to UW Medicine for care. Regardless, this exclusion was necessary to help assure that patients using UW Medicine for COVID-19 acute care but returning to another healthcare system for follow-up care were excluded from our study. Further, cardiovascular medication use was defined as documentation of a refill for patients' cardiovascular medication recorded in their EHR. This might not represent all chronic use of medication, such as prescriptions from outside of the UW medical system, and does not reflect if patients follow the instructions of their medication. Other limitations include errors that may be found in medical records such as those occurring in the transcription or recording of information, differences in clinician decisions to document specific diseases/conditions, and errors in omission regarding other variables we extracted from the EHR. Finally, the sample size for stratified analyses by specific medications may have been too small to provide the power needed for showing significant associations.

In the future, studies should focus on increasing sample sizes and following the cohorts for longer periods of time. There is emerging evidence that COVID-19 can cause long-term health issues, including cardiovascular distress. Understanding how these results may change when being evaluated over a longer time period could have additional benefits for clinical decisions and policy-makers as COVID-19 enters an endemic phase.

Our study demonstrates that the risk of death for individuals with COVID-19 is increased in individuals that have a pre-existing cardiovascular medication prescription. The higher risk that patients who have a pre-existing cardiovascular medication prescription have for death after a COVID-19 diagnosis should be at the forefront of decision making for clinicians managing these patients. In addition, more research is needed to understand the protective effect, if any, from treatment for cardiovascular complications that may arise following COVID-19. More details on their impact and mechanisms for reducing risk of death and other adverse outcomes for these individuals may also provide valuable data for treating COVID-19 patients in the future.

Table 1. Characteristics of Patients Using Cardiovascular Medications by COVID-19 Status

	COVID Positive		COVID Negative		Overall	
	Incident (N=970)	Prevalent (N=1009)	Incident (N=8452)	Prevalent (N=6572)	Incident (N=9422)	Prevalent (N=7581)
Self-Identified Gender*						
Male	555 (57.2%)	591 (58.6%)	4670 (55.3%)	3647 (55.5%)	5225 (55.5%)	4238 (55.9%)
Female	415 (42.8%)	418 (41.4%)	3781 (44.7%)	2925 (44.5%)	4196 (44.5%)	3343 (44.1%)
Age						
18-40	158 (16.3%)	111 (11.0%)	1244 (14.7%)	609 (9.3%)	1402 (14.9%)	720 (9.5%)
41-60	399 (41.1%)	389 (38.6%)	2860 (33.8%)	1939 (29.5%)	3259 (34.6%)	2328 (30.7%)
61-80	365 (37.6%)	431 (42.7%)	3754 (44.4%)	3339 (50.8%)	4119 (43.7%)	3770 (49.7%)
80+	48 (4.9%)	78 (7.7%)	594 (7.0%)	685 (10.4%)	642 (6.8%)	763 (10.1%)
Age						
Mean (SD)	56.6 (15.0)	59.8 (15.1)	59.3 (15.8)	63.0 (14.9)	59.0 (15.7)	62.6 (14.9)
Median [Min, Max]	58.0 [19.0, 96.0]	61.0 [20.0, 101]	61.0 [18.0, 104]	65.0 [18.0, 103]	61.0 [18.0, 104]	64.0 [18.0, 103]
Race						
White	624 (64.3%)	655 (64.9%)	6252 (74.0%)	4818 (73.3%)	6876 (73.0%)	5473 (72.2%)
Non-White**	346 (35.7%)	354 (35.1%)	2200 (26.0%)	1754 (26.7%)	2546 (27.0%)	2108 (27.8%)
Insurance						
Self-pay	435 (44.8%)	454 (45.0%)	3453 (40.9%)	2842 (43.2%)	3888 (41.3%)	3296 (43.5%)
Medicare	160 (16.5%)	202 (20.0%)	1812 (21.4%)	1531 (23.3%)	1972 (20.9%)	1733 (22.9%)
Commercial	194 (20.0%)	157 (15.6%)	1910 (22.6%)	1356 (20.6%)	2104 (22.3%)	1513 (20.0%)
Medicaid	116 (12.0%)	131 (13.0%)	875 (10.4%)	534 (8.1%)	991 (10.5%)	665 (8.8%)
Other	65 (6.7%)	65 (6.4%)	402 (4.8%)	309 (4.7%)	467 (5.0%)	374 (4.9%)
Primary Language Spoken						
English	788 (81.2%)	806 (79.9%)	7775 (92.0%)	5980 (91.0%)	8563 (90.9%)	6786 (89.5%)

Table 1. Characteristics of Patients Using Cardiovascular Medications by COVID-19 Status

	COVID Positive		COVID Negative		Overall	
	Incident (N=970)	Prevalent (N=1009)	Incident (N=8452)	Prevalent (N=6572)	Incident (N=9422)	Prevalent (N=7581)
Spanish	87 (9.0%)	81 (8.0%)	213 (2.5%)	150 (2.3%)	300 (3.2%)	231 (3.0%)
Other	95 (9.8%)	122 (12.1%)	464 (5.5%)	442 (6.7%)	559 (5.9%)	564 (7.4%)
Comorbidities						
Autoimmune Disease	137 (14.1%)	219 (21.7%)	1205 (14.3%)	1290 (19.6%)	1342 (14.2%)	1509 (19.9%)
Diabetes	237 (24.4%)	389 (38.6%)	1705 (20.2%)	1966 (29.9%)	1942 (20.6%)	2355 (31.1%)
Respiratory Disease	183 (18.9%)	261 (25.9%)	1493 (17.7%)	1419 (21.6%)	1676 (17.8%)	1680 (22.2%)
Liver Disease	82 (8.5%)	137 (13.6%)	724 (8.6%)	591 (9.0%)	806 (8.6%)	728 (9.6%)
Hypertension	515 (53.1%)	707 (70.1%)	4193 (49.6%)	4754 (72.3%)	4708 (50.0%)	5461 (72.0%)
Kidney Disease	141 (14.5%)	268 (26.6%)	1045 (12.4%)	1202 (18.3%)	1186 (12.6%)	1470 (19.4%)
Stroke	48 (4.9%)	89 (8.8%)	421 (5.0%)	527 (8.0%)	469 (5.0%)	616 (8.1%)
Heart Disease	268 (27.6%)	425 (42.1%)	2409 (28.5%)	3060 (46.6%)	2677 (28.4%)	3485 (46.0%)
Other Vascular Disease	181 (18.7%)	308 (30.5%)	1653 (19.6%)	1822 (27.7%)	1834 (19.5%)	2130 (28.1%)
Cancer	217 (22.4%)	292 (28.9%)	2450 (29.0%)	2178 (33.1%)	2667 (28.3%)	2470 (32.6%)
Outcomes						
Hospitalized	30 (3.1%)	21 (2.1%)	196 (2.3%)	79 (1.2%)	226 (2.4%)	100 (1.3%)
Death	37 (3.8%)	87 (8.6%)	401 (4.7%)	325 (4.9%)	438 (4.6%)	412 (5.4%)
No Hospitalization/Death	903 (93.1%)	901 (89.3%)	7855 (92.9%)	6168 (93.9%)	8758 (93.0%)	7069 (93.2%)

*Counts might not match total patient counts due to missingness in the data.
**Includes: American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander and Unknown.

Table 2. Cardiovascular Medication Types in COVID-19 Positive and Negative Patients by Incident or Prevalent

	Positive		Negative		Overall	
Medication Type	Incident (N=970)	Prevalent (N=1009)	Incident (N=8452)	Prevalent (N=6572)	Incident (N=9422)	Prevalent (N=7581)
Antianginal	42 (4.3%)	78 (7.7%)	397 (4.7%)	520 (7.9%)	439 (4.7%)	598 (7.9%)
Antiarrhythmic	14 (1.4%)	30 (3.0%)	197 (2.3%)	309 (4.7%)	211 (2.2%)	339 (4.5%)
Anticoagulants	131 (13.5%)	197 (19.5%)	1442 (17.1%)	1446 (22.0%)	1573 (16.7%)	1643 (21.7%)
Antihyperlipidemic	428 (44.1%)	610 (60.5%)	3837 (45.4%)	3947 (60.1%)	4265 (45.3%)	4557 (60.1%)
Antihypertensive	423 (43.6%)	564 (55.9%)	3660 (43.3%)	3804 (57.9%)	4083 (43.3%)	4368 (57.6%)
Beta Blockers	288 (29.7%)	412 (40.8%)	2841 (33.6%)	2823 (43.0%)	3129 (33.2%)	3235 (42.7%)
Calcium Blockers	251 (25.9%)	325 (32.2%)	2111 (25.0%)	2204 (33.5%)	2362 (25.1%)	2529 (33.4%)
Cardiotonics	3 (0.3%)	15 (1.5%)	72 (0.9%)	103 (1.6%)	75 (0.8%)	118 (1.6%)
Cardiovascular Agents	103 (10.6%)	126 (12.5%)	903 (10.7%)	768 (11.7%)	1006 (10.7%)	894 (11.8%)
Pressors	38 (3.9%)	31 (3.1%)	285 (3.4%)	194 (3.0%)	323 (3.4%)	225 (3.0%)
ACE Inhibitors*	251 (25.9%)	314 (31.1%)	1886 (22.3%)	2070 (31.5%)	2137 (22.7%)	2384 (31.4%)

*ACE Inhibitors are a subclass of medication and therefore represented among other classes, primarily hypertensives, in this table.

Table 3: Risk of Hospitalization or Death in Patients With Incident and Prevalent Cardiovascular Medication Use in COVID-19 Positive Patients Compared to COVID-19 Negative Patients

Outcomes for COVID+ Patients	**Unadjusted Model**		**Adjusted for Demographics***		**Adjusted for Comorbidities****		**Fully Adjusted Model*****	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Prevalent Use of CVD Medication								
Hospitalization								
All CVD Medications	1.63 (0.98-2.70)	0.06	1.32 (0.77-2.26)	0.32	1.49 (0.90-2.48)	0.13	1.17 (0.60-2.29)	0.64
Type of Medication								
Antihyperlipidemic	1.39 (0.75-2.57)	0.29	1.32 (0.67-2.58)	0.42	1.22 (0.66-2.27)	0.53	1.26 (0.62-2.55)	0.52
Antihypertensives	1.84 (1.05-3.22)	0.03	1.75 (0.98-3.10)	0.06	1.75 (1.00-3.10)	0.05	1.65 (0.93-2.95)	0.09
Beta Blockers	1.72 (0.99-3.01)	0.05	1.61 (0.91-2.82)	0.10	1.56 (0.89-2.73)	0.12	1.48 (0.84-2.62)	0.18
Death								
All CVD Medications	2.10 (1.68-2.61)	<0.001	2.03 (1.61-2.57)	<0.001	1.94 (1.55-2.43)	<0.001	1.88 (1.48-2.38)	<0.001
Type of Medication								
Antihyperlipidemic	2.47 (1.79-3.42)	<0.001	2.48 (1.78-3.46)	<0.001	2.27 (1.64-3.16)	<0.001	2.29 (1.63-3.23)	<.0001
Antihypertensives	2.05 (1.41-2.97)	<0.001	2.18 (1.48-3.19)	<0.001	1.97 (1.35-2.86)	<0.001	2.11 (1.44-3.11)	<0.001
Beta Blockers	2.29 (1.62-3.24)	<0.001	2.31 (1.61-3.30)	<0.001	2.17 (1.53-3.08)	<0.001	2.18 (1.51-3.13)	<0.001
Incident Use of CVD Medication								
Hospitalization								
All CVD Medications	1.29 (0.88-1.86)	0.18	1.29 (0.89-1.88)	0.18	1.30 (0.90-1.90)	0.16	1.30 (0.90 – 1.90)	0.17
Type of Medication								
Antihyperlipidemic	1.39 (0.72-2.57)	0.29	1.07 (0.60-1.91)	0.82	1.22 (0.66-2.27)	0.53	1.12 (0.62-2.00)	0.71
Antihypertensives	0.93 (0.51-1.68)	0.80	0.91 (0.50-1.68)	0.77	0.96 (0.53-1.76)	0.92	0.92 (0.50-1.70)	0.80
Beta Blockers	1.31 (0.76-2.25)	0.33	1.26 (0.73-2.17)	0.41	1.31 (0.76-2.25)	0.33	1.29 (0.75-2.23)	0.36
Death								
All CVD Medications	0.75 (0.54-1.05)	0.09	0.81 (0.58-1.14)	0.23	0.74 (0.52-1.04)	0.08	0.80 (0.57-1.13)	0.20
Type of Medication								
Antihyperlipidemic	0.85 (0.51-1.42)	0.53	0.88 (0.52-1.49)	0.64	0.86 (0.52-1.45)	0.58	0.91 (0.54-1.53)	0.72
Antihypertensives	0.85 (0.51-1.42)	0.54	0.89 (0.52-1.51)	0.67	0.90 (0.53-1.50)	0.67	0.91 (0.54-1.54)	0.72
Beta Blockers	0.76 (0.46-1.28)	0.30	0.80 (0.48-1.34)	0.39	0.72 (0.43-1.21)	0.21	0.80 (0.47-1.33)	0.39

*Covariates in model: Age, Race, Gender, Insurance Status and Primary Language Spoken. **Covariates in model: Heart Disease, Autoimmune Disease, Diabetes, Respiratory Disease, Non-Autoimmune Liver Disease, Hypertension, Kidney Disease and Stroke. ***Covariates included in model: Age, Race, Gender, Insurance Status, Primary Language Spoken, Heart Disease, Autoimmune Disease, Diabetes, Respiratory Disease, Non-Autoimmune Liver Disease, Hypertension, Kidney Disease and Stroke.

Appendix 1: ICD-10 Codes Used to Determine Comorbidities

Comorbidity Category	ICD-10 Code	Description
Autoimmune Disease	D86*	Sarcoidosis
	D89.0	Polyclonal hypergammaglobulinemia
	D89.1	Cryoglobulinemia
	D89.2	Hypergammaglobulinemia, unspecified
	D89.3	Immune reconstitution syndrome
	D89.4*	Mast cell activation syndrome and related disorders
	D89.81*	Graft-versus-host disease
	D89.82	Autoimmune lymphoproliferative syndrome [ALPS]
	D89.83*	Cytokine release syndrome
	D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified
	D89.9	Disorder involving the immune mechanism, unspecified
	G36*	Other acute disseminated demyelination
	G61*	Inflammatory polyneuropathy
	G70*	Myasthenia gravis and other myoneural disorders
	K50*	Crohn's disease [regional enteritis]
	K51*	Ulcerative colitis
	K74.3	Primary biliary cirrhosis
	K75.4	Autoimmune hepatitis
	K83.01	Primary sclerosing cholangitis
	K90.0	Celiac disease
	L10*	Pemphigus
	L11*	Other acantholytic disorders
	L12*	Pemphigoid
	L13*	Other bullous disorders
	L40*	Psoriasis
	M04*	Autoinflammatory syndromes
	M05*	Rheumatoid arthritis with rheumatoid factor
	M06*	Other rheumatoid arthritis
	M08*	Juvenile arthritis
	M10*	Gout
	M11*	Other crystal arthropathies

	M1A*	Chronic gout
	M30*	Polyarteritis nodosa and related conditions
	M31*	Other necrotizing vasculopathies
	M32*	Systemic lupus erythematosus (SLE)
	M33*	Dermatopolymyositis
	M34*	Systemic sclerosis [scleroderma]
	M35*	Other systemic involvement of connective tissue
	M36*	Systemic disorders of connective tissue in diseases classified elsewhere
	M45*	Ankylosing spondylitis
	M46.8*	Other specified inflammatory spondylopathies
	M46.9*	Unspecified inflammatory spondylopathy
Diabetes	E08*	Diabetes mellitus due to underlying condition
	E09*	Drug or chemical induced diabetes mellitus
	E10*	Type 1 diabetes mellitus
	E11*	Type 2 diabetes mellitus
	E13*	Other specified diabetes mellitus
	O24*	Diabetes mellitus in pregnancy, childbirth, and the puerperium
Endocrine Disorder, Not Diabetes	E00*	Congenital iodine-deficiency syndrome
	E01*	Iodine-deficiency related thyroid disorders and allied conditions
	E02	Subclinical iodine-deficiency hypothyroidism
	E03*	Other hypothyroidism
	E04*	Other nontoxic goiter
	E05*	Thyrotoxicosis [hyperthyroidism]
	E06*	Thyroiditis
	E07*	Other disorders of thyroid
	E20*	Hypoparathyroidism
	E21*	Hyperparathyroidism and other disorders of parathyroid gland
	E22*	Hyperfunction of pituitary gland
	E23*	Hypofunction and other disorders of the pituitary gland
	E24*	Cushing's syndrome
	E25*	Adrenogenital disorders
	E26*	Hyperaldosteronism
	E27*	Other disorders of adrenal gland

E28*	Ovarian dysfunction
E29*	Testicular dysfunction
E30*	Disorders of puberty, not elsewhere classified
E31*	Polyglandular dysfunction
E32*	Diseases of thymus
E34*	Other endocrine disorders
E40	Kwashiorkor
E41	Nutritional marasmus
E42	Marasmic kwashiorkor
E43	Unspecified severe protein-calorie malnutrition
E44*	Protein-calorie malnutrition of moderate and mild degree
E45	Retarded development following protein-calorie malnutrition
E46	Unspecified protein-calorie malnutrition
E50*	Vitamin A deficiency
E51*	Thiamine deficiency
E52	Niacin deficiency [pellagra]
E53*	Deficiency of other B group vitamins
E54	Ascorbic acid deficiency
E55*	Vitamin D deficiency
E56*	Other vitamin deficiencies
E58	Dietary calcium deficiency
E59	Dietary selenium deficiency
E60	Dietary zinc deficiency
E61*	Deficiency of other nutrient elements
E63*	Other nutritional deficiencies
E64*	Sequelae of malnutrition and other nutritional deficiencies
E66*	Overweight and obesity
E70*	Disorders of aromatic amino-acid metabolism
E71*	Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism
E72*	Other disorders of amino-acid metabolism
E73*	Lactose intolerance
E74*	Other disorders of carbohydrate metabolism
E75*	Disorders of sphingolipid metabolism and other lipid storage disorders
E76*	Disorders of glycosaminoglycan metabolism
E77*	Disorders of glycoprotein metabolism
E78*	Disorders of lipoprotein metabolism and other lipidemias

	E79*	Disorders of purine and pyrimidine metabolism
	E80*	Disorders of porphyrin and bilirubin metabolism
	E83*	Disorders of mineral metabolism
	E84*	Cystic fibrosis
	E85*	Amyloidosis
	E88*	Other and unspecified metabolic disorders
	E89.0	Postprocedural hypothyroidism
	E89.2	Postprocedural hypoparathyroidism
	E89.3	Postprocedural hypopituitarism
	E89.4*	Postprocedural ovarian failure
	E89.5	Postprocedural testicular hypofunction
	E89.6	Postprocedural adrenocortical (-medullary) hypofunction
Respiratory	J41*	Simple and mucopurulent chronic bronchitis
	J43*	Emphysema
	J44*	Other chronic obstructive pulmonary disease
	J45*	Asthma
	J47*	Bronchiectasis
	J62*	Pneumoconiosis due to dust containing silica
	J63*	Pneumoconiosis due to other inorganic dusts
	J66*	Airway disease due to specific organic dust
	J67*	Hypersensitivity pneumonitis due to organic dust
	J68.4	Chronic respiratory conditions due to chemicals, gases, fumes and vapors
	J70.1	Chronic and other pulmonary manifestations due to radiation
	J70.3	Chronic drug-induced interstitial lung disorders
	J70.4	Drug-induced interstitial lung disorders, unspecified
	J82.81	Chronic eosinophilic pneumonia
	J82.83	Eosinophilic asthma
	J84*	Other interstitial pulmonary diseases
	J94.1	Fibrothorax
	J96.1*	Chronic respiratory failure
	J96.2*	Acute and chronic respiratory failure
Liver Disease	K70*	Alcoholic liver disease
	K71*	Toxic liver disease

	K72*	Hepatic failure, not elsewhere classified
	K73*	Chronic hepatitis, not elsewhere classified
	K74*	Fibrosis and cirrhosis of liver
	K75*	Other inflammatory liver diseases
	K76*	Other diseases of liver
Hypertension	I10	Essential (primary) hypertension
	I11*	Hypertensive heart disease
	I12*	Hypertensive chronic kidney disease
	I13*	Hypertensive heart and chronic kidney disease
	I15*	Secondary hypertension
	I16*	Hypertensive crisis
	O10*	Pre-existing hypertension complicating pregnancy, childbirth and the puerperium
	O11*	Pre-existing hypertension with pre-eclampsia
	O13*	Gestational [pregnancy-induced] hypertension without significant proteinuria
	O14*	Pre-eclampsia
	O15*	Eclampsia
	O16*	Unspecified maternal hypertension
Heart Failure	I11.0	Hypertensive heart disease with heart failure
	I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
	I50*	Heart failure
Chronic Kidney Disease	I12*	Hypertensive chronic kidney disease
	I13*	Hypertensive heart and chronic kidney disease
	N01*	Rapidly progressive nephritic syndrome
	N02*	Recurrent and persistent hematuria
	N03*	Chronic nephritic syndrome
	N04*	Nephrotic syndrome
	N05*	Unspecified nephritic syndrome
	N06*	Isolated proteinuria with specified morphological lesion
	N07*	Hereditary nephropathy, not elsewhere classified

	N08	Glomerular disorders in diseases classified elsewhere
	N18*	Chronic kidney disease (CKD)
Stroke/TIA	G45*	Transient cerebral ischemic attacks and related syndromes
	G46*	Vascular syndromes of brain in cerebrovascular diseases
	I60*	Nontraumatic subarachnoid hemorrhage
	I61*	Nontraumatic intracerebral hemorrhage
	I62*	Other and unspecified nontraumatic intracranial hemorrhage
	I63*	Cerebral infarction
	I69.0*	Sequelae of nontraumatic subarachnoid hemorrhage
	I69.1*	Sequelae of nontraumatic intracerebral hemorrhage
	I69.2*	Sequelae of other nontraumatic intracranial hemorrhage
	I69.3*	Sequelae of cerebral infarction
Coronary Heart Disease	I20*	Angina pectoris
	I21*	Acute myocardial infarction
	I22*	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
	I24*	Other acute ischemic heart diseases
	I25*	Chronic ischemic heart disease
Other Heart Disease	I30*	Acute pericarditis
	I31*	Other diseases of pericardium
	I32	Pericarditis in diseases classified elsewhere
	I33*	Acute and subacute endocarditis
	I34*	Nonrheumatic mitral valve disorders
	I35*	Nonrheumatic aortic valve disorders
	I36*	Nonrheumatic tricuspid valve disorders
	I37*	Nonrheumatic pulmonary valve disorders
	I38	Endocarditis, valve unspecified
	I39	Endocarditis and heart valve disorders in diseases classified elsewhere
	I40*	Acute myocarditis
	I41	Myocarditis in diseases classified elsewhere
	I42*	Cardiomyopathy
	I43	Cardiomyopathy in diseases classified elsewhere
	I44*	Atrioventricular and left bundle-branch block

	I45*	Other conduction disorders
	I46*	Cardiac arrest
	I47*	Paroxysmal tachycardia
	I48*	Atrial fibrillation and flutter
	I49*	Other cardiac arrhythmias
	I51.0	Cardiac septal defect, acquired
	I51.1	Rupture of chordae tendineae, not elsewhere classified
	I51.2	Rupture of papillary muscle, not elsewhere classified
	I51.3	Intracardiac thrombosis, not elsewhere classified
	I51.4	Myocarditis, unspecified
	I51.5	Myocardial degeneration
	I51.7	Cardiomegaly
	I51.81	Takotsubo syndrome
	I51.89	Other ill-defined heart diseases
	I51.9	Heart disease, unspecified
	I52	Other heart disorders in diseases classified elsewhere
	I5A	Non-ischemic myocardial injury (non-traumatic)
Other Non-Coronary Vascular Disease	I26*	Pulmonary embolism
	I27*	Other pulmonary heart diseases
	I28*	Other diseases of pulmonary vessels
	I70*	Atherosclerosis
	I71*	Aortic aneurysm and dissection
	I72*	Other aneurysm
	I73*	Other peripheral vascular diseases
	I74*	Arterial embolism and thrombosis
	I75*	Atheroembolism
	I76	Septic arterial embolism
	I77*	Other disorders of arteries and arterioles
	I78*	Diseases of capillaries
	I79*	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
	I80*	Phlebitis and thrombophlebitis
	I81	Portal vein thrombosis
	I82*	Other venous embolism and thrombosis
	I83*	Varicose veins of lower extremities

I85*	Esophageal varices
I86*	Varicose veins of other sites
I87*	Other disorders of veins
I88*	Nonspecific lymphadenitis
I89*	Other noninfective disorders of lymphatic vessels and lymph nodes
I99.8	Other disorder of circulatory system
I99.9	Unspecified disorder of circulatory system

Note: A * at the end of a code indicates that all ICD-10 codes beginning with the preceding characters are to be included

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