

Effects of statins on outcomes in Hispanic patients with COVID-19

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ABSTRACT

The Hispanic population is regarded among those who are at greater risk of adverse prognoses due to higher rates of diabetes and obesity in the USA during the COVID-19 pandemic. Statin medications are speculated to help treat the infection by decreasing inflammation caused by COVID-19. In this retrospective, observational study, outcomes of statin use were assessed among Hispanic patients with COVID-19 by screening all patients hospitalized between March, 2020 and March, 2021 at a tertiary care hospital in El Paso, Texas, resulting in a total of 1039 patients. The patients were categorized into a group of either being on statins or not. The considered outcomes were mechanical ventilation, intensive care unit (ICU) hospitalization, oxygen supplementation at discharge, hospital length of stay, and mortality. Patients receiving statins were observed to be older with more comorbidities. In the propensity-scores adjusted analysis, no association was found between statin use and: mortality (adjusted risk ratio (aRR)=0.96, p=0.754), mechanical ventilation (aRR=0.91, p=0.503), ICU transfer (aRR=0.96, p=0.395), and O₂ supplementation at discharge (aRR=1.03, p=0.729). These outcomes were also evaluated in patients who had myocardial infarction and stroke with COVID-19. Among these patients, association was found between statin use and: a reduced risk of mortality (aRR=0.61, p=0.005), mechanical ventilation (aRR=0.53, p=0.012) and ICU transfers (aRR=0.81, p=0.005). These results may not give us a reason to start patients on statins for the specific treatment of COVID-19, but it may be sufficient evidence to suggest statins should not be discontinued during hospitalization due to COVID-19.

INTRODUCTION

SARS-CoV-2 is the causal agent of the current global pandemic since 2019. Evidence has suggested that the virus enters and infects cells by interacting with human ACE2 like a receptor. ACE2 has been found in multiple organs in the body, explaining the multiple organ failures in people infected with COVID-19. Another receptor that has been connected to viral uptake is CD147.¹ It is an extracellular matrix metalloproteinase inducer or basigin expressed on many cells and is thought to be involved in the remodeling of the extracellular matrix in wound healing,

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The Hispanic population has a substantial prevalence of diabetes mellitus and obesity.
- ⇒ COVID-19 invades the body through the binding of CD147, an extracellular matrix metalloproteinase inducer or basigin found on the surface of cells in inflammatory states.
- ⇒ Recent studies show that statins may help in decreasing inflammation through the downregulation of NF-κB, and thus lowering the expression of CD-147.
- ⇒ Since statins lower cholesterol synthesis, it may prevent COVID-19 from appropriating lipid rafts and releasing particles.

WHAT THIS STUDY ADDS

- ⇒ Statin use in Hispanic patients with COVID-19 does not increase the rate of mortality, mechanical ventilation, intensive care unit (ICU) transfer, and O₂ supplementation at the time of discharge for living patients.
- ⇒ Hispanic patients suffering from a myocardial infarction or stroke concurrently with statin use may benefit with a reduced risk of mortality, mechanical ventilation, and ICU transfer than those not on statins.
- ⇒ The use of statins does not contribute to worsening outcomes compared with Hispanic patients not on statins during hospitalization.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The use of statin medications should not be discontinued among Hispanic patients admitted to the hospital due to COVID-19 infection.
- ⇒ COVID-19 infected patients who concurrently suffer a myocardial infarction or stroke may benefit from having statin medications added to their treatment regimen.
- ⇒ This study may help shed light in the practice of research studies on medications focused on minority populations, such as Hispanics, in COVID-19 studies.

inflammatory diseases, and cancer.² With diabetes and obesity being considered chronic inflammatory conditions, CD147 is often upregulated.



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Once infection occurs, a cytokine storm is appreciated in most patients, activating the coagulation cascade which leads to disseminated intravascular coagulation, specifically leading to pulmonary intravascular coagulopathy.³

It has been recently suggested that statins may help in the treatment of SARS-CoV-2 infections. Statins have traditionally been used as 3-hydroxyl-3-methyl-glutaryl-coenzyme A reductase inhibitors to lower serum cholesterol by the liver. It is also suggested that statins may also have a pleiotropic effect in reducing C reactive protein (CRP) independent of low-density lipoprotein (LDL) reduction.¹ As cholesterol production is lowered, the liver expresses increased LDL receptors, leading to increased uptake of low-density lipoprotein cholesterol (LDL-C) in the serum to compensate for the lowered cholesterol production. In addition, one of the most important pleiotropic effects of statin medications is the inhibition of nuclear factor kappa B (NF- κ B), helping with anti-inflammation.¹ Through the downregulation of NF- κ B, there is a decrease in interleukin 1 (IL-1) and IL-6, leading to a decrease in the release of CRP from the liver. The decrease in CRP contributes to the anti-inflammatory effects of statin therapy. Both effects of statins help in the reduction of adverse effects of COVID-19. Statins have also been observed to reduce the infectivity of COVID-19 in the body. In a recent study, it has been shown that with the pretreatment of cultured THP-1 monocytes with atorvastatin, pravastatin, or fluvastatin, there was a decrease in CD147 translocation to the cell surface. The downregulation of CD147 in pulmonary cells decreases the ability of the virus to infect cells.¹ In addition to reducing CD147, statin's effects on inhibiting cholesterol biosynthesis can help regulate cell membrane lipid rafts. Viruses may disrupt cholesterol homeostasis to help with viral assembly and proliferation. Using statins, cholesterol biosynthesis can be disrupted and subsequently may decrease viral production.

SARS-CoV-2 can specifically cause worsening prognosis in patients with diabetes and obesity.⁴ In the USA, some ethnic minorities are at a greater risk for adverse prognosis due to COVID-19. Hispanics have higher rates of diabetes and obesity in both adults (80%) and children (five times higher) than non-Hispanic whites.^{5,6} Despite this, the effects of statins on COVID-19 outcomes among Hispanic patients have not been assessed. We hypothesized that Hispanic patients with COVID-19 receiving statins can produce better outcomes than patients without statins. Thus, we sought to determine the effects of statins on COVID-19-associated outcomes through a large single-center study among Hispanic patients.

MATERIAL AND METHODS

We conducted a retrospective cohort study at a tertiary care hospital providing care support to a predominantly Hispanic population living on the Mexico-US border. A patient list of 4000 was requested from the University Medical Center (UMC) of El Paso from March, 2020 to March, 2021. Any adults aged between 18 years and 85 years, Hispanic ethnicity, positive test for COVID-19 using RT-PCR and hospitalized at UMC for over 48 hours were considered eligible for the study. Patients discharged from the emergency department, patients with cancer, patients on chemotherapy, immunosuppressive or immunotherapy,

HIV, organ transplant patients, and patients co-infected with influenza A or B were excluded from this study.

Outcomes

The outcomes were all measured objectively from patient charts. The primary outcomes included mortality, mechanical ventilation, intensive care unit (ICU) transfer, while secondary outcomes included hospital length of stay (HLOS), and oxygen (O₂) supplementation at the time of discharge.

Groups

As per our objectives, all patients were divided into two groups (patients with statin therapy and patients without statin therapy). Patients on statin therapy were defined as patients who were recorded taking statins prior to being admitted to the hospital and patients who were given statin therapy during admission. The types of statin therapies were recorded in the study through log detail and included atorvastatin, simvastatin, rosuvastatin, and pravastatin. In addition, a comparative group was created that included all the same variables except for statin therapy.

Covariates

Age and gender were collected as demographic variables. We collected risk factors and comorbidities that include body mass index (BMI), vitamin D level, troponin, smoking, neurological symptoms, gastrointestinal (GI) symptoms, respiratory symptoms, cardiac symptoms, diabetes mellitus (DM), metabolic syndrome, myocardial infarction (MI), stroke, pneumothorax, GI bleeding, thrombocytopenia, deep vein thrombosis (DVT), eye symptoms, hypertension, hyperlipidemia, and end-stage renal disease. We also collected treatment profiles including remdesivir, dexamethasone, prednisone, hydroxychloroquine, azithromycin, aspirin, selective serotonin reuptake inhibitors (SSRI), vitamin D therapy, convalescent plasma, monoclonal antibodies, and therapeutic anticoagulants/warfarin.

Statistical analysis

Quantitative data were described either using mean and SD or median and IQR. Qualitative data were summarized using frequency and percentages. Association between patient characteristics with statin use was assessed using an unpaired t-test, Wilcoxon rank-sum test, χ^2 test, and Fisher's exact test as appropriate with the distribution and type of variables. The effect of statin use on each outcome was determined using a relative risk regression model with an inverse probability treatment weighting method.⁷ The weight was determined by estimating propensity of statin using a multivariable logistic regression model. Most of the baseline characteristics without missing values including age, gender, smoking, remdesivir treatment, dexamethasone treatment, azithromycin, SSRI, vitamin D therapy, prednisone treatment, hydroxychloroquine, convalescent plasma, monoclonal antibodies, neurological symptoms, GI symptoms, respiratory symptoms, cardiac symptoms, MI, stroke, pneumothorax, GI bleeding, thrombocytopenia, hypertension, hyperlipidemia, metabolic syndrome, and DM were included in the propensity score model. We further validated our findings using propensity score-matched analysis using a relative risk model. Furthermore,

the unadjusted effect of statins on each outcome was determined using relative risk models according to each major comorbidity (hypertension, hyperlipidemia, metabolic syndrome, DM, stroke, MI, and pneumothorax). Afterwards, we determined the effect of statins on each outcome in a subgroup of patients with stroke and MI using propensity scores weighted relative risk models. In the subgroup analyses, only age, gender, BMI, metabolic syndrome, hypertension, hyperlipidemia, DM, aspirin, and SSRI were used for forming propensity scores for statin compared with non-statin groups. Risk ratios (RRs), 95% CIs, and p values were used to summarize the findings of the study. Statistical significance was considered at p values less than 5%. Forest plots were created to summarize critical findings in

this study. All statistical analysis and data management were conducted using Stata V.17.

RESULTS

After assessing eligibility criteria, a total of 1039 patients were included in the study. Of these 1039 patients, 456 were on statin therapy. The study sample included patients with a mean age of 58.9 years and a BMI of 30.9 kg/m². The sample also resulted in 57.9% men, 11.2% smokers, 53.4% patients with DM, 52% hypertensive patients, and 15% patients with hyperlipidemia. Table 1 shows the differences in baseline characteristics between the statin and non-statin groups. Patients on statins were seen to be significantly

Table 1 Comparisons of baseline clinical and treatment profiles between patients with or without statin

Factor	Statin use			P value
	Overall	No	Yes	
N	1039	583	456	
Demographics				
Age (years), mean (SD)	58.88 (15.49)	54.69 (16.29)	64.20 (12.56)	<0.001
Gender, male	598 (57.89%)	342 (59.17%)	256 (56.26%)	0.37
Risk factors and comorbidities				
BMI (kg/m ²), mean (SD)	30.89 (6.41)	31.19 (6.35)	30.12 (6.29)	0.011
Vit D level, median (IQR)	27.85 (18.80, 40.00)	26.20 (17.25, 40.15)	30.30 (20.60, 40.00)	0.11
Troponin, mean (SD)	0.91 (12.11)	0.25 (1.99)	1.65 (17.54)	0.096
Smoking, yes	116 (11.16%)	64 (10.98%)	52 (11.40%)	0.84
Neurological symptoms	275 (26.47%)	152 (26.07%)	123 (26.97%)	0.78
GI symptoms	673 (64.77%)	400 (68.61%)	273 (59.87%)	0.004
Respiratory symptoms	878 (84.50%)	504 (86.45%)	374 (82.02%)	0.057
Cardiac symptoms	191 (18.38%)	111 (19.04%)	80 (17.54%)	0.57
Diabetes mellitus	555 (53.42%)	261 (44.77%)	294 (64.47%)	<0.001
Metabolic syndrome	341 (46.84%)	115 (31.94%)	226 (61.41%)	<0.001
Myocardial infarction	70 (6.74%)	28 (4.80%)	42 (9.21%)	0.006
Stroke	22 (2.12%)	8 (1.37%)	14 (3.07%)	0.081
Pneumothorax	29 (2.79%)	22 (3.77%)	7 (1.54%)	0.036
GI bleeding	32 (3.08%)	17 (2.92%)	15 (3.29%)	0.72
Thrombocytopenia	123 (11.84%)	66 (11.32%)	57 (12.50%)	0.56
DVT	568 (90.59%)	305 (91.87%)	235 (88.68%)	0.21
Eye symptoms	3 (0.29%)	2 (0.34%)	1 (0.22%)	1.00
Hypertension	540 (51.97%)	232 (39.79%)	308 (67.54%)	<0.001
Hyperlipidemia	156 (15.01%)	45 (7.72%)	111 (24.34%)	<0.001
End-stage renal disease	37 (3.56%)	18 (3.09%)	19 (4.17%)	0.4
Treatments				
Remdesivir	668 (64.29%)	380 (65.18%)	288 (63.16%)	0.51
Dexamethasone	811 (78.06%)	461 (79.07%)	350 (76.75%)	0.41
Prednisone	223 (21.46%)	125 (21.44%)	98 (21.49%)	1.00
Hydroxychloroquine	25 (2.41%)	15 (2.57%)	10 (2.19%)	0.84
Azithromycin	561 (53.99%)	310 (53.17%)	251 (55.04%)	0.57
Aspirin	332 (31.95%)	97 (16.64%)	235 (51.54%)	<0.001
SSRI	105 (10.11%)	45 (7.72%)	60 (13.16%)	0.005
Vit D therapy	537 (51.68%)	286 (49.06%)	251 (55.04%)	0.061
Convalescent plasma	91 (8.76%)	52 (8.92%)	39 (8.55%)	0.91
Monoclonal antibodies	19 (1.83%)	7 (1.20%)	12 (2.63%)	0.1
Therapeutic anticoagulants/warfarin	388 (38.88%)	192 (37.28%)	164 (38.95%)	0.64

All data were expressed with N (%), otherwise explained.

BMI, body mass index; DVT, deep vein thrombosis; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor.

Table 2 Unadjusted effect of statin use on each outcome

Outcomes	Statin		P value
	No	Yes	
N	583	456	
HLOS, median (IQR)	12.00 (8.00–19.00)	12.30 (8.00–20.00)	0.46
Mortality			0.82
Discharged from hospital	456 (78.76%)	355 (78.02%)	
Died	123 (21.24%)	100 (21.98%)	
Mechanical ventilation			0.88
No	465 (79.76%)	366 (80.26%)	
Yes	118 (20.24%)	90 (19.74%)	
ICU transfer			0.37
No	165 (28.30%)	141 (30.92%)	
Yes	418 (71.70%)	315 (69.08%)	
O ₂ supplementation at time of discharge			0.26
No	268 (58.26%)	193 (54.21%)	
Yes	192 (41.74%)	163 (45.79%)	

ICU, intensive care unit; O₂, oxygen; HLOS, hospital length of stay.

older (64 ± 12.7 years vs 54.7 ± 16.3 years, $p < 0.001$). Statin patients were also noticed to have significantly lower LDL levels ($p = 0.02$). Additionally, patients taking statins had reported more comorbidities, with a larger number of patients having DM (64.5% vs 44.8%, $p < 0.001$), metabolic syndrome (61.4% vs 31.9%, $p = 0.006$), hypertension (67.5% vs 39.8%, $p < 0.001$), and hyperlipidemia (24.3% vs 7.7%, $p < 0.001$). Patients in the statin group had statistically more MI cases ($p = 0.006$) and less pneumothorax cases (0.036). There were no differences in COVID-19-related treatments between groups. However, statin patients were more likely to receive aspirin ($p < 0.001$) and SSRI ($p = 0.005$) therapy than patients not taking statins.

The median HLOS was not found to be statistically different between the statin and non-statin groups (12 days vs 12.3 days, $p = 0.46$). No significant differences in mortality, mechanical ventilation, ICU transfer, and O₂ supplementation at the time of discharge were observed between groups in the unadjusted analysis (table 2). Specifically, the rate of mortality (22% vs 21.2%, $p = 0.82$), mechanical ventilation use (19.7% vs 20.2%, $p = 0.88$), ICU transfer (69.1% vs 71.7%, $p = 0.37$), and O₂ supplementation at the time of discharge (45.8% vs, 41.7%, $p = 0.26$) were found comparable between the statin and non-statin groups (table 2).

After creating propensity scores, most of the baseline characteristics were found to be balanced between groups except for age, GI symptoms, DM, metabolic syndrome, MI, hypertension, and hyperlipidemia (table 3). The propensity scores adjusted analysis (table 4) confirmed that statin use was not significantly associated with mortality (RR=0.96, $p = 0.754$), mechanical ventilation (RR=0.91, $p = 0.503$), ICU admission (RR=0.96, $p = 0.395$), and O₂ supplementation at the time of discharge (RR=1.03, $p = 0.729$). These findings were confirmed in propensity score matched analysis as well.

Our results show the unadjusted effect of statin on each outcome in the subgroup of patients with specific comorbidity. Statin use yielded a significantly reduced risk of mortality (RR=0.32, $p = 0.014$) in patients with a history of stroke. In addition, patients with MI receiving statin did

have a significantly decreased risk of mortality (RR=0.72, $p = 0.024$), mechanical ventilation (RR=0.56, $p = 0.011$), and ICU transfer (RR=0.84, $p = 0.037$). Compared with the non-statin group, the statin group did not show a significant reduction in the risk of unfavorable outcomes in patients with major comorbidities (figure 1).

Statin appeared to be a protective medication with regard to mechanical ventilation, ICU transfer, and O₂ supplementation at discharge in those patients who had experienced either MI or stroke (table 5). Patients with a prescribed statin as part of their treatment regimen had 39% less risk of having mortality ($p = 0.005$) due to COVID-19 infection, were 47% less likely to receive mechanical ventilation ($p = 0.012$), and had 19% less risk to be transferred to the ICU ($p = 0.005$). The reduction in the HLOS (difference = -1.4, $p = 0.527$) was not found to be associated with statin use among patients with MI or stroke. In the sensitivity analyses after additionally adjusting for the duration of symptoms in the propensity model, statin use was associated with a reduced risk of mortality and ICU transfer.

DISCUSSION

In this large cohort of Hispanic patients with COVID-19 infections, statin use was not found to be associated with reduced mortality, mechanical ventilation, ICU transfer, or need of O₂ supplementation at the time of discharge. From the results, we were unable to find supporting evidence for the primary regimen use of statin medications for managing patients with COVID-19. However, our study showed favorable outcomes with statin use in a subgroup of patients with either MI or stroke.

Previous studies have shown mixed results on the benefit of using statins in the treatment of COVID-19 infection. A nationwide study conducted in Denmark revealed no association in mortality between patients with or without statin therapy.⁸ Similarly, a study conducted in Singapore showed no difference in mortality, intubation, or hypoxia; however, it did show a significant difference in ICU admission.⁹ Both

Table 3 Comparisons of baseline clinical and treatment profiles between patients with or without statin after matching propensity scores between groups

Factor	Propensity matched statin		P value
	No	Yes	
N	454	454	
Demographics			
Age, mean (SD)	60.03 (13.34)	64.18 (12.58)	<0.001
Gender, male	265 (58.37%)	256 (56.39%)	0.590
Risk factors and comorbidities			
BMI, mean (SD)	30.90 (6.23)	30.11 (6.30)	0.072
Vit D level, median (IQR)	27.2 (18.1–41.9)	30.30 (20.6–40)	0.330
Troponin, mean (SD)	0.29 (2.20)	1.66 (17.56)	0.140
Smoking	49 (10.79%)	52 (11.45%)	0.750
Neurological symptoms	124 (27.31%)	122 (26.87%)	0.880
GI symptoms	301 (66.30%)	272 (59.91%)	0.046
Respiratory symptoms	392 (86.34%)	373 (82.16%)	0.083
Cardiac symptoms	90 (19.82%)	80 (17.62%)	0.390
Diabetes mellitus	230 (50.66%)	293 (64.54%)	<0.001
Metabolic syndrome	112 (36.60%)	225 (61.31%)	<0.001
Myocardial infarction	26 (5.73%)	42 (9.25%)	0.044
Stroke	8 (1.76%)	14 (3.08%)	0.200
Pneumothorax	10 (2.20%)	7 (1.54%)	0.460
GI bleeding	17 (3.74%)	15 (3.30%)	0.720
Thrombocytopenia	56 (12.33%)	57 (12.56%)	0.920
DVT	238 (93.70%)	234 (88.64%)	0.043
Eye symptoms	2 (0.44%)	0 (0.00%)	0.160
Hypertension	224 (49.34%)	306 (67.40%)	<0.001
End-stage renal disease	18 (3.96%)	19 (4.19%)	0.870
Hyperlipidemia	45 (9.91%)	110 (24.23%)	<0.001
Treatments			
Remdesivir	299 (65.86%)	286 (63.00%)	0.370
Dexamethasone	363 (79.96%)	349 (76.87%)	0.260
Prednisone	99 (21.81%)	97 (21.37%)	0.870
Hydroxychloroquine	10 (2.20%)	10 (2.20%)	1.000
Azithromycin	255 (56.17%)	250 (55.07%)	0.740
Aspirin	81 (17.84%)	233 (51.32%)	<0.001
SSRI	43 (9.47%)	60 (13.22%)	0.075
Vit D therapy	242 (53.30%)	250 (55.07%)	0.590
Convalescent plasma	46 (10.13%)	39 (8.59%)	0.430
Monoclonal antibodies	5 (1.10%)	11 (2.42%)	0.130
Therapeutic anticoagulants/warf	156 (38.42%)	163 (38.90%)	0.890

All data were expressed with N (%), otherwise explained.
 BMI, body mass index; DVT, deep vein thrombosis; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor.

studies done in Denmark and Singapore showed similar results to our study, showing no difference in outcomes with statin therapy. However, a study conducted in Stockholm, Sweden presented an overall decrease in deaths, ICU admission and mechanical ventilation of about 30%

in statin users.¹⁰ In contrast, a study conducted in Hubei Province, China showed a mortality rate of 5.5% in patients on statin versus 6.8% in patients without statins.¹¹ Additionally, a retrospective study showed a mortality rate of 2.4% in statin patients compared with 3.7% in non-statin

Table 4 Adjusted effect of statin use on each outcome

Outcomes	Propensity score adjusted model			Propensity score matched model		
	RR	95% CI	P value	RR	95% CI	P value
Mortality	0.96	(0.75 to 1.23)	0.754	0.95	(0.75 to 1.21)	0.705
Mechanical ventilation	0.91	(0.70 to 1.19)	0.503	0.92	(0.71 to 1.18)	0.513
ICU transfer	0.96	(0.87 to 1.05)	0.395	0.96	(0.88 to 1.04)	0.345
O ₂ supplementation at time of discharge	1.03	(0.86 to 1.23)	0.729	1.06	(0.90 to 1.26)	0.458

ICU, intensive care unit; O₂, oxygen; RR, risk ratio.

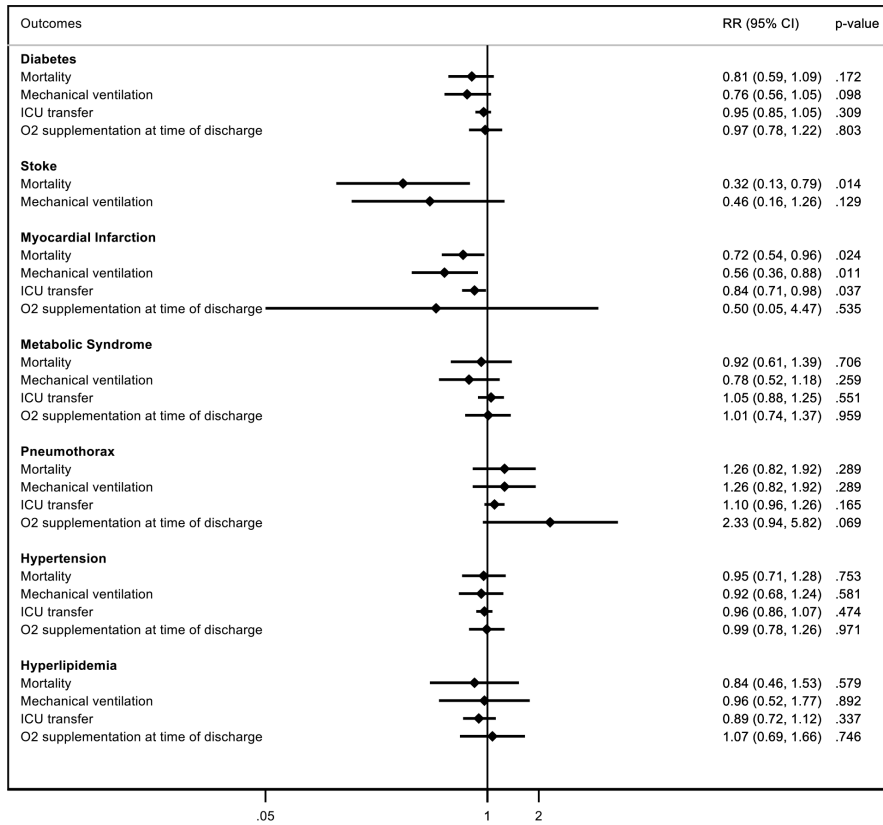


Figure 1 Effect of statin use compared with non-statin use on primary outcomes in the subgroup of patients with major comorbidities. RR, risk ratio; ICU, intensive care unit; O₂, oxygen.

patients.¹² Among studies conducted in patients with type 2 diabetes, one study observing the effects of statin revealed an increase in deaths in patients on statin medication than those without (12.8% vs 9.8%).¹³ In contrast, another study observing the same effect showed a 12% decrease in mortality in patients on statin therapy compared with those without.¹⁴ A review of the literature suggests there is a need for more research to confirm the efficacy of statins in the treatment of COVID-19.

However, in our study, among those patients with MI or strokes, statin therapy was associated with a significantly lower risk of mortality, mechanical ventilation, and ICU transfer than those not on statin therapy without any difference with oxygen supplementation at discharge and HLOS between groups. These results may be due to the anti-inflammatory properties of statin medications, decreasing the detrimental coagulation effects of the infection.¹⁴ Previous studies showed a decrease in inflammatory

markers in patients infected with COVID-19 and taking statin medications.¹¹

Through the activation of the clotting cascade from cytokine storms in COVID-19 infections, patients are at risk of MI and stroke. This is increasingly dangerous in Hispanic patients as they have a higher risk of cardiovascular disease due to the higher incidence of diabetes, obesity, and hypertension when compared with non-Hispanic whites.¹⁵ Through the use of statins, patients not only reduce their LDL cholesterol, but also the degree of inflammation, oxidative stress, and amount of proinflammatory mediators on the endothelium. It is speculated that statins are able to lower the degree of inflammation through their ability to decrease the toll-like receptor expression on immune cells.¹⁶ Decreased expressivity may lead to less inflammation contributing to the lower detrimental outcomes. In addition, statins are also able to increase the production of nitric oxide, the amount of circulating endothelial progenitor cells, and inhibit apoptosis of endothelium, thus reducing the detrimental effects of the disseminated intravascular coagulation.¹⁷ With all the effects of statin therapy, patients infected with the virus may have lower adverse effects from the MI, stroke, and pneumothorax caused through the cytokine storm.

Previous studies have shown that there has been an increase in the incidence of thromboembolic disorders in patients with COVID-19. A multisite study conducted in the Netherlands showed that patients with COVID-19 had similar thromboembolic patterns to patients who develop disseminated intravascular coagulation.¹⁸ Another study conducted in France showed that out of 34 consecutive

Table 5 Propensity scores-adjusted effect of statin on each outcome among patients with either stroke or myocardial infarction

Outcome variables	RR	95% CI	P value
Mortality	0.61	0.43 0.86	0.005
Mechanical ventilation	0.53	0.32 0.87	0.012
ICU transfer	0.81	0.69 0.94	0.005
O ₂ supplementation at time of discharge	0.49	0.06 0.67	0.490

ICU, intensive care unit; O₂, oxygen; RR, risk ratio.

patients, 27 patients (79%) presented with DVT.¹⁹ A meta-analysis conducted on the effects of statin therapy showed a decrease in the development of venous thromboembolism, while no statin therapy showed an increase in recurrence.¹⁶ While these studies did show the benefits of using statins in thromboembolic disorders, more research needs to be conducted on determining the effects on other thrombotic disorders, such as MI, stroke, and pneumothorax.

Compared with our study, we observed that these studies do not focus on a minority population that has a high prevalence of diabetes, such as the Hispanic population. There have not been many known COVID-19 studies evaluating medication effects exclusively on minority patients, especially the Hispanic population. With Hispanic patients having a unique set of comorbidities, studies like ours can help in their treatment of this infection. Through this study, we hope to change the narrative of the COVID-19 pandemic and aid in the treatment of those most susceptible to this virus. We also evaluated outcomes other than morbidity and mortality, such as ICU transfer, mechanical ventilation, and oxygen treatment postdischarge among living patients. Additionally, our study included the investigation of the multiple coagulation disorders that are seen in patients infected with COVID-19, such as MI and stroke. Our study also solely focused on the effects of statins and not concurrently with aspirin. Our results may have been limited due to the lack of randomness from selecting patients, such as specifically selecting patients on statin regimens. Differences may also be observed due to the severity of illnesses, such as comorbidities and secondary effects of the infection. Furthermore, we only collected information on statin use but not the duration of statin use. In addition, there may have been limitations in the size of the cohort, particularly for subgroup analyses, and future studies should be concluded to verify this.

CONCLUSION

We did not observe a significant association between statin medication use and patient mortality, mechanical ventilation, ICU transfer, O₂ supplementation at the time of discharge, nor HLOS. Thus, our study does not suggest benefit, nor any harm associated with statin use in Hispanic patients infected with COVID-19, and we therefore suggest that pre-existing statin use should not be discontinued during hospitalization due to COVID-19. There were, however, promising results found for the use of statin medications as part of a secondary COVID-19 treatment regimen for patients with comorbid MI or stroke.

Contributors SK and FD designed this study. SK, JE, TL, KT and KH participated in collecting data. FD and AD participated in data analysis. SK, FD and AD participated in interpreting the data. SK participated in self-drafting the manuscript. FD and AD participated in critical revision of the manuscript. All authors read and approved the final manuscript. FD and AD are responsible for the overall content as guarantors.

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REFERENCES

- Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: could an old friend help in the fight against COVID-19? *Br J Pharmacol* 2020;177:4873–86.
- Guindole D, Gabison EE. Role of CD147 (EMMPRIN/Basigin) in tissue remodeling. *Anat Rec* 2020;303:1584–9.
- Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol* 2021;113:45–57.
- Zhou Y, Chi J, Lv W, et al. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). *Diabetes Metab Res Rev* 2021;37:e3377.
- Aguayo-Mazzucato C, Diaque P, Hernandez S, et al. Understanding the growing epidemic of type 2 diabetes in the Hispanic population living in the United States. *Diabetes Metab Res Rev* 2019;35:e3097.
- Mackey K, Ayers CK, Kondo KK, et al. Racial and Ethnic Disparities in COVID-19-Related Infections, Hospitalizations, and Deaths: A Systematic Review. *Ann Intern Med* 2021;174:362–73.
- Dwivedi AK, Mallawaarachchi I, Lee S, et al. Methods for estimating relative risk in studies of common binary outcomes. *J Appl Stat* 2014;41:484–500.
- Butt JH, Gerds TA, Schou M, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. *BMJ Open* 2020;10:e044421.
- Tan WYT, Young BE, Lye DC, et al. Statin use is associated with lower disease severity in COVID-19 infection. *Sci Rep* 2020;10:17458.
- Bergqvist R, Ahlqvist VH, Lundberg M, et al. HMG-CoA reductase inhibitors and COVID-19 mortality in Stockholm, Sweden: a registry-based cohort study. *PLoS Med* 2021;18:e1003820.
- Zhang X-J, Qin J-J, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab* 2020;32:176–87.
- Fan Y, Guo T, Yan F, et al. Association of statin use with the in-hospital outcomes of 2019-Coronavirus disease patients: a retrospective study. *Front Med* 2020;7:584870.
- Cariou B, Goronflot T, Rimbert A, et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: results from the CORONADO study. *Diabetes Metab* 2021;47:101202.
- Saeed O, Castagna F, Agalliu I, et al. Statin use and in-hospital mortality in patients with diabetes mellitus and COVID-19. *J Am Heart Assoc* 2020;9:e018475.
- Shaw PM, Chandra V, Escobar GA, et al. Controversies and evidence for cardiovascular disease in the diverse Hispanic population. *J Vasc Surg* 2018;67:960–9.
- Greco S, D'Amuri A, Giorgini E, et al. Role of statins in Coronavirus-related disease (COVID-19): a retrospective cohort study in northern Italy. *High Blood Press Cardiovasc Prev* 2021;28:355–64.
- Florêncio FKZ, Tenório MdeO, Macedo Júnior ARA, et al. Aspirin with or without statin in the treatment of endotheliitis, thrombosis, and ischemia in coronavirus disease. *Rev Soc Bras Med Trop* 2020;53:e20200472.
- Klok FA, Kruij MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–7.
- Nahum J, Morichau-Beauchant T, Daviaud F, et al. Venous thrombosis among critically ill patients with coronavirus disease 2019 (COVID-19). *JAMA Netw Open* 2020;3:e2010478.