Long-term outcomes of patients with pre-existing coronary artery disease after SARS-CoV-2 infection

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Summary

Background The long-term outcomes of patients with pre-existing coronary artery disease (CAD) after SARS-CoV-2 infection are unknown.

Methods Patients with pre-existing CAD were classified as COVID+ or COVID– based on the polymerase-chain-reaction test in the Montefiore Health System between March 11, 2020, and January 12, 2024. The final cohorts comprised 1380 hospitalised with COVID-19, 1702 non-hospitalised with COVID-19, 7264 contemporary COVID– controls, and 8492 historical controls (January 1, 2016–December 31, 2019). Primary outcomes were all-cause mortality, new-onset congestive heart failure (CHF), myocardial infarction (MI), stroke, and major adverse cardiovascular events (MACE). Cox and Fine–Gray regression models with multivariate adjustment, propensity matching, and inverse probability weighting were applied. Outcomes were also analysed with respect to inflammatory and haematologic biomarkers obtained during acute infection.

Findings Compared to contemporary controls, patients hospitalised with COVID-19, but not patients not hospitalised with COVID-19, had higher future risk of MACE (adjusted HR = 1.58 [1.38, 1.80]), mortality, CHF, MI, and stroke up to four years post-infection ($p < 0.05$). Analysis using propensity-score matching and inverse probability weighting corroborated the results of multivariate regression. Sensitivity analyses using historical controls and a cohort without excluding early death or loss to follow-up showed consistent results. Among patients hospitalised for COVID-19, elevated neutrophil-to-lymphocyte ratio, ferritin, D-dimer, creatinine, low haemoglobin, and abnormal platelets were associated with increased risk for MACE.

Interpretation Severe COVID-19 is associated with long-term cardiovascular risk in patients with pre-existing CAD. Abnormal biomarkers during acute infection were associated with increased risk for MACE. These findings underscore the need for monitoring for cardiovascular risk in patients with pre-existing CAD.

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Keywords: Cardiovascular risk factors; Post-acute sequelae of SARS-CoV-2 infection (PASC); Socioeconomic status; Inflammatory markers; D-dimer; C-reactive protein

Introduction

The emergence of COVID-19 has introduced a new layer of complexity to cardiovascular risk. Individuals who survive severe SARS-CoV-2 infection have been reported to be at elevated risk of major adverse cardiovascular events (MACE) for up to two years post-infection.[1–5] Notably, the impact of severe COVID-19 on long-term MACE risk appears comparable in magnitude to that of coronary artery disease (CAD) itself.[4] CAD is a causal risk factor for MACE because atherosclerotic plaque buildup and arterial narrowing directly predispose patients to events such as myocardial infarction (MI), congestive heart failure (CHF), and stroke. Given this inherently elevated baseline risk in patients with CAD, an in-depth examination of the interplay between COVID-19 and the unique risk profile imposed by CAD is warranted.

There is some evidence that SARS-CoV-2 can contribute to the destabilization of atherosclerotic plaques. Coronary autopsy specimens from patients with CAD who died of COVID-19 showed SARS-CoV-2 infiltration in plaque-resident macrophages, leading to

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Research in context

Evidence before this study

Respiratory viral infections such as influenza have been shown to increase the risk of thromboembolic and cardiovascular events. There is evidence that SARS-CoV-2 infection contributes to the destabilization of atherosclerotic plaques. However, the impact of SARS-CoV-2 infection on long-term cardiovascular outcomes in individuals with a history of coronary artery disease (CAD) is unknown.

Added value of this study

This longitudinal study assessed the impact of COVID-19 on long-term cardiovascular outcomes among patients with pre-existing CAD up to 4 years post-infection. Patients with a history of CAD who were hospitalised for COVID-19 had elevated risk of first-time major adverse cardiovascular events, myocardial infarction, congestive heart failure, stroke, and all-cause mortality, independent of age, sex, race, ethnicity, pre-existing comorbidities, and socioeconomic status. Abnormal biomarkers such as neutrophil-to-lymphocyte ratio, haemoglobin, platelets, ferritin, D-dimer, and creatinine during acute COVID-19 were independent predictors of downstream cardiovascular risk.

Implications of all the available evidence

Individuals with pre-existing CAD who have had a severe COVID-19 disease course should be carefully monitored for adverse cardiovascular events.

overexpression of pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α.[6] These cytokines were associated with endothelial cell damage and heightened expression of tissue factor, suggesting an enhanced pro-thrombotic state. Importantly, histopathologic evidence of plaque rupture was observed in several specimens, with disruption of the fibrous cap, intraplaque haemorrhage, and luminal thrombus formation. These factors could hinder the capacity of arterial smooth muscle cells to maintain a stable fibrous cap, which could weaken the structural integrity of the plaque and predispose the coronary plaque to rupture. Coronary arteries of patients with CAD who were exposed to SARS-CoV-2 were more likely than controls to exhibit plaque ruptures, erosions, fibrosis, and diffuse lesions.[7] As a result, what might have otherwise remained a relatively stable plaque may be transformed by the viral invasion into a focal point of heightened vulnerability for acute ischaemic events. Thus, beyond merely amplifying systemic risk factors such as inflammation, coagulopathy, and hypoxia,[8–10] severe COVID-19 may actively exploit the pathological vulnerabilities of atherosclerotic plaques, potentially posing a persistent threat long after the acute infection phase.

Cardiovascular outcomes post-COVID-19 have also been shown to be impacted by socioeconomic status and social determinants of health.[11,12] Marginalized communities often face higher SARS-CoV-2 infection risk due to overcrowded housing, limited healthcare access, and employment in high-risk or public-facing roles.[13,14] These structural inequities can also delay diagnosis and treatment of chronic conditions, compound comorbidities such as hypertension and diabetes, and ultimately heighten the long-term risk of MACE after SARS-CoV-2 infection.[15,16]

The goal of this study was to investigate the association between COVID-19 and all-cause mortality, as well as first-time CHF, MI, and stroke in patients with pre-existing CAD up to four years post-infection. We also assessed the impact of socioeconomic status and biomarkers at the time of infection as potential contributors to cardiovascular outcomes. An improved understanding of these risk factors may provide guidance to the development of preventive and therapeutic strategies for COVID-19 survivors with CAD.

Methods

Data sources

This retrospective cohort study was approved by the Einstein-Montefiore Institutional Review Board with an exemption for informed consent (#2021–13658). Electronic health records (EHR) came from the Montefiore Health System (January 1, 2016–January 12, 2024), which consists of multiple hospitals and outpatient clinics in the Bronx and its environs. EHR were extracted using Observational Medical Outcomes Partnership (OMOP) common data model as previously described.[17–34] A large team of data scientists and engineers created, maintained, curated, and validated data extraction. To ensure data quality, this team routinely performed manual chart review of all relevant variables on subsets of patients over the last few years. As retrospective studies are susceptible to patient selection biases, confounders, and competing risks, we corroborated our findings using propensity score (PS) matching, inverse probability weighting (IPW), and multivariate regression to account for potential confounders. In addition, we also performed sensitivity analyses. With a large and diverse patient population, these findings are likely generalizable, although additional studies are needed to achieve broader generalizability.

Study cohort

Inclusion criteria were adults (≥21 years old) with a prior diagnosis of CAD at index date but without prior history of outcomes (MI, CHF, or stroke). Patients were grouped into COVID+ and COVID– cohorts. Patients

classified as COVID+ were those tested positive by polymerase chain reaction (PCR) at least once and index date was defined as date of first positive test. COVID– controls consisted of those who never tested positive and index date was defined as date of first negative test. Patients who did not return to our health system 30 days or more after index date (lost to follow-up) were excluded. Patients who experienced outcomes (MI, CHF, stroke, or mortality) within 30 days of index date were also excluded. A sensitivity analysis was performed in which these 30 days exclusions were not applied.

Patients who were hospitalised during acute COVID-19 were 1:1 PS matched with COVID– controls on age, sex, race, ethnicity, pre-existing comorbidities, insurance, and income of Zone Improvement Plan (ZIP) code. Similarly, patients in the non-hospitalised COVID+ group were matched with COVID– controls using the same criteria. This process yielded two cohorts, each consisting of two matched COVID+ and COVID– groups. IPW was also performed with the same covariates.

In addition to contemporary controls, a sensitivity analysis was performed using pre-pandemic historical controls (January 1, 2016–December 31, 2019). Note that both contemporary and historical control groups were not stratified by hospitalisation status, as hospitalisations often reflected diverse causes (e.g., physical trauma, stroke, sepsis, terminal illness, etc.), making comparisons to COVID-19-related hospitalisations less meaningful.

Variables

Demographic data included age at index date, sex (self-reported by patients in the EHR), race, and ethnicity. Insurance and median household income of each patient's ZIP code were collected. Pre-existing comorbidities at index date included hypertension (HTN), type-2 diabetes (T2DM), chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease (CKD), liver disease, and tobacco use as defined by ICD-10 codes. Sociodemographic data were available for all patients and those who had no diagnosis of comorbidities or outcomes in the EHR were assumed to not have experienced the outcome or had the comorbidity. To assess severity of SARS-CoV-2 infection, patients with COVID-19 were stratified based on hospitalisation during the acute phase of the infection. Among the hospitalised COVID+ cohort, the following biomarkers at time of infection were collected: neutrophil-to-lymphocyte ratio (NLR), haemoglobin (g/dL), platelets (110×10^9 cells/L), ferritin (μg/L), D-dimer (μg/mL), creatinine (mg/dL), C-reactive protein (mg/dL), lactate dehydrogenase (U/L), aspartate aminotransferase (U/L), and temperature (°C).

Outcomes

Outcome events included all-cause mortality, MI, CHF, stroke, and MACE (defined as a composite of the four individual outcomes) recorded in the EHR >30 days to up to 4 years after index date. Follow-up time was calculated in months from the index date to either the date of first diagnosis (for patients who developed the outcome) or to the date of death or last recorded visit (for patients who did not develop the outcome) up to January 12, 2024.

Statistical analysis

Python (v3.10.12) and RStudio (v4.3.2) were used for data processing and statistical analyses. *p*-values less than 0.05 were considered statistically significant. For group comparison of categorical variables, the chi-square test was used and for group comparison of continuous variables, the independent t-test was used. Risk of outcomes was assessed using Cox proportional hazards models for all-cause mortality and MACE and Fine–Gray subdistribution competing risk regression models for CHF, MI, and ischaemic or hemorrhagic stroke to account for mortality as a competing risk. We evaluated the proportional hazards assumption using Schoenfeld residuals and time-by-covariate interaction terms and found no evidence of violation. When analysing the unmatched cohort, the covariates adjusted for included age, sex, race, ethnicity, pre-existing comorbidities, insurance (private insurance as baseline), and median income of ZIP code (divided into four quartiles with the highest income quartile as baseline). Univariate analysis was used in PS-matched and IPW-adjusted cohorts, which were matched and adjusted according to the same covariates. Among patients hospitalised with COVID-19, biomarkers at time of COVID-19 hospitalisation were assessed[35,36] and analysed with respect to risk of MACE.

Role of funders

No specific funding was received for the work presented in this manuscript.

Results

Cohort selection

Fig. 1 shows the patient selection flowchart. From March 11, 2020 to January 12, 2024, 212,590 adults (≥21 years old) had a SARS-CoV-2 PCR test performed for suspicion of respiratory infection. After only including patients with pre-existing CAD with no history of MI, CHF, or stroke, 3893 patients who were COVID+ and 8167 patients who were COVID– were identified. 304 (7.81%) of the patients in the COVID+ group died during the acute (within 30 days) infection. Of those who did not die or experience MACE within the first 30 days of PCR test, 507 (14.13%) in the COVID+ group and 865 (10.64%) in the COVID– group were lost to follow-up within the first 30 days. There were 3082 patients in the COVID+ group and 7264 patients in the COVID– group who returned to our health system ≥30

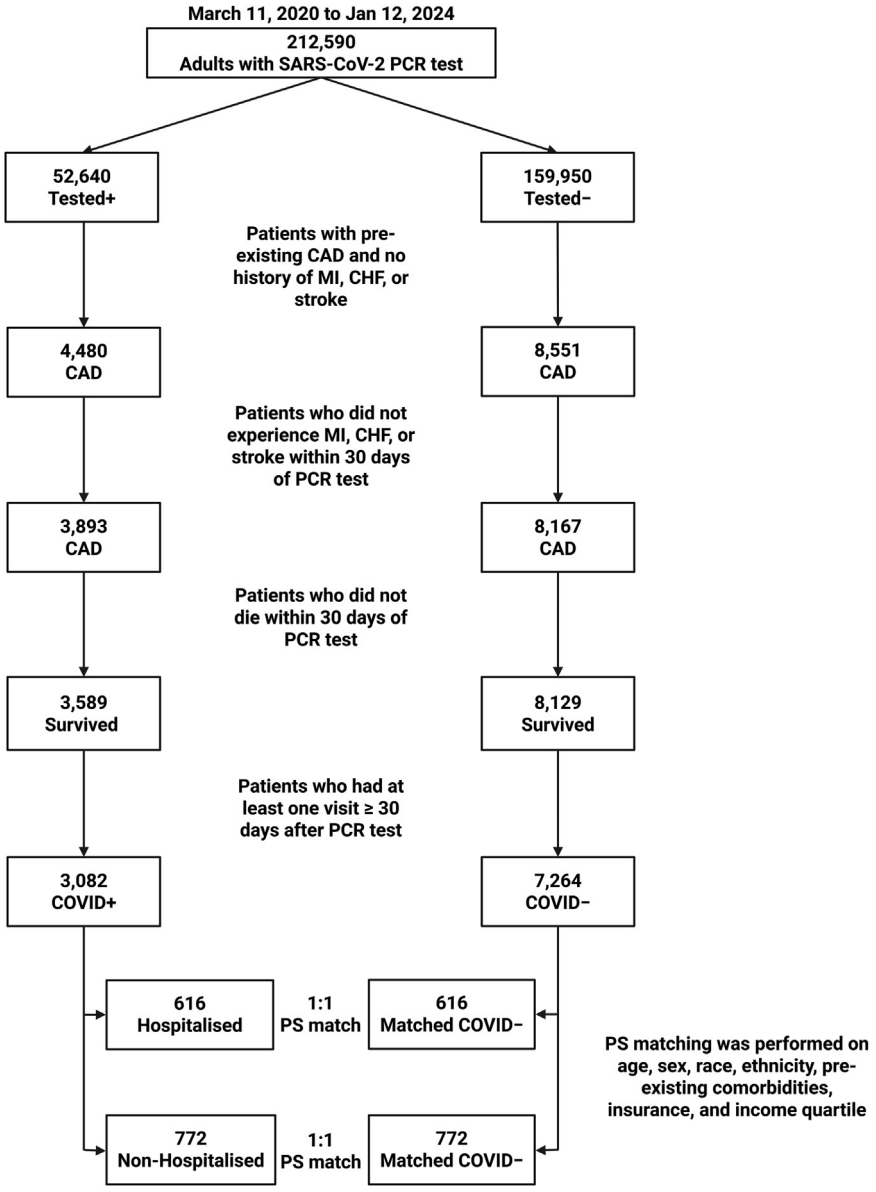

Fig. 1: Patient selection flowchart. PCR, polymerase chain reaction; CAD, coronary artery disease; MI, myocardial infarction; CHF, congestive heart failure; PS, propensity score.

days after index date for any medical reason. Of the 1380 patients who were hospitalised for COVID-19, 616 were 1:1 PS matched to COVID− controls and of the 1702 COVID+ who were not hospitalised for COVID-19, 772 were 1:1 PS matched to COVID− controls.

Table 1 shows the characteristics of patients with pre-existing CAD but no history of MI, CHF, or stroke with and without COVID-19 (unmatched cohort). Those with COVID-19 were on average older by a year (66.37 vs. 65.30 years, independent t-test $p < 0.005$), more likely to be Black (30.79% vs. 25.40%, chi-square $p < 0.005$), more likely to have all pre-existing comorbidities (chi-square $p < 0.005$ for all) besides tobacco use, less likely to be on private insurance (32.06% vs. 34.62%, chi-square $p = 0.010$), more likely to be self-pay (4.09% vs. 2.06%, chi-square $p < 0.005$), less likely to live in a ZIP code in the lower 25th percentile of median income (25.63% vs. 28.26%, chi-square $p = 0.010$), more likely to live in a ZIP code in the 25–50th percentile of median income (27.09% vs. 23.77%, chi-square $p < 0.005$), and less likely to live in a ZIP code in the top 25th percentile of median income (21.61% vs. 23.46%, chi-square $p = 0.040$). Sex disaggregated demographic data are shown in Supplementary Table S1.

Main analysis

Table 2 shows the Cox proportional and Fine–Gray subdistribution adjusted hazard ratios (HR) for COVID-19 and risk of cardiovascular outcomes. After adjusting for age, sex, race, ethnicity, pre-existing comorbidities, insurance, and median income of ZIP code, patients hospitalised for COVID-19 were more likely to experience all-cause mortality, MI, CHF, stroke, and MACE compared to the COVID– group. Adjusting for the same covariates via IPW showed similar results. However, in the PS matching process, patients who were not matched had to be excluded which reduced statistical power, and only risk of MI and MACE were significantly higher in the COVID+ hospitalised group compared to the COVID– group. Patients not hospitalised with COVID-19 were at higher risk of CHF than patients in the COVID– group in multivariate regression. Supplementary Table S2 shows the full results of multivariate models with all covariates. Patients on Medicare and Medicaid were at higher risk of MI, CHF, and MACE.

IPW-adjusted Kaplan–Meier and cumulative incidence curves for the outcomes are shown in Fig. 2. For all outcomes, patients hospitalised with COVID-19 had worse outcomes compared to those who were non-hospitalised with COVID-19 and COVID–. The outcomes of patients non-hospitalised with COVID-19 were mostly similar to the COVID– group, except for CHF which showed the non-hospitalised COVID-19 group to be at higher risk compared to the COVID– group.

To investigate the potential association of outcomes with biomarkers, we evaluated MACE with respect to biomarkers obtained during acute COVID-19. Table 3 shows the multivariate Cox-proportional adjusted HRs for biomarkers at time of infection and risk of MACE among patients hospitalised for COVID-19. NLR ≥10 (adjusted HR = 1.45 [1.11, 1.89]), haemoglobin ≤9.2 g/dL (adjusted HR = 2.01 [1.46, 2.76]), platelets ≤110 × 10^9 cells/L (adjusted HR = 1.82 [1.22, 2.72]), ferritin ≥700 μg/L (adjusted HR = 1.34 [1.03, 1.73]), D-dimer ≥1.5 μg/mL (adjusted HR = 1.46 [1.14, 1.87]), and creatinine ≥1.1 mg/dL (adjusted HR = 1.30 [1.00, 1.69]) were associated with further elevated risk of MACE. C-reactive protein ≥15 mg/dL, lactate dehydrogenase ≥400 U/L, aspartate aminotransferase ≥100 U/L, and temperature ≥38.0 °C at time of infection were not associated with risk of MACE.

Sensitivity analyses

The COVID– contermporary control group in this main analysis might have been contaminated with patients exposed to COVID-19 that were not documented in our EHR. We thus also analysed using pre-pandemic (January 1, 2016–December 31, 2019) controls (n = 8492). The results were similar to those using contermporary controls (Appendix 1).

	COVID+ (n = 3082)	COVID– (n = 7264)	*p*-value
Follow up time (years), mean ± SD	1.72 ± 1.02	1.96 ± 0.98	**<0.005**
Age, mean ± SD	66.37 ± 13.58	65.30 ± 12.17	**<0.005**
Female, n (%)	1695 (55.00%)	3968 (54.63%)	0.74
Race and ethnicity, n (%)			
Non-Hispanic White	457 (14.83%)	1138 (15.67%)	0.29
Black	949 (30.79%)	1845 (25.40%)	**<0.005**
Asian	127 (4.12%)	290 (3.99%)	0.80
Other race	1549 (50.26%)	3991 (54.94%)	**<0.005**
Hispanic	1261 (40.91%)	2897 (39.88%)	0.34
Pre-Existing comorbidities, n (%)			
Hypertension	2692 (87.35%)	6013 (82.78%)	**<0.005**
Type-2 diabetes	1710 (55.48%)	3459 (47.62%)	**<0.005**
COPD	258 (8.37%)	195 (2.68%)	**<0.005**
Asthma	812 (26.35%)	1575 (21.68%)	**<0.005**
Chronic kidney disease	945 (30.66%)	1409 (19.40%)	**<0.005**
Liver disease	867 (28.13%)	1436 (19.77%)	**<0.005**
Tobacco use	1620 (52.56%)	3781 (52.05%)	0.65
Insurance, n (%)			
Medicaid	819 (26.57%)	2004 (27.59%)	0.30
Medicare	1149 (37.28%)	2595 (35.72%)	0.14
Private	988 (32.06%)	2515 (34.62%)	**0.010**
Self-Pay	126 (4.09%)	150 (2.06%)	**<0.005**
Income group of ZIP code, n (%)			
Lower 25% (≤$38,066)	790 (25.63%)	2053 (28.26%)	**0.010**
25–50% ($38,768–$49,679)	835 (27.09%)	1727 (23.77%)	**<0.005**
50–75% ($50,164–$62,918)	791 (25.67%)	1780 (24.50%)	0.22
Top 25% (>$63,048)	666 (21.61%)	1704 (23.46%)	**0.040**
Hospitalised due to COVID-19, n (%)	1380 (44.78%)	–	–
Outcomes, n (%)			
All-cause mortality	129 (4.19%)	148 (2.04%)	**<0.005**
Myocardial infarction	124 (4.02%)	186 (2.56%)	**<0.005**
Congestive heart failure	342 (11.10%)	585 (8.05%)	**<0.005**
Ischaemic or hemorrhagic stroke	108 (3.50%)	188 (2.59%)	**0.010**
Major adverse cardiovascular events	527 (17.10%)	924 (12.72%)	**<0.005**

SD, standard deviation; COPD, chronic obstructive pulmonary disease; ZIP, Zone Improvement Plan. Bolded values reflect statistical significance ($p < 0.05$).

Table 1: **Characteristics of patients with pre-existing coronary artery disease but no history of myocardial infarction, congestive heart failure, or stroke with and without COVID-19 (unmatched).**

Our main analysis excluded patients who were lost to follow-up, died, or experienced MACE within 30 days of the index date, which might have introduced survivor biases. We thus performed sensitivity analysis in which these exclusions were not applied (Appendix 2). The results were largely consistent with main analysis, except that patients with COVID-19 were at much greater risk of mortality when not excluding those who died acutely.

Discussion

This study investigated the association between COVID-19 and all-cause mortality, first-time CHF, MI, stroke and MACE in patients with pre-existing CAD up to four years post-infection. Patients hospitalised with COVID-19, but not with non-hospitalised COVID-19, had

Outcome	COVID+ Hospitalised vs. COVID–		COVID+ Non-Hospitalised vs. COVID–	
	Adjusted HR [95% CI]	*p*-value	Adjusted HR [95% CI]	*p*-value
Multivariate regression				
All-cause mortality	2.27 [1.72, 3.00]	**<0.005**	1.20 [0.83, 1.72]	0.33
Myocardial infarction	1.85 [1.40, 2.46]	**<0.005**	1.12 [0.79, 1.60]	0.52
Congestive heart failure	1.51 [1.27, 1.79]	**<0.005**	1.22 [1.01, 1.48]	**0.041**
Ischaemic or hemorrhagic stroke	1.62 [1.21, 2.17]	**<0.005**	1.01 [0.71, 1.43]	0.98
Major adverse cardiovascular events	1.58 [1.38, 1.80]	**<0.005**	1.08 [0.92, 1.26]	0.36
Outcome	**COVID+ Hospitalised vs. COVID–**		**COVID+ Non-Hospitalised vs. COVID–**	
	HR [95% CI]	*p*-value	HR [95% CI]	*p*-value
Inverse probability weighting-adjusted				
All-cause mortality	2.30 [1.70, 3.11]	**<0.005**	1.04 [0.71, 1.51]	0.86
Myocardial infarction	1.76 [1.36, 2.28]	**<0.005**	1.12 [0.83, 1.50]	0.47
Congestive heart failure	1.63 [1.37, 1.94]	**<0.005**	1.18 [0.98, 1.43]	0.081
Ischaemic or hemorrhagic stroke	1.67 [1.28, 2.18]	**<0.005**	1.00 [0.74, 1.36]	0.98
Major adverse cardiovascular events	1.60 [1.38, 1.86]	**<0.005**	1.02 [0.87, 1.21]	0.77
Propensity-Score matching				
All-cause mortality	1.64 [0.89, 3.01]	0.11	0.59 [0.29, 1.21]	0.15
Myocardial infarction	2.24 [1.26, 3.99]	**0.0060**	1.36 [0.65, 2.85]	0.42
Congestive heart failure	1.17 [0.85, 1.62]	0.34	1.13 [0.76, 1.66]	0.54
Ischaemic or hemorrhagic stroke	1.67 [0.98, 2.84]	0.059	1.24 [0.63, 2.44]	0.54
Major adverse cardiovascular events	1.31 [1.01, 1.70]	**0.043**	0.93 [0.68, 1.26]	0.62

Multivariate models were adjusted for age, sex, race, ethnicity, all collected comorbidities, insurance status, and quartile of Zone Improvement Plan code median household income. Propensity score and inverse probability weighting-adjusted models were matched for the same covariates. Bolded values reflect statistical significance ($p < 0.05$).

Table 2: **Cox-proportional (all-cause mortality and major adverse cardiovascular events) and Fine–Gray subdistribution (myocardial infarction, congestive heart failure, and ischaemic or hemorrhagic stroke) adjusted hazard ratios (HR) for different outcomes grouped by COVID-19 status (COVID+ hospitalised and COVID+ non-hospitalised vs. COVID–).**

elevated adjusted risk of all-cause mortality, first-time CHF, MI, stroke, and composite MACE. Such risk posed by hospitalised COVID-19 was similar in magnitude to that of established cardiovascular risk factors such as pre-exisitng HTN, COPD, T2DM and CKD. Abnormal biomarker levels (NLR, haemoglobin, platelets, ferritin, D-dimer, and creatinine) during acute COVID-19 hospitalisation were associated with greater

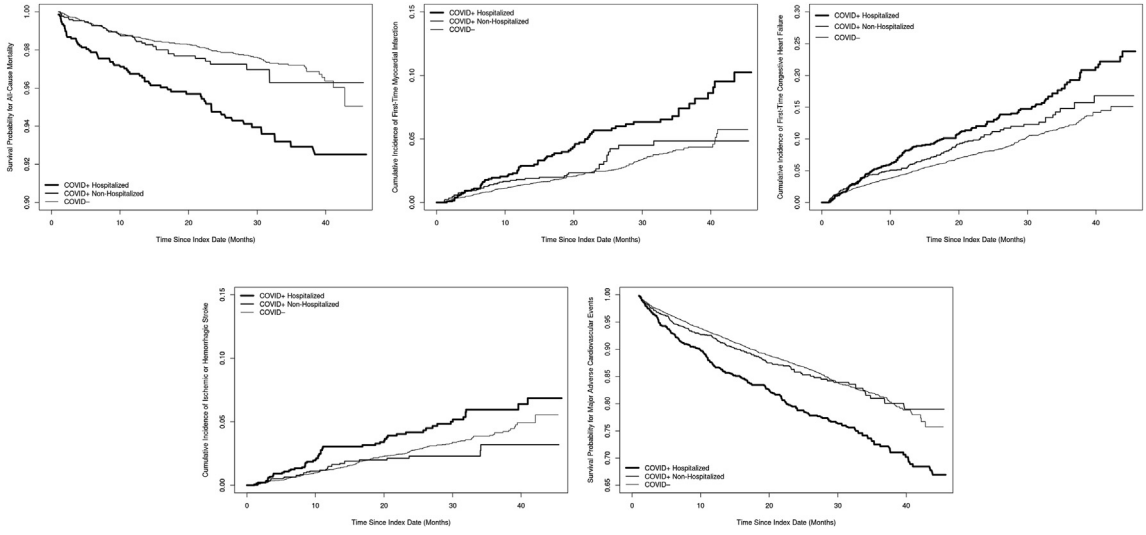

Fig. 2: Kaplan–Meier (all-cause mortality and major adverse cardiovascular events) and cumulative incidence function (myocardial infarction, congestive heart failure, and ischaemic or hemorrhagic stroke) up to 45 months post-index date among COVID+ hospitalised (n = 1380), COVID+ non-hospitalised (n = 1702), and COVID– (n = 7264) groups. The three groups were inverse probability weighted according to age, sex, race, ethnicity, all collected comorbidities, insurance status, and quartile of Zone Improvement Plan code median household income.

adjusted risk for future MACE. Sensitivity analyses further supported these main findings.

Patients with CAD who were hospitalised with COVID-19 are at higher risk of MACE

Our findings highlight the significant cardiovascular burden associated with patients with CAD who were hospitalised for COVID-19. CAD is an important causal risk factor of cardiovascular events due to atherosclerotic plaque buildup and rupture, with studies suggesting that COVID-19 interacts directly with these pathological processes. SARS-CoV-2 virions have been shown to infiltrate plaque-resident macrophages within atherosclerotic lesions, inducing a hyperinflammatory state that releases pro-inflammatory cytokines, damages the endothelium, and weakens the fibrous cap, ultimately increasing the likelihood of plaque rupture.[6] Optical coherence tomography studies have corroborated these findings, revealing higher rates of plaque rupture, erosion, and fibrosis in patients with COVID-19 compared to controls, suggesting that SARS-CoV-2 may actively exploit pre-existing vulnerabilities in the coronary vasculature.[7]

Non-hospitalised COVID-19 status however did not confer elevated risk of cardiovascular outcomes compared to comtempory and historical COVID– controls, indicating COVID-19 disease severity played a key role in driving long-term cardiovascular complications. This is consistent with prior studies that show that severe COVID-19 induces systemic inflammation, endothelial dysfunction, hypoxia, and coagulopathy, which act synergistically to exacerbate thrombotic and cardiovascular risk.[37–41] Abnormal values of NLR, haemoglobin, platelets, ferritin, D-dimer, and creatinine were linked to elevated risk of future MACE among patients hospitalised for COVID-19, further supporting the notion that COVID-19-related cardiovascular insults may persist beyond the acute phase of infection, leading to a risk trajectory that exacerbates the vulnerabilities imposed by CAD.

The link between viral infection and cardiovascular events is not new. Viral infections such as influenza have been shown to increase the risk of thromboembolic and cardiovascular events.[42–45] With the emergence of SARS-CoV-2, these associations have extended to COVID-19 as well.[1–5] A meta-analysis of 81 studies concluded that among patients with COVID-19, having pre-existing CAD increased the risk of hospitalisation, intensive-care unit admission, and mortality[46] and a recent study reported that COVID-19 imposes a CAD-equivalent risk factor for MACE.[4] Our results are consistent with these prior observations.

Socioeconomic status

When risk of MACE was analysed with respect to socioeconomic variables, having Medicare compared to private insurance was associated with higher risk of MACE, consistent with the 65 years or older eligibility requirement for Medicare.[47] Most sociodemographic variables were largely not associated with risk of cardiovascular outcomes, except for Hispanics who were at elevated risk of MACE, which might reflect the high prevalence of hypercholesterolaemia, HTN, obesity, T2DM, or tobacco use in this population.[48]

Biomarker predictor	Adjusted HR [95% CI]	p-value
Neutrophil/lymphocyte ratio ≥10	1.45 [1.11, 1.89]	**0.0060**
Haemoglobin ≤9.2 g/dL	2.01 [1.46, 2.76]	**<0.005**
Platelets ≤110 × 10^9 cells/L	1.82 [1.22, 2.72]	**<0.005**
Ferritin ≥700 µg/L	1.34 [1.03, 1.73]	**0.029**
D-dimer ≥1.5 µg/mL	1.46 [1.14, 1.87]	**<0.005**
Creatinine ≥1.1 mg/dL	1.30 [1.00, 1.69]	**0.049**
C-Reactive protein ≥15 mg/dL	1.23 [0.93, 1.62]	0.15
Lactate dehydrogenase ≥400 U/L	1.09 [0.82, 1.45]	0.56
Aspartate aminotransferase ≥100 U/L	0.85 [0.50, 1.44]	0.55
Temperature ≥38.0 °C	0.91 [0.60, 1.39]	0.67

Bolded values reflect statistical significance ($p < 0.05$).

Table 3: **Cox-proportional adjusted hazard ratios (HR) for biomarkers at time of infection and risk of major adverse cardiovascular events among patients hospitalised for COVID-19. In addition to the biomarker, models adjusted for age, sex, race, ethnicity, and pre-existing comorbidities.**

Clinical implications

These findings have potential implications for clinical practice, as our cohort comprised of patients with CAD with no prior history of MI, CHF, or stroke at baseline, a subgroup in which preventing a first-time MACE is paramount to avoiding substantial, and potentially irreversible, morbidity, mortality, and declines in quality of life.[49] What is particularly striking is that the risk posed by hospitalised COVID-19 (adjusted HR = 1.58 [1.38, 1.80]) was similar in magnitude to that of established cardiovascular risk factors such as HTN (1.28 [1.05, 1.55]), COPD (1.50 [1.23, 1.83]), T2DM (1.13 [1.02, 1.27]), and CKD (1.51 [1.34, 1.69]).[50–53] Our data indicate that patients with CAD should be classified as high risk for first-time adverse cardiovascular events following hospitalisation for COVID-19.

Given these findings, proactive measures to mitigate long-term risk may warrant consideration. Specifically, intensifying the management of traditional cardiovascular risk factors (e.g., HTN, T2DM, and dyslipidemia), alongside the adjunctive use of anti-inflammatory or anti-coagulant therapies, may be considered to help reduce the risk of first-time cardiovascular complications.[54–57] In addition, considering structured post-discharge care, including routine assessments for heart failure, arrhythmias, and ischaemic events, may be justified, given emerging evidence of persistent risk among survivors of severe COVID-19.[58–61]

Furthermore, these observations underscore the value of integrating cardiovascular considerations into COVID-19 treatment protocols, including prioritization of vaccination and early therapeutic interventions to

avert progression to severe disease.[62–65] In CAD patients who have elevated inflammatory or coagulation markers during acute COVID-19, early administration of anti-inflammatory agents (e.g., corticosteroids or interleukin-6 inhibitors) and prophylactic anti-coagulation may help mitigate downstream cardiovascular risk.[66,67] Although our findings identify associations between these serum abnormalities and increased long-term MACE risk, they do not demonstrate that correcting these abnormalities would directly reduce that risk. Further research into the molecular mechanisms linking SARS-CoV-2 infection to cardiovascular dysfunction is essential to determine whether targeted interventions can modify long-term outcomes, particularly in individuals with underlying cardiovascular disease.

Limitations

Our study has several limitations. Data were limited to those who returned to our health system for care over the study period after the index date and it is possible that patients who had more severe COVID-19 or had more urgent health concerns were more likely to return to our health system. However, return care included any visit, including regular medical checkup in both COVID+ and COVID– cohorts. We relied on the accuracy of the EHR, which in datasets of this size could have some inaccuracies or mis-documentations. We did not use at home SARS-CoV-2 tests because they were not reliably documented in our EHR. Patients could be misclassified as COVID– if they were tested positive elsewhere and such misclassification likely underestimated any potential impact of the infection. However, cases of severe COVID-19 were unlikely to have been missed due to the need for inpatient admission, as Montefiore Health System is the predominant healthcare provider in the Bronx. We did not investigate the association of COVID-19 vaccination with outcomes because individuals could have been vaccinated at nearby pharmacies or other facilities. We also did not study associations of various COVID-19 treatments with outcomes because there were many combinations of treatments which were heterogeneous and not systematically administered throughout time, especially during the early pandemic. We did not study the contribution of acute inflammatory markers to outcomes in the non-hospitalised COVID-19 group because these laboratory tests were usually not clinically indicated in these patients. As our cohort is diverse, consisting of large proportions of racial minorities in an underserved population, our findings may not be representative of less diverse populations. Future research should include multicentre studies to enhance generalizability, particularly in populations with different demographic and socioeconomic characteristics. Although we corrected for all major confounds using multivariate regression, IPW, and PS matching, there could still be unintentional patient selection biases and residual confounders.

Conclusions

In patients with a history of coronary artery disease, those hospitalised for COVID-19, but not those not hospitalised COVID-19, are at elevated risk of first-time cardiovascular events up to four years post-infection compared to COVID– controls. Patients exhibiting abnormal blood biomarkers (NLR, haemoglobin, platelets, ferritin, D-dimer, and creatinine) at time of infection were especially susceptible. These findings emphasize the importance of long-term monitoring of survivors of severe COVID-19 with cardiovascular risk factors such as coronary artery disease.

Contributors

R.H.–conceptualisation, formal analysis, investigation, methodology, validation, visualisation, writing—original draft, writing—review & editing.

P.L.–methodology, writing—original draft, writing—review & editing.

S.Q.–formal analysis, investigation, validation, writing—review & editing.

S.C.–methodology, validation.

S.H.–data curation, methodology, validation.

T.Q.D.–conceptualisation, supervision, validation, writing—original draft, writing—review & editing.

All authors read and approved the final version of the manuscript. Roham Hadidchi and Tim Q. Duong have accessed and verified the underlying data.

Data sharing statement

The data underlying this study are not publicly available due to institutional and IRB restrictions involving patient privacy and confidentiality. De-identified summary data and analysis code are available from the corresponding author upon reasonable request and contingent upon institutional approval and execution of a data use agreement. Please contact Tim Q. Duong at tim.duong@einsteinmed.edu. Code used to perform analysis in this study is available at https://doi.org/10.5281/zenodo.15377430.[68]

Declaration of interests

Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105778.

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