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# Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching



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## Keywords

Hydroxymethylglutaryl-CoA reductase inhibitors;  
Mortality;  
Critical care;  
Mechanical ventilation;  
COVID-19

## Abstract:

**Background:** Statins have been associated with a reduction in inflammatory markers and improved endothelial function. Whether statins offer any benefit in COVID-19 needs to be elucidated.

**Objective:** To determine the association between antecedent statin use and severe disease outcomes among COVID-19 patients.

**Methods:** A retrospective cohort study on 1014 patients with confirmed COVID-19 diagnosis. Outcomes were mortality, need for mechanical ventilation, and intensive care admission. Patients were classified into statin-users vs statin non-users based on antecedent use of statins. Multivariable regression analysis was performed adjusting for confounders such as age, sex, race, BMI, smoking, insurance, and comorbidities. Propensity score matching was performed to achieve a 1:1 balanced cohort.

**Results:** A total of 1014 patients (Median age 65 (IQR 53–73); 530 (52.3%) males; 753 (74.3%) African Americans; median BMI 29.4 (IQR 25.1–35.9); 615 (60.7%) with Medicare insurance) were included in the study. About 454 patients (44.77%) were using statins as home medication. Antecedent statin use was associated with significant decrease in mortality in the total cohort (OR, 0.66; 95% CI, 0.46 – 0.95;  $p = 0.03$ ). Among the propensity score matched (PSM) cohort of 466 patients (233 statin users and 233 statin non-users), all the baseline characteristics had similar distribution among the two groups. Statin users had significant reduction in mortality in the PSM cohort as well (OR, 0.56; 95% CI, 0.37 – 0.83;  $p = 0.004$ ).

**Conclusions:** Statin use was associated with significant reduction in mortality among COVID-19 patients. These findings support the pursuit of randomized clinical trials to explore the possible benefits of statins in COVID-19.

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Conflict of interest: All authors report no conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Submitted October 19, 2020. Accepted for publication March 2, 2021.

## Introduction

With the pandemic of COVID-19 now affecting almost every aspect of life, with no definitive cure, some researchers are looking into the role of existing drugs to determine if they might affect the clinical outcomes in COVID-19. One of the drugs being scrutinized currently is the family of statins. In the United States alone, almost a quarter of the population above the age of 40 years are on a statin medication.<sup>1</sup> In the past, studies have tried to elucidate the role of statins in other viral infections including influenza,<sup>2-4</sup> Ebola virus,<sup>5,6</sup> and MERS.<sup>7</sup> Some observational studies have noted the association of statins with a significant decrease in the mortality from influenza,<sup>4</sup> and community-acquired pneumonia.<sup>8</sup> The results of a randomized control trial (RCT) reported by Calfee et al.<sup>9</sup> found improved survival with simvastatin therapy compared to placebo, in patients with hyperinflammatory sub phenotype of acute respiratory distress syndrome (ARDS). On the contrary, some other studies have noted no role of statins in mortality from ARDS.<sup>10,11</sup> Hypertension, coronary artery disease as well as diabetes have been reported as the most common comorbidities among COVID-19 patients.<sup>12-14</sup> Statins are a commonly prescribed medication among patients with these comorbidities, thereby one might wonder if statins have any role in COVID-19 disease.

Statins have immunomodulating properties and modulate the immune response at different levels including *T* cell signaling, antigen presentation, immune cell migration, and cytokine production.<sup>15,16</sup> Because of these anti-inflammatory and immunomodulating properties, studies have suggested that statins might play a beneficial role in COVID-19 disease<sup>17-22</sup> whereas some note increased levels of proinflammatory interleukin-18 (IL-18) among patients receiving statins, contributing to higher mortality in ARDS.<sup>23</sup> A recent in-silico study has shown that statins bind to the main protease of the SARS-CoV-2 virus, thereby statins might reduce infectivity.<sup>24</sup>

Several studies indicate that endothelial cell dysfunction is characteristic of COVID-19 and identify the critical role of endothelium in the hyperinflammatory and procoagulant state seen in COVID-19.<sup>25-27</sup> Additionally, there is evidence of SARS-CoV-2 infection of vascular endothelial cells<sup>27,28</sup> and statins have been known to induce cytoprotective genes, protect against vascular injury and reverse endothelial dysfunction.<sup>29-31</sup> These vasculoprotective effects of statins along with anti-inflammatory and immunomodulatory actions led us to explore if statins have any role in clinical outcomes in COVID-19 patients.

The primary objective of this study is to determine if antecedent use of statins as a home medication had any association with mortality among COVID-19 patients who presented to the hospital. This study also explored if there was any association of statins with other severe disease clinical outcomes such as the need for mechanical ventilation and intensive care unit (ICU) requirement in COVID-19 patients. Additionally, it was investigated if the intensity of statins had any correlation with the same clinical outcomes.

## Methods

This is a retrospective cohort study on 1014 adult patients with a confirmed COVID-19 diagnosis who presented to the hospital. The study was approved by the Detroit Medical Center (DMC) and Wayne State University Institutional Review Board; a waiver for informed consent form was granted (IRB application # 20-06-2426). No external funding was received for conducting the study.

Adult patients ( $\geq 18$  years of age) with a confirmed COVID-19 diagnosis (either via nasopharyngeal or oropharyngeal swab) were included in the study. Testing for COVID-19 was done at DMC, one of the largest academic medical centers and healthcare providers in southeast Michigan. DMC comprises four distinct hospitals in Michigan, however for this study only 2 hospitals (Detroit Receiving and Harper/Hutzel University Hospital) were included. These hospitals primarily cater to the underserved patient population of downtown Detroit.

A list of all the patients who presented to the 2 hospitals between March 10, 2020, and June 30, 2020, and had a laboratory-confirmed COVID-19 PCR diagnosis was collated in collaboration with institutional information technology services. There were a total of 1105 patients. Patients under the age of 18 years, any readmission during the time frame, pregnant patients, and patients transferred to an outside hospital for Extracorporeal membrane oxygenation (ECMO) were excluded from the study. A total of 91 patients were excluded based on these criteria. Information on the statin use was collected from the medication list in the EMR. Due to the lack of integration between the outpatient EMR and the inpatient EMR, the information to trace the medication refills could not be reliably collected. However, in our hospital system, patient/caretaker history is usually taken into account at the time of patient intake by a trained medical assistant or registered nurse. Patients were classified into 2 groups- statin users, patients with documentation of statins as home medication at the time of hospitalization, and statin non-users, patients with no documentation of antecedent use of statin medication. The type and dose of statins were also noted and the patients on statins were classified into 3 groups, based on the dose of home statin medication into low, moderate, and high dose statin based upon the American College of Cardiology and American Heart Association classification of statin intensity.<sup>32</sup> Data points were manually collected and coded for each patient.

The main outcome for this study was mortality, and the secondary outcomes explored were the need for mechanical ventilation and ICU admission among COVID-19 patients. All of the patients included in the study had a documented outcome (mortality/discharged status) at the time of data collection. Additionally, the data on prior comorbidities, BMI, smoking status, disposition upon emergency department (ED) visit (discharge home, inpatient floor admission, and direct ICU admission), maximum oxygenation requirement during hospitalization were collected. It was also noted if the patients received antibiotics, corticosteroids, remde-

sivir, and therapeutic anticoagulation during the course of hospitalization. The institutional criteria used for administering the above medications are provided in supplementary Table 1. Data were collected for 11 prominent comorbidities (as defined in supplementary Table 1) including diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, chronic kidney disease, preexisting lung disease, end-stage renal disease on dialysis, chronic liver disease, any cancer, and any history of stroke. Charts were screened to determine if the patient required transfer to ICU from inpatient floors. Demographic data including age, sex, insurance status, and race were also collected.

Categorical variables have been described as frequency and percentages. Age was categorized into two groups (18–64 years, and 65 and older). Baseline characteristics of the two groups—statin users and statin non-users, were compared using *t*-test and Mann-Whitney *U* test for continuous variables and Chi-square test for the nominal variables. An unadjusted odds ratio was calculated using Chi-square test. An adjusted odds ratio was calculated using binary logistic regression. Variables in the fully adjusted models were age, sex, BMI, race, smoking status, and comorbidities which included diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, preexisting lung disease, chronic kidney disease, end-stage renal disease on dialysis, chronic liver disease, any cancer and any history of stroke; along with statin use. Age and BMI were taken as continuous variables and comorbidities as categorical variables for the adjusted model. The 95% confidence intervals (CI) were estimated using a binomial distribution. A *p*-value of less than 0.05 was determined to be significant. To obtain an optimal model, stepwise regression with Forward (Wald) selection was performed. The optimal model only included covariates that contributed significantly to the model, and these variables were age, sex, diabetes mellitus, preexisting lung diseases, hypertension, and statin use. Further, to explore the dose-response relationship of statins in terms of changes in clinical outcomes, binary logistic regression was performed using statin non-users as the referent group, and comparison was made with low, moderate, and high dose statin users. Propensity score matching was performed to obtain a 1:1 matched cohort using the ‘nearest-neighbor’ approach without replacement, with a match tolerance of 0.1. Propensity score was defined as the predicted probability of the patient using statins given the patient’s demographics, BMI, and comorbidities. The covariates used to calculate the propensity score included age, sex, African American race, BMI, insurance, smoking status, diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, preexisting lung disease, chronic kidney disease, end-stage renal disease on dialysis, chronic liver disease, any cancer and history of stroke. Baseline characteristics of the two groups were compared for the matched cohort to validate the propensity score model. Binary logistic regression was conducted on the propensity score matched (PSM) cohort for primary as well as secondary outcomes. Sensitivity analyses were performed after excluding the patients who were dis-

charged home from the ER. Further, an exploratory analysis was conducted on the ICU patients to assess the association of antecedent statin use with mortality in the ICU patients with COVID-19. Statistical analyses were completed using IBM SPSS Statistics software (version 26).

## Results

### Baseline characteristics of the total cohort

The total cohort of our study consisted of 1014 patients with a median age of 65 (IQR 53–73) years. We had an almost equal distribution of males and females (males:  $n = 530$ , 52.3%) and African American was the predominant race ( $n = 753$ , 74.3%). The distribution of BMI was not normal in our cohort [median 29.4 (IQR 25.1–35.9)] and almost half of the patients were obese ( $n = 477$ , 47%). Hypertension ( $n = 792$ , 78.1%), diabetes ( $n = 434$ , 42.85) and preexisting lung diseases ( $n = 325$ , 32.1%) were the three most common comorbidities. Of the 1014 patients included in our study, 454 patients were antecedent statin users, with documentation of statin as home medication, while 560 patients were statin non-users, not on any statin medications at home. Close to 45% ( $n = 205$ ) of the statin-users had been prescribed a high dose of statins per the records and atorvastatin was the most commonly prescribed statin ( $n = 309$ , 30.4%). For 19 patients, the dose of statins was not recorded in the clinical notes, thereby their intensity of home statin dose could not be determined. BMI information was missing for 7 patients. Upon comparison of the baseline characteristics in the two groups; statin users vs statin non-users, we found that the distribution of sex, race, and BMI was similar across the two groups. Whereas the two groups differed in the age distribution, preexisting lung diseases, coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, chronic kidney disease, end stage renal disease on dialysis, and history of stroke. Patients using statins were older compared to the ones who were not using statins ( $p < 0.001$ ). The details about the baseline characteristics of the cohort and their distributions in the two groups have been outlined in Table 1. Table 2 describes the intensity/dose and type of statins among the statin users group.

### Clinical course of the total cohort

Mortality for the total cohort was 29.3% ( $n = 297$ ). During the course of their admission, 24.7% ( $n = 250$ ) required mechanical ventilation, and more than 80% ( $n = 823$ ) required some kind of supplemental oxygen during their admission. About 15.1% ( $n = 153$ ) patients were admitted directly to ICU from the ED, and additional 184 patients required admission to ICU from the medical floors. One-third of the total patients (33.2%) who came to the hospital required intensive care services during their treatment. Less than 10% ( $n = 92$ ) were discharged from the ED

**Table 1** Baseline characteristic of patients.

Characteristic	Cohort ( <i>n</i> = 1014)	Unmatched			Propensity score matched		
		Statin ( <i>n</i> = 454)	Non-Statin ( <i>n</i> = 560)	<i>p</i> -value	Statin ( <i>n</i> = 233)	Non Statin ( <i>n</i> = 233)	<i>p</i> -value
<b>Age, (years) n (%)</b>							
Median (IQR)	65 (53–73)	67 (60–74)	61 (47–72)	< 0.001	66 (59–73)	67 (57–75)	0.16
18–30	36 (3.6)	1 (0.2)	35 (6.3)		1 (0.4)	3 (1.3)	
31–45	108 (10.7)	17 (3.7)	91 (16.3)		8 (3.4)	21 (9)	
46–64	357 (35.2)	165 (36.3)	192 (34.3)		97 (41.6)	69 (29.6)	
≥65	513 (50.6)	271 (59.7)	242 (43.2)		127 (54.5)	140 (60.1)	
<b>Sex, n (%)</b>							
Male	530 (52.3)	240 (52.9)	290 (51.8)	0.73	125 (53.6)	130 (55.8)	0.64
Female	484 (47.7)	214 (47.1)	270 (48.2)		108 (46.4)	103 (44.2)	
<b>Race/ ethnicity, n (%)</b>							
African American	753 (74.3)	340 (74.9)	413 (73.8)	0.68	186 (79.8)	173 (74.2)	0.15
Other races	261 (25.7)	114 (25.1)	147 (26.3)		47 (20.2)	60 (25.8)	
<b>BMI</b>							
Median (IQR)	29.4 (25.1–35.9)	29.4 (24.9–35.2)	29.4 (25.4–36.8)	0.36	30 (25.7–35.5)	28.8 (24.8–35.6)	0.27
< 18.5 (underweight)	28 (2.8)	11 (2.4)	17 (3)		4 (1.7)	8 (3.4)	
18.5–24.9 (normal)	217 (21.4)	108 (23.8)	109 (19.5)		49 (21)	51 (21.9)	
25–29.9 (overweight)	285 (28.1)	126 (27.8)	159 (28.4)		63 (27)	69 (29.6)	
≥ 30 (obese)	477 (47)	209 (46)	268 (47.9)		117 (50.2)	105 (45.1)	
<b>Comorbidities, n (%)</b>							
Preexisting lung disease	325 (32.1)	171 (37.7)	154 (27.5)	< 0.001	80 (34.3)	71 (30.5)	0.37
Coronary artery disease	221 (21.8)	163 (35.9)	58 (10.4)	< 0.001	52 (22.3)	52 (22.3)	1
Hypertension	792 (78.1)	420 (92.5)	372 (66.4)	< 0.001	201 (86.3)	200 (85.8)	0.89
Diabetes mellitus	434 (42.8)	263 (57.9)	171 (30.5)	< 0.001	117 (50.2)	116 (49.8)	0.93
Hyperlipidemia	292 (28.8)	239 (52.6)	53 (9.5)	< 0.001	69 (29.6)	53 (22.7)	0.09
Congestive Heart Failure	139 (13.7)	101 (22.2)	38 (6.8)	< 0.001	29 (12.4)	33 (14.2)	0.59
Stroke	104 (10.3)	82 (18.1)	22 (3.9)	< 0.001	26 (11.2)	22 (9.4)	0.54
Cancer	90 (8.9)	47 (10.4)	43 (7.7)	0.137	25 (10.7)	23 (9.9)	0.76
Chronic liver disease	38 (3.7)	13 (2.9)	25 (4.5)	0.182	8 (3.4)	10 (4.3)	0.63
CKD	114 (11.2)	68 (15)	46 (8.2)	< 0.001	32 (13.7)	31 (13.3)	0.89
ESRD on dialysis	101 (10)	64 (14.1)	37 (6.6)	< 0.001	27 (11.6)	30 (12.9)	0.66
Smoking	402 (39.6)	202 (44.5)	200 (35.7)	0.004	98 (42.1)	96 (41.2)	0.85
<b>Insurance</b>							
Uninsured	17 (1.7)	5 (1.1)	12 (2.1)	< 0.001	2 (0.9)	2 (0.9)	0.94
Medicaid	281 (27.7)	86 (18.9)	195 (34.8)		49 (21)	53 (22.7)	
Medicare	615 (60.7)	340 (74.9)	275 (49.1)		168 (72.1)	162 (69.5)	
Private	101 (10)	23 (5.1)	78 (13.9)		144 (6)	16 (6.9)	

to home and 75.8% (*n* = 769) required inpatient floor admission. A total of 324 patients (32%) received corticosteroids during the course of hospitalization and 766 (75.5%) received antibiotics. About 18.6% of the total patients (*n* = 189) received therapeutic anticoagulation therapy. The clinical course of the total cohort has been summarized in [Table 3](#).

### Statins and clinical outcomes in the total cohort

In the unadjusted analysis, antecedent statin use had no significant association with mortality (OR, 1.10; 95% CI, 0.84 – 1.44; *p* = 0.49), ICU admission (OR, 1.24; 95% CI, 0.96 – 1.61; *p* = 0.11), or the need for mechanical ventilation (OR, 1.18; 95% CI, 0.89 – 1.58; *p* = 0.23). Similarly, in the

**Table 2** Description of intensity and type of statins among the statin user group in the total cohort.

Intensity of Statins, n (%)	
Low	41 (9)
Moderate	189 (41.6)
High	205 (45.1)
Type of statins, n (%)	
Atorvastatin	309 (30.4)
Pravastatin	35 (3.4)
Rosuvastatin	39 (3.8)
Simvastatin	65 (6.4)
Lovastatin	6 (0.6)

minimally adjusted models (adjusted only for demographic factors), no association was noted between statin use and any of the severe disease outcomes explored by this study (supplemental Table 2). In multivariable regression analysis, after adjusting for age, sex, race, BMI, insurance, smoking status, and 11 comorbidities, antecedent statin use was associated with a significant decrease in mortality (OR, 0.66; 95% CI, 0.46 – 0.95;  $p = 0.03$ ). However, no similar association was noted for the need for ICU admission (OR, 0.92; 95% CI,

0.66 – 1.29;  $p = 0.64$ ) or the need for mechanical ventilation (OR, 0.80; 95% CI, 0.55 - 1.15;  $p = 0.22$ ). The results of stepwise regression further validate these findings. In the optimal model, statin users had a significant reduction in the all-cause mortality (OR, 0.64; 95% CI, 0.47 – 0.87;  $p = 0.005$ ), while no significant association was noted between statin use and ICU admission ( $p = 0.21$ ), or the need for mechanical ventilation ( $p = 0.6$ ). The results of the analyses exploring the association between statins and clinical outcomes have been summarized in Table 4.

Upon doing the regression analyses to explore the dose-response relationship of statins in the total cohort, we found no significant association between the dose of statin and mortality, and other clinical outcomes explored by us. Statin non-users group was taken as the reference category.

### Baseline characteristics of the PSM cohort

Using 1:1 propensity score matching, a balanced cohort of 466 patients (233 statin users and 233 statin non-users) was obtained. All the baseline characteristics had a similar distribution in the PSM cohort. These details have been outlined in Table 1.

**Table 3** Clinical course of the patients.

Characteristic	Cohort ( <i>n</i> = 1014)	Unmatched		Propensity score matched	
		Statin ( <i>n</i> = 454)	Non-Statins ( <i>n</i> = 560)	Statin ( <i>n</i> = 233)	Non-Statins ( <i>n</i> = 233)
Mortality	297 (29.3)	138 (30.4)	159 (28.4)	58 (24.9)	87 (37.3)
Mechanical Ventilation	250 (24.7)	120 (26.4)	130 (23.2)	56 (24)	71 (30.5)
ICU Admission	337 (33.2)	163 (35.9)	174 (31.1)	82 (35.2)	91 (39.1)
Admission disposition					
ER Visit Only (Discharged from ER)	92 (9.1)	16 (3.5)	76 (13.6)	10 (4.3)	17 (7.3)
Inpatient floor admission	769 (75.8)	365 (80.4)	404 (72.1)	188 (80.7)	178 (76.4)
Direct ER to ICU Admission	153 (15.1)	73 (16.1)	80 (14.3)	35 (15)	38 (16.3)
Maximum supplemental oxygen during admission					
Room air only	191 (18.8)	60 (13.2)	131 (23.4)	34 (14.6)	32 (13.7)
Nasal Canula	317 (31.3)	154 (33.9)	163 (29.1)	76 (32.6)	67 (28.8)
Venti-mask	51 (5)	20 (4.4)	31 (5.5)	10 (4.3)	13 (5.6)
Non-Rebreather	172 (17)	82 (18.1)	90 (16.1)	45 (19.3)	44 (18.9)
High Flow Oxygen	30 (3)	16 (3.5)	14 (2.5)	10 (4.3)	5 (2.1)
BPAP/CPAP	3 (0.3)	2 (0.4)	1 (0.2)	2 (0.9)	1 (0.4)
Mechanical Ventilation	250 (24.7)	120 (26.4)	130 (23.2)	56 (24)	71 (30.5)
Treatment during admission					
Corticosteroids	324 (32)	154 (33.9)	170 (30.4)	82 (35.2)	72 (30.9)
Remdesivir	8 (0.8)	4 (0.9)	4 (0.7)	2 (0.9)	1 (0.4)
Anticoagulation	189 (18.6)	94 (20.7)	95 (17)	53 (22.7)	48 (20.6)
Antibiotics	766 (75.5)	359 (79.1)	407 (72.7)	185 (79.4)	182 (78.1)



**Table 4** Association between statins and severe disease outcomes- Mortality, Mechanical ventilation and ICU admission.

Characteristic	Mortality		ICU Admission		Mechanical ventilation	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Total cohort						
Unadjusted	1.10 (0.84–1.44)	0.49	1.24 (0.96–1.61)	0.11	1.18 (0.89–1.58)	0.23
Fully adjusted*	0.66 (0.46–0.95)	0.03	0.92 (0.66–1.29)	0.64	0.80 (0.55–1.15)	0.22
Optimal Model**	0.64 (0.47–0.87)	0.005	NS	0.21	NS	0.6
Propensity score matched cohort						
PS matched	0.56 (0.37–0.83)	0.004	0.85 (0.58–1.23)	0.39	0.72 (0.48–1.09)	0.12
Intensity of statins (Total cohort)						
No statin	Reference		Reference		Reference	
Low	0.66 (0.30–1.41)	0.28	0.78 (0.38–1.61)	0.5	0.62 (0.28–1.40)	0.25
Moderate	0.66 (0.43–1.01)	0.06	0.93 (0.62–1.37)	0.7	0.76 (0.49–1.17)	0.21
High	0.78 (0.51–1.19)	0.25	0.84 (0.57–1.25)	0.39	0.88 (0.57–1.35)	0.55
Intensity of statins (Propensity score matched)						
No statin	Reference		Reference		Reference	
Low	0.81(0.40–1.64)	0.55	0.79(0.39–1.58)	0.5	0.75(0.35–1.6)	0.45
Moderate	0.52(0.31–0.87)	0.01	0.94(0.59–1.49)	0.78	0.69(0.40–1.17)	0.16
High	0.54(0.29–0.99)	0.047	0.59(0.33–1.06)	0.08	0.77(0.42–1.42)	0.41

\*Adjusted for age, sex, race, BMI, insurance, and comorbidities which include preexisting lung diseases, smoking, hypertension, coronary artery disease, diabetes mellitus, chronic kidney disease, ESRD on dialysis, congestive heart failure, any cancer, chronic liver disease, hyperlipidemia and history of previous stroke.

\*\*Variables in the optimal model- age, sex, diabetes mellitus, hypertension, preexisting lung disease, and statin use. NS- Not significant, OR- odds ratio, CI- confidence interval.

### Statins and clinical outcomes in PSM cohort

The results of the analyses on the PSM cohort further validate our findings of the association of antecedent statin use with reduced mortality. In the PSM cohort, statin use was found to be associated with reduced mortality (OR, 0.56; 95% CI, 0.37 – 0.83;  $p = 0.004$ ). However, no significant association was noted between statin use and ICU admission (OR, 0.85; 95% CI, 0.58 – 1.23;  $p = 0.39$ ), or the need for mechanical ventilation (OR, 0.72; 95% CI, 0.48 – 1.09;  $p = 0.12$ ). In the PSM cohort, a significant statin dose-response relationship was noted in terms of reduction in mortality among statin users. Compared to the statin non-users, statin users on low statins dose had no significant association with mortality (OR, 0.81; 95% CI, 0.40 – 1.64;  $p = 0.55$ ). However, statin users on moderate and high dose of statins had significant reduction in mortality compared to statin non-users ((OR, 0.52; 95% CI, 0.31 – 0.87;  $p = 0.01$ ) for patients on moderate dose of statins; (OR, 0.54; 95% CI, 0.29 – 0.99;  $p = 0.047$ ) for patients on high dose of statins). Further details on the results of these analyses in the PSM cohort have been outlined in [Table 4](#).

### Sensitivity analyses

Additionally, fully adjusted multivariable regression analyses performed after excluding the patients who were dis-

charged home from ER, demonstrated that antecedent statin use was associated with reduced mortality in the hospitalized patients with COVID-19 (OR, 0.64; 95% CI, 0.44 – 0.92;  $p = 0.02$ ). However similar to the results of analyses on the total cohort and PSM cohort, no significant association was noted between statin use and ICU admission (OR, 0.88; 95% CI, 0.63 – 1.23;  $p = 0.46$ ) or the need for mechanical ventilation (OR, 0.79; 95% CI, 0.54 – 1.15;  $p = 0.22$ ) among the hospitalized COVID-19 patients. Further exploratory multivariable regression analysis performed on ICU patients in the total cohort (OR, 0.55; 95% CI, 0.31 – 0.99;  $p = 0.049$ ) and PSM cohort (OR, 0.52; 95% CI, 0.28 – 0.95;  $p = 0.03$ ), showed a significant association between antecedent statin use and reduced mortality among ICU patients with COVID-19.

### Discussion

Antecedent statin use was associated with a significant decrease in all-cause mortality among COVID-19 patients in this retrospective study in the models adjusted for all the known confounders including demographic factors as well as different comorbidities. The protective benefit of statins seen with COVID-19 may be postulated because of the cardioprotective effects of statin therapy. Anti-inflammatory and immunomodulating properties of statins<sup>17–22</sup> along with their

vasculoprotective effects<sup>29–31</sup> are other factors that might be responsible for the protective effect of statins. Another possible explanation could be that statins can modulate SARS-CoV-2 virus entry by acting on the ACE2 and CD147 receptors and lipid raft engagements.<sup>33</sup> Additionally, induction of the MYD88 gene has been reported to occur in other coronavirus infections, which can lead to activation of the NF- $\kappa$ B pathway and marked inflammation.<sup>7,34</sup> Statins inhibit the MYD88 gene, hence inhibiting the activation of the NF- $\kappa$ B pathway<sup>7,35</sup> and possibly preventing marked inflammation in COVID-19 patients.

In the total cohort of this study, patients using statins were older and had a significantly more severe burden of comorbidities such as coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, preexisting lung diseases, chronic kidney disease, and history of stroke. A growing number of recent observational studies have demonstrated a significant association of these comorbidities with worse clinical outcomes in COVID-19.<sup>22, 36–42</sup> Hence, the lack of significant association between antecedent statin use and mortality in the results of unadjusted analysis in this study can be attributed to the cardiovascular comorbidities for which statins are routinely prescribed. When multivariable adjustments were made with binary logistic regression to adjust for demographics and comorbidities, this study demonstrated a significant association between antecedent statin use and reduced mortality among COVID-19 patients. These results were further validated in the PSM cohort to minimize any likelihood of known confounding due to selection bias. Recent studies looking at the role of statins among COVID-19 patients, either antecedent use or current in-hospital use, have noted similar beneficial effects on mortality.<sup>43,44</sup> The use of statins prior to admission was found to be associated with a reduced risk of severe disease and a faster time to recovery in COVID-19 patients.<sup>45</sup> Additionally, a recent meta-analysis on the effect of statins in COVID-19 patients noted a 30% reduction in severe disease outcomes,<sup>46</sup> similar to what is noted in our study.

To our knowledge, this is the first study exploring the dose-response relationship of statins in terms of improvement in clinical outcomes among COVID-19 patients. In the PSM cohort of this study, patients on moderate and high dose of statins had a significant reduction in mortality compared to statin non-users, while the patients on low dose statins did not have a significant association with reduced mortality. This is consistent with the literature which reports that high dose statin therapy confers both primary and secondary prevention from cardiovascular events.<sup>47,48</sup>

This study did not find any significant association between antecedent statin use and ICU admission or the need for mechanical ventilation, in the total cohort or the PSM cohort. Interestingly, among the ICU patients with COVID-19, statin use was associated with reduced mortality in both the total cohort and the PSM cohort. It has been recently reported that a large number of patients admitted to the hospital with COVID-19 can develop ARDS.<sup>49,50</sup> Statins might be playing a role in assisting in the recovery of these critically ill

patients by reducing lung inflammation and injury, as well as via its endothelial stabilizing properties. However, further studies are needed to validate these findings and to understand the underlying mechanisms that might be contributing to this.

Although reporting clinically relevant findings, our study does have a few limitations. This is a retrospective cohort analysis in which data was collected from the documented clinical records. Hence the possibility of selection and information bias cannot be negated. This study did not look into compliance with the home medication regime since the information on medicine refills was not available in the EMR. We relied on the data of home medications provided at the time of hospitalization by the patient or as mentioned in the patient's previous records when available.

Moreover, our cohort only consisted of those COVID-19 patients who presented to the hospital. This might limit the generalization of the results and more community-based studies are warranted. Additionally, it must be acknowledged that patients taking statins might be more health-conscious in general and well-connected with their medical providers, whose comorbidities might be better managed. They might have taken other steps such as presenting earlier in the course of infection, which could have led to an improved prognosis with COVID-19. Even though we have performed propensity score matching as well as multivariable adjustments to minimize the confounding related to selection bias; in an ideal scenario, RCTs can provide the best evidence regarding the effect of statins on clinical outcomes in COVID-19. However, until the results from ongoing RCTs are available, in the light of the current pandemic, this study reports that the use of statins is safe and recommends continued adherence to guideline-recommended statin therapy for patients with pre-existing comorbidities for which statins have been proven to be effective.

## Conclusion

Statin use was associated with a significant reduction in mortality among COVID-19 patients in this retrospective study. Hence, the use of statin therapy seems safe amid the current global pandemic. Even though strong methodology including propensity score matching and sensitivity analyses further validate the findings of this study, consideration should be given to randomized control trials exploring the possible benefits of statin use in COVID-19 patients.

## Author contributions

PL conceptualized the study and performed the lead role in data acquisition, data analysis, data interpretation, along with supervising the project, drafting the manuscript and reviewing it for critical intellectual content. SK was the equal contributor in study conceptualization, data analysis, data interpretation, drafting the manuscript and review-



ing the manuscript. SB, TM conceptualized the study, collected the data and made supporting contribution editing the manuscript. All the authors read and approved the final manuscript; agree to be accountable for all aspects of the work.

## Data sharing and accessibility

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request and appropriate permission from the institutional IRB.

## Acknowledgments

We extend our gratitude to the Research Design and Analysis Unit at Wayne State University for their assistance with the analyses of the project. We are also grateful to the three anonymous reviewers whose valuable and insightful suggestions have immensely helped us in improving our manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2021.03.002.

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