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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%, \( p < 0.001 \)) and 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.

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.³ 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 primary¹¹,¹² and secondary prevention¹³,¹⁴ of cardiovascular events and mortality. Besides these well-known effects, statins also reduce C-reactive protein (CRP) and pro-inflammatory cytokine levels¹⁵–¹⁷ and demonstrate various anti-inflammatory¹⁸ and immunomodulatory¹⁹,²⁰ 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

| Characteristics                  | Not on statins at admission | On statins at admission | Overall | p-value |
|----------------------------------|-----------------------------|-------------------------|---------|---------|
| Number of participants, n (%)    | 139 (54.5)                  | 116 (45.5)              | 255     |         |
| Age in years, mean (SD)          | 62.4 (17.7)                 | 69 (10.6)               | 64.4 (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/m², 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**

| Antiplabelets, 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 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 | Number of patients | 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.

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 0.003-0.92 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 analyses 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.
Among the 54% of cohort who had SOFA score available at the time of admission, statins were associated with decrease in mortality (OR 0.14, 95% CI 0.03 - 0.61, p = 0.008) 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.

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. 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.

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 intubation during hospitalization compared to the non-statins group. Adjusting for these variables, the use of statins was associated with a lower odds of in-hospital mortality (OR 0.14, 95% CI 0.03 - 0.61, p = 0.008) 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.
and coronary artery disease (CAD). These co-morbidities are known to contribute a high mortality in SARS-CoV-2 patients. 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. 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. 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. 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. 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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