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Association of Pre-Admission Statin Use With Reduced In-Hospital Mortality in COVID-19

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ABSTRACT

Background: Coronavirus disease-19 (COVID-19) infection is associated with an uncontrolled systemic inflammatory response. Statins, given their anti-inflammatory properties, may reduce the associated morbidity and mortality. This study aimed to determine the association between statin use prior to hospitalization and in-hospital mortality in COVID-19 patients.

Methods: In this retrospective study, clinical data were collected from the electronic medical records of patients admitted to the hospital with confirmed COVID-19 infection from March 1, 2020 to April 24, 2020. A multivariate regression analysis was performed to study the association of pre-admission statin use with in-hospital mortality.

Results: Of 255 patients, 116 (45.5%) patients were on statins prior to admission and 139 (54.5%) were not. The statin group had a higher proportion of end stage renal disease (ESRD) (13.8% vs. 2.9%, $p = 0.001$), diabetes mellitus (63.8% vs. 35.2%, $p<0.001$), hypertension (87.9% vs. 61.1%, $p < 0.001$) and coronary artery disease (CAD) (33.6% vs. 5%, $p < 0.001$). On multivariate analysis, we found a statistically significant decrease in the odds of in-hospital mortality in patients on statins before admission (OR 0.14, 95% CI 0.03- 0.61, $p = 0.008$). In the subgroup analysis, statins were associated with a decrease in mortality in those with CAD (OR 0.02, 95% CI 0.0003−0.92 $p = 0.045$) and those without CAD (OR 0.05, 95% CI 0.005 −0.43, $p = 0.007$).

Conclusions: Our study suggests that statins are associated with reduced in-hospital mortality among patients with COVID-19, regardless of CAD status. More comprehensive epidemiological and molecular studies are needed to establish the role of statins in COVID-19.

Key Indexing Terms: Statins; Covid-19; Mortality. **[Am J Med Sci 2021;361(6):725–730.]**

INTRODUCTION

Coronavirus disease-19 (COVID-19), caused by SARS-CoV-2, was first reported in December 2019 in Wuhan, China, and subsequently spread to over 200 countries, leading to a worldwide pandemic.[1] At present, there is no specific treatment or vaccine for this virus, and efforts to understand risks factors, susceptibilities and therapeutics have been going on across the world. SARS-CoV-2 infection has been shown to trigger a cytokine storm with resultant uncontrolled systemic inflammatory response, causing acute respiratory distress syndrome (ARDS), multiple organ dysfunction and eventually death in severe cases.[2,3] Underlying cardiovascular disease has been shown to be associated with increased mortality among patients with COVID-19.[4–8] There exists an urgent need to find safe and effective therapies to reduce the morbidity and mortality associated with COVID-19. Already existing drugs that target the host immune response to mitigate the effect of COVID-19 are of broad interest.

Statins decrease low-density lipoprotein (LDL) levels,[9,10] and are well established in the primary[11,12] and secondary prevention[13,14] of cardiovascular events and mortality. Besides these well-known effects, statins also reduce C-reactive protein (CRP) and pro-inflammatory cytokine levels[15-17] and demonstrate various anti-inflammatory[18] and immunomodulatory[19,20] effects. These pleotropic effects of statins are evidence of beneficial effects in a variety of diseases like inflammatory bowel diseases,[21-23] autoimmune diseases,[24] chronic obstructive pulmonary disease (COPD),[25,26] cancer[27-29] and various infections.[30-32] Furthermore, several observational studies in patients with influenza have shown a mortality benefit with statin therapy.[26,33,34]

Given these multifaceted benefits of statins, we aimed to study the effects of statins on the outcomes of patients admitted to the hospital with COVID-19 infection.

METHODS

We performed a retrospective review of patients above 18 years of age admitted to Albert Einstein Medical Center in Philadelphia with confirmed COVID-19 infection from March 1, 2020 to April 24, 2020. A diagnosis of COVID-19 infection was made using a standardized RT-PCR nasal swab test.

The following data was collected retrospectively from the electronic medical record (EMR)- patients' demographic characteristics, including age, gender, race and body mass index (BMI); comorbidities, presenting symptoms, relevant laboratory values on admission and home medications at the time of admission. We also collected data regarding length of hospital stay, need for intubation, duration of mechanical ventilation and in-hospital mortality via chart review.

Statistical analysis

We compared baseline characteristics, laboratory values and presenting symptoms among those who were on statins before admission to those who were not on statins. We reported categorical variables as numbers (percentages) and continuous variables as means (standard deviation). We performed a multivariable regression analysis to study association of statin use with in-hospital mortality. We adjusted for known confounders of mortality from prior literature and also variables accounting for differences among statin users and non-users. The model with the lowest Akaike's Information Criterion was selected and used to estimate the odds ratio (OR) for the association. We defined statistical significance as p value<0.05. We used Stata, version 12.1 (Stat Corp, College Station, Texas) to perform statistical analysis.

RESULTS

This study included 255 inpatients admitted with COVID-19 with a mean age of 65.4 ± 15.2 years, 51% (n = 100) were male and 60% (n = 153) were African American. The mean body mass index (BMI) was 29.5 ± 9.1. The most common comorbidities in this cohort were hypertension (n = 187, 73.3%), diabetes mellitus (n = 123, 48.2%) and obstructive lung disease (n = 51, 19.9%). (Table 1)

There were 116 (45.5%) patients who were on statins before admission and 139 (54.5%) patients who were not on statins. The mean age of those on statins was higher (69 ± 10.6 years) than those not on statins (62.4 ± 17.7 years, p <0.001). The statin group had a higher proportion of end stage renal disease (ESRD) (13.8% vs. 2.9%, p = 0.001), diabetes mellitus (63.8% vs. 35.2%, p<0.001), hypertension (87.9% vs. 61.1%, p < 0.001) and coronary artery disease (CAD) (33.6% vs. 5%, p < 0.001) than the non-statin group. There were also more patients in the statin group on an angiotensin

Table 1. Baseline characteristics comparing participants who were on statins at admission with those who were not on statins.

	Not on statins at admission	On statins at admission	Overall	p-value
Characteristics				
Number of participants, n (%)	139 (54.5)	116 (45.5)	255	
Age in years, mean (SD)	62.4 (17.7)	69 (10.6)	65.4 (15.2)	<0.001
Female gender, n (%)	68 (48.9)	57 (49.1)	125 (49)	0.972
African American race, n (%)	76 (54.7)	77 (66.4)	153 (60)	0.057
Body mass index in kg/m^2, mean (SD)	29.7 (8.3)	29.4 (9.9)	29.5 (9.1)	0.811
Asthma, n (%)	9 (6.5)	10 (8.6)	19 (7.4)	0.516
COPD, n (%)	15 (10.8)	17 (14.7)	32 (12.5)	0.354
Cirrhosis, n (%)	6 (4.3)	3 (2.6)	9 (3.5)	0.456
Diabetes mellitus, n (%)	49 (35.2)	74 (63.8)	123 (48.2)	<0.001
End stage renal disease, n (%)	4 (2.9)	16 (13.8)	20 (7.8)	0.001
Coronary artery disease, n (%)	7 (5)	39 (33.6)	46 (18)	<0.001
Hypertension, n (%)	85 (61.1)	102 (87.9)	187 (73.3)	<0.001
SOFA on admission, mean (SD)	3.4 (3.6)	4.4 (3.5)	3.9 (3.6)	0.13
PaO2: FiO2 ratio	278.6 (153.3)	268 (164.6)	274.3 (157.5)	0.704
Home Medications				
Antiplatelets, n (%)	29 (20.8)	66 (56.9)	95 (37.2)	<0.001
ACEI/ARB, n (%)	33 (23.7)	54 (46.5)	87 (34.1)	<0.001
NSAIDs, n (%)	11 (7.9)	10 (8.7)	21 (8.3)	0.822
Home anticoagulation, n (%)	18 (12.9)	19 (16.4)	37 (14.5)	0.439
Prednisone, n (%)	13 (9.3)	5 (4.3)	18 (7.1)	0.117

Abbreviations: SOFA, Sequential Organ Failure Assessment; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; NSAID, Non-steroidal anti-inflammatory drug.

Table 2. Baseline laboratory values at admission.

	Not on statins at admission	On statins at admission	Total	Number of patients	p-value
Total leukocyte count (x 10^3 cells/microliter), mean (SD)	8.1 (4.3)	8.0 (5.4)	8.1 (4.8)	253	0.83
Segmented leukocytes (%), mean (SD)	70.95 (13.3)	80.4 (75.5)	75.1 (50.9)	213	0.179
Lymphocytes (%), mean (SD)	15.9 (9.8)	16.0 (8.0)	15.9 (9.0)	212	0.892
Neutrophil to lymphocyte ratio (NLR), mean (SD)	8.7 (14.4)	7.0 (8.9)	7.9 (12.3)	209	0.317
Lactate (mmol/L), mean (SD)	2.4 (2.2)	2.0 (1.5)	2.2 (1.9)	165	0.2
Creatinine (mg/dL), mean (SD)	1.8 (2.3)	2.4 (2.3)	2.1 (2.4)	250	0.054
CRP (mg/dL), mean (SD)	160.3 (123.8)	128.4 (104.8)	145.3 (115.8)	104	0.161
Fibrinogen (mg/dL), mean (SD)	547.2 (188.3)	633.2 (164.9)	578.3 (183.8)	72	0.056
Procalcitonin (ng/ml), mean (SD)	2.7 (8.8)	1.4 (3.9)	2.1 (7.0)	137	0.322
Lactate dehydrogenase (U/L), mean (SD)	481.1 (359)	452.1 (270.0)	467.6 (320.1)	155	0.576
Ferritin (mcg/L), mean (SD)	1456 (2311)	2308 (3257)	1842 (2803)	159	0.056
B-type natriuretic peptide (pg/ml), mean (SD)	267.9 (676.4)	400.6 (704.3)	340.8 (691.2)	91	0.365

converting enzyme inhibitor (ACEI) / Angiotensin receptor blocker (ARB) (46.5% vs. 23.7%, $p<0.001$) and an anti-platelet medication (56.9% vs. 20.8%, $p<0.001$). Laboratory parameters on admission did not significantly differ between the two groups as shown in Table 2. The statin group had a trend towards higher ferritin ($p = 0.056$) and higher fibrinogen ($p = 0.056$). Sequential Organ Failure Assessment (SOFA) score on admission was available for 134 (52.5%) patients did not differ significantly between the two groups (4.4 ± 3.5 vs. 3.5 ± 3.6, $p = 0.13$). PaO2/Fio2 (PF ratio) on admission was available in 132 (51.8%) patients and did not differ significantly between the two groups (268 ± 164.6 vs. 278.6 ± 153, $p = 0.704$).

During the course of hospitalization, 22.3% ($n = 54$) of the study population required mechanical ventilation and 28.8% ($n = 65$) required intensive care unit (ICU) admission. A total of 53 patients (20.1%) died and 38 patients (14.9%) required hospice care. There was no difference between the two groups in terms of requirement of mechanical ventilation ($p = 0.353$), days on the ventilator ($p = 0.253$), days on vasopressors ($p = 0.787$), requirement of continuous renal replacement therapy (CRRT) ($p = 0.5$) and in-hospital mortality (Table 3). Steroids were given in 9.3% of patients in the statin group as compared to 7.1% of patients in the non-statin group. ($p = 0.117$).

On multivariate analysis, we found a statistically significant decrease in the odds of in-hospital mortality in patients on statins before admission (OR 0.14, 95% CI 0.03- 0.61, $p = 0.008$), after adjusting for age, gender, BMI, ESRD, intubation during hospitalization, creatinine, neutrophil: lymphocyte ratio (NLR), hypertension, diabetes mellitus, CAD, anti-platelets and ACEI/ARBs (Fig. 1 and Table 4). Other factors significantly associated with in-hospital mortality as seen in Fig. 1 were age (OR 2.2, 95% CI 1.3- 3.8, $p = 0.004$), ESRD (OR 27.1, 95% CI 2.08- 353.6, $p = 0.012$) intubation (OR 126.30, 95% CI 28.20- 565.73, $p<0.001$) and NLR (OR 1.58, 95% CI 1.05 −2.38, $p = 0.028$).

We performed subgroup analysis to study the effect of statins on mortality among patients with and without CAD separately. In the adjusted analysis, statins were associated with a decrease in mortality in those with CAD (OR 0.02, 95% CI 0.0003−0.92 $p = 0.045$) and also among those without CAD (OR 0.05, 95% CI 0.005 −0.43, $p = 0.007$). Similarly, statin use was significantly associated with reduction in mortality in separate analysis for patients with diabetes (p value=0.01) and a trend towards reduction in mortality in those without diabetes mellitus (p value=0.07). There was no effect modification of ESRD and hypertension on the association of statin use with mortality.

Table 3. Measures of health care utilization comparing participants who were on statins at admission with those who were not on statins.

	Not on statins at admission	On statins at admission	Total	p-value
CRRT, % (n)	6.5 (9)	13.8 (16)	9.8 (25)	0.5
Mechanical Ventilation, % (n)	21.5 (28)	23.2 (26)	22.3 (54)	0.755
Days on mechanical ventilation, mean (SD)	2.8 (5.1)	2.0 (3.3)	2.4 (4.4)	0.253
Days in the ICU, mean (SD)	2.4 (4.7)	1.8 (3.3)	2.1 (4.1)	0.343
Death, % (n)	23 (32)	18.3 (21)	20.1 (53)	0.353
Hospice, % (n)	17.3 (24)	12.1 (14)	14.9 (38)	0.246

Abbreviations: CRRT, Continuous Renal Replacement Therapy; ICU, Intensive Care Unit.

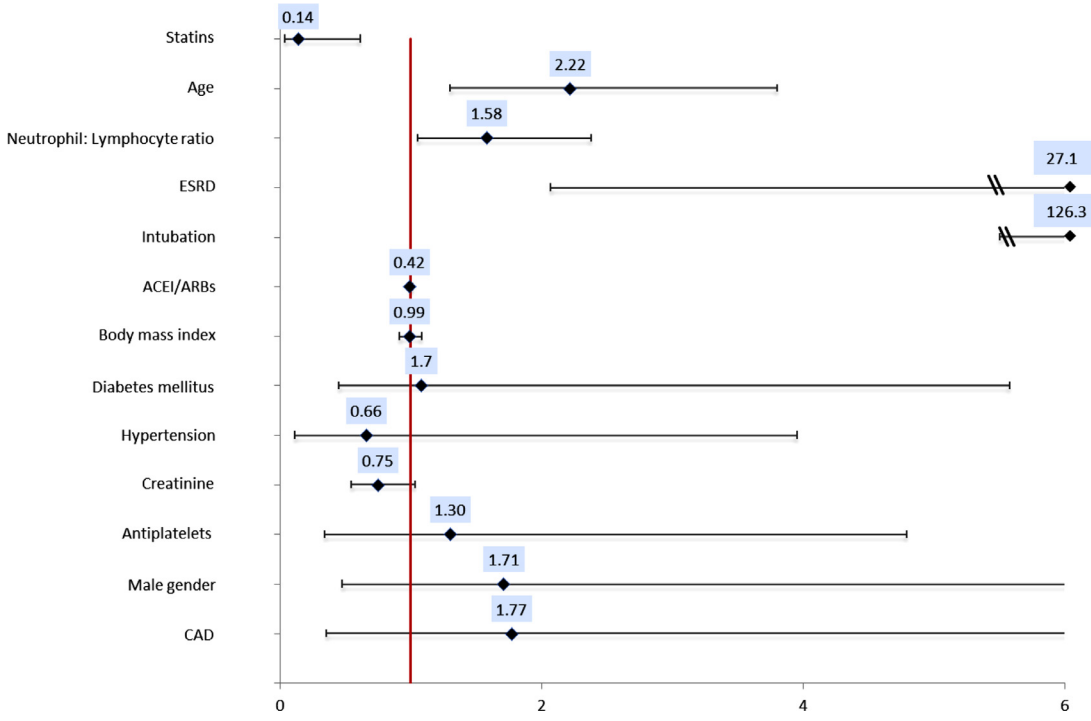

FIG. 1. Forest plot based on the results of the multivariate analysis. This figure depicts the of odds ratio (OR) and confidence interval for in-hospital mortality in COVID-19. OR for age and NLR is shown for increments of 10. Increase in age, neutrophil: lymphocyte ratio, presence of ESRD and intubation during hospitalization were all associated with an increased risk of in-hospital mortality. Use of statins pre-admission was associated with decrease in the odds of in-hospital mortality (OR 0.14, 95% CI 0.03- 0.61, $p = 0.008$). All other variables including gender, body mass index, hypertension, diabetes, coronary artery disease and antiplatelets or ACEI/ARBs before admission were not associated with in hospital mortality. *Abbreviations*: ESRD, End Stage Renal Disease; ACEI, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker.

Among the 54% of cohort who had SOFA score available at the time of admission, statins were associated with decrease in mortality (OR 0.03 95% CI 0.002 −0.38, $p = 0.006$) after adjusting for SOFA score in addition to the previous adjusted confounders, including, age, sex, gender, BMI, ESRD, intubation during hospitalization, creatinine, NLR, hypertension, diabetes mellitus, CAD, anti-platelets and ACEI/ARBs.

Table 4. Results of multivariable regression analysis for association of statin use with in hospital mortality in patients with COVID 19.

	Odds ratios	95% confidence interval	P-value
Statins	0.14	0.03 - 0.61	0.008
Age	2.2[a]	1.3 - 3.8	0.004
Neutrophil: lymphocyte ratio (NLR)	1.58[a]	1.05 - 2.38	0.028
End stage renal disease	27.1	2.08 - 353.6	0.012
Intubation	126.3	28.2 - 565.73	<0.001
Male gender	1.6	0.45 - 5.49	0.482
BMI	0.99	0.91 - 1.08	0.908
Hypertension	0.66	0.11 - 3.95	0.654
Diabetes mellitus	1.7	0.47 - 6.24	0.412
Coronary artery disease	1.7	0.35 - 8.8	0.486
Anti-platelets	1.3	0.34 - 4.98	0.698
ACEI/ARBs	0.42	0.09−1.87	0.256
Creatinine at admission	0.7	0.54−1.03	0.079

Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BMI, Body Mass Index.
[a] Odds ratios for age and NLR are shown for increments of 10 for clinical relevance and ease of depiction.

DISCUSSION

Some observational studies have reported an association of statins with reduction in adverse cardiovascular outcomes and mortality in patients admitted with influenza and/or pneumonia.[26,34,35] It is therefore conceivable that statins can offer a protective effect in acute viral illness of COVID-19. Progress in the development of effective vaccines and antiviral drugs, although the focus of much research, has been disappointing and time consuming. Therefore, utilizing statins to mitigate the inducing effect of COVID-19 on the immune system merits exploration. Additionally, an in-silico molecular modeling study by Wang et al. to identify FDA approved drugs targeting SARS-CoV-2 identified rosuvastatin as the sixth potentially usable drug that may have clinical utility in COVID-19.[36]

Our study suggests that statins are associated with reduced in-hospital mortality among patients with COVID-19 infection. Patients in the statin group were older in age and had a higher prevalence of end stage renal disease (ESRD), diabetes mellitus, hypertension

and coronary artery disease (CAD). These co-morbidities are known to contribute a high mortality in SARS-CoV-2 patients.[6,37-44] Hence, this group represents a higher risk group and would be expected to have worse outcomes. On the contrary, multivariate analysis found statin use to be associated with lower odds of mortality in patients with COVID-19, compared to those not on statins.

There are several proposed mechanisms for the effect of statins on disease caused by SARS-CoV-2. In addition to the indirect effect of statins on decreasing cardiovascular complications by anti-inflammatory and immunomodulatory effect, various studies have shown direct effect on viral particles.[45] It is postulated that some of the pleiotropic effects of statins such as the downregulation of CD147 expression and function, lipid raft disruption, autophagy activation, and attenuation of both the inflammatory response and the coagulation activation are relevant in the infection and replication of SARS-CoV-2 in host cells.[46] However it is unknown if any of these mechanisms are responsible for the observed association or it is an epiphenomenon.

The same dilemma was faced by Kruger et al., who at a time when it was recommended that statins be stopped during an acute infection, described a significantly lower mortality rate in patients with bacteremia who continued statin therapy during the hospital admission.[47] In the study those who continued statins had the lowest mortality, followed by those who stopped statins on admission and highest mortality was seen in the no statin group.[47] They considered the possibility that statins had a synergistic effect with antibiotic therapy or that they played an immunomodulatory role.

We did not find any difference in levels of inflammatory markers at admission between the statin and no statin group. Based on our findings, the reduction in mortality by statins was unlikely to be mediated by the level of inflammatory markers on admission.

To minimize any bias by indication, we separately analyzed those with CAD and those without CAD. We found that, on multivariable analysis, statin use before admission was associated with reduction in mortality in both these groups.

Our study has several limitations common to retrospective studies. Data regarding the duration of statin therapy prior to presentation, specific type and dose of statins, and whether they were continued or stopped during the hospitalization was not available. Also given the retrospective nature of this study, we are unable to eliminate hidden confounding. We also could not compare the interaction of statins with some of the other potential treatments of COVID-19 like antiviral drugs. However, the protective effect of statins in our study was consistent among all subgroups and after adjusting for all available confounders.

Our study builds evidence that statins may be helpful in mitigating effects of COVID-19. Given their low cost, great safety profile and worldwide availability, they portend great potential. More comprehensive epidemiological and molecular studies are needed to establish the role of statins in COVID-19 including role of continuation of therapy, de novo initiation of therapy and potential harms associated with statin use in those with COVID-19.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the manuscript.

DECLARATION OF COMPETING INTEREST

No conflict of interest for any of the authors.

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