Original Article

Long-Term Major Adverse Cardiovascular Events in Patients with Moderate and Severe COVID-19: A Focus on Early Statin Use and Previous CVD

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Abstract

Background: *Limited data exist regarding the status of long-term cardiovascular disease (CVD) outcomes of hospitalized COVID-19 patients. We aimed to examine the efficacy of early statin use after SARS-CoV-2 pneumonia and the impact of prior CVD on the incidence of cardiovascular events.*

Methods: *A prospective cohort study was performed on hospitalized COVID-19 patients. The primary endpoint was major adverse cardiovascular events (MACE) as a composite of cardiovascular mortality, stroke, heart failure, venous thromboembolism (VTE), revascularization, and nonfatal myocardial infarction (MI). The secondary endpoints comprised MACE components, all-cause mortality, readmission for COVID-19, and impaired functional classes.*

Results: *The mean age of the 858 participants was 55.52±13.97 years, and the median follow-up time was 13 months (11.5-15). Men comprised 63.9% of the patients. Overall, MACE occurred in 84 subjects (9.8%), and 98 patients (11.4%) received ventilation. A multivariate Cox regression model was employed to explore the association between statin use and outcomes, and the following hazard ratios were obtained: MACE (0.831 [0.529 to 0.981]; P=0.044), All-cause mortality (1.098 [0.935 to 1.294]; P=0.255), stroke (0.118 [0.029 to 0.48]; P=0.003), revascularization (0.103 [0.029 to 0.367]; P<0.0001), poor functional capacity (0.827 [0.673 to 1.018]; P=0.073), nonfatal MI (0.599 [0.257 to 1.394]; P=0.234), VTE (0.376 [0.119 to 1.190]; P=0.096), and decompensated heart failure (0.137 [0.040 to 0.472]; P=0.002). Prior CVD predicted MACE (2.953 [1.393 to 6.271]; P=0.005), all-cause death (1.170 [0.960 to 1.412]; P=0.102), and VTE (2.770 [0.957 to 8.955]; P=0.051).*

Conclusion: *Previous CVD is a robust predictor of long-term MACE and VTE. Early statin use might decrease the incidence rates of MACE, ischemic stroke, revascularization, and readmission for heart failure.*

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Introduction

Since the onset of the 2019 coronavirus pandemic (COVID-19), we have observed various legacies, including a wide range of cardiac manifestations. The predominant clinical picture of the pandemic leading to complications and mortality was severe acute respiratory syndrome because of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The presumed etiologies of myocardial injury in COVID-19 patients subtend myopericarditis, hypoxic damage, stress-induced cardiomyopathy, hypercoagulable state, ischemic events due to plaque rupture, vasospasm or microvascular disease, right-sided pressure overload, and dysrhythmias.[1-4] The systemic inflammatory cascade due to the abundant release of cytokine plays a central role in the different characteristics of the disease, in particular concerning cardiovascular complications.[5]

Pre-existing cardiovascular disease (CVD), such as coronary artery disease, hypertension, and heart failure, is associated with acute cardiac events and the prognosis and severity of SARS-CoV-2 infection. Putative mechanisms that might explain this relationship include declined cardiovascular reserve, attenuated immune response, increased systemic inflammation, virus-mediated endothelial dysfunction, and angiotensin-converting enzyme 2 (ACE-2) receptor linking. ACE-2 is a host surface protein used for virus entry by binding to the viral spike (S) protein. In addition, SARS-CoV-2 infection usually triggers a cytokine storm, whereby mediators, including tumor necrosis factor-α and pro-inflammatory interleukins (IL-1β and IL-6), are released. Thus, the immune system overproduces chemokines, which, in concert with the upregulation of coagulation factors, might lead to thromboembolic disorders and multi-organ damage. Furthermore, COVID-19 causes coagulation abnormalities in a substantial proportion of patients, which can result in thromboembolic events.[6, 7] Although cardiovascular events rise early after acute COVID-19 or during short-term periods, few investigations have addressed long-term CVD outcomes. Additionally, the long-term benefits of statins in COVID-19 patients need confirmation with high certainty. Therefore, we sought to assess the impact of early statin therapy on the frequency of subsequent major adverse cardiovascular events (MACE) in these patients. A high risk of acute myocardial infarction (MI) and ischemic stroke was reported during 3 weeks of new SARS-CoV-2 infection in a comprehensive study.[8] With this in mind, an extensive cohort study of 153 760 COVID-19 survivors for at least 30 days examined the incidence of cardiovascular outcomes compared with 5.6 million controls. The results revealed that all endpoints, including all-cause mortality, MACE, stroke, MI, dysrhythmias, heart failure, and thromboembolic events, increased over the 12-month follow-up period.[9] Likewise, another retrospective cohort study on an unvaccinated population subtending 2 similar groups with 690 892 subjects (COVID-19 survivors for 1 month matched with controls in a 1:1 ratio) reported that the rates of all major CVD outcomes were substantially lower in the non-COVID-19 group during 12 months.[10]

In the present study, we aimed to explore the long-term incidence of MACE in a cohort of COVID-19 patients with a history of CVD.

Methods

The current prospective cohort study enrolled all consecutive hospitalized patients with a diagnosis of COVID-19 in a general hospital in Tehran. The study was started in August 2020 during the early peaks of the COVID-19 outbreak in Iran. All eligible COVID-19 cases were enrolled consecutively according to admission ID over 12 months. The eligibility criteria for inclusion were a positive polymerase chain reaction (PCR) test or a high clinical likelihood of SARS-CoV-2 accompanied by evidence of pneumonia in computed tomography (CT), age between 18 and 85 years, first episode COVID-19 infection, and informed consent. Patients were excluded in cases of mild disease (outpatient management), rapid discharge under 24 hours, incomplete demographic records, lack of molecular tests, and missing contact data. The empirical administration of medications such as corticosteroids, azithromycin, hydroxychloroquine, and nonspecific antivirals, including lopinavir/ritonavir, ribavirin, and remdesivir, was at the discretion of the infectious disease specialist. Data were collected on the prescription of statins during and after index hospitalization. The demographic characteristics, hemodynamic variables, and laboratory data were obtained using the general in-patient database. The missing files were filled out using the paper file review and online interviews. The initial files of 1012 consecutive COVID-19 patients were assessed. After the selection of 883 eligible subjects, 858 patients completed the follow-up process. (The study flow chart can be found in the supplements.) Vaccination with non-RNA vectors was administered to the majority of the population that survived at least 30 days after index hospitalization. All the vaccinated patients received at least 2 doses at a 3-month

interval.

COVID-19 was diagnosed through a positive PCR or reactive antibody test combined with constitutional manifestations such as cough, dyspnea, fever, myalgia, and weakness. Furthermore, a highly probable diagnosis was established if the patient had clinical manifestations consistent with SARS-CoV-2 pneumonia and thoracic CT results in favor of infiltrative pneumonia. The symptomatic interval after the latency period of the illness was reported in days, and follow-up duration was measured in months. Venous thromboembolism (VTE) was defined as deep vein thrombosis, pulmonary embolism, or a combination of both. Nonfatal MI was characterized according to the fourth universal definition of MI.[11] All kinds of revascularization procedures for significant coronary artery disease in case of either unstable angina, MI, or symptomatic chronic coronary syndrome were considered a distinct secondary endpoint. Impaired New York Heart Association (NYHA) functional class (FC) was determined as an FC of II or higher.[12] Worsening or de novo heart failure was detected via the clinical signs and symptoms of congestion, such as dyspnea, orthopnea, crackles, peripheral edema, and reduced ejection fraction (EF) and/or diastolic dysfunction in echocardiography. An EF under 50% was specified to characterize heart failure with a reduced EF. However, subsequent hospitalizations for episodes of heart failure were considered an endpoint, confirmed via the patient's documents. A history of previous CVD at baseline was defined as prior coronary artery disease, including MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and heart failure. Ventilation support during index hospitalization encompassed both tracheal intubation and noninvasive positive pressure ventilation (NIPPV) with facial masks. Treatment with statins was defined as a period of 15 days or more. A moderate-intensity dose was defined as using either atorvastatin of 20 mg/day or Rosuvastatin of 10 mg/day. A high-intensity statin regimen was determined as an atorvastatin dose ≥40 mg/d or rosuvastatin ≥20 mg/d. The electrocardiographic (ECG) rhythm was determined via the first ECG in hospitalized patients, classified into sinus or atrial fibrillation (AF) rhythm. The severity of COVID-19 was determined using the ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults.[13] This guideline classifies moderate and more severe illnesses as follows:

1. Moderate illness: patients with lower respiratory disease (including pneumonia) with oxygen saturation (O_2 sat) ≥ 94%

2. Severe illness: individuals suffering lower respiratory disease with a declined O_2 sat (<94%), partial arterial oxygen pressure to the fraction of inspired O2 (PaO_2/FiO_2 ratio) <300 mmHg, a respiratory rate >30 per minute, and pulmonary infiltrations involving at least one-half of the lung parenchymal tissue.

3. Critical illness: subjects with pneumonia, respiratory compromise warranting ventilation support, septic shock, and/or multiple target organ failure

The primary endpoint of the study was MACE, defined as a composite of cardiovascular mortality, stroke, hospitalization for decompensated heart failure, VTE, repeat revascularization by PCI or CABG, and nonfatal MI. The secondary endpoints encompassed all the components of MACE as separate outcomes, all-cause mortality, new-onset hypertension, readmission due to COVID-19, and impaired NYHA FC.

A follow-up duration of at least 6 months was ascertained for all the patients to show long-term CVD complications. Nonetheless, we expected to reach a median time of 12 months or more. The routine follow-up of the patients was performed through regular bimonthly phone interviews and online visits via visual applications. Outpatient visits in cardiology clinics were also considered for a minority of challenging cases. Medical records of readmission were also reviewed in the event of readmission. The follow-up was terminated if the patient died or was unavailable over 2 sessions.

The Ethics Committee of Tehran University of Medical Sciences approved the current research protocol (code: IR.TUMS.THC.REC.1400.055). The study also complied with the principles of the Declaration of Helsinki.

The Kolmogorov-Smirnov and Leven tests were employed to examine the normality of the distribution and equality of variances, respectively. Continuous variables were displayed as mean±standard deviation (SD) or median (with interquartile ranges or 25^{th} and 75^{th} percentiles) based on normal or skewed distributions, respectively. Categorical variables were expressed using percentages and crude numbers. The independent t and Mann-Whitney U tests were utilized to compare the differences regarding the continuous variables between 2 groups with and without normal distributions, respectively. The χ^2 test was applied to show differences in the comparison of multiple categorical variables between the groups. The Fisher exact test was considered for situations where the expected/observed count in 1 or more cells was less than 5. We assessed both univariate and multivariate relationships between baseline variables and adverse outcomes via Cox regression analysis. Univariate hazard ratios, which had a $P<0.3$, were entered into a stepwise backward conditional multivariate analysis. Moreover, the proportional hazards of MACE and secondary endpoints were illustrated using Kaplan-Meier graphs.

Statistical significance was ascertained with a $P<0.05$ in all tests. The statistical analyses were conducted via IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA).

Results

The present prospective cohort study evaluated 858 patients admitted with moderate and severe COVID-19. The median (interquartile range) follow-up duration was 13 months (11.5-15). The mean age of the participants was 55.52±13.97 years, and men comprised the majority of the population (63.9%, n=549). Table 1 presents the baseline characteristics of the participants according to their history of prior CVD. The results revealed that 72.4 % (n=621) of the participants were on statin treatment as either a new medication or continuing the previous use. The majority of the patients who received statins during index admission had a history of longstanding use before their COVID-19 infection. In other words, new-onset prescriptions of statins were recorded in 20.9% (n=180) of the participants. However, COVID-19 patients with and without prior CVD had a similar rate of new statin use. Statins were initiated in 27 subjects with prior CVD (out of 100) compared with 153 patients without prior CVD (out of 521). Thus, 27.1% vs 29.36% of the patients received statins as a new treatment, respectively (*P*=0.353). The rest of the participants on statins had received this medication before hospital admission. Among those who used statins, 74 patients in the CVD (+) group and 369 ones in the CVD (-) group consumed atorvastatin (74.2% vs 70.8%; *P*=0.315), and the others were on rosuvastatin.

Table 1. Baseline characteristics of the study participants according to previous CVD*

	History of CVD		*P*
	CVD (+) (n=149)	CVD (-) (n=709)	
Age	58.13±12.10	54.95±13.28	0.012
Sex			0.211
Female	31.5 (47)	37.0 (262)	
Cough	34.9 (52)	37.1 (263)	0.613
Dyspnea at presentation	33.6 (50)	40.2 (285)	0.131
Chest pain	83.2 (124)	80.8 (573)	0.495
Fever and chills	45.0 (67)	44.9 (318)	0.980
Prior lung disease (COPD/ILD)	14.1 (21)	9.4 (67)	0.089
Chronic kidney disease	11.4 (17)	5.8 (41)	0.013
DM	37.6 (56)	22.8 (162)	0.022
HTN	58.4 (87)	25.1 (178)	<0.0001
Prior stroke	1.3 (2)	0.4 (3)	0.180
Current tobacco smoker	10.7 (16)	10.2 (72)	0.831
Underlying malignancy	3.7 (4)	1.6 (8)	0.170
Chemotherapy	1.3 (2)	0.98 (7)	0.450
Corticosteroid treatment	18.1 (27)	23.7 (168)	0.140
Regular NSAID use	10.7 (16)	9.4 (67)	0.755
Statin (overall)	67.1 (100)	73.5 (521)	0.114
Moderate-intensity statins	48.9 (73)	51.3 (364)	0.256
High-intensity statins	10.7 (16)	11.6 (72)	0.554
Antiplatelet	38.3 (25)	34.8 (247)	0.428
Anticoagulant	6.0 (9)	5.2 (37)	0.686
ECG rhythm (sinus)	81.9 (122)	85.2 (604)	0.309
Ventilation support	14.8 (22)	10.7 (76)	0.158
BMI	28.88±5.04	28.64±4.67	0.576
SBP (mmHg)	126.14±15.79	125.52±15.65	0.658
DBP (mmHg)	74.24±11.57	75.82±10.98	0.113
Temperature	37.35±1.08	37.33±1.03	0.788
WBC (per µL)	7118±397	7111±378	0.991
Lymph percentage	15.92±3.98	14.12±2.94	0.145
Hemoglobin (g/dL)	14.17±1.93	14.24±1.76	0.696
Platelet (* 103 per µL)	200.73±8.39	198.32±8.41	0.760
CRP	29.70±3.16	25.92±2.80	0.161
ESR	44.48±12.4	43.31±11.53	0.617
Creatinine (mg/dL)	1.17±0.07	1.08±0.05	0.135
FBS (mg/dL)	103.33±33.48	96.88±22.43	0.672
LDH*	634 (515-741)	606 (498-767)	0.608
O2 saturation**	90 (88-93)	91 (87-94)	0.304
Respiratory rate**	18 (17-20)	18 (17-20)	0.072
Heart rate***	74 (70.75-88)	75 (67-90)	0.445
COVID symptoms duration (d)**	7 (3.75-9.25)	7 (5-10)	0.038
Hospital stay (d)**	7 (5-10)	6 (5-8)	0.014
Total follow-up duration (mon)**	13 (11-15)	13 (11.5-15)	0.140

*Continuous variables are expressed as mean±SD or medians (interquartile ranges), while categorical variables are shown using percentages (counts).
**These variables are expressed in medians (interquartile ranges).
MI, Myocardial infarction; AF, Atrial fibrillation; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ESR, Erythrocyte sedimentation rate; CRP,

C-reactive protein; BMI, Body mass index; WBC, White blood cells; DM, Diabetes mellitus; LDH, Lactate dehydrogenase; HTN, Hypertension; CHF, Congestive heart failure; COVID-19, Coronavirus disease 2019; FBS, Fasting blood sugar; COPD, Chronic obstructive pulmonary disease; ILD, Interstitial lung disease; CVD, Cardiovascular disease; NSAID, Non-steroidal anti-inflammatory drug

Table 2. Frequency of MACE and secondary outcomes among the study participants with respect to the baseline CVD history and treatment with statins*

	Statin Use		*P*	Prior CVD		*P*	Total
	No	Yes		CVD (-)	CVD (+)		
MACE	19.4 (46)	6.1 (38)	0.000	9 (64)	13.4 (20)	0.082	9.8 (84)
All-cause death	7.4 (19)	9.8 (59)	0.082	8.9 (63)	10.1 (15)	0.648	9.1 (78)
Cardiovascular death	0.8 (2)	1.1 (7)	0.135	1.3 (9)	2.0 (3)	0.507	1.4 (12)
Stroke	4.2 (10)	0.5 (3)	0.000	1.7 (12)	0.7 (1)	0.311	1.5 (13)
Revascularization	10.1 (24)	0.5 (3)	0.000	3.0 (21)	4.0 (6)	0.322	3.1 (27)
Decreased functional capacity (NYHA FC ≥II)	78.1 (185)	45.1 (280)	0.000	54.3 (385)	53.7 (80)	0.892	54.2 (465)
Nonfatal MI	4.2 (10)	2.6 (16)	0.209	3.0 (21)	3.4 (5)	0.799	3.0 (26)
Venous thromboembolism	3.4 (8)	0.8 (5)	0.006	1.1 (8)	3.4 (5)	0.034	1.5 (13)
Hospitalization for heart failure	8.0 (19)	0.6 (4)	0.000	2.8 (20)	2.0 (3)	0.413	2.7 (23)
Readmission for COVID-19	7.2 (17)	6.3 (39)	0.135	6.8 (48)	5.4 (8)	0.389	6.5 (56)
New-onset hypertension	7.6 (18)	3.9 (24)	0.024	5.1 (36)	4.0 (6)	0.589	4.9 (42)

*P values are expressed as 0.000 points to numbers <0.0001.
MI, Myocardial infarction; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification

Table 3. Univariate Cox regression, showing the predictors of MACE outcomes and all-cause mortality

Predictor	MACE HR (95% CI)	*P*	All-Cause Mortality HR (95% CI)	*P*
Age	0.998 (0.93-1.014)	0.822	1.020 (1.004-1.037)	0.015
BMI	1.008 (0.965-1.054)	0.712	0.991 (0.945-1.039)	0.710
Heart rate (per 1 unit increase)	0.987 (0.974-1.001)	0.071	0.999 (0.986-1.013)	0.932
Temperature	0.895 (0.726-1.105)	0.303	0.848 (0.681-1.057)	0.143
Respiratory rate	0.959 (0.898-1.023)	0.201	0.957 (0.895-1.023)	0.197
O2 SAT	1.017 (0.982-1.052)	0.353	0.966 (0.947-0.986)	0.001
Creatinine	1.142 (0.897-1.455)	0.281	1.142 (0.883-1.476)	0.312
ICU stay	1.074 (1.012-1.139)	0.019	1.131 (1.088-1.175)	0.000
COVID-19 symptoms duration (d)	0.995 (0.946-1.045)	0.827	1.008 (0.961-1.057)	0.753
Sex (male vs female)	1.105 (0.693-1.762)	0. 676	0.968 (0.837-1.121)	0.666
Cough (+ vs -)	1.001 (0.632-1.538)	0.998	0.960 (0.822-1.112)	0.582
Dyspnea (+ vs -)	0.754 (0.478-1.190)	0.226	1.070 (0.926-1.235)	0.359
HTN (+ vs -)	0.777 (0.488-1.238)	0.289	1.008 (0.865-1.173)	0.923
DM (+ vs -)	1.190 (0.707-2.003)	0.513	0.948 (0.808-1.113)	0.513
CVD (+ vs -)	1.598 (0.956-2.672)	0.074	1.157 (0.960-1.394)	0.126
MI (+ vs -)	2.626 (0.798-8.641)	0.112	1.362 (0.802-2.311)	0.253
CHF (+ vs -)	1.889 (0.451-7.915)	0.384	1.349 (0.672-2.709)	0.400
Stroke (+ vs -)	20.29 (0.01-267.7)	0.617	20.27 (0.120-65.400)	0.642
Previous lung disease (+ vs -)	1.354 (0.651-2.816)	0.417	1.401 (1.113-1.764)	0.004
CKD (+ vs -)	1.027 (0.322-3.277)	0.964	1.200 (0.907-1.587)	0.202
Cancer (+ vs -)	0.919 (0.286-2.950)	0.887	0.947 (0.521-1.721)	0.858
Smoking (+ vs -)	1.370 (0.588-3.194)	0.466	1.007 (0.799-1.270)	0.951
Hookah smoking (+ vs -)	1.496 (0.675-3.319)	0.321	0.781 (0.615-0.991)	0.042
Corticosteroids (+ vs -)	0.874 (0.491-1.555)	0.646	0.951 (0.803-1.125)	0.558
ECG rhythm (sinus vs AF)	1.217 (0.625-2.367)	0.563	0.960 (0.790-1.166)	0.680
Ventilation support (+ vs -)	2.102 (1.219-3.625)	0.008	4.121 (2.573-6.600)	0.000
Vaccination (+ vs -)	0.658 (0.401-1.079)	0.097	0.003 (0.01-0.033)	0.000
Vaccine doses	1.223 (0.955-1.567)	0 .110	1.101 (0.918-1.113)	0.825
Antiplatelets (+ vs -)	1.436 (0.918-2.245)	0.113	0.952 (0.823-1.101)	0.506
Anticoagulants (+ vs -)	3.272 (1.865-5.682)	0.000	0.759 (0.563-1.023)	0.071
Statins (+ vs -)	0.722 (0.466-0.994)	0.041	1.087 (0.933-1.267)	0.282

MI, Myocardial infarction; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification; MI, Myocardial infarction; AF, Atrial fibrillation; BMI, Body mass index; DM, Diabetes mellitus; HTN, Hypertension; CHF, Congestive heart failure; CKD, Chronic kidney disease; O2 SAT, Oxygen saturation at baseline

Table 4. Univariate and multivariate Cox regression, showing the impact of prior CVD on long-term cardiovascular outcomes after COVID-19

Outcomes HR (95% CI)	Previous CVD			
	Univariate	*P*	Multivariate	*P*
MACE[1]	1.598 (0.956- 2.672)	0.074	2.953 (1.393- 6.271)	0.005
All-cause mortality[2]	1.157 (0.960- 1.394)	0.126	1.170 (0.960- 1.412)	0.102
Cardiovascular mortality[3]	1.591 (0.431- 5.877)	0.486	1.519 (0.364- 6.341)	0.566
Stroke[4]	0.532 (0.069- 4.107)	0.545	0.421 (0.050- 3.533)	0.426
Revascularization[5]	1.701 (0.685 -4.225)	0.253	1.381 (0.502- 3.797)	0.532
Decreased functional capacity (NYHA FC ≥ II) [6]	1.160 (0.911 -1.476)	0.229	1.124 (0.880-1.436)	0.347
Nonfatal MI[7]	1.461 (0.548 -3.893)	0.448	1.156 (0. 710-3.342)	0.255
Venous thromboembolism[8]	3.726 (1.214 -11.439)	0.022	2.770 (0.957- 8.955)	0.051
Hospitalization for heart failure[9]	0.872 (0.258 -2.943)	0.825	0.690 (0.437-3.471)	0.453
Readmission for COVID-19 [10]	0.962 (0.455 -2.037)	0.920	0.672 (0.493- 2.335)	0.345
New-onset hypertension[11]	0.945 (0.398- 2.247)	0.898	0.569 (0.155- 2.084)	0.395

[1]Adjusted for heart rate, respiratory rate, ICU stay length, history of cancer, corticosteroids on admission, statin therapy, ventilation support, vaccination, number of vaccine doses, and treatment with anticoagulants and antiplatelets.
[2]Adjusted for initial body temperature, O2 saturation, ICU stay length, statin use, cough, anticoagulants, vaccination, ventilation support, and age.
[3]ICU stay length, vaccination, sex, DM, corticosteroids on admission, ventilation support, and respiratory rate
[4]Adjusted for sex, BMI, ECG rhythm, body temperature, O2 SAT, ventilation support, and use of statins, anticoagulants, and antiplatelets
[5]Adjusted for sex, BMI, DM, corticosteroid, O2 SAT, ventilation support, statins, chest pain, symptom duration, lung disease, smoking, and antiplatelet use
[6]Adjusted for sex, O2 SAT, antiplatelet, lung disease, age, CKD, RR, and vaccine
[7]Adjusted for sex, BMI, corticosteroid, O2 SAT, statin use, symptom duration, vaccine, and HTN
[8] Adjusted for statin use, ventilation support, symptom duration, vaccination, DM, and body temperature
[9]Adjusted for BMI, corticosteroid use, O2 SAT, statin, DM, age, cough, HTN, ECG rhythm, RR, and ICU stay
[10]Adjusted for sex, BMI, symptom duration, body temperature, cancer, RR, body temperature, ICU stay, and anticoagulant use
[11]Adjusted for age, sex, BMI, DM, cancer, hookah use, RR, creatinine, ICU stay, and anticoagulant use
MI, Myocardial infarction; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification; MI, Myocardial infarction; AF, Atrial fibrillation; BMI, Body mass index; DM, Diabetes mellitus; HTN, Hypertension; CHF, Congestive heart failure; CKD, Chronic kidney disease; O2 SAT, Oxygen saturation at baseline; ICU, Intensive care unit; RR, respiratory rate

Overall, 98 patients (11.4%) received ventilation support modalities. The total number of patients who had 1 or more components of MACE was 84 (9.8% of the subjects). Additionally, 78 cases of all-cause mortality (9.1% of the participants) were recorded. Twenty patients (2.3%) died during the index hospitalization or up to 1 month following admission. Table 2 demonstrates the distribution of primary and secondary outcomes based on a history of CVD and the statin use profile. Likewise, Table S1 (in supplements) provides the same proportions among subjects who were discharged alive and who survived the first COVID-19 course. Also shown are univariate (Table 3) and multivariate (Table 4) proportional hazard ratios using Cox regression analysis pertaining to MACE and all-cause mortality. Moreover, univariate and multivariable Cox regression models showing the effects of statin therapy on cardiovascular outcomes are presented in a separate table (Table S2 in supplements).

The following values concern the incidence of cardiovascular endpoints in vaccinated compared with unvaccinated subjects, respectively:

MACE: 9.5% vs 11.8% (*P*=0.0.74), all-cause mortality: 0.2% vs 32.1% (*P*<0.0001), cardiovascular mortality: 0.2% vs 6.2% (*P*<0.0001), nonfatal MI: 2.9% vs 3.9% (*P*=0.472), stroke: 1.8% vs 0.6% (*P*=0.229), revascularization: 3.2% vs 0.85% (*P*=0.006), and VTE: 1.5% vs 1.7% (*P*=0.870).

The prevalence of baseline CVD was higher among unvaccinated patients than vaccinated patients (23.0% vs 16.2%; *P*=0.034).

A multivariate Cox regression model showed the final predictors of in-hospital mortality. The corresponding hazard ratios (95% CI) with P values are as follows:

The baseline pulse rate: 1.089 (0.993-1.196; *P*=0.071), the hospital stay time: 1.032 (1.004-1.060; *P*=0.022), serum creatinine: 1.376 (0.957-1.978; *P*=0.085), ventilation support: 0.276 (0.079-0.962; *P*=0.043), and antiplatelets in the treatment regimen: 0.91 (0.843-0.978; *P*=0.034).

Kaplan-Meier graphs were used to depict the differential hazards of MACE and secondary endpoints in subjects with and without baseline CVD (Figure 1A-1F). Figure 2A-2F also illustrates the risk of similar events in cases with and without a statin regimen. Each figure contains 6 graphs representing the risks pertaining to MACE, all-cause mortality, stroke, revascularization, decreased functional capacity (NYHA FC ≥ II), and nonfatal MI. Figure 3 (in the supplementary files) depicts the proportional hazards of VTE, hospitalization for heart failure, and readmission owing to recurrent COVID-19.

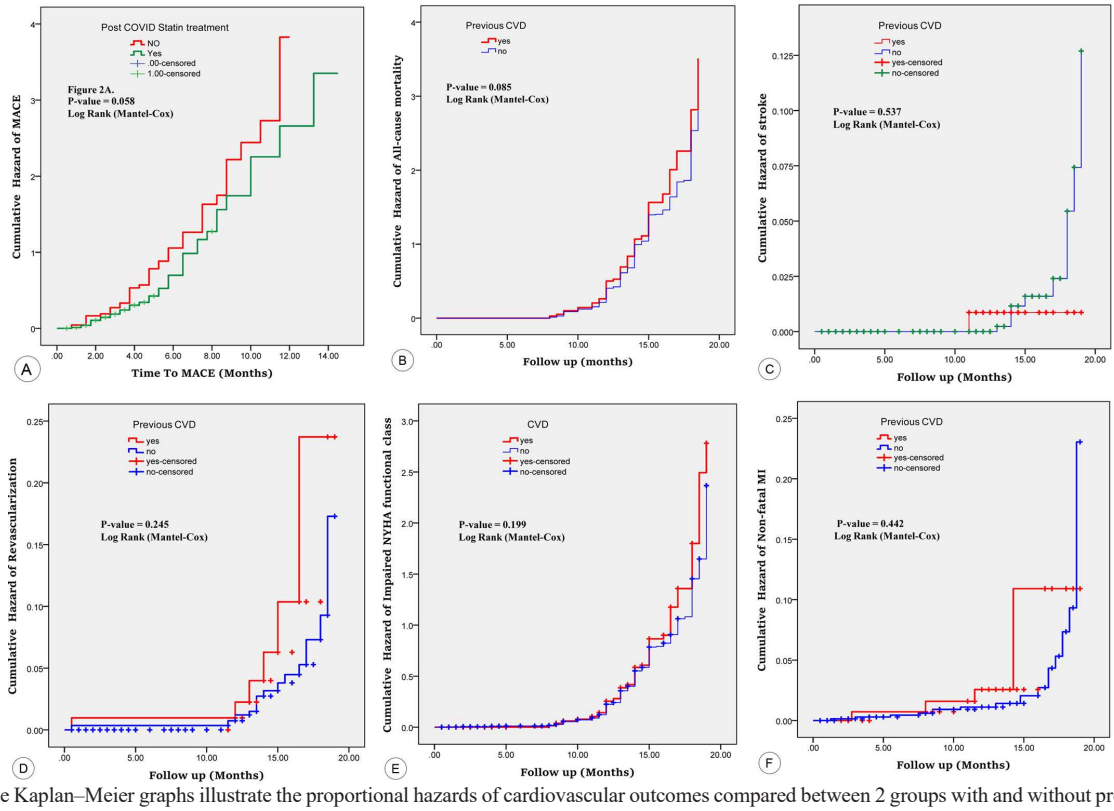

Figure 1. The Kaplan–Meier graphs illustrate the proportional hazards of cardiovascular outcomes compared between 2 groups with and without previous CVD. A) MACE, B) all-cause mortality, C) Stroke, D) Revascularization, E) Decreased functional capacity (NYHA FC ≥ II), and F) Nonfatal MI
CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification; MI, Myocardial infarction

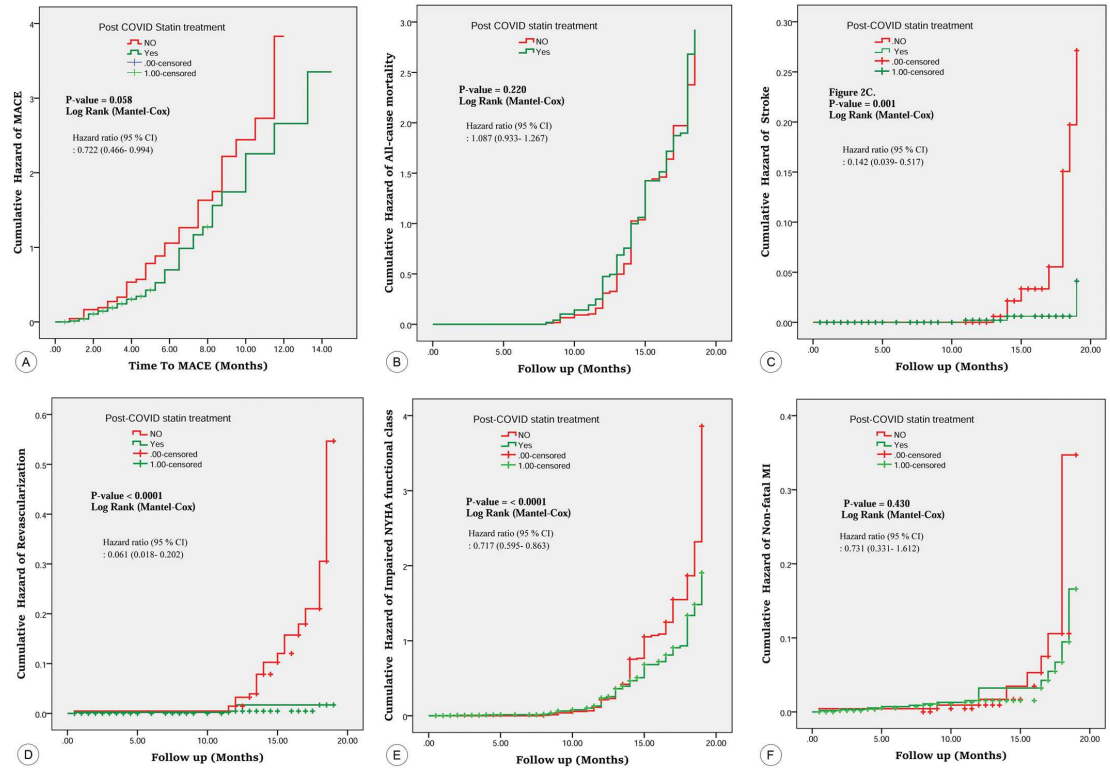

Figure 2. The Kaplan–Meier graphs show the cumulative hazard of cardiovascular outcomes compared between those with and without statin treatment after COVID-19. A) MACE, B) All-cause mortality, C) Stroke, D) Revascularization, E) Decreased functional capacity (NYHA FC ≥ II), and F) Nonfatal MI
MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification; MI, Myocardial infarction

Discussion

In the present study, we found that the incidence rate of MACE was strikingly high in patients with moderate and severe SARS-CoV-2 infection. Likewise, we also detected a substantial increase in other cardiovascular outcomes over a median of 13 months. In addition, a history of prior CVD was associated with the occurrence of MACE and VTE over a long-term follow-up after COVID-19 hospitalization. Furthermore, the risks related to MACE, stroke, revascularization, and readmission for heart failure decreased markedly in patients treated with statins after SARS-CoV-2 infection. Similarly, the use of statins may have a potential decreasing effect on VTE and impaired functional class; however, the statistical significance was not enough to confirm the hypothesis. Neither a history of CVD nor treatment with statins affected the long-term impact of hypertension and readmission due to COVID-19. We also observed that prior CVD and statin use could not predict in-hospital mortality of COVID-19 in a multivariate analysis. On the contrary, increased heart rate, the need for ventilation, and the use of antiplatelet agents were associated with hospital death.

In contrast to previous studies with a similar follow-up time, we observed higher incidence rates of cardiovascular events.[9, 10] Compared with a study by Wang et al,[10] we found high frequencies of MACE (9.8% vs 1.5%), all-cause mortality (9.1% vs 0.3 %), and readmission for heart failure (2.7% vs 0.8%). The incidence rates of stroke (1.5% vs 0.7%), nonfatal MI (3.1% vs 0.2%), and VTE (1.5% vs 0.5 %) were also higher in our results. In the aforementioned study (TriNet X US collaborative networks), MACE was determined as a composite of MI, stroke, dysrhythmias, and heart failure, encompassing fewer components than those incorporated in our definition. The baseline risk factors of atherosclerotic CVD were also less prevalent than those in the current study. Wang and colleagues had younger patients (mean age =43 vs 55 y), with lower frequencies of male sex, smoking, chronic kidney disease, diabetes mellitus, and hypertension. Furthermore, we enrolled SARS-CoV-2 patients with moderate and severe disease, whereas the TriNetX US collaborative networks registry enrolled all COVID-19 cases, including the majority of mild illnesses. We designed a prospective cohort, while the TriNetX study had a retrospective design. Moreover, we performed an active direct follow-up schedule with live visits, whereas Wang and colleagues only reviewed hospital records.

Xie et al[9] performed another comprehensive retrospective cohort, which confirmed the excess burden of all cardiovascular outcomes due to COVID-19 (compared with the control group) over 12 months of follow-up.[9] The incidence rates of MACE (6.8%) and MI (0.8%) were still lower than those in our investigation, whereas the proportions of heart failure (2.8%), VTE (1.6%), and stroke (1.6%) were similar. In their study, MACE was characterized as a constellation of all-cause mortality, stroke, and MI. Conversely, a recent study on 47 780 cases of COVID-19 demonstrated that all-cause mortality was as high as 12.3% (higher than our reported value), and MACE was 4.9%, which is lower than our observed incidence. Nonetheless, that study defined MACE as the summation of MI, stroke, heart failure, and new dysrhythmias. The mean follow-up was 140 days in the aforementioned investigation, and participants were older than our cases on average (66 vs 55 years).[14]

In-hospital (and 30-day) mortality rates were substantially higher in most previous reports than in our study.[15-17] The finding might reflect the variety of baseline risk profiles, including age, disease severity, and medical and intensive care facilities. Based on recent evidence, there is a consensus on the increased likelihood of cardiovascular events during the acute and subacute post-COVID-19 phase as well as in longer periods.[9, 10, 18, 19] Moreover, a few reports have raised concerns about cardiovascular complications, including early thrombotic events after vaccination, that could occur due to immunological mechanisms.[20] Nevertheless, recent large cohorts have proven the safety of COVID-19 vaccines by showing no excess risks of CVD, even among people with a history of CVD.[21] Furthermore, a study based on a Korean nationwide COVID-19 registry compared 62 727 unvaccinated subjects and 168 310 fully vaccinated cases using 2 doses of mRNA vaccines or viral vector vaccine against SARS-CoV-2.[22] During the 31 to 120 days following COVID-19, a composite diagnosis of acute MI and ischemic stroke was less likely (58.4%) in patients with complete vaccination.

In the current study, we found declines in the incidence of MACE (unadjusted), all-cause mortality, cardiovascular mortality, nonfatal MI, stroke, and VTE in vaccinated participants, which seems consistent with earlier reports. Still, MACE displayed a tendency toward meaning (limit), and the rate of revascularization increased unexpectedly in the vaccinated group. In contrast to most prior studies, we used only a non-RNA platform of vaccines. In addition, the unvaccinated group had a higher prevalence rate of CVD at baseline, whereas high-risk patients, including those with a history of established CVD are considered a priority group for COVID-19 vaccination.[23]

The concept that highlights the incremental effects of previous CVD and cardiovascular risk factors on the acute risk and severity of SARS-CoV-2 infection is well known.[6, 24] Nevertheless, a dearth of evidence concerning long-term cardiovascular outcomes limits the insights in this regard. Hence, the long-term implications of prior CVD after COVID-19 seem controversial. We examined the impact of established CVD on the future outcomes of COVID-19 patients and found that baseline CVD was an independent predictor of MACE and VTE. A long-term follow-up

in a large cohort, including 428 650 COVID-19 patients without pre-existing CVD and diabetes mellitus, showed no increase in MACE and thrombotic events.[18] Conversely, another study demonstrated that a negative history of CVD mitigated the risk of MACE after COVID-19 vaccination, although the difference was nonsignificant among those with prior CVD.[21] Multiple studies have declared that a history of CVD or cardiomyopathies is associated with an increased risk of MACE and mortality.[9,15] In a study by Xie et al,[9] using the United States Department of Veterans Affairs COVID-19 registry, both subgroups of CVD (+) and CVD (-) had elevated risks of MACE compared with the contemporary control group. However, the difference in hazard ratios was nonsignificant (1.53 [1.48-1.59] vs 1.34 [1.28-1.40]).

In the current investigation, the potential benefit of statin treatment for at least 2 weeks following SARS-CoV-2 infection was depicted. We found that statin therapy reduced the adjusted hazards of MACE, ischemic stroke, urgent revascularization, and hospitalization related to heart failure. To our knowledge, there are no studies yet to assess the long-term effects of statins on survival and cardiovascular complications after severe COVID-19. In the absence of evidence, it may be advisable to revisit a number of surveys assessing the short-term effects of statins on acute COVID-19. Debates also exist vis-à-vis the effectiveness of statins in the acute context of SARS-CoV-2 infection. A recent meta-analysis of 8 cohorts matched with 14 446 COVID-19 patients found the benefits of statins in reducing in-hospital mortality.[25] In contrast, a few studies have shown no change in mortality rates in COVID-19 patients receiving statins[26] A recent trial among Iranian COVID-19 patients admitted to the ICU (the INSPIRATION-S trial) failed to show benefits of using statins compared with placebo regarding mortality and thrombotic events.[27] A reverse-causal bias may occur, reflecting a higher underlying cardiovascular risk burden among those receiving statins than in controls. Accordingly, a worse prognosis might be observed among those under treatment. Statins inhibit the production of isoprenoids, the co-factorial components of small molecules GTP-ase, and interlayers in the top-down regulation of transcriptional inflammatory factors, including NF-κB. Statins modify the immune response by decreasing antigen presentation, altering adhesion, and reducing the migration of immune cells.[28] SARS-CoV-2 has been associated with increased thromboembolic events through the activation of the coagulation system, the progression of atherosclerosis, microvascular thrombosis formation, and plaque instability.[29] The enhancement of the underlying immune response to the cytokine storm contributed to Acute respiratory distress syndrome, multiple organ failure, and disseminated intravascular coagulation during the COVID-19 pandemic. Statins may exert advantageous effects by acting in these pathophysiologic pathways.[30]

The present study has several strengths as well as multiple limitations. To date, it has been the first prospective investigation performed on COVID-19 patients with severe and moderate disease over a long-term follow-up. Moreover, there are limited studies exploring extended long-term MACE outcomes and thrombotic events after COVID-19. In addition, this work is the first of its kind on a population in Iran, patients who have only received adenoviral (non-RNA) vector-based vaccines. However, there are also some noticeable caveats. Firstly, a non-randomized observation scheme with an uneven number of subjects in the study groups can prevent the causality statement and optimal sensitivity analyses. Secondly, we had considerable missing data regarding several lab tests, echocardiography reports, and medications used during index hospitalization, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, autoimmune disorders, and antiviral agents. There are also concerns regarding the potential adverse cardiovascular effects of such drugs as hydroxychloroquine, azithromycin, ritonavir-lopinavir, ribavirin, and corticosteroids. Since the evolution of the pandemic, paradigm shifts in the empirical treatment of SARSCoV-2 in acute settings have been remarkable. The development of various vaccines, new variants of the virus secondary to mutations or genetic alterations, dynamic healthcare-related policies, and so many other variables could have influenced the epidemiologic changes and risk profile of the participants. We were not able to control many of these factors and confounders. Thirdly, we did not evaluate the incidence of pericarditis and myocarditis because of insufficient echocardiographic data during follow-up and substantial missing records of troponin levels. We also did not define and detect probable cases of prolonged COVID-19 due to a lack of definite criteria.

Conclusion

We demonstrated that the long-term cardiovascular outcomes of COVID-19 were relatively frequent and noteworthy. A population of COVID-19 patients with moderate and severe disease require stringent follow-up and risk factor modification in order to improve cardiovascular prognosis. Prior CVD is a robust predictor of long-term MACE and VTE. Early treatment with statins might decrease 1-year MACE, ischemic stroke, revascularization, and readmission for heart failure.

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Supplementary Material

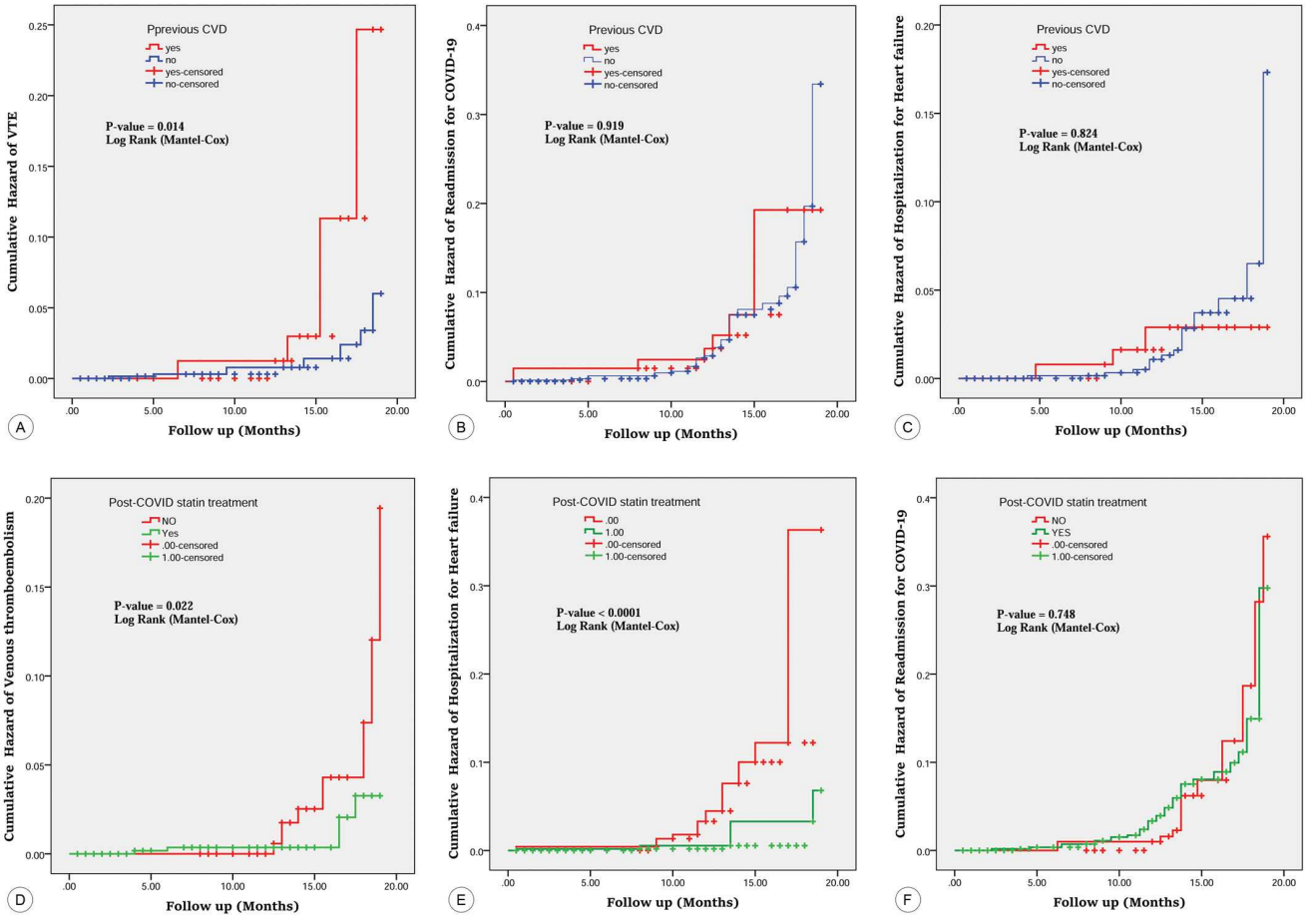

Figure 3S. (3A -3F). The Kaplan–Meier graphs show the cumulative hazard of cardiovascular outcomes.
Figures 3 A, 3B, and 3C refer to the risks of VTE, readmission for COVID-19, and hospitalization for heart failure, respectively. These montages (3A-C) compare the groups with and without prior CVD. Figures 3 D-F refers to the comparison between those with and without statin treatment.

Supplementary Material

Table S1. Univariate and multivariate Cox regression, showing the impact of statin treatment after COVID-19 on long-term cardiovascular outcomes

Outcomes HR (95% CI)	Treatment with Statins			
	Univariate	*P*	Multivariate	*P*
MACE[1]	0.722 (0.466-0.994)	0.041	0.831 (0.529-0.981)	0.044
All-cause mortality[2]	1.087 (0.933-1.267)	0.282	1.098 (0.935-1.294)	0.255
Cardiovascular mortality[3]	3.524 (0.192-6.46)	0.180	5.91 (0.108-15.46)	0.967
Stroke[4]	0.142 (0.039-0.517)	0.003	0.118 (0.029-0.48)	0.003
Revascularization[5]	0.061 (0.018-0.202)	0.000	0.103 (0.029-0.367)	<0.0001
Decreased functional capacity (NYHA FC ≥ II)[6]	0.717 (0.595- 0.863)	0.000	0.827(0.673-1.018)	0.073
Nonfatal MI[7]	0.731 (0.331- 1.612)	0.437	0.599 (0.257-1.394)	0.234
Venous thromboembolism[8]	0.293 (0.096 -0.898)	0.032	0.376 (0.119-1.190)	0.096
Hospitalization for heart failure[9]	0.102 (0.035 -0.300)	0.000	0.137 (0.040-0.472)	0.002
Readmission for COVID-19[10]	1.097 (0.620 -1.940)	0.750	NA	
New-onset hypertension[11]	0.630 (0.342 -1.162)	0.739	NA	

[1]The adjustments were made for heart rate, respiratory rate, ICU stay length, history of cancer, corticosteroids on admission, statin therapy, ventilation support, vaccination, number of vaccine doses, and treatment with anticoagulants and antiplatelets after COVID-19 infection.
[2]The adjustments were performed for initial body temperature, O2 saturation, ICU stay length, statin use, cough at presentation, treatment with anticoagulants, vaccination, ventilation support, and age.
[3]The adjustments were performed for age, DM, history of cancer, smoking, initial body temperature, RR, ICU stay length, and ventilation support.
[4]Adjusted for sex, ECG rhythm, ICU stay, anticoagulants, total hospital stay, chest pain, temperature, O2 SAT, and ventilation support
[5]Adjusted for total hospital stay, BMI, RR, symptom duration, chest pain, DM, prior CVD, lung disease, O2 SAT, ventilation support, sex, and antiplatelets
[6]Adjusted for sex, lung disease, O2 SAT, RR, and antiplatelets
[7]Adjusted for age, sex, BMI, HTN, anticoagulants, total hospital stay, cough, dyspnea, DM, CVD, lung disease, O2 SAT, ventilation support, and symptom duration.
[8]Adjusted for symptom duration, cough DM, CVD, temperature, ventilation support
[9]Adjusted for BMI, age, HTN, RR, ICU stay, total hospital stay, cough, dyspnea, DM, CVD, O2 SAT, ECG rhythm, and antiplatelets
[10]Adjusted for sex, BMI, symptom duration, body temperature, cancer, RR, body temperature, ICU stay, and anticoagulant use
[11]Adjusted for age, sex, BMI, DM, cancer, hookah use, RR, creatinine, ICU stay, and anticoagulant use
MI, Myocardial infarction; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification; AF, Atrial fibrillation; BMI, Body mass index; DM, Diabetes mellitus; HTN, Hypertension; CHF, Congestive heart failure; CKD, Chronic kidney disease; O2 SAT, Oxygen saturation at baseline; ICU, Intensive care unit; RR, respiratory rate

Table S2. Frequency of cardiovascular outcomes among patients who survived more than 30 days (discharged alive) with respect to baseline CVD history and treatment with statins*

	Statin Use		*P*	Prior CVD		*P*	Total
	No	Yes		CVD (-)	CVD (+)		
MACE	19.4 (46)	6.3 (38)	0.000	9.3 (64)	13.5 (20)	0.080	10.0 (84)
All-cause death	4.4 (11)	7.9 (47)	0.063	6.4 (44)	9.5 (14)	0.180	6.9 (58)
Cardiovascular death	0.83 (2)	1.33 (8)	0.076	1.3 (9)	2.0 (3)	0.423	1.4 (12)
Stroke	4.2 (10)	0.5 (3)	0.000	1.7 (12)	0.7 (1)	0.301	1.6 (13)
Revascularization	10.1 (24)	0.5 (3)	0.000	3.0 (21)	4.0 (6)	0.322	3.2 (27)
Decreased functional capacity (NYHA FC ≥ II)	78.1 (185)	46.4 (279)	0.000	54.1 (384)	53.7 (80)	0.723	55.4 (464)
Nonfatal MI	4.2 (10)	2.7 (16)	0.242	3.0 (21)	3.4 (5)	0.799	3.1 (26)
Venous thromboembolism	3.4 (8)	0.8 (5)	0.012	1.2 (8)	3.4 (5)	0.047	1.6 (13)
Hospitalization for heart failure	8.0 (19)	0.7 (4)	0.000	2.9 (20)	2.0 (3)	0.399	2.7 (23)
Readmission for COVID-19	7.2 (17)	6.5 (39)	0.078	7.0 (48)	5.4 (8)	0.310	6.7 (56)
New-onset hypertension	7.6 (18)	4.0 (24)	0.031	5.2 (36)	4.1 (6)	0.556	5.0 (42)

*P values are expressed as 0.000 points to numbers <0.0001.
MI, Myocardial infarction; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; MACE, Major adverse cardiovascular events; NYHA FC, New York Heart Association Functional Classification

Table S3. History of CVD and related conditions in patients with and without vaccination

	Vaccinated (n=665)	Unvaccinated (-) (n=193)	*P*
Prior stroke	0.6 (2)	0.51 (1)	0.180
Heart failure	3.6 (24)	2.07 (4)	0.651
Revascularization (PCI/CABG)	10.22 (68)	12.95 (25)	0.222
Myocardial infarction	6.16 (41)	4.14 (8)	0.821
Stable ischemic heart disease	10.67 (71)	15.02 (29)	0.071
Coronary artery disease (total)	16.84 (112)	19.17 (37)	0.358