Risk of Cardiovascular Events After COVID-19

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We aimed to determine absolute and relative risks of either symptomatic or asymptomatic SARS-CoV-2 infection for late cardiovascular (CV) events and all-cause mortality. We conducted a retrospective double cohort study of patients with either symptomatic or asymptomatic SARS-CoV-2 infection (COVID-19+ cohort) and its documented absence (COVID-19− cohort). The study investigators drew a simple random sample of records from all patients under the Oregon Health & Science University Healthcare (n = 65,585), with available COVID-19 test results, performed March 1, 2020 to September 13, 2020. Exclusion criteria were age <18 years and no established Oregon Health & Science University care. The primary outcome was a composite of CV morbidity and mortality. All-cause mortality was the secondary outcome. The study population included 1,355 patients (mean age 48.7 ± 20.5 years; 770 women [57%], 977 White non-Hispanic [72%]; 1,072 ensured [79%]; 563 with CV disease history [42%]). During a median 6 months at risk, the primary composite outcome was observed in 38 of 319 patients who were COVID-19+ (12%) and 65 of 1,036 patients who were COVID-19− (6%). In the Cox regression, adjusted for demographics, health insurance, and reason for COVID-19 testing, SARS-CoV-2 infection was associated with the risk for primary composite outcome (hazard ratio 1.71, 95% confidence interval 1.06 to 2.78, p = 0.029). Inverse probability-weighted estimation, conditioned for 31 covariates, showed that for every patient who was COVID-19+, the average time to all-cause death was 65.5 days less than when all these patients were COVID-19−: average treatment effect on the treated −65.5 (95% confidence interval −125.4 to −5.61) days, p = 0.032. In conclusion, either symptomatic or asymptomatic SARS-CoV-2 infection is associated with an increased risk for late CV outcomes and has a causal effect on all-cause mortality in a late post-COVID-19 period. © 2022 Elsevier Inc. All rights reserved. (Am J Cardiol 2022;00:1−8)

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See page 7 for disclosure information.

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Introduction

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor-binding domain.[1,2] Myocardial injury in COVID-19 can be caused by both direct injury and secondary effects from the systemic inflammation and hypercoagulable state.[3] Postacute or "long" COVID-19 has been described in patients with persistent symptoms or complications after the end of the acute phase of infection.[4,5] Acute COVID-19 cardiovascular (CV) manifestations have been described in great depth.[6−8] However, the impact of COVID-19 on long-term CV outcomes is incompletely understood.[8,9] The COVID-19 pandemic disrupted the delivery of standard CV care,[10] which led to increased CV mortality in populations presumably unexposed to the SARS-CoV-2 virus.[11,12] Although higher than expected all-cause mortality during the pandemic has been recognized,[13] it is unclear whether either asymptomatic or symptomatic SARS-CoV-2 infections may have played a causal role. To address these knowledge gaps, we
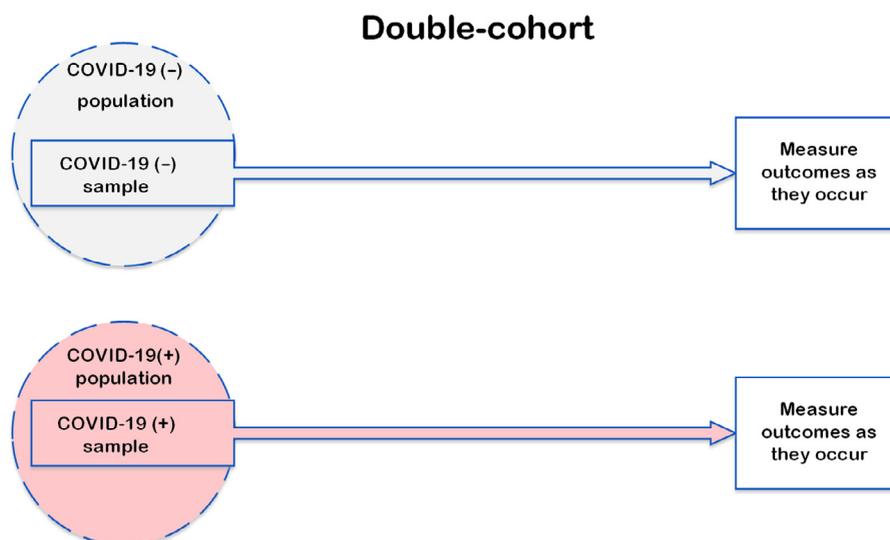
Double-cohort

Figure 1. Study design and analysis.

conducted a retrospective double cohort study to determine: (1) absolute (attributable) risk, (2) relative conditional risk, and (3) causal inference effect of either symptomatic or asymptomatic SARS-CoV-2 infection on postacute (late) CV events and all-cause mortality.

Methods

We conducted a retrospective double cohort study at the Oregon Health & Science University (OHSU). OHSU Healthcare included all OHSU inpatient and outpatient clinical sites, including OHSU Hospital, Hillsboro Medical Center, and Adventist Medical Center. The study has been approved by the OHSU Institutional Review Board and was registered (*http://www.clinicaltrials.gov*. Unique identifier: NCT04555187).

OHSU Healthcare's electronic medical records (EMRs) of adult (aged ≥18 years) patients were eligible for inclusion in the study if there was a positive or negative COVID-19 test performed between March 1, 2020 and September 13, 2020. We excluded records of children and those without evidence of established medical care. The study investigators drew a simple random sample of records from the pool of all EMRs with available results of the COVID-19 test. A COVID-19 episode was defined as the documented presence (COVID-19+) or absence (COVID-19−) of SARS-CoV-2 infection by the polymerase chain reaction test. See detailed definitions of exposure in the Supplementary Methods.

We collected information on patient demographic characteristics, past medical history and medications, COVID-19 symptoms and treatment, electrocardiogram, and echocardiogram measurements, in accordance with the definitions and timeline of COVID-19 episodes. Healthy status was documented by regular annual check-ups and an absence of any medical history documented in the EMR. The study timeline is shown in Figure 1. Study outcomes occurred at any time on or after the first day of the first COVID-19 episode, either (+) or (−). If there were 2

COVID-19 episodes, the first set of outcomes occurred before the first day of the second COVID-19 episode, and second set of outcomes occurred on or after the first day of the second COVID-19 episode. If neither a primary nor secondary outcome occurred, such record was censored on the last date the patient was known to be alive and event-free, which per the study design was the date when the study investigator collected EMR data.

The primary outcome was defined as a composite of CV death, acute heart failure, acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-STEMI, or unstable angina), incident stroke or transient ischemic attack, another acute or new CV outcome prompting healthcare utilization (deep venous thrombosis, pulmonary embolism, pulmonary hypertension, myocarditis, endocarditis, hypertension emergency, or kidney injury[14]), critical care utilization (intensive care unit [ICU] bed) because of either primary or secondary CV condition, or development of a life-threatening arrhythmia (sustained ventricular tachycardia/ventricular fibrillation or resuscitated sudden cardiac arrest), whichever came first. Secondary outcomes included (1) all-cause death and (2) any documented cardiac arrhythmia. A mortality and morbidity classification committee adjudicated and reviewed outcomes.

Normally distributed continuous variables were summarized as means and SD and compared using a 2-sided *t* test. Chi-square test was used to compare categoric variables in patients with 2 levels of COVID-19 exposure: positive (COVID-19+ cohort) and negative (COVID-19− cohort). COVID-19+ cohort included patients with COVID-19+ episodes (either first or second or both). COVID-19− cohort included patients who had COVID-19− episodes only and did not have any COVID-19+ episodes. The unadjusted Kaplan−Meier survivor functions were plotted for 2 levels of exposure for the primary and secondary outcomes. We used the log-rank test for the equality of survivor functions across 2 levels of exposure. Incidence rate and incidence rate difference were calculated to assess the absolute risk and absolute risk difference between 2 levels of exposure.

To answer a question of whether either asymptomatic or symptomatic SARS-CoV-2 infection is associated with outcomes independently from known COVID-19 risk factors, prevalent CV disease (CVD), and CV risk factors, we constructed 2 Cox proportional hazards models. The proportional hazards assumption was tested using *stcox* PH-assumptions suite of tests implemented in STATA (StataCorp, College Station, Texas LP, College Station, Texas). Model 1 was adjusted for demographic (age, gender, and race-ethnicity group categories, defined as White non-Hispanic vs non-White or Hispanic) and socioeconomic characteristics (insurance status) and reason for testing (presence or absence of COVID-19 symptoms during the COVID-19 episode). Model 2, in addition to covariates included in Model 1, was adjusted for CV and COVID-19 risk factors (history of CVD, cerebrovascular, liver disease, diabetes mellitus, conditions with an elevated risk of thromboembolism, immunocompromised status, and use of any prescription medication).

Additionally, we use the causal inference approach and counterfactual analytical framework to investigate the hypothetically causal average treatment effect on the treated (ATET) of COVID-19 exposure on the study outcomes. The ATET estimation has several advantages over the hazard ratio as an effect estimator. First, the ATET measures the effect in the same time units as the time to outcome instead of in a relative conditional probability. Second, the models used to estimate ATET are more flexible because there are no assumptions of linearity and proportional hazards and no risk of model overfitting if too many covariates are included. Nevertheless, ATET estimation requires the assumptions of conditional independence, sufficient overlap, and correct adjustment for censoring. Estimating the ATET requires a significantly weaker version of the conditional independence assumption than estimating the average treatment effect in population.

We used inverse probability-weighted (IPW) estimators, using weighted averages of the observed outcome to calculate the potential outcome means and ATET. The IPW estimators were implemented in a three-step approach. First, we estimated the parameters of a treatment assignment model (predicting probabilities of a subject to be included in a COVID-19+ or COVID-19− cohort) and computed the component of the estimated weights that accounts for data missing because each subject was only observed after receiving one of the possible treatment levels, either COVID-19+ or COVID-19−. The model was conditioned for 31 covariates, including demographic and socioeconomic characteristics (age, gender, race, and ethnicity, health insurance status), the reason for COVID-19 testing, medical history of CVD, cerebrovascular, respiratory, kidney, liver, blood, systemic, endocrine disease, diabetes mellitus, addiction, conditions with immunocompromised and thromboembolic risk, use of prescription medications (including renin-angiotensin-aldosterone system blocking drugs, atrioventricular nodal agents, antiplatelet or anticoagulant, and immunosuppressants), and the presence and type of COVID-19 symptoms (fever, fatigue, runny nose, headache, muscle and body aches, cough, shortness of breath, ageusia or anosmia, and nausea). Next, we estimated the parameters of a time-to-censoring model and computed

the component of estimated weights that accounts for data lost to censoring. In this retrospective study, the censoring time was determined by a random day when a study investigator collected EMR data unless a patient used healthcare and experienced potential outcome. Thus, we assumed that the time-to-censoring was random. We conditioned the model predicting time-to-censoring for the same 31 covariates as described previously for the model predicting treatment assignment. At the final third step, we used both estimated weights to compute weighted averages of the outcomes for the COVID-19+ cohort.

We conducted balance checks for the treatment assignment model. We tested an overlap assumption that each study participant has a sufficient positive probability of being assigned to each treatment level. These checks depend only on the estimated probabilities of COVID-19+ cohort assignment and are not affected by the censoring of the outcome. We observed (Supplementary Table 1) that the weighted standardized differences are much closer to 0 than the raw standardized differences, and the weighted variance ratios are much closer to 1 than the raw variance ratios; therefore, the model-based treatment weights balanced the covariates. We conducted a formal test of the hypothesis that the weighted constructed from the treatment assignment model balances the covariates. We observed that we do not reject the null hypothesis that the treatment assignment model is well specified (p = 0.965; Supplementary Figure 1). Thus, we used this model to look for evidence that the overlap condition is violated. Supplementary Figure 1 showed that the densities for the probability to be included in the COVID-19+ cohort were evenly distributed and showed sufficient overlap, and the maximum probability to be included in either COVID-19+ or COVID-19− cohort was sufficiently <1. However, the densities for the probability of being included in the COVID-19− cohort violated the overlap assumption, indicating that there were unmeasured patient characteristics that increased the probability for a patient to belong to the COVID-19− cohort, likely because many of these patients underwent unrelated to COVID-19 medical procedures and were tested for COVID-19 as a part of hospital precautions. Therefore, we reported only ATET estimators and not average treatment effect in population estimators. We conducted a sensitivity analysis in a subgroup with available body mass index (BMI) data and adjusted all analyses for BMI.

Statistical analyses were performed using STATA MP 17 (StataCorp LP, College Station, Texas). A 2-sided p <0.05 was considered statistically significant. STATA do-files are available at https://github.com/Tereshchenko lab/statistics.

Results

Between March 1, 2020 and September 13, 2020, the OHSU Healthcare performed 99,711 COVID-19 tests for 65,585 patients. The study investigators included a random sample of 1,355 eligible patient records. Clinical characteristics of the patient population are presented in Table 1. Patients who were COVID-19+ were younger, more likely to be non-White or Hispanic, and less likely to be ensured than patients who were COVID-19−. Furthermore, patients

Table 1
Baseline clinical and demographic characteristics in COVID19 (+) and (−) cohorts

Characteristic	Covid19(+) cohort (n = 319)	Covid19(-) cohort (n = 1,036)	p-Value
Age ± SD (years)	**46.7 ± 18.5**	**49.4 ± 21.1**	**0.032**
Body mass index ± SD (kg/m^2)	**31.3 ± 11.4) (n=241)**	**28.9 ± 9.7 (n=723)**	**0.004**
Women	186 (58.3%)	584 (56.4%)	0.541
White non-Hispanic	**158 (49.5%)**	**819 (79.1%)**	**<0.0001**
Insured	**226 (70.6%)**	**846 (81.7%)**	**<0.0001**
Healthy	61 (19.1%)	212 (20.5%)	0.602
Cardiovascular disease Hx	129 (40.4%)	434 (41.9%)	0.645
Hypertension Hx	86 (27.0%)	321 (31.0%)	0.170
Atrial fibrillation or SVT Hx	**15 (4.7%)**	**83 (8.0%)**	**0.046**
VT or SCA Hx	3 (0.9%)	8 (0.8%)	0.770
Heart failure Hx	14 (4.4%)	64 (6.2%)	0.230
Any CHD Hx	**12 (3.8%)**	**87 (8.4%)**	**0.005**
Dyslipidemia on LLD	73 (22.9%)	276 (26.6%)	0.180
Noncoronary atherosclerosis Hx	**2 (0.6%)**	**32 (3.1%)**	**0.014**
Noncoronary heart disease	13 (4.1%)	58 (5.6%)	0.286
Cerebrovascular disease Hx	16 (5.0%)	57 (5.5%)	0.737
Respiratory disease Hx	98 (30.7%)	264 (25.5%)	0.064
Liver disease Hx	**38 (11.9%)**	**75 (7.2%)**	**0.008**
Kidney disease Hx	32 (10.0%)	114 (11.0%)	0.624
Thromboembolism risk Hx	7 (2.2%)	41 (4.0%)	0.136
Diabetes mellitus Hx	**81 (25.4%)**	**196 (18.9%)**	**0.012**
Immunocompromised Hx	53 (16.6%)	204 (19.7%)	0.220
Smoking & addiction Hx	68 (21.3%)	225 (21.7%)	0.879
Endocrine disease Hx	**31 (9.7%)**	**147 (14.2%)**	**0.039**
Blood disease Hx	56 (17.6%)	163 (15.7%)	0.440
Systemic disease Hx	4 (1.3%)	13 (1.3%)	0.999
On any Rx medication	**177 (55.5%)**	**504 (48.6%)**	**0.033**
RAAS medication use	47 (14.7%)	153 (14.8%)	0.988
AV nodal agents use	41 (12.9%)	172 (16.6%)	0.108
Anticoagulant/antiplatelet use	51 (16.0%)	213 (20.6%)	0.071
Immunosuppressant use	31 (9.7%)	112 (10.8%)	0.579

SVT = supraventricular tachycardia; VT = ventricular tachycardia; SCA = sudden cardiac arrest; Hx = history; CHD = coronary heart disease; AV = atrioventricular; LLD = lipid-lowering drugs.

who were COVID-19+ were more likely to have been prescribed medication and have a history of liver disease and/or diabetes mellitus (Table 1). There was no difference in CVD history between the 2 exposure cohorts.

There was a significant difference in the reasons for COVID-19 testing between 2 cohorts: patients in the COVID-19+ cohort were twice as likely to be symptomatic than patients in the COVID-19− cohort (Table 2). All COVID-19+ episodes were confirmed by a polymerase chain reaction test, whereas 17 COVID-19− episodes (0.02%) were detected by an antibody test. All known COVID-19 symptoms were more frequently observed in patients who were COVID-19+ (Table 2). The most frequent COVID-19 symptoms were cough and fever. In addition to the symptoms listed in Table 2, patients who were COVID-19+ also had abdominal pain, ear pain, dizziness, vertigo, hemoptysis, and dark stool. Notably, 20% of patients who were COVID-19+ were asymptomatic.

Most patients had a single COVID-19 episode, either positive or negative. A total of 4 of 319 patients (1.25%) had reinfection that occurred 58.5 ± 23.6 days (range 33 to 89 days) after the first COVID-19+ episode. A total of 31 patients experienced COVID-19+ episode 94.5 ± 61.3 days (range 15 to 247 days) after COVID-19− episode. A total of 35 patients had COVID-19− episode 145.5 ± 90.9 days (range 36 to 371 days) after COVID-19+ episode. Because

only a small number of patients experienced reinfection or 2 different types of COVID-19 episodes, we were precluded from completing a meaningful crossover analysis.

During a median of 178 days at risk, the primary composite outcome was observed in a total of 103 patients, 38 of whom were from the COVID-19+ cohort (12%), and 65 were from COVID-19− cohort (6%). Acute heart failure was diagnosed in 7, sudden cardiac arrest/ventricular fibrillation in 2, STEMI in 1, non-STEMI in 5, incident stroke in 5, endocarditis in 3, DVT/pulmonary embolism in 6, acute kidney dysfunction in 24, critical care use because of an acute primary or secondary CV condition in 25, and CV death in 25. Those who developed primary outcome were more likely to have greater severity of COVID-19 (Table 3). However, only 26% of them were hospitalized because of COVID-19, and only 13% used ICU beds.

Among participants in the COVID-19+ cohort, the incidence rate of the primary outcome was higher (178.6 per 1,000 person-years of follow-up) than among participants in the COVID-19− cohort (149.2 per 1,000 person-years of follow-up). However, the incidence rate difference in the primary outcome between the 2 levels of exposure did not reach statistical significance (29.4, 95% confidence interval −38.04 to 96.8 per 1,000 person-years of follow-up, p = 0.379).

In unadjusted survival analysis, patients who were COVID-19+ had a significantly higher probability of

Table 2
COVID-19 exposure characteristics

Characteristic of Covid19 episode	Covid19(+) cohort (n = 319)	Covid19(-) cohort (n = 1,036)	*p*-Value
Reason for testing: symptomatic patient	255 (79.9%)	383 (36.8%)	<0.0001
Fever, chills	133 (41.7%)	127 (12.3%)	<0.0001
Weakness, fatigue	52 (16.3%)	81 (7.8%)	<0.0001
Muscle and body aches	84 (26.3%)	78 (7.5%)	<0.0001
Runny nose, congestion, sore throat	100 (31.4%)	151 (14.6%)	<0.0001
Cough	147 (46.1%)	151 (14.6%)	<0.0001
Shortness of breath, difficulty breathing	75 (23.5%)	99 (9.6%)	<0.0001
Loss of taste (ageusia) or smell (anosmia)	54 (16.9%)	10 (1.0%)	<0.0001
Nausea, vomiting	42 (13.2%)	60 (5.8%)	<0.0001
Anorexia	5 (1.6%)	2 (0.2%)	0.003
Diarrhea	32 (10.0%)	47 (4.5%)	<0.0001
Headache	90 (28.2%)	119 (11.5%)	<0.0001
Confusion	4 (1.3%)	9 (0.9%)	0.537
Pain or pressure in the chest	22 (6.9%)	28 (2.7%)	0.001
Other symptoms	19 (6.0%)	30 (2.9%)	0.010

Table 3
Comparison of patient characteristics by the primary outcome

Characteristic	Primary outcome YES (n = 103)	Primary outcome NO (n = 1,252)	*P*-value
Age ± SD (years)	66.9 ± 18.7	47.3 ± 20.0	<0.0001
Body mass index ± SD (kg/m^2)	29.6 ± 8.3 (n=85)	29.4 ± 10.4 (n=879)	0.843
Female	53 (51.5%)	717 (57.3%)	0.252
White non-Hispanic	81 (78.6%)	896 (71.6%)	0.124
Insured	88 (85.4%)	984 (78.6%)	0.101
Healthy	1 (1.0%)	272 (21.7%)	<0.0001
Cardiovascular disease history	84 (81.6%)	479 (38.3%)	<0.0001
On any Rx medication	90 (87.4%)	584 (46.6%)	<0.0001
COVID-19-related hospital admission	18 (25.7%)	14 (10.1%)	0.003
COVID-19-related ICU admission	13 (12.6%)	0	<0.0001
On any Rx medication during COVID-19 episode	77 (74.8%)	334 (26.7%)	<0.0001
Remdesivir during COVID-19 episode	6 (5.8%)	10 (0.8%)	<0.0001
Hydroxychloroquine during COVID-19 episode	3 (2.9%)	4 (0.3%)	<0.0001

Rx = prescribed; ICU = intensive care unit.

developing the primary composite outcome than patients who were COVID-19− (Figure 2). In unadjusted Cox regression analysis, COVID-19+ exposure was associated with a >50% higher risk of the primary outcome (Table 4). After adjustment for demographic characteristics, health insurance status, and reason for COVID-19 testing (Model 1), COVID-19 infection remained associated with the primary outcome. However, the association attenuated after additional adjustment for prevalent CVD, CV, and COVID-19 risk factors in Model 2. Proportional hazards assumption was confirmed for all Cox regression models with the primary composite outcome.

In the COVID-19+ cohort, the average time to the primary composite outcome was estimated to be 163.8 days or approximately 5.4 months longer than when everyone in the COVID-19+ cohort was COVID-19−. The estimated average time to the primary composite outcome when all in the COVID-19+ cohort were COVID-19− was 148.5 days or approximately 4.9 months (Table 4).

During median 190 days at risk, there were 32 all-cause deaths: 10 deaths in the COVID-19+ cohort and 22 in the COVID-19− cohort. Among participants in the COVID-19+ cohort, the incidence rate of the all-cause death was 41.6 per 1,000 person-years of follow-up, compared with 45.1 per 1,000 person-years of follow-up among participants in the COVID-19− cohort. There was no statistically significant incidence rate difference (−3.4, 95% confidence interval −35.4 to 28.5 per 1,000 person-years of follow-up, p = 0.855) in the all-cause death between 2 cohorts.

In the Kaplan−Meier survival analysis, there were no differences in all-cause mortality between the COVID-19− and COVID-19+ cohorts (Figure 2). In unadjusted Cox regression analysis, COVID-19+ exposure was associated with nonsignificant risk (Table 4). Notably, the proportional hazards assumption was violated for all Cox regression models with the all-cause death outcome.

Importantly, causal inference analysis using IPW estimators, conditioned for 31 covariates as described previously, showed that for every patient who was COVID-19+, the average time to all-cause death was estimated to be 65.5 days shorter than when all these patients were COVID-19−. The estimated average time to all-cause death when all these patients were COVID-19− was 98.6 days (Table 4). Sensitivity analyses in a subgroup with available BMI data showed consistent results that are similar to the main analyses results (Supplementary Table 2).
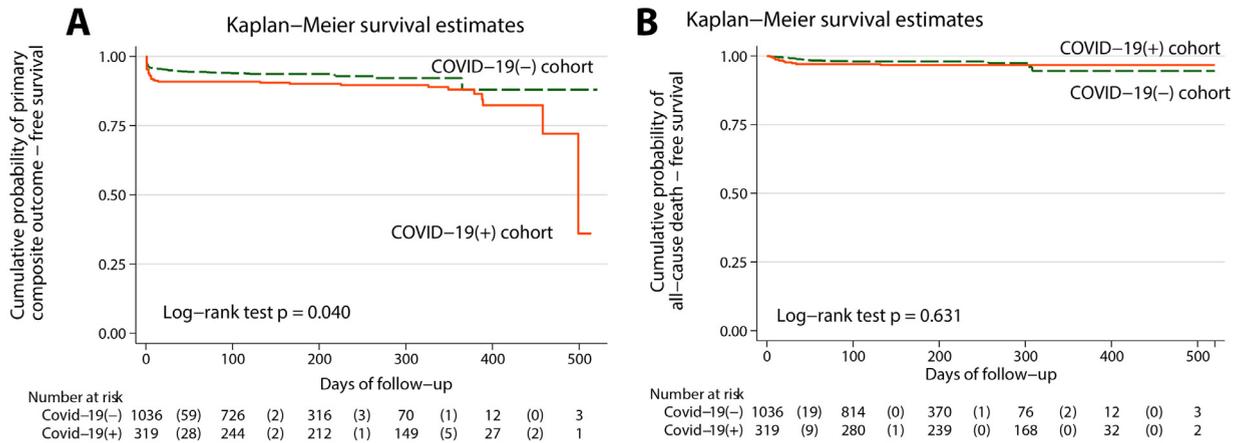
Figure 2. (A) The estimated unadjusted Kaplan−Meier survivor functions for the primary composite outcome in COVID-19+ (solid line) and COVID-19− (dashed line) cohorts. (B) The estimated unadjusted Kaplan−Meier survivor functions for all-cause mortality in COVID-19+ COVID-19+ (solid line) and COVID-19− (dashed line) cohorts. The table below the graph shows the number at risk in each group at every 100 days of follow-up. The number of primary composite outcome events at every 100 days of follow-up is shown in parenthesis.

Table 4
Association of COVID-19 exposure with the study outcomes in survival analyses

Model	Composite primary outcome Estimate (95% CI)	p-Value	All-cause death Estimate (95% CI)	p-Value
Unadjusted Cox HR	1.54 (1.02-2.34)	0.042	1.21 (0.56-2.63)	0.631
Cox model 1 HR	1.71 (1.06-2.78)	0.029	1.27 (0.52-3.12)	0.600
Cox model 2 HR	1.47 (0.90-2.38)	0.122	1.08 (0.44-2.65)	0.874
POM for COVID-19 (-) cohort, days	148.5 (72.4 − 224.5)	<0.0001	98.6 (45.7-151.5)	<0.0001
ATET for COVID-19 (+) versus COVID-19 (-), days	+163.8 (34.3 − 293.3)	0.013	-65.5 (-125.4 to -5.61)	0.032

HR = hazard ratio; POM = potential outcome means; ATET = average treatment effect on treated.

Another prespecified secondary outcome, documented cardiac arrhythmia, was recorded in only 10 study participants: 4 in the COVID-19+ cohort and 9 in the COVID-19− cohort. Therefore, we did not conduct survival analyses because of the small number of documented cardiac arrhythmia outcomes.

Discussion

In this retrospective double cohort study, after rigorous adjustment for demographic and socioeconomic characteristics, reasons for COVID-19 testing, acute COVID-19 symptoms, medical history, risk factors of both COVID-19 and CVD, and use of medications, we found that either symptomatic or asymptomatic SARS-CoV-2 infection was associated with increased risk of late CV outcomes, occurring at least 30 days (on average 10 months) after SARS-CoV-2 infection. Importantly, we demonstrated this effect of COVID-19 on CV events, regardless of initial presenting COVID-19 symptoms. This finding highlights the importance of COVID-19 prevention and suggests that careful follow-up might be needed for any patient who experienced SARS-CoV-2 infection, either symptomatic or asymptomatic, to monitor for late CV events. Also importantly, our study was the first to demonstrate the causal effect of either symptomatic or asymptomatic SARS-CoV-2 infection on

all-cause death occurring during the postacute or late COVID-19 period.

There is both pathophysiologic basis and clinical evidence of significant CV risk after COVID-19.[15] Several recent studies confirmed the risks of long-term CV consequences of COVID-19 and showed a wide range of an estimated disease burden.[6,16−19] Our double cohort study showed similar estimates of absolute (attributable) and relative risks of SARS-CoV-2 infection for the development of late CV outcomes, as reported by Xie et al.[9]

Relatively few longitudinal COVID-19 CV studies have been reported to date. A prospective echocardiographic study of hospitalized, symptomatic patients with COVID-19 reported a decrease in both left and right-sided cardiac function 3 months after hospital discharge.[20] Preliminary findings of the prospective longitudinal study C-MORE (Capturing MultiORgan Effects of COVID-19)[21] showed that more than half of the patients experienced symptoms at 6 months after COVID-19, limiting their ability to exercise. C-MORE investigators also noted a dissociation between symptoms and objective measures of CV health.[21] Our study did not ascertain the duration of the COVID-19 symptoms,[22] which should be further studied in future prospective studies.

Our study contributed to the growing body of knowledge showing the CV implications of SARS-CoV-2 infection regardless of its symptoms. A large study of the English National Immunisation Database of COVID-19

vaccination, using self-controlled case series methods, showed that SARS-CoV-2 infection was associated with a substantial increase in the risk of hospitalization or death from myocarditis, pericarditis, and cardiac arrhythmia.[23] The distinct mechanism of SARS-CoV-2 infection includes ACE2 downregulation, diminishing the protective, anti-inflammatory role of ACE2, facilitating myocardial injury and fibrosis as the virus' long-term sequelae.[24] Frequently observed nonspecific cardiac pathology in COVID-19 highlights the importance of appropriate control in study design assessing CV risks of SARS-CoV-2 infection.[25,26] Of note, any pandemic or epidemic, regardless of the type of a pathogen, might be associated with increased CV mortality.[27] The double cohort design used in this study allowed us to demonstrate the causal nature of SARS-CoV-2 infection with CV events.

Our COVID-19− and COVID-19+ cohorts had a similar absolute number of all-cause deaths, consistent with the notion about indirect consequences of the pandemic, including the healthcare systems' redistributed resources toward patients with COVID-19 and the reduced standards of healthcare delivery.[28] Using a counterfactual analytical framework and conditioning for 31 covariates, we showed that all-cause death in the COVID-19+ cohort occurred 2 months sooner than if the patients did not experience SARS-CoV-2 infection. Our finding of a causal effect of either symptomatic or asymptomatic SARS-CoV-2 infection on all-cause mortality supports previous reports linking excess all-cause mortality during the pandemic with SARS-CoV-2 infection.[13]

We found that patients who were COVID-19+ were more likely to be non-White or Hispanic and less likely to be ensured than patients who were COVID-19−. Furthermore, other studies have shown that racial and ethnic minority groups have a significantly higher risk of COVID-19 positivity and that socioeconomic determinants were strongly associated with outcomes.[27−29] This recurrent disproportionality suggests that health inequities and socioeconomic determinants play a significant role in the ongoing COVID-19 pandemic and that interventions should be aimed at mitigating these negative impacts.

As in any retrospective cohort study, investigators had no control over the quality and completeness of the available EMR data. The likelihood of unobserved and unmeasured confounding cannot be eliminated entirely because an observational study is susceptible to confounding bias. A total of 2 cohorts assembled from the different COVID-19+ and COVID-19− populations may differ in multiple important ways that influenced the outcomes. We cannot completely rule out the violation of the conditional independence assumption. In our observational study, the treatment (SARS-CoV-2 infection exposure) was not randomly assigned, so potential outcomes are not independent of the exposure. We assumed that after conditioning on the covariates, the treatment assignment was as good as random. Nevertheless, we cannot be 100% sure that we observed, measured, and conditioned enough covariates. We also note that this small study was conducted in a single healthcare system. Validation of the study findings in alternative populations will increase the chances that the observed association is causal.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.06.023.

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