Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

The association of statins use with survival of patients with COVID-19 ☆

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ABSTRACT

Background: Statins are frequently prescribed for patients with dyslipidemia and diabetes mellitus. These comorbidities are highly prevalent in coronavirus disease 2019 (COVID-19) patients. Statin's beneficial effect on mortality in COVID-19 infection has been reported in several studies. However, these findings are still inconclusive.

Methods: We conducted a retrospective observational study among 6,095 patients with laboratory confirmed COVID-19 hospitalized in Mount Sinai Health System between March 1st 2020 and May 7th 2020. Patients were stratified into two groups: statin use prior to or during hospitalization ($N = 2,423$) versus no statins ($N = 3,672$). We evaluated in-hospital mortality as a primary outcome using propensity score matching and inverse probability treatment weighted (IPTW) analysis. In additional analysis, we compared continuous use of statins ($N = 1,108$) with no statins, continuous use of statins with discontinuation of statins ($N = 644$), and discontinuation of statins with no statins.

Results: Among 6,095 COVID-19 patients, statin use prior to or during hospitalization group were older (70.8 ± 12.7 years versus 59.2 ± 18.2 years, $p<0.001$) and had more comorbidities compared to no statins group. After matching by propensity score (1,790 pairs), there were no significant differences in-hospital mortality between patients with statins and those without [28.9% versus 31.0%, $p = 0.19$, odds ratio (OR) 95% confidence interval (CI): 0.91 (0.79–1.05)]. This result was confirmed by IPTW analysis [OR (95% CI): 0.96 (0.81–1.12), $p = 0.53$]. In the additional analysis comparing continuous use of statins with no statins group, in-hospital mortality was significantly lower in continuous use of statins compared to no statins group [26.3% versus 34.5%, $p<0.001$, OR (95% CI): 0.68 (0.55–0.82)] after matching by propensity score (944 pairs), as well as IPTW analysis [OR (95% CI): 0.77 (0.64–0.94), $p = 0.009$]. Finally, comparison of continuous use of statins with discontinuation of statins showed lower in-hospital mortality in continuous use of statins group [27.9% versus 42.1%, $p<0.001$, OR (95% CI): 0.53 (0.41–0.68)].

Conclusions: Use of statins prior to or during hospitalization was not associated with a decreased risk of in-hospital mortality, however, continuous use of statins was associated with lower in-hospital mortality compared to no statin use and discontinuation of statins.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly leading to pneumonia and potentially to acute respiratory distress syndrome.

The most common comorbidities among COVID-19 patients are hypertension, diabetes mellitus, and coronary artery disease and many of these patients are treated with hydroxy–methyl-glutaryl-coenzyme A reductase inhibitors, known as statins. Statins are known to have anti-inflammatory and antithrombotic effects [1,2].

☆ This study was approved by the institutional review boards (#2000495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

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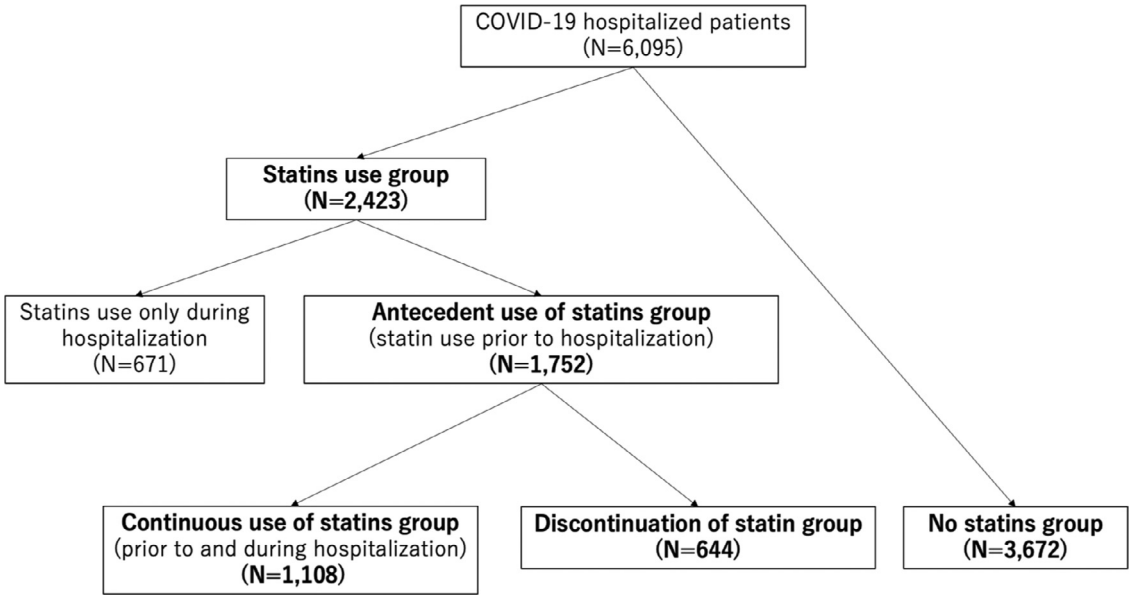

Fig. 1. Patient flowchart.

Table 1
Baseline characteristics of statin use group (either statin use prior to or during hospitalization) and no statins group.

	All hospitalizations			Propensity matched hospitalizations			
	No statinsN=3672n (%)	Statins use*N* = 2423n (%)	*p*-value	No statinsN=1790n (%)	Statins use*N* = 1790n (%)	*p*-value	SMD
Age, years (mean, SD)	59.2 (18.2)	70.8 (12.7)	<0.001	69.6 (13.8)	69.4 (12.8)	0.78	0.009
Male, n (%)	2035 (55.4)	1391 (57.4)	0.13	1035 (57.8)	1023 (57.2)	0.71	0.014
Race, n (%)			<0.001			0.85	0.039
White	792 (21.6)	611 (25.2)		424 (23.7)	437 (24.4)		
African American	890 (24.2)	631 (26.0)		497 (27.8)	494 (27.6)		
Hispanic	1034 (28.2)	637 (26.3)		442 (24.7)	456 (25.5)		
Asian	166 (4.5)	128 (5.3)		92 (5.1)	81 (4.5)		
Other	790 (21.5)	416 (17.2)		335 (18.7)	322 (18.0)		
Asthma, n (%)	158 (4.3)	146 (6.0)	0.003	79 (4.4)	94 (5.3)	0.28	0.039
COPD, n (%)	97 (2.6)	140 (5.8)	<0.001	74 (4.1)	92 (5.1)	0.18	0.048
Hypertension, n (%)	747 (20.4)	1269 (52.5)	<0.001	634 (35.4)	754 (42.1)	<0.001	0.14
Diabetes mellitus, n (%)	431 (11.7)	901 (37.2)	<0.001	369 (20.6)	485 (27.1)	<0.001	0.15
Chronic Kidney Disease, n (%)	192 (5.2)	487 (20.1)	<0.001	162 (9.1)	231 (12.9)	<0.001	0.12
Obstructive Sleep Apnea, n (%)	56 (1.5)	69 (2.9)	0.001	36 (2.0)	41 (2.3)	0.65	0.019
Obesity, n (%)	229 (6.2)	252 (10.4)	<0.001	135 (7.5)	152 (8.5)	0.33	0.035
HIV, n (%)	55 (1.5)	50 (2.1)	0.12	32 (1.8)	36 (2.0)	0.71	0.016
Cancer, n (%)	237 (6.5)	241 (10.0)	<0.001	149 (8.3)	163 (9.1)	0.44	0.028
Atrial fibrillation, n (%)	126 (3.5)	255 (10.6)	<0.001	109 (6.1)	125 (7.0)	0.31	0.036
Heart Failure, n (%)	99 (2.7)	309 (12.8)	<0.001	85 (4.7)	145 (8.1)	<0.001	0.137
Temperature, °C (mean, SD)	37.4 (0.7)	37.3 (0.6)	0.001	37.3 (0.6)	37.3 (0.6)	0.67	–
Heart Rate, /min (mean, SD)	97.6 (14.9)	96.2 (15.0)	<0.001	97.6 (15.0)	96.3 (14.8)	0.009	–
Respiratory Rate, /min (mean, SD)	22.5 (5.7)	22.8 (6.2)	0.049	23.1 (5.9)	22.8 (5.8)	0.087	–
SBP, mmHg (mean, SD)	135.6 (16.4)	142.2 (17.1)	<0.001	139.5 (16.5)	141.5 (16.8)	<0.001	–
DBP, mmHg (mean, SD)	79.5 (9.2)	79.4 (8.9)	0.75	79.9 (9.3)	79.5 (8.8)	0.28	–
O_2 Saturation,% (mean, SD)	92.4 (5.7)	91.7 (5.4)	<0.001	91.4 (6.8)	91.8 (4.9)	0.028	–
White blood cell, 10^3/μL (mean, SD)	8.89 (5.98)	8.86 (5.98)	0.82	9.02 (5.64)	8.84 (6.07)	0.36	–
Hemoglobin, g/dL (mean, SD)	13.3 (2.2)	12.6 (2.4)	<0.001	13.1 (2.3)	12.8 (2.3)	<0.001	–
Creatinine, mg/dL (median [IQR])	0.93 [0.73, 1.32]	1.23 [0.88, 2.10]	<0.001	1.89 [1.01, 3.91]	1.68 [0.94, 3.21]	0.002	–
CRP, mg/L (median [IQR])	114.0 [52.3, 202.6]	108.8 [51.6, 190.8]	0.097	129.0 [61.3, 220.6]	109.2 [51.6, 194.0]	<0.001	–
D-Dimer, μg/mL (median [IQR])	1.55 [0.80, 3.41]	1.79 [0.98, 3.48]	<0.001	1.94 [1.03, 4.00]	1.71 [0.95, 3.34]	0.001	–
Therapeutic anticoagulation	957 (26.1)	1011 (41.7)	<0.001	647 (36.1)	749 (41.8)	0.001	–
Steroid treatment	1056 (28.8)	834 (34.4)	<0.001	606 (33.9)	641 (35.8)	0.23	–

SD, standard deviation; SMD, standardized mean difference; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein.

Table 2
In-hospital outcomes for patients who used statins prior to or during hospitalization group versus no statins group, antecedent use of statins group versus no statins group, continuous use of statins group versus no statins group, discontinuation of statins group versus no statins group, and discontinuation of statins group versus continuation of statins group.

	All hospitalizations			Propensity matched hospitalizations		
	No statinsN=3672n (%)	Statins use*N* = 2423n (%)	*p*-value	No statinsN=1790n (%)	Statins use*N* = 1790n (%)	*p*-value
ICU admission, n (%)	642 (17.5)	480 (19.8)	0.024	356 (19.9)	385 (21.5)	0.25
Endotracheal intubation, n (%)	448 (12.2)	329 (13.6)	0.12	254 (14.2)	272 (15.2)	0.42
In-hospital death, n (%)	744 (20.3)	736 (30.4)	<0.001	555 (31.0)	518 (28.9)	0.19
	No statins N=3672 n (%)	Antecedent use of statins *N* = 1752 n (%)	*p*-value	No statins N=1329 n (%)	Antecedent use of statins *N* = 1329 n (%)	*p*-value
ICU admission, n (%)	642 (17.5)	284 (16.2)	0.26	256 (19.3)	225 (16.9)	0.13
Endotracheal intubation, n (%)	448 (12.2)	184 (10.5)	0.075	187 (14.1)	160 (12.0)	0.13
In-hospital death, n (%)	744 (20.3)	566 (32.3)	<0.001	442 (33.3)	418 (31.5)	0.34
	No statins N=3672 n (%)	Continuous use of statins *N* = 1108 n (%)	*p*-value	No statins N=944 n (%)	Continuous use of statins *N* = 944 n (%)	*p*-value
ICU admission, n (%)	642 (17.5)	185 (16.7)	0.57	196 (20.8)	154 (16.3)	0.015
Endotracheal intubation, n (%)	448 (12.2)	117 (10.6)	0.15	139 (14.7)	102 (10.8)	0.013
In-hospital death, n (%)	744 (20.3)	307 (27.7)	<0.001	326 (34.5)	248 (26.3)	<0.001
	No statins N=3672 n (%)	Discontinuation of statins *N* = 644 n (%)	*p*-value	No statins N=541 n (%)	Discontinuation of statins *N* = 541 n (%)	*p*-value
ICU admission, n (%)	642 (17.5)	99 (15.4)	0.21	90 (16.6)	96 (17.7)	0.69
Endotracheal intubation, n (%)	448 (12.2)	67 (10.4)	0.22	60 (11.1)	66 (12.2)	0.64
In-hospital death, n (%)	744 (20.3)	259 (40.2)	<0.001	183 (33.8)	227 (42.0)	0.007
	Discontinuation of statins N=644 n (%)	Continuation of statins *N* = 1108 n (%)	*p*-value	Discontinuation of statins N=541 n (%)	Continuation of statins *N* = 541 n (%)	*p*-value
ICU admission, n (%)	99 (15.4)	185 (16.7)	0.98	96 (17.7)	88 (16.3)	0.57
Endotracheal intubation, n (%)	67 (10.4)	117 (10.6)	0.98	67 (12.4)	57 (10.5)	0.39
In-hospital death, n (%)	259 (40.2)	307 (27.7)	<0.001	228 (42.1)	151 (27.9)	<0.001

ICU, intensive care unit.

Although the previous two randomized clinical trials failed to prove favorable effect of statins in acute respiratory distress syndrome patients [3,4], a report showed statins' ability to inhibit SARS-CoV-2 entry into host cells by directly binding the main protease of the coronavirus [5], led to the speculation of potential therapeutic benefits of statins in treatment of COVID-19. The study of nursing home residents reported the association of statin use with higher chance of asymptomatic infection, which also suggested the potential protective benefits of statins [6]. The effect of in-hospital use of statins by COVID-19 patients was reported to be favorable in preventing 28-day mortality in a retrospective study [7]. In several other retrospective studies, the benefits of antecedent use of statins before admission were equivocal [8–14]. Moreover, despite the favorable results of using statin on survival in recent meta-analyses, the studies exposures included in these meta-analyses were heterogenous: some studied the effect of antecedent use of statins while others studied in-hospital use of statins [15–17]. However, it remains unclear whether statin use during or prior to hospitalization or continuous use of statins from the period antecedent to hospital admission through hospitalization period is beneficial to COVID-19 patients. The aim of this study was to investigate the association between mortality of hospitalized COVID-19 patients and use of statins prior to admission or during admission. Moreover, we also aimed to investigate whether continuous use of statins before and during hospitalization was effective to decrease the mortality due to COVID-19.

Methods

In this study, 6095 hospitalized patients with laboratory confirmed COVID-19 were retrospectively analyzed using medical records at the Mount Sinai Health System in New York, USA, between March 1st 2020 and May 7th 2020 [18–27]. Identification of COVID-19 required a nasopharyngeal swab, which was tested using a polymerase chain reaction. Patients' demographics, comorbidities, and clinical outcomes were extracted from electronic medical records. Firstly, patients were stratified into two groups: patients who were prescribed statins anytime during the study period, either prior to admission or during admission (statin use group, $N = 2423$) and patients who were not receiving statins throughout the study period (no statins group, $N = 3672$) and compared these two groups. Types of statins included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rousvastatin, and simvastatin. Secondly, we also compared statin use prior to hospitalization regardless of continuation or discontinuation during hospitalization (antecedent use of statins group) ($N = 1752$) and no statins group ($N = 3672$). Additionally, we compared continuous use of statins (statin use prior to and during hospitalization) ($N = 1108$) and no statins group ($N = 3672$). Finally, we compared discontinuation of statins ($N = 644$) with continuous use of statins ($N = 1108$) and discontinuation of statins ($N = 644$) with no statin ($N = 3672$) (Fig. 1). Differences in baseline characteristics between groups were evaluated using analysis of variance for continuous variables and the χ^2 test for categorical variables. Continuous variables are presented as mean ± standard deviation or median [interquartile range] depending on what is appropriate for the data distribution, and categorical variables were expressed as percentages. All vital signs were recorded at time of admission. In-hospital mortality was assessed as a primary outcome.

We conducted propensity score matched analysis. The following variables were used to estimate propensity score: age, sex, race, asthma, chronic obstructive pulmonary disease, obstructive sleep

Table 3
Comparison of baseline characteristics of patients with antecedent use of statins with no statins group.

	All hospitalizations			Propensity matched hospitalizations			
	No statinsN=3672n (%)	Antecedent use of statins*N* = 1752n (%)	*p*-value	No statinsN=1329n (%)	Antecedent use of statins*N* = 1329n (%)	*p*-value	SMD
Age, years (mean, SD)	59.2 (18.2)	71.5 (12.5)	<0.001	71.1 (14.3)	70.7 (12.8)	0.45	0.029
Male, n (%)	2035 (55.4)	1004 (57.3)	0.20	756 (56.9)	749 (56.4)	0.81	0.011
Race, n (%)			<0.001			0.83	0.047
White	792 (21.6)	455 (26.0)		354 (26.6)	237 (17.8)		
African American	890 (24.2)	418 (23.9)		341 (25.7)	326 (24.5)		
Hispanic	1034 (28.2)	495 (28.3)		346 (26.0)	357 (26.9)		
Asian	166 (4.5)	96 (5.5)		51 (3.8)	61 (4.6)		
Other	790 (21.5)	288 (16.4)		237 (17.8)	231 (17.4)		
Asthma, n (%)	158 (4.3)	110 (6.3)	0.002	66 (5.0)	66 (5.0)	1.00	<0.001
COPD, n (%)	97 (2.6)	103 (5.9)	<0.001	70 (5.3)	73 (5.5)	0.86	0.01
Hypertension, n (%)	747 (20.4)	982 (56.1)	<0.001	563 (42.4)	621 (46.7)	0.026	0.088
Diabetes mellitus, n (%)	431 (11.7)	684 (39.1)	<0.001	329 (24.8)	395 (29.7)	0.005	0.112
Chronic Kidney Disease, n (%)	192 (5.2)	382 (21.8)	<0.001	152 (11.4)	203 (15.3)	0.004	0.11
Obstructive Sleep Apnea, n (%)	56 (1.5)	54 (3.1)	<0.001	34 (2.6)	28 (2.1)	0.521	0.03
Obesity, n (%)	229 (6.2)	187 (10.7)	<0.001	116 (8.7)	105 (7.9)	0.48	0.03
HIV, n (%)	55 (1.5)	39 (2.2)	0.07	26 (2.0)	30 (2.3)	0.69	0.021
Cancer, n (%)	237 (6.5)	187 (10.7)	<0.001	123 (9.3)	127 (9.6)	0.84	0.01
Atrial fibrillation, n (%)	126 (3.5)	187 (10.7)	<0.001	100 (7.5)	115 (8.7)	0.31	0.041
Heart Failure, n (%)	99 (2.7)	236 (13.5)	<0.001	82 (6.2)	132 (9.9)	<0.001	0.139
Temperature, °C (mean, SD)	37.4 (0.7)	37.3 (0.6)	0.037	37.3 (0.6)	37.3 (0.6)	0.031	–
Heart Rate, /min (mean, SD)	97.6 (14.9)	95.6 (15.4)	<0.001	97.3 (14.8)	95.9 (15.3)	0.023	–
Respiratory Rate, /min (mean, SD)	22.5 (5.7)	22.6 (6.4)	0.453	23.1 (5.8)	22.6 (5.9)	0.066	–
SBP, mmHg (mean, SD)	135.6 (16.4)	142.1 (17.4)	<0.001	139.9 (16.7)	141.4 (16.7)	0.024	–
DBP, mmHg (mean, SD)	79.5 (9.2)	79.2 (8.9)	0.335	79.8 (9.6)	79.4 (8.8)	0.90	–
O_2 Saturation,% (mean, SD)	92.4 (5.7)	91.6 (5.6)	<0.001	91.1 (6.3)	91.5 (5.4)	0.20	–
White blood cell, 10^3/μL (mean, SD)	8.9 (6.0)	8.7 (5.4)	0.24	9.0 (5.5)	8.7 (5.2)	0.17	–
Hemoglobin, g/dL (mean, SD)	13.3 (2.2)	12.5 (2.3)	<0.001	13.1 (2.3)	12.6 (2.3)	<0.001	–
Creatinine, mg/dL (median [IQR])	0.93 [0.73, 1.32]	1.25 [0.89, 2.15]	<0.001	1.10 [0.81, 1.72]	1.18 [0.85, 1.90]	0.004	–
CRP, mg/L (median [IQR])	114.0 [52.3, 202.6]	108.3 [52.2, 189.9]	0.22	128.3 [62.8, 225.8]	111.6 [52.9, 191.6]	<0.001	–
D-Dimer μg/mL (median [IQR])	1.55 [0.80, 3.41]	1.76 [0.98, 3.39]	0.001	2.01 [1.10, 3.94]	1.71 [0.95, 3.33]	<0.001	–
Therapeutic anticoagulation	957 (26.1)	647 (36.9)	<0.001	497 (37.4)	489 (36.8)	0.78	–
Steroid treatment	1056 (28.8)	553 (31.6)	0.037	476 (35.8)	436 (32.8)	0.11	–

SD, standard deviation; SMD, standardized mean difference; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; ICU, intensive care unit.

apnea, obesity, hypertension, diabetes mellitus, chronic kidney disease, human immunodeficiency virus, cancer, atrial fibrillation, and heart failure. We performed this analysis with and without multiple imputation for missing data. In addition, we also conducted inverse probability weighted (IPTW) analysis.

All statistical calculations and analyses were performed in R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) with packages of Matchit and Mice. Values of $p<0.05$ were considered statistically significant.

This study was approved by the institutional review boards (#2,000,495) and conducted in accordance with the principles of the Declaration of Helsinki. The waiver of patients' informed consent was also approved by the institutional review boards.

Results

Among 6095 COVID-19 patients, statin use group patients (39.8%, $N = 2423$) were older (70.8 ± 12.7 years versus 59.2 ± 18.2 years, $p<0.001$) and had more comorbidities including asthma, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, atrial fibrillation, and heart failure compared to no statins group (60.2%, $N = 3672$) (Table 1). Vital signs at admission and laboratory findings are also shown in Table 1. Notably, statins group had lower oxygen saturation (91.7 ± 5.4% versus 92.4 ± 5.7%, $p<0.001$) and higher D-dimer level [1.79 (0.98, 3.48) μg/mL versus 1.55 (0.80, 3.41) μg/mL, $p<0.001$) (Table 1). Crude in-hospital outcomes are shown in Table 2. In-hospital mortality was higher in the statins group than no statins group (30.4% versus 20.3%, $p<0.001$) (Table 2).

After propensity score matched analysis (1790 pairs), the baseline characteristics were comparable between the two groups (Table 1). There were no significant differences in-hospital mortality between patients with statins versus those without [28.9% versus 31.0%, $p = 0.19$, odds ratio (OR) 95% confidential interval (CI): 0.91 (0.79–1.05)] (Table 2). The analysis with multiple imputation showed a similar result [OR (95% CI): 0.94 (0.82–1.09), $p = 0.40$]. IPTW analysis showed that the statins group had similar in-hospital mortality compared to no statins group [OR (95% CI): 0.88 (0.76–1.02), $p = 0.08$].

Secondly, in the analysis of comparing antecedent use of statins group (statin use prior to hospitalization regardless of continuation or discontinuation of statins during hospitalization) ($N = 1752$) with no statins group ($N = 3672$) (Fig. 1), antecedent use of statins group was older and more likely to have comorbidities compared to no statins group (Table 3). Crude in-hospital outcomes are shown in Table 2. In-hospital mortality was higher in the antecedent statins group than no statins group (32.3% versus 20.3%, $p<0.001$) (Table 2). After propensity score matched analysis with well-balanced standardized mean differences <0.10 (1329 pairs) (Table 3), there was no significant difference in-hospital mortality [31.5% versus 33.3%, $p = 0.34$, OR (95% CI): 0.92 (0.78–1.08), $p = 0.58$) (Table 2) as well as multiple imputation [OR (95% CI):

Table 4
Baseline characteristics of patients from continuous use of statins group and from no statins group.

	All hospitalizations			Propensity matched hospitalizations			
	No statinsN=3672n (%)	Continuous use of statins*N* = 1108n (%)	*p*-value	No statinsN=944n (%)	Continuous use of statins*N* = 944n (%)	*p*-value	SMD
Age, years (mean, SD)	59.2 (18.2)	71.12 (12.3)	<0.001	71.2 (14.7)	70.4 (12.3)	0.17	0.063
Male, n (%)	2035 (55.4)	663 (59.8)	0.01	557 (59.0)	563 (59.6)	0.82	0.013
Race, n (%)			<0.001			0.72	0.066
White	792 (21.6)	294 (26.5)		259 (27.4)	246 (26.1)		
African American	890 (24.2)	265 (23.9)		247 (26.2)	237 (25.1)		
Hispanic	1034 (28.2)	316 (28.5)		248 (26.3)	256 (27.1)		
Asian	166 (4.5)	66 (6.0)		39 (4.1)	50 (5.3)		
Other	790 (21.5)	167 (15.1)		151 (16.0)	155 (16.4)		
Asthma, n (%)	158 (4.3)	67 (6.0)	0.021	53 (5.6)	53 (5.6)	1	<0.001
COPD, n (%)	97 (2.6)	62 (5.6)	<0.001	51 (5.4)	52 (5.5)	1	0.005
Hypertension, n (%)	747 (20.4)	627 (56.6)	<0.001	457 (48.4)	484 (51.3)	0.231	0.057
Diabetes mellitus, n (%)	431 (11.7)	445 (40.2)	<0.001	284 (30.1)	327 (34.6)	0.039	0.097
Chronic Kidney Disease, n (%)	192 (5.2)	274 (24.7)	<0.001	138 (14.6)	181 (19.2)	0.01	0.12
Obstructive Sleep Apnea, n (%)	56 (1.5)	33 (3.0)	0.003	28 (3.0)	25 (2.6)	0.78	0.019
Obesity, n (%)	229 (6.2)	114 (10.3)	<0.001	90 (9.5)	89 (9.4)	1.00	0.004
HIV, n (%)	55 (1.5)	20 (1.8)	0.562	18 (1.9)	19 (2.0)	1.00	0.008
Cancer, n (%)	237 (6.5)	117 (10.6)	<0.001	98 (10.4)	96 (10.2)	0.94	0.007
Atrial fibrillation, n (%)	126 (3.5)	128 (11.6)	<0.001	82 (8.7)	92 (9.7)	0.47	0.037
Heart Failure, n (%)	58 (1.8)	142 (12.9)	<0.001	78 (8.3)	111 (11.8)	0.014	0.12
Temperature, °C (mean, SD)	37.4 (0.7)	37.3 (0.5)	0.109	37.3 (0.60)	37.3 (0.5)	0.04	–
Heart Rate, /min (mean, SD)	97.6 (14.9)	94.4 (14.6)	<0.001	97.6 (15.1)	94.6 (14.6)	<0.001	–
Respiratory Rate, /min (mean, SD)	22.5 (5.7)	22.2 (5.4)	0.088	23.1 (5.4)	22.2 (5.5)	<0.001	–
SBP, mmHg (mean, SD)	135.6 (16.4)	142.9 (16.4)	<0.001	139.5 (17.0)	142.8 (16.1)	<0.001	–
DBP, mmHg (mean, SD)	79.5 (9.2)	79.4 (8.5)	0.664	79.6 (9.3)	79.6 (8.5)	0.86	–
O_2 Saturation,% (mean, SD)	92.4 (5.7)	91.9 (4.6)	0.005	91.2 (6.1)	91.8 (4.6)	0.014	–
White blood cell, 10^3/μL (mean, SD)	8.9 (6.0)	8.5 (5.2)	0.039	9.1 (5.6)	8.5 (5.4)	0.01	–
Hemoglobin, g/dL (mean, SD)	13.3 (2.2)	12.4 (2.3)	<0.001	13.0 (2.3)	12.5 (2.3)	<0.001	–
Creatinine, mg/dL (median [IQR])	0.93 [0.73, 1.32]	1.23 [0.88, 2.18]	<0.001	1.15 [0.86, 1.89]	1.17 [0.86, 1.88]	0.48	–
CRP, mg/L (median [IQR])	114.0 [52.3, 202.6]	102.1 [46.8, 182.3]	0.003	129.9 [59.5, 222.4]	100.9 [46.3, 177.2]	<0.001	–
D-Dimer μg/mL (median [IQR])	1.55 [0.80, 3.41]	1.72 [0.94, 3.24]	0.073	1.97 [1.06, 4.00]	1.65 [0.92, 3.02]	<0.001	–
Therapeutic anticoagulation	957 (26.1)	478 (43.1)	<0.001	380 (40.3)	388 (41.1)	0.74	–
Steroid treatment	1056 (28.8)	385 (34.7)	<0.001	341 (36.1)	329 (34.9)	0.60	–

SD, standard deviation; SMD, standardized mean difference; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein.

0.95 (0.80–1.14)]. IPTW analysis showed a similar result [OR (95% CI): 0.96 (0.81–1.12), $p = 0.53$].

In the analysis comparing continuous use of statins (statins use prior to and during hospitalization) ($N = 1108$) versus no statins group ($N = 3672$) (Fig. 1), continuous use of statins group was older and more likely to have comorbidities compared to no statins group (Table 4). Crude in-hospital outcomes are shown in Table 2. In-hospital mortality was higher in continuous use of statins group than no statins group (27.7% versus 20.3%, $p<0.001$) (Table 2). In the propensity score matched 944 pairs (Table 4), in-hospital mortality was significantly lower in continuous statins use compared to no statins group [26.3% versus 34.5%, $p<0.001$, OR (95% CI): 0.68 (0.55–0.82)] (Table 2). Multiple imputation showed similar results [0.75 (0.61–0.93), $p = 0.007$]. After adjustment with IPTW, continuous use of statins was also associated with decreased risk of in-hospital mortality [OR (95% CI): 0.77 (0.64–0.94), $p = 0.009$].

Furthermore, patients in the continuous use of statins group had more comorbidities such as chronic kidney disease and heart failure than patients in the discontinuous use of statins group (Online Table 1). In-hospital mortality was significantly lower in the continuous statins use group compared to the discontinuation of statins group (27.7% versus 40.2%, $p<0.001$). In the propensity score-matched 541 pairs (Online Table 1), in-hospital mortality was significantly lower in continuous use of statins group compared to discontinuation of statins group [27.9% versus 42.1%, $p<0.001$, OR (95% CI): 0.53 (0.41–0.68)]. Similar results were obtained with IPTW adjustment [OR (95% CI): 0.54 (0.43–0.67)]. Patients who discontinued use of statins had more comorbidities and had significantly higher in-hospital mortality in propensity matching analysis [42.0% vs. 33.8%, $p = 0.007$, OR (95% CI): 1.41(1.11–1.81)] as well as in IPTW analysis [OR (95% CI): 1.61 (1.28–2.02)] compared to patients in the no statins group (Online Table 2).

Discussion

In this study, almost 40% of patients were prescribed statins prior to or during the admissions due to COVID-19 infection and patients with antecedent use of statins were older and had more cardiovascular comorbidities, in line with previous studies [11,13,14]. The most important findings in our study are: 1) use of statins anytime either prior to or during hospitalization was not associated with lower in-hospital mortality compared to patients who did not receive statins; 2) statin use prior to admission alone did not demonstrate survival benefit compared to patients who were never on statins, however; 3) patients with continuous use of statins showed lower in-hospital mortality compared to patients who were never treated with statins; 4) among patients who were receiving statins prior to hospitalization, discontinuation of statins was associated with higher in-hospital mortality compared to continuous use of statins.

In a previous report, in-hospital use of statins were associated with 28-day mortality benefit in various models of statistical analyses, in which whether statins were antecedently prescribed was not clarified among the cohort [7]. Some studies examined the effect of antecedent use of statins to COVID-19 showed in-hospital mortality benefit with no difference in secondary outcomes such as intensive care unit admission rate, mechanical ventilation rate, length of stay [11,13,14], while other studies showed no significant difference in mortality [8-10,12]. In these studies, continuous use of statins during hospitalization was not clearly mentioned or investigated. The protective role of antecedent use of statins to prevent the occurrence of critically ill COVID-19 infection is still questionable given the result from previous reports, however.

We demonstrated that continuous use of statins (before and during hospitalization) was beneficial compared to the no statins and discontinuation of statins for patients with COVID-19. Interestingly, in-hospital mortality was even worse in the statins discontinuation group than in the no statins group. This effect can be attributable to statin rebound that leads to vascular dysfunction. This effect previously was described in animal studies [28]. This result further strengthens the fact that discontinuation of statins is harmful to COVID-19 patients.

SARS-CoV-2 virus is known to cause significant effects on the expression and function of angiotensin-converting-enzyme inhibitor-2 in the vasculature and evidence of coronary endothelial dysfunction and endotheliitis in the postmortem analysis [29,30]. Statins are experimentally known to have protective effects on vascular endothelium function such as mitigating unfavorable outcomes caused by reduced nitric oxide in endothelium by inducing endothelial nitric oxide synthase [31,32] as well as immune-modulatory effects by inhibiting the expression of adhesion molecules between immune cells and the blood vessel wall and reducing immune cell investment within the blood vessel wall [33–35]. These protective effects of statins may explain these clinically favorable effects of statins in COVID-19 infection. The current study could suggest that statins should be prescribed to patients with cardiovascular comorbidities for primary prevention as described in guidelines not to mention for secondary prevention of cardiovascular and cerebrovascular diseases. During hospitalization due to COVID-19 infection, statins should be continued as much as tolerable unless there are contraindications.

Our study is not without limitations. Since this is an observational study, we could not adjust for unobserved confounders such as the severity of illness that may affect the ability to continue statins in patients with severe disease. The effect of severity of the illness on the decision to continue or discontinue statins could be considerable [36]. Medication adherence before hospitalization was not taken into account in the study. Prior history of coronary artery disease and cerebrovascular disease were not included as covariates.

Conclusion

Use of statins prior to or during hospitalization was not associated with a decreased risk of in-hospital mortality, however, continuous use of statins might have potential benefit of a decreased risk of in-hospital mortality due to COVID-19.

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None

Author contributions

All authors, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Supplementary materials

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