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CLINICAL RESEARCH STUDY

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Statin Use in Hospitalized Patients with COVID-19: A Comprehensive Analysis of the New York City Public Hospital System

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ABSTRACT

INTRODUCTION: Statins have been commonly used for primary and secondary cardiovascular prevention. We hypothesized that statins may improve in-hospital outcomes for hospitalized patients with Coronavirus disease 2019 (COVID-19) due to its known anti-inflammatory effects.

METHODS: We conducted a retrospective study at the largest municipal health care system in the United States, including adult patients who were hospitalized for COVID-19 between March 1 and December 1, 2020. The primary endpoint was in-hospital death. Propensity score matching was conducted to balance possible confounding variables between patients receiving statins during hospitalization (statin group) and those not receiving statins (non-statin group). Multivariate logistic regression was used to evaluate the association of statin use and other variables with in-hospital outcomes.

RESULTS: There were 8897 patients eligible for study enrollment, with 3359 patients in the statin group and 5538 patients in the non-statin group. After propensity score matching, both the statin and non-statin groups included 2817 patients. Multivariate logistic regression analysis showed that the statin group had a significantly lower risk of in-hospital mortality (odds ratio 0.71; 95% confidence interval, 0.63-0.80; $P < .001$) and mechanical ventilation (OR 0.80; 95% confidence interval, 0.71-0.90; $P < .001$) compared with the non-statin group.

CONCLUSION: Statin use was associated with lower likelihood of in-hospital mortality and invasive mechanical ventilation in hospitalized patients with COVID-19.

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KEYWORDS: COVID-19; In-hospital mortality; Mechanical ventilation; Statin

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has placed a significant strain on health care systems around the world, with more than 230 million cases and 4.5 million deaths to date.[1] The United States, and particularly, New York City, have been severely affected, particularly during the spring of 2020.[2,3]

The causal agent for COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades the host's cells via the angiotensin-converting enzyme 2 (ACE2) receptor.[4] This receptor is expressed in the cells of many organs, including endothelial cells of blood vessels. Direct endothelial cell viral infection leads to recruitment of immune cells, causing widespread microvascular dysfunction.[5]

Cardiovascular disease is commonly present in patients with COVID-19.[6] Statins, or 3-hydroxy-3-methylglutaryl

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coenzyme A (HMG-CoA) inhibitors, have been used for primary and secondary prevention of atherosclerotic disease by lowering low-density lipoprotein.[7] Several studies have also proposed that the anti-inflammatory role of statins can suppress inflammatory cell infiltration and reduce inflammatory markers in addition to their lipid-lowering effect.[8] It is unknown whether this anti-inflammatory effect of statin therapy can have therapeutic effects in clinical entities other than cardiovascular disease such as infections or inflammatory diseases. In prior studies, the use of statins has been proven to reduce mortality in patients with seasonal influenza and was proposed as a treatment for the Middle Eastern Respiratory Syndrome infection.[9,10] As such, our study aims to evaluate whether statin use is associated with improved in-hospital outcomes in hospitalized patients with moderate-to-severe COVID-19.

CLINICAL SIGNIFICANCE

- The use of statins was independently associated with a significantly lower risk of in-hospital mortality and mechanical ventilation in patients hospitalized with COVID-19 infection in our hospital system.
- Statin use still had a significant association with reduced in-hospital mortality and mechanical ventilation after the COVID-19 patient surge period.
- In patients admitted to the intensive care unit, statin use was also associated with a lower rate of in-hospital mortality.

MATERIAL AND METHODS

Study Design and Patient Population

We conducted a retrospective observational cohort study at New York City Health + Hospitals, the largest municipal health care system in the United States, serving more than one million residents within the New York City metropolitan area. We included adult patients who tested positive for SARS-CoV-2 via polymerase chain reaction assays of nasopharyngeal specimens and who were hospitalized in one of the 11 acute care hospitals within the New York City Health + Hospitals system during the study period (March 1 through December 1, 2020).

All patients were classified into 2 groups: the statin group and the non-statin group. The statin group included patients who received at least one of the US Food and Drug Administration-approved statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) during their hospitalizations. The non-statin group included those patients who did not receive any statins during their hospitalizations. Patients were excluded if they remained hospitalized at the end of the study period or there was missing information about body mass index.

Baseline characteristics including age, sex, history of hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation, stroke/transient ischemic attack, pulmonary hypertension, chronic obstructive pulmonary disease, and asthma were collected. Medications that were commonly used in patients with COVID-19 or were proposed as possibly having a therapeutic effect on COVID-19 by prior studies (hydroxychloroquine,[11] remdesivir,[12] glucocorticoid,[13] ceftriaxone,[14] azithromycin,[14] piperacillin-tazobactam,[15] vancomycin,[15] cefepime,[15] angiotensin-converting enzyme inhibitors [ACEi],[16] angiotensin receptor blockers [ARB],[16] angiotensin receptor–neprilysin inhibitor [ARNi],[16] tocilizumab[17]) were also collected as possible confounding variables. Patients were selected based on eligibility criteria, and patient data were retrieved from our electronic medical record system.

The study was approved by the Biomedical Research Alliance of New York (BRANY) Institutional Review Board (IRB number 20-12-228-373). Informed consent was waived based on the retrospective nature of our study carrying minimal risks to the study population.

Study Outcomes and Statistical Analysis

The primary outcome of the study was in-hospital mortality. The secondary outcomes included intensive care unit (ICU) admission and need for invasive mechanical ventilation. Continuous variables were described as mean ± standard deviation. Categorical variables were reported as absolute numbers and percentages. The standardized mean difference (SMD) was calculated to assess the difference between the 2 groups. Propensity score matching using nearest neighbor matching with a caliper of 0.1 standard deviations of the logit of the propensity scores was conducted to improve the comparability between the 2 groups. The baseline characteristics were incorporated into the propensity score matching model.

The following sociodemographic, clinical, and therapeutic variables were included in our analyses. Age and sex have been proven to be significant sociodemographic risk factors for severe COVID-19 infection.[18] Hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, and stroke/transient ischemic attack were associated with the severity of COVID-19 infection, as demonstrated by prior studies.[18-30] Medications that were considered as possible confounders included: antibiotics for empiric treatment of possible superimposed bacterial infection in patients hospitalized with COVID-19 (ceftriaxone, azithromycin, piperacillin-tazobactam, vancomycin, cefepime) or medications (hydroxychloroquine, remdesivir, glucocorticoid, tocilizumab) that were proposed to affect in-hospital outcomes of COVID-19. One-to-one ratio matching was adopted based on sample size. An SMD <0.1 is considered well matched between the 2 groups. Univariate logistic regression was performed individually for each study outcome: in-hospital mortality, ICU admission, and mechanical ventilation. Those variables with P value < .1 in the univariate analyses

Table 1 Baseline Demographic and Clinical Comorbidities Between Statin Group and Non-Statin Group

	Unmatched			Matched		
	Statin Group	Non-Statin Group	SMD	Statin Group	Non-Statin Group	SMD
Number of patients	3359	5538		2817	2817	
Age, years: mean (SD)	67.39 (12.95)	59.97 (17.06)	0.490	66.50 (13.08)	67.76 (14.65)	0.091
Male sex (%)	2017 (60.0)	3446 (62.2)	0.045	1694 (60.1)	1718 (61.0)	0.017
Hypertension (%)	1235 (36.8)	1036 (18.7)	0.412	868 (30.8)	840 (29.8)	0.022
Diabetes mellitus (%)	1066 (31.7)	809 (14.6)	0.415	734 (26.1)	682 (24.2)	0.043
Obesity (%)	1264 (37.6)	2109 (38.1)	0.009	1053 (37.4)	1020 (36.2)	0.024
Coronary artery disease (%)	317 (9.4)	131 (2.4)	0.304	183 (6.5)	126 (4.5)	0.089
Heart failure (%)	361 (10.7)	208 (3.8)	0.272	229 (8.1)	190 (6.7)	0.053
Atrial fibrillation (%)	216 (6.4)	151 (2.7)	0.178	147 (5.2)	125 (4.4)	0.036
Asthma (%)	159 (4.7)	225 (4.1)	0.033	135 (4.8)	130 (4.6)	0.008
Chronic obstructive pulmonary disease (%)	164 (4.9)	139 (2.5)	0.126	110 (3.9)	114 (4.0)	0.007
Pulmonary hypertension (%)	26 (0.8)	22 (0.4)	0.049	19 (0.7)	16 (0.6)	0.014
Stroke/transient ischemic attack (%)	260 (7.7)	108 (2.0)	0.272	128 (4.5)	101 (3.6)	0.049
Hydroxychloroquine (%)	1877 (55.9)	3399 (61.4)	0.112	1661 (59.0)	1706 (60.6)	0.033
Azithromycin (%)	2135 (63.6)	4056 (73.2)	0.209	1890 (67.1)	1930 (68.5)	0.030
Ceftriaxone (%)	1951 (58.1)	3608 (65.1)	0.146	1718 (61.0)	1780 (63.2)	0.045
Piperacillin-tazobactam (%)	698 (20.8)	1154 (20.8)	0.001	597 (21.2)	593 (21.1)	0.003
Cefepime (%)	581 (17.3)	844 (15.2)	0.056	472 (16.8)	491 (17.4)	0.018
Vancomycin (%)	1009 (30.0)	1589 (28.7)	0.030	848 (30.1)	856 (30.4)	0.006
Remdesivir (%)	162 (4.8)	271 (4.9)	0.003	135 (4.8)	127 (4.5)	0.013
ACEi/ARB/ARNi (%)	955 (28.4)	607 (11.0)	0.450	626 (22.2)	572 (20.3)	0.047
Tocilizumab (%)	212 (6.3)	316 (5.7)	0.025	184 (6.5)	182 (6.5)	0.003
Glucocorticoid (%)	728 (21.7)	946 (17.1)	0.116	615 (21.8)	626 (22.2)	0.009

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; SMD = standardized mean difference.

were incorporated into the multivariate logistic regression model. The threshold of statistical significance was $P < .05$. All analyses were conducted using R 3.6.3 version (RStudio software, RStudio, Boston, Mass).

RESULTS

A total of 8897 patients were eligible for study enrollment after excluding 160 patients who had not been discharged at the end of the study period, 60 patients who were not admitted to our acute care hospitals, and 1682 that did not have available body mass index. There were 3359 patients found to be in the statin group and 5538 patients in the non-statin group. After propensity score matching, both the statin and non-statin groups contained 2817 patients, with mean age around 67 years, 67% of whom were male. Hypertension, obesity, and diabetes mellitus were the 3 most common comorbidities. The matched cohorts were balanced for age, sex, comorbidities including hypertension, diabetes, obesity, coronary artery disease, heart failure, atrial fibrillation, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, stroke/transient ischemic attack, and prescriptions of other medications with SMD <0.10 (Table 1).

Characteristics of the Study Population

A total of 80.4% (7152 of 8897) of our patients were admitted between March and April when New York City was the epicenter of COVID-19. Of these patients, a total 64.1% (4587 of 7152) of the patients who were admitted between March and April were not given a statin (Figure 1). Across all the acute care hospitals located in different geographic areas of New York City, statin use was variable between different institutions (Figure 2).

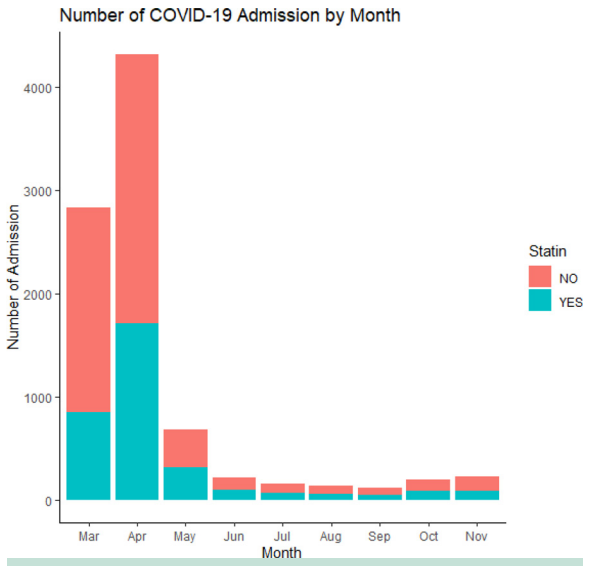

Figure 1 Number of COVID-19 admissions by month.

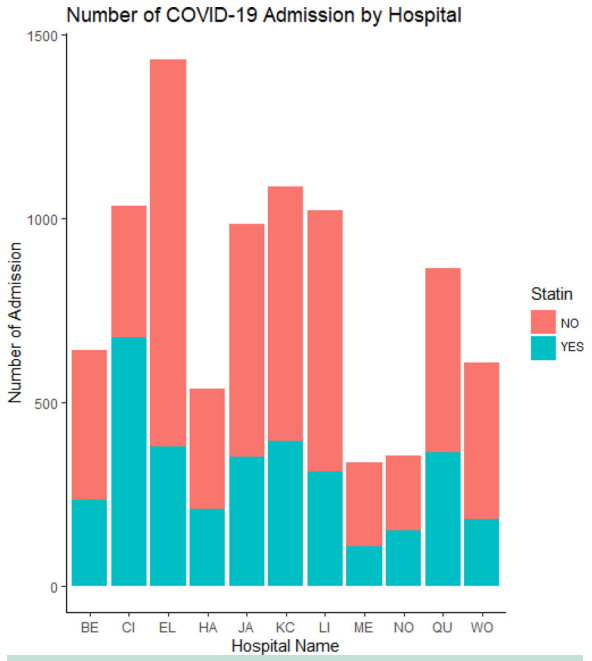

Figure 2 Number of COVID-19 admissions by hospitals.
BE = NYC Health + Hospitals/Bellevue; CI = NYC Health + Hospitals/Coney Island; EL = NYC Health + Hospitals/Elmhurst; HA = NYC Health + Hospitals/Harlem; JA = NYC Health + Hospitals/Jacobi; KC = NYC Health + Hospitals/Kings County; LI = NYC Health + Hospitals/Lincoln; ME = NYC Health + Hospitals/Metropolitan; NO = NYC Health + Hospitals/North Central Bronx; QU = NYC Health + Hospitals/Queens; WO = NYC Health + Hospitals/Woodhull.

Primary Outcome: In-Hospital Mortality

A total of 29.0% (817 of 2817) of patients in the statin group and 37.1% (1045 of 2817) patients in the non-statin group died during hospitalization of COVID-19. Multivariate logistic regression analysis showed that the statin use was associated with a significantly lower likelihood for in-hospital death compared with the non-statin group (odds ratio [OR] 0.71; 95% confidence interval [CI], 0.63-0.80; $P < .001$]. In addition, increasing age and coronary artery disease were significant risk factors for in-hospital mortality.

We noticed that the univariate and multivariate logistic regression analysis suggested that hypertension was a protective factor against in-hospital mortality, but a significant interaction between hypertension and ACEi/ARB/ARNi use ($P = .03$) existed. After adding the interaction variables of hypertension and ACEi/ARB/ARNi use in the multivariate logistic regression model, hypertension was no longer a significant protective factor ($P = .10$). ACEi/ARB/ARNi use was statistically significantly associated with reduced in-hospital mortality (OR 0.41; 95% CI, 0.34-0.50; $P < .001$), suggesting the effect of hypertension was largely attributed to ACEi/ARB/ARNi use (Table 2).

Secondary Outcomes

ICU admission. Regarding admission to the ICU, 21.1% (594 of 2817) of patients in the statin group required admission to the ICU compared with 22.8% (642 of 2817) of patients in the non-statin group. Multivariate logistic regression analysis showed that the statin group had a trend toward a lower likelihood for ICU admission, although this association did not reach the threshold of statistical significance (OR 0.90; 95% CI, 0.79-1.02; $P = .092$]. Additionally, for the statin group patients, increasing age was associated with reduced ICU admission (Table 3).

Mechanical ventilation. Among patients to whom statin was administered, 24.2% (683 of 2817) needed mechanical ventilation, and 28.5% (803 of 2817) of the patients without statin use during hospitalization underwent mechanical ventilation. Multivariate logistic regression demonstrated that during the hospitalization, mechanical ventilation occurred

Table 2 Univariate and Multivariate Logistic Regression Analyses for In-Hospital Mortality

Variable	Univariate (Odds ratio, 95% CI).	Multivariate (Odds ratio, 95% CI).	After Adding Interaction (Odds ratio, 95% CI).
Statin	0.69 (0.62-0.77), $P < .001$	0.71 (0.63-0.80), $P < .001$	0.72 (0.64-0.80), $P < .001$
Age	1.04 (1.03-1.04), $P < .001$	1.03 (1.03-1.04), $P < .001$	1.03 (1.03-1.04), $P < .001$
Male sex	1.09 (0.97-1.22), $P = .142$		
Hypertension	0.82 (0.72-0.92), $P = .001$	0.77 (0.67-0.88), $P < .001$	0.88 (0.76-1.02), $P = .100$
Diabetes mellitus	0.91 (0.80-1.03), $P = .151$		
Obesity	1.02 (0.91-1.15), $P = .686$		
Coronary artery disease	1.49 (1.17-1.87), $P = .001$	1.59 (1.24-2.04), $P < .001$	1.67 (1.29-2.15), $P < .001$
Heart failure	0.94 (0.76-1.16), $P = .554$		
Atrial fibrillation	1.21 (0.94-1.55), $P = .143$		
Asthma	0.72 (0.54-0.94), $P = .019$	0.80 (0.59-1.08), $P = .148$	0.82 (0.60-1.11), $P = .209$
Chronic obstructive pulmonary disease	1.28 (0.97-1.68), $P = .083$	1.22 (0.91-1.63), $P = .176$	1.22 (0.90-1.63), $P = .196$
Pulmonary hypertension	0.50 (0.20-1.09), $P = .106$		
Stroke/transient ischemic attack	0.80 (0.59-1.06), $P = .126$		
ACEi/ARB/ARNi* hypertension	0.68 (0.48-0.95), $P = .027$		0.68 (0.48-0.97), $P = .034$

*Interaction.ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor.

Table 3 Univariate and Multivariate Logistic Regression Analyses for Intensive Care Unit Admission

Variable	Univariate (Odds ratio, 95% CI).	Multivariate (Odds ratio, 95% CI).	After Adding Interaction (Odds ratio, 95% CI).
Statin	0.91 (0.80-1.03), $P = .122$	0.90 (0.79-1.02), $P = .092$	0.89 (0.78-1.01), $P = .070$
Age	0.98 (0.98-0.99), $P < .001$	0.99 (0.98-0.99), $P < .001$	0.99 (0.98-0.99), $P < .001$
Male sex	1.53 (1.34-1.75), $P < .001$	1.45 (1.27-1.67), $P < .001$	1.45 (1.27-1.67), $P < .001$
Hypertension	0.82 (0.71-0.95), $P = .007$	0.90 (0.78-1.04), $P = .162$	0.90 (0.78-1.04), $P = .162$
Diabetes mellitus	0.99 (0.85-1.14), $P = .844$		
Obesity	1.31 (1.15-1.49), $P < .001$	1.27 (1.11-1.46), $P < .001$	1.27 (1.11-1.46), $P < .001$
Coronary artery disease	1.07 (0.81-1.39), $P = .65$		
Heart failure	0.67 (0.51-0.87), $P = .004$	0.76 (0.57-1.00), $P = .051$	0.68 (0.44-1.01), $P = .066$
Atrial fibrillation	1.15 (0.86-1.52), $P = .342$		
Asthma	0.64 (0.45-0.89), $P = .010$	0.71 (0.49-1.00), $P = .055$	0.71 (0.49-1.00), $P = .056$
Chronic obstructive pulmonary disease	0.72 (0.50-1.01), $P = .068$	0.90 (0.61-1.28), $P = .563$	0.90 (0.61-1.28), $P = .571$
Pulmonary hypertension	1.05 (0.45-2.22), $P = .895$		
Stroke/transient ischemic attack	1.16 (0.84-1.57), $P = .348$		
Statin*heart failure	1.27 (0.74-2.19), $P = .385$		1.23 (0.71, 2.13), $P = .463$

*Interaction.

significantly less frequently in the statin group compared with the non-statin group (OR 0.80; 95% CI, 0.71-0.90); $P < .001$). Male sex and obesity are also significant predictors of higher risk of requiring mechanical ventilation. Despite the fact that heart failure appears to be a significant protective factor for mechanical ventilation, a possible interaction between statin use and heart failure exists ($P = .23$). After introducing the interaction variable of statin use and heart failure, the effect of heart failure was no longer significant ($P = .40$) (Table 4).

Subgroup Analysis

We performed subgroup analyses using the outcome of ICU admission and mechanical ventilation as surrogates for COVID-19 severity, and the results showed that the statin group is associated with a reduced in-hospital mortality in both ICU (OR 0.69; 95% CI, 0.55-0.86) and non-ICU patients (OR 0.69; 95% CI, 0.61-0.79; *P*-interaction .955). But for patients who required mechanical ventilation, statin therapy failed to show a significant reduction in hospital mortality (OR 0.81; 95% CI, 0.65-1.01, *P*-interaction .160).

Sensitivity Analysis

We reassessed the effect of statin use on in-hospital mortality from May 16 to December 1, 2020 after the surge period in New York City.[31] After applying propensity score matching (Table 5), the statin group still had a significant reduced in-hospital mortality (OR 0.54; 95% CI, 0.33-0.87; $P = .013$) and mechanical ventilation rate (OR 0.57; 95% CI, 0.38-0.85; $P = .006$), but not ICU admission (OR 0.82; 95% CI, 0.60-1.12; $P = .204$).

DISCUSSION

Our study found that the use of statins was independently associated with a significantly lower risk of in-hospital

Table 4 Univariate and Multivariate Logistic Regression Analyses for Mechanical Ventilation

Variable	Univariate (Odds ratio, 95% CI).	Multivariate (Odds ratio, 95% CI).	After Adding Interaction (Odds ratio, 95% CI).
Statin	0.80 (0.71-0.90), $P < .001$	0.80 (0.71-0.90), $P < .001$	0.81 (0.72-0.92), $P = .001$
Age	0.99 (0.99-1.00), $P < .001$	1.00 (0.99-1.00), $P = .307$	1.00 (0.99-1.00), $P = .299$
Male sex	1.26 (1.11-1.42), $P < .001$	1.30 (1.15-1.48), $P < .001$	1.30 (1.15-1.48), $P < .001$
Hypertension	0.86 (0.75-0.98), $P = .023$	0.92 (0.80-1.06), $P = .243$	0.92 (0.80-1.06), $P = .241$
Diabetes mellitus	0.91 (0.79-1.05), $P = .198$		
Obesity	1.52 (1.35-1.72), $P < .001$	1.58 (1.39-1.80), $P < .001$	1.58 (1.39-1.80), $P < .001$
Coronary artery disease	1.04 (0.80-1.35), $P = .740$		
Heart failure	0.69 (0.54-0.88), $P = .003$	0.74 (0.57-0.96), $P = .023$	0.86 (0.60-1.21), $P = .403$
Atrial fibrillation	0.83 (0.62-1.11), $P = .218$		
Asthma	0.76 (0.55-1.01), $P = .066$	0.79 (0.57-1.07), $P = .136$	0.79 (0.57-1.07), $P = .133$
Chronic obstructive pulmonary disease	0.88 (0.64-1.20), $P = .432$		
Pulmonary hypertension	0.36 (0.11-0.91), $P = .054$	0.42 (0.12-1.07), $P = .105$	0.43 (0.13-1.10), $P = .116$
Stroke/transient ischemic attack	1.14 (0.84-1.51), $P = .392$		
Statin*Heart failure	0.74 (0.45-1.21), $P = .226$		0.74 (0.45-1.22), $P = .242$

*Interaction.

Table 5 Baseline Demographic and Clinical Comorbidities Between Statin Group and Non-Statin Group in Post-Surge Period

	Unmatched			Matched		
	Statin Group	Non-Statin Group	SMD	Statin Group	Non-Statin Group	SMD
Number of patients	586	722		377	377	
Age, years: mean (SD)	66.21 (13.58)	55.64 (18.36)	0.655	63.83 (13.83)	64.81 (15.58)	0.066
Male sex (%)	348 (59.4)	403 (55.8)	0.072	216 (57.3)	217 (57.6)	0.005
Hypertension (%)	263 (44.9)	157 (21.7)	0.506	139 (36.9)	124 (32.9)	0.084
Diabetes mellitus (%)	217 (37.0)	126 (17.5)	0.451	116 (30.8)	102 (27.1)	0.082
Obesity (%)	217 (37.0)	244 (33.8)	0.068	124 (32.9)	125 (33.2)	0.006
Coronary artery disease (%)	65 (11.1)	14 (1.9)	0.377	26 (6.9)	14 (3.7)	0.142
				155		
Heart failure (%)	86 (14.7)	32 (4.4)	0.354	32 (8.5)	30 (8.0)	0.019
Atrial fibrillation (%)	49 (8.4)	24 (3.3)	0.216	26 (6.9)	22 (5.8)	0.043
Asthma (%)	38 (6.5)	44 (6.1)	0.016	25 (6.6)	28 (7.4)	0.031
Chronic obstructive pulmonary disease (%)	44 (7.5)	20 (2.8)	0.216	19 (5.0)	15 (4.0)	0.051
Pulmonary hypertension (%)	3 (0.5)	2 (0.3)	0.037	3 (0.8)	1 (0.3)	0.073
Stroke/transient ischemic attack (%)	73 (12.5)	21 (2.9)	0.364	20 (5.3)	17 (4.5)	0.037
Hydroxychloroquine (%)	6 (1.0)	10 (1.4)	0.033	4 (1.1)	4 (1.1)	< 0.001
Azithromycin (%)	168 (28.7)	296 (41.0)	0.261	122 (32.4)	134 (35.5)	0.067
Ceftriaxone (%)	195 (33.3)	365 (50.6)	0.356	144 (38.2)	154 (40.8)	0.054
Piperacillin-tazobactam (%)	106 (18.1)	205 (28.4)	0.246	82 (21.8)	81 (21.5)	0.006
Cefepime (%)	73 (12.5)	86 (11.9)	0.017	52 (13.8)	49 (13.0)	0.023
Vancomycin (%)	145 (24.7)	242 (33.5)	0.194	110 (29.2)	112 (29.7)	0.012
Remdesivir (%)	117 (20.0)	212 (29.4)	0.219	92 (24.4)	91 (24.1)	0.006
ACEi/ARB/ARNi (%)	235 (40.1)	118 (16.3)	0.547	111 (29.4)	109 (28.9)	0.012
Tocilizumab (%)	14 (2.4)	20 (2.8)	0.024	10 (2.7)	10 (2.7)	<0.001
Glucocorticoid (%)	75 (12.8)	100 (13.9)	0.031	55 (14.6)	56 (14.9)	0.007

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor—neprilysin inhibitor; SMD = standardized mean difference.

mortality and mechanical ventilation in patients hospitalized with COVID-19.

COVID-19 can generate an accentuated immune response, which activates a systemic inflammatory cascade, often termed "cytokine storm."[32,33] Interaction of the SARS-CoV-2 with the host immune system results in inhibition of lymphopoiesis and accelerated lymphocyte apoptosis.[34] In later stages of the infection, continued virus replication disrupts host endothelial-epithelial barrier, precipitating the release of inflammatory cytokines and infiltration of monocytes and neutrophils.[32,35] End-organ damage pathognomonic of COVID-19-associated inflammation occurs in the manifestation of acute respiratory distress syndrome with associated alveolitis and endothelial inflammation.[35] Levels of inflammatory markers including C-reactive protein, interleukin-6, procalcitonin, ferritin, erythrocyte sedimentation rate, and serum amyloid A have been found strongly associated with the severity of COVID-19, whereas survivors of COVID-19 had significantly lower levels of interleukin-6.[36,37] Activation of the immune system and the subsequent inflammation are fundamental to the pathophysiology of COVID-19. Therefore, they form the basis of currently available treatment target options and monitors of disease progression.[36,37]

Anti-inflammatory agents such as dexamethasone, tocilizumab, and baricitinib are proven efficacious treatments for selected patients with severe COVID-19.[12,13,38,39] Given that the proven benefit of these agents is attributed to their anti-inflammatory properties, the association of statins with lower in-hospital mortality identified by our study suggests that this can also be attributed to their anti-inflammatory effects.

The anti-inflammatory effects of statins have been well studied and reported, independent of their cholesterol-lowering effects. In vitro studies have uniformly found statins to reduce the expression of cellular adhesion molecules, thereby inhibiting leukocyte adhesion to endothelial cells.[40,41] Specifically, they have been found to lower the expression of the integrin dimer CD11b and monocyte chemotactic protein-1 on monocytes, and selectively inhibit leukocyte function antigen-1.[8,40] By binding to a novel regulatory site within the β_2 integrin, statins inhibit leukocyte function antigen-1 and adhesion of lymphocytes to endothelial cells.[40,42] This selective inhibition results in termination of the inflammatory cascade at a preliminary stage.

Clinical studies have corroborated these findings; the use of high-dose atorvastatin was associated with a significant reduction in the levels of C-reactive protein, interleukin-1, interleukin-6, tumor necrosis factor, and adhesions molecules.[43] Another HMG-CoA-reductase inhibitor, simvastatin showed a similar significant reduction in C-reactive protein and interleukin-6 levels.[44] The PRINCE study validated these findings by demonstrating that pravastatin significantly reduced C-reactive protein levels independent of

changes in lipid levels and may have distinctive anti-inflammatory effects.[45] The JUPITER study showed similar findings; the use of rosuvastatin significantly reduced C-reactive protein levels and cardiovascular events.[46] Although preliminary results from randomized controlled trials studying the role of statins in acute respiratory distress syndrome did not find a significant improvement in outcomes,[47,48] on secondary analysis, statins demonstrated a mortality benefit when used within 48 hours of development of acute respiratory distress syndrome in patients with the hyperinflammatory sub-phenotype.[47,49] Moreover, the anti-inflammatory property of statins has been applied in the treatment of non-cardiovascular diseases such as multiple sclerosis and rheumatoid arthritis.[50,51] Statins showed modest, albeit clinically apparent anti-inflammatory effects in high-grade rheumatoid arthritis. These effects are postulated secondary to suppression of Th1-related immune responses and tumor necrosis factor-alpha in the synovial membranes.[52] Evidence from meta-analysis also suggests that statins may have a role in reducing cancer-related mortality and reducing exacerbations in patients with chronic obstructive pulmonary disease.[53]

There have been studies evaluating the use of statins in COVID-19 patients. However, they differ from our study in remarkable ways. Saeed et al,[54] in their retrospective observational study of COVID-19 patients, found statins to be associated with a lower hospital mortality selectively in patients with diabetes mellitus. They concluded that there was no difference in hospital mortality based on statin use in patients without history of diabetes. In our study, statins continued to demonstrate an association with significantly lower hospital mortality regardless of diabetes status. Our cohorts were balanced not only for diabetes, but also hypertension, obesity, coronary artery disease, heart failure, and atrial fibrillation, among others, with a larger sample and an analysis that employed propensity score matching and multivariate logistic regression. Also, their single-center study was conducted during the initial COVID-19 surge, when treatment protocols were in flux and underwent rapid changes, making study groups heterogeneous. Our study evaluated the role of statins, both during the initial surge period in New York City and after it, assessing for consistency in results, and was conducted in 11 different hospitals within the country's largest municipal health care system. The randomized controlled trial INSPIRATION-S (Intermediate versus Standard-Dose Prophylactic Anticoagulation in Critically Ill Patients with COVID-19) studied the effect of statins on in-hospital mortality in critically ill COVID-19 patients admitted to the ICU.[55] The investigators did not find atorvastatin to improve outcomes in these patients. It is important to note that the study excluded patients who were routinely taking statins prior to hospitalization and tested only the 20-mg dosage form of atorvastatin. Statin use could have influenced disease progression in the early stages of infection prior to hospitalization. We included all of the most common forms of statin therapy, as well as patients, irrespective of statin use prior to hospitalization. In addition, our findings suggested that the use of renin-angiotensin-aldosterone system inhibitors were associated with significantly reduced in-hospital mortality in addition to the effect of statin therapy. Increasing age was found associated with a lower rate of ICU admission in our patient population, suggesting that age was likely incorporated into selection criteria for ICU admission in patients with COVID-19 infection, especially during the surge period. Haas et al[56] mentioned in their article that age could be considered to forgo ICU treatment in times of scarcity to prioritize younger patients. Overall, statin use in such a largely diverse population derived from the largest municipal hospital system in the nation was found to be associated with lower in-hospital mortality regardless of disease severity. However, further investigation with randomized trials evaluating for dose-dependent effects of statins on COVID-19 outcomes, and effect of different agents within the same class of drugs are needed. The effect of routine use of statins on the early stages of COVID-19 infection also needs to be assessed.

Strengths and Limitations

The strengths of our study include a large study population from multiple hospitals across New York City, an epicenter of the COVID-19 pandemic. We used a strict methodology using propensity score matching and multivariate logistic regression to control for possible confounding factors. We did not restrict our analysis to a predefined and limited in-hospital length of stay, allowing for accurate capturing of endpoints. Our study also evaluated the pandemic during 2 different phases, the surge and the period following it. To achieve this, we used a robust analysis incorporating subgroup analyses and sensitivity analyses of patients in the post-COVID-19 surge period.

We recognize that our study has important limitations. Although propensity-matched analysis was performed, being a retrospective study conducted from electronic medical records, the possibility of unmeasured confounders exists. An important bias to consider in retrospective studies is the "healthy user effect." It has been demonstrated that patients who adhere to statin use tend to be younger, engage in healthier lifestyles, and see their primary care physician more often.[57,58]

In addition, errors in medication reconciliation and documentation are possible, especially amidst soaring hospital admissions during the pandemic. Also, the duration of treatment with statins and medication noncompliance prior to hospitalization were not accounted for in the analysis, and these carry the potential to affect outcomes. Another limitation is the possible significant different criteria for ICU admission across all of our different facilities. These also vary based on provider assessment, ICU bed capacity, and available hospital resources.

CONCLUSION

In this multicenter study from the largest municipal health care system in the United States, located in the epicenter of

the COVID-19 pandemic, statin use was associated with a lower risk of in-hospital mortality and mechanical ventilation for hospitalized COVID-19 patients.

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