



Impact of In-hospital Statin Use on Mortality in COVID-19 Patients from a Majority African American Population

Nitish Sood , Dhairya Shukla MPH , Pranjal Mishra ,
Saloni Sharma , Sahil Gandhi , Daniel F. Linder PhD ,
Priyank Shah MD

PII: S0147-9563(23)00071-7
DOI: <https://doi.org/10.1016/j.hrtlng.2023.03.005>
Reference: YMHL 2182

To appear in: *Heart & Lung*

Received date: 19 August 2022
Revised date: 7 March 2023
Accepted date: 10 March 2023

Please cite this article as: Nitish Sood , Dhairya Shukla MPH , Pranjal Mishra , Saloni Sharma , Sahil Gandhi , Daniel F. Linder PhD , Priyank Shah MD , Impact of In-hospital Statin Use on Mortality in COVID-19 Patients from a Majority African American Population, *Heart & Lung* (2023), doi: <https://doi.org/10.1016/j.hrtlng.2023.03.005>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights:

- As of August 18th, 2022, the COVID-19 pandemic has claimed over 6,400,000 lives worldwide and over 1,000,000 lives in the United States.
- Prior retrospective studies exist in the literature, documenting that statins have a mortality benefit in patients hospitalized with COVID-19. These studies have focused on populations with a high proportion of Caucasians.
- This retrospective study examines a population that is majority African American and found no benefit of statins in patients hospitalized with COVID-19 in mortality, survival time, need for ICU care, length of ICU stay, need for ventilator, duration of intubation, or need for dialysis.
- Further research should be done examining the interplay between COVID-19, statins, and race/ethnicity to better elucidate whether statins have any beneficial effect in decreasing mortality caused by COVID-19.

Journal Pre-proof

Impact of In-hospital Statin Use on Mortality in COVID-19 Patients from a Majority

African American Population

Nitish Sood^a, Dhairya Shukla, MPH^a, Pranjali Mishra^a, Saloni Sharma^a, Sahil Gandhi^a, Daniel F.

Linder, PhD^a, Priyank Shah, MD^b

a. Medical College of Georgia, 1120 15th St, Augusta, GA 30912, USA

b. Department of Cardiology, Phoebe Putney Memorial Hospital, Albany, GA, USA.

Corresponding Author: Nitish Sood

1120 15th Street

Augusta, GA 30912

(678) 538-7214

NSood@augusta.edu

Journal Pre-proof

Abstract

Background: The COVID-19 pandemic has claimed over 6.4 million lives globally. Finding effective medications to reduce mortality in hospitalized COVID-19 patients remains critical. No previous study has been published on the effects of statin use in a majority African American COVID-19 patient population.

Objective: This study aims to assess the relationship between in-hospital statin use and mortality in this population.

Methods: A retrospective chart review of patients diagnosed with COVID-19 from March 2020 to June 2020 admitted to the Phoebe Putney Health System in Albany, Georgia, an early epicenter of the COVID-19 pandemic, was conducted. The outcomes of 735 hospitalized COVID-19 positive patients from over 40 counties in Georgia were analyzed. The primary outcome of interest was all-cause mortality, with secondary outcomes of interest of ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis. Multivariate logistic regression and Cox proportional hazards analysis were conducted to examine the effect of in-hospital statin use and mortality.

Results: 186 of 735 total patients were prescribed statins in-hospital. 83.8% were African American. Multivariate logistic regression found in-hospital statin use was not significantly associated with the primary outcome – all-cause mortality ($p=0.23$). Similar findings were seen in need for ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis ($p>0.05$). Additionally, results from a Cox proportional hazards model found in-hospital statin use was not associated with survival time. Sensitivity analysis conducted on only African American patients validated that in-hospital statin use was not associated with all-cause mortality in these patients. Of note, immunosuppression and severe disease

Impact of In-Hospital Statin Use on Mortality

presentation were associated with a six-fold increase in risk of mortality and the largest decreases in survival time.

Conclusion: It is possible statins have no mortality benefit for this patient population, but further research beyond this association study would need to be conducted to determine this conclusively. From this study, the best clinical recommendation would be to continue statins for COVID-19 patients with pre-hospital statin use and to launch a randomized clinical trial to definitively determine the efficacy of statins in the treatment of hospitalized COVID-19 patients.

Key Words: Cardiovascular; Emergency Medicine; Evidence-based Medicine; Infectious Diseases; Intubation; Length of Stay; Lipids; Outcomes Research

Introduction

Coronavirus Disease 2019 (COVID-19) was declared a worldwide pandemic by the World Health Organization on March 11, 2020.¹ As of August 18th, 2022, the pandemic has claimed over 6,400,000 lives worldwide and over 1,000,000 lives in the United States according to the Johns Hopkins Coronavirus Resource Center.² The virus works primarily by binding to angiotensin-converting receptor 2 on alveolar epithelial cells, whereby it activates the innate and adaptive immune systems and results in inflammation caused by a pro-inflammatory cytokine storm.³ While multiple therapies have been tried against COVID-19, no definitive cure has yet been found. Physicians must continue to evaluate previously approved drugs as adjunct therapies to reduce the clinical course severity of COVID-19. Statins are Food and Drug Administration approved 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors typically used to lower LDL-Cholesterol and reduce the risk of myocardial infarction or stroke.⁴

Due to statins' pleiotropic anti-inflammatory effects and ability to lower C-reactive protein, as demonstrated in the JUPITER trial, calls have also emerged for further research into the use of statins to improve outcomes in infectious diseases.⁵⁻⁸ Statins have been previously shown to be efficacious in observational cohort studies in reducing risk of sepsis in hospitalized patients as well as mortality from both bacterial and viral infections, suggesting the possibility of a similar effect in COVID-19 patients.⁹⁻¹¹ Recently concluded observational studies have found statins to be associated with a reduced risk of mortality in COVID-19 patients and Rodriguez-Nava et al 2020 found atorvastatin users had a longer time-to-mortality than atorvastatin non-users in COVID-19 patients admitted to the Intensive Care Unit (ICU).¹²⁻¹⁵

As physicians continue to alter the therapeutic protocol for COVID-19 patients, having more information about the effectiveness of these medications in different populations is especially valuable information. Positive effects of statin use for COVID-19 patients has been

Impact of In-Hospital Statin Use on Mortality

seen in previous observational studies; however, no study has yet been published on the impact of statin use on mortality in a majority African American patient population. This study aims to assess the impact of in-hospital statin use on outcomes for hospitalized COVID-19 patients in a predominantly African American population.

Journal Pre-proof

Methods

Participants and Data Collection

Following Institutional Review Board approval from Augusta University IRB Committee B (1603044-2), aggregate patient visit data was collected from Phoebe Putney Health System electronic medical records (Meditech and Athena Health). The authors abstracted each data element from each chart by manually reviewing each patient's medical record and extracting the relevant information. Each data point was then entered into a table by the research team. To ensure accuracy, the table was reviewed by a physician who independently verified each data point against the corresponding medical record. The system consists of 3 hospitals serving over 40 counties with an aggregate population of approximately 825,000 in rural South-west Georgia. Patients admitted to one of three Phoebe Putney hospitals between March 2, 2020 and June 13, 2020 for any reason with a confirmed positive COVID-19 test were included in the study. Criteria for a positive COVID-19 test included a positive initial or repeat nasopharyngeal swab for COVID-19 using a polymerase chain reaction (PCR). If the initial negative test result had been judged as a likely false-negative due to poor sampling technique or there was a high clinical pretest probability of COVID-19, a repeat test was performed on in-patients during hospitalization. Transfers from one in-system hospital to another were merged and considered as a single visit. Atorvastatin (lipitor) was administered to all patients who received a statin in-hospital. Patients taking a different statin at home were given an equivalent atorvastatin dose while hospitalized.

The primary outcome of interest was in-hospital mortality. Secondary outcomes of interest were need for ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis. The intervention of interest was in-hospital statin use. Variables

Impact of In-Hospital Statin Use on Mortality

relating to the intervention of interest were pre-admission statin use, duration of statin use, statin dosage, and statin use time from admission to discharge. The demographic and comorbid variables of age, gender, race, body mass index, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, peripheral arterial disease, chronic kidney disease, asthma, immunosuppression, COVID-19 disease presentation severity, and tobacco use were controlled for in the analyses. Severe COVID-19 disease presentation was defined as progression to one of the following: severe pneumonia as defined by the CURB-65 criteria, septic shock, or acute respiratory distress syndrome. All comorbidities were adjudicated based on the 10th version of the International Classification of Diseases (ICD-10).

Data Analysis

Analyses were conducted with R software (version 4.0.0) and Excel (version 2019). Bivariate descriptive statistics for the outcomes of interest and covariates by statin use group are reported as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Two-sample independent t-tests with Bonferroni corrections were used for testing differences in continuous variables, while chi-squared tests with Bonferroni corrections were used for testing homogeneity of categorical variables. The Bonferroni correction was used in the univariate analysis to adjust for the increased likelihood of a type 1 error arising from comparison of multiple endpoints and possible significant correlation between the endpoints.¹⁶ Logistic regression was conducted to analyze the relationship between mortality and statin use, while controlling for pre-admission statin use, duration of statin use, statin dosage, and statin use time from admission to discharge, age, gender, race, body mass index, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, chronic obstructive

Impact of In-Hospital Statin Use on Mortality

pulmonary disease, coronary artery disease, congestive heart failure, peripheral arterial disease, chronic kidney disease, asthma, immunosuppression, COVID-19 disease presentation severity, and tobacco use. Bidirectional stepwise regression was utilized to build the final model for mortality. In addition to analyzing mortality as a binary outcome, time-to-event analysis of the time from admission to mortality or discharge (treated as censored) was conducted by fitting a Cox proportional hazards model of time to mortality regressed onto in-hospital statin use and the covariates.¹⁷ All statistical analysis and hypothesis tests were performed at significance level $\alpha = 0.05$. All authors reviewed the manuscript and take responsibility for accuracy and completeness of data presented.

Results

The researchers conducted a retrospective analysis of 735 patients in Albany, Georgia diagnosed with COVID-19 to determine the effect of in-hospital statin use on mortality, need for ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis. 84% of these patients were African American, and 116 (17%) died during hospitalization. Of the 186 patients who received statins in-hospital, 153 (82%) survived to hospital discharge, while 33 (18%) did not.

Patients with in-hospital statin use were more likely to be older (66.8 years old) and have a history significant for hypertension (95.2%) and diabetes (60.2%). In contrast, patients without in-hospital statin use were younger (58.6) and less likely to have a history of hypertension (70.7%) or diabetes (36.1%). Other demographics, co-morbidities, and severity of disease at presentation were not significantly different between the two groups (Table 1). That patients with in-hospital statin use were more likely to be older, hypertensive, and diabetic likely reflects clinical indications for statin usage.

Table 1. Descriptive Table Comparing Baseline Demographics and Co-Morbidities of Patients with and without In-hospital Statin Use. All binary data are presented as counts (percentages) and continuous data are presented as mean (SE) unless otherwise indicated. P-values were adjusted using the Bonferroni correction.

The primary outcome of mortality and secondary outcomes: need for ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis were compared between patients with and without in-hospital statin use using the chi-squared test and two-sample t-tests with Bonferroni corrections. The most prevalent secondary outcome of interest was need for ICU hospitalization, occurring in 25.7% of all patients (Table 2). In contrast, the need for dialysis occurred in fewer than 7% of all patients. No significant difference was found in all-cause mortality between the in-hospital statin group (17.7%) and in the no in-

Impact of In-Hospital Statin Use on Mortality

hospital statin group (15.1%). Similar findings were observed in the need for ICU stay (29.6% in the in-hospital statin group and 24.4% in the no in-hospital statin group), length of ICU stay (11.7 days and 9.3 days), need for mechanical ventilator (19.9% and 18.4%), duration of intubation (7.7 days and 7.0 days), and need for dialysis (9.1% and 5.8%).

Table 2. Descriptive Table Comparing Secondary Outcomes of Interest by In-hospital Statin Use. All binary data are presented as counts (percentages) and all continuous data are presented as mean (SE), unless otherwise indicated. P-values were adjusted using the Bonferroni correction.

To adjust for the potential confounding effects of comorbidities, demographics, severity of disease upon presentation, and others, a multivariable logistic regression was performed (Table 3). Results from logistic regression analysis showed that after controlling for relevant covariates, neither in-hospital nor pre-admission statin use impacted mortality (Table 3). Multivariable logistic regressions (results not shown) also showed that in-hospital statin use did not impact any of the secondary outcomes of interest. Bidirectional stepwise regression was performed to identify a model that is parsimonious in the number of covariates. A logistic regression model was then fit using only those covariates that were identified in the final model from the stepwise regression procedure. Results from this final logistic regression analysis also indicated no statistically significant relationship between in-hospital or pre-admission statin use and the primary outcome (Table 3).

To adjust for the differences in hypertension and diabetes diagnoses between the two groups, a sensitivity analysis was conducted including only patients with hypertension or diabetes. All-cause mortality in this group did not differ between the two groups, further validating the results.

Five variables were found to be significantly associated with mortality in this patient population: increased age, male sex, obesity, severe disease presentation, and

Impact of In-Hospital Statin Use on Mortality

immunosuppression (Table 3). Of these variables, immunosuppression and severe disease presentation had the highest associations with mortality, with both associated with a 6-fold increase in likelihood of mortality. Male sex and obesity were associated with a two-fold increase in mortality, and every additional year of age was associated with an additional 5% risk of mortality.

Table 3. Multivariate Logistic Regression Examining the Effect of In-Hospital Statin Use on Mortality.

Time to mortality was also analyzed as an outcome of interest. Results from a Cox proportional hazards regression model including the variables of interest and control variables showed that in-hospital statin use was not associated with time to mortality, indicating patients who received in-hospital were not more likely to live longer than patients who did not receive in-hospital statins. However, increased age, male sex, severe disease presentation, and immunosuppression were associated with decreased survival time. Of these variables, positive immunosuppression status and severe disease presentation had the greatest reduction in survival times, with more than a three-fold increase in the hazards of mortality when compared to patients who were not immunosuppressed and more than two and a half times the hazards of mortality in those with severe disease presentation compared to those without.

Table 4. Cox Proportional Hazards Model Examining Factors Influencing Time-to-mortality. Significance was determined if $p < 0.05$.

A sensitivity analysis conducted on African American patients validated that in-hospital statin use was not associated with all-cause mortality. A subsequent sensitivity analysis found that in patients with hypertension or diabetes, all-cause mortality did not differ between the two groups.

Discussion

This study found that the use of statins during hospitalization for COVID-19 did not improve either the primary or secondary outcomes being investigated. Therefore, the data does not support the initiation of statins for COVID-19 patients who are not typically indicated for statin use. However, if COVID-19 patients are already taking statins, they should continue taking them, as statins are known to have long-term cardiovascular benefits, and the study did not find that statin use significantly decreased any of the outcomes of interest.

Our study also found that in-hospital statin use was not associated with the need for ICU care, length of ICU stay, need for mechanical ventilator, duration of intubation, and need for dialysis. These findings suggest that statin use in COVID-19 patients from a majority African American population may not have a significant impact on disease severity or organ dysfunction. Wei et al.¹⁸ conducted a retrospective study and found that decreased levels of low-density lipoprotein (LDL) and total cholesterol were associated with increased COVID-19 disease severity. They found that patients with COVID-19 develop hypolipidemia when they begin to show mild symptoms, and the level of dyslipidemia correlates with disease severity. This suggests a complex interplay between statins and COVID-19 on lipid levels, and even a possible cause of statin-induced exacerbations of COVID-19. While this study did not find any such evidence of an exacerbation, this may help explain why despite the anti-inflammatory properties of statins, there was no significant impact on the secondary outcomes of interest.

The findings of this study stand in contrast to many other studies, which demonstrate positive clinical outcomes for patients with statin usage.^{12, 13, 19, 20} This may be attributed to possible differential effects of statin therapy among African Americans and white patients. Currently, conflicting research exists on whether African Americans initiating statin therapy

Impact of In-Hospital Statin Use on Mortality

have similar lipid-lowering effects²¹ or have decreased lipid-lower effects than white patients do²².

In addition, while these results show that neither African American patients nor white patients had significant improvements in the primary or secondary endpoints, the study may have been underpowered to detect any significant benefit for non-African Americans as 84% of the study population were African Americans.

As the use of in-hospital statins did not influence any outcomes of interest in this study, this suggests that patients hospitalized with COVID-19 receiving statins prior to hospitalization should continue to be on statins. However, the secondary outcomes of interest in this study largely compromised of measures of respiratory or renal function, and did not include factors such as inflammatory markers or thromboembolic events, which prior studies have found were reduced by statin use.¹²⁻¹⁴

Additionally, anti-inflammatory characteristics associated with statin use found in other studies suggest an overall health benefit to consider. Statins have been previously shown to mediate multiple inflammatory pathways, including through circulating neutrophil counts, C-reactive protein, and interleukin 6. These pathways have been linked with the COVID-19-associated multiorgan syndrome, with significant amounts of inflammation mediating both intrapulmonary and extrapulmonary organ damage seen in this condition.²³ Indeed, RCTs have demonstrated the beneficial effect of statins *in vivo* in reducing proinflammatory cytokine release in patients with bacterial and viral pneumonia.

Studies have previously shown that African American patients are less likely to receive guideline recommended statin therapy for the management of dyslipidemia and cardiovascular disease. This is a complex and multifactorial issue, as explored by Nanna et al.²⁴ who suggested

Impact of In-Hospital Statin Use on Mortality

factors including decreased access to healthcare, insurance status, financial barriers, and trust in clinicians are among the causes of this issue. As African Americans are more likely to suffer from dyslipidemia compared to other racial and ethnic groups, the decreased access to statins in this population may exacerbate existing health disparities. While our study did not find a significant association between statin use and outcomes in COVID-19 patients, it is possible that statins may have a beneficial effect in certain subgroups of patients. The underuse of statins in African American patients could lead to missed opportunities for cardiovascular risk reduction and improved outcomes. Thus, efforts to address disparities in statin therapy are warranted, including strategies to improve access to healthcare, increase awareness and education among patients and providers, and promote guideline-adherent statin prescribing practices.

Certain limitations must be taken into consideration when analyzing the results of the study. First, the present analysis does not indicate the length of time a patient was on statins prior to admission for COVID-19 therapy. As such, patients with in-hospital statin usage include de novo statin patients and long-time statin patients, while patients with no in-hospital statin usage include those who have never received statins and long-time statin patients who were discontinued at admission. Third, retrospective chart reviews are more likely to suffer from confounding and selection bias.²⁵ However, as no randomized clinical trials have been conducted on this topic, such studies are critical in elucidating the relationship between statin use and mortality in hospitalized COVID-19 patients. Fourth, while many comorbid conditions, patient demographics, and details of statin therapy were all controlled for, the presence of other treatments were not controlled for, which could have served as confounders for statin therapy and possibly falsely insignificant results.

Conclusion

As COVID-19 continues to remain a world pandemic and a threat at large, identifying measures that can improve clinical outcomes for COVID-19 patients remains of paramount importance. Statins are known to have pleiotropic anti-inflammatory effects that can target inflammatory pathways involved in COVID-19 infection.^{5, 26} Although the exact pathways and molecules by which statins can modulate COVID-19 infection remains unidentified, many studies have found improved clinical outcomes with statin usage.¹²⁻¹⁴ Furthermore, the negative side effects of statins are well documented and relatively mild in comparison to the complications of COVID-19 infection. However, the results of this study do not show a significant positive benefit of in-hospital statin use as a standalone therapy for COVID-19 treatment. Therefore, the best clinical recommendation would be to continue statins for COVID-19 patients with pre-hospital statin use and to launch a randomized clinical trial to definitively determine the efficacy of statins in the treatment of hospitalized COVID-19 patients.

Acknowledgements

The authors acknowledge the help provided by Jennifer Hill and Krista Barfield for their help in data abstraction. DFL acknowledges an internal Augusta University Early Career Award that partially supported this work.

References:

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed.* Mar 19 2020;91(1):157-160. doi:10.23750/abm.v91i1.9397
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis.* May 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
3. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents.* May 2020;55(5):105954. doi:10.1016/j.ijantimicag.2020.105954
4. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol.* 2005;45:89-118. doi:10.1146/annurev.pharmtox.45.120403.095748
5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* Nov 20 2008;359(21):2195-207. doi:10.1056/NEJMoa0807646
6. Castiglione V, Chiriaco M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother.* Jul 1 2020;6(4):258-259. doi:10.1093/ehjcvp/pvaa042
7. Fedson DS, Opal SM, Rordam OM. Hiding in Plain Sight: an Approach to Treating Patients with Severe COVID-19 Infection. *mBio.* Mar 20 2020;11(2)doi:10.1128/mBio.00398-20
8. Dashti-Khavidaki S, Khalili H. Considerations for Statin Therapy in Patients with COVID-19. *Pharmacotherapy.* May 2020;40(5):484-486. doi:10.1002/phar.2397
9. Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet.* Feb 4 2006;367(9508):413-8. doi:10.1016/S0140-6736(06)68041-0
10. Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest.* Apr 2007;131(4):1006-12. doi:10.1378/chest.06-1997
11. Mortensen EM, Restrepo MI, Anzueto A. The Potential Role of Statins in Severe Sepsis. In: Rello J, Restrepo MI, eds. *Sepsis: New Strategies for Management.* Springer Berlin Heidelberg; 2008:19-28.
12. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care.* Jul 14 2020;24(1):429. doi:10.1186/s13054-020-03154-4
13. Zhang XJ, Qin JJ, Cheng X, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell Metab.* Aug 4 2020;32(2):176-187 e4. doi:10.1016/j.cmet.2020.06.015
14. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *J Am Coll Cardiol.* Aug 4 2020;76(5):533-546. doi:10.1016/j.jacc.2020.06.007
15. Santosa A, Franzén S, Nätman J, Wettermark B, Parmryd I, Nyberg F. Protective effects of statins on COVID-19 risk, severity and fatal outcome: a nationwide Swedish cohort study. *Sci Rep.* Jul 14 2022;12(1):12047. doi:10.1038/s41598-022-16357-2
16. Lee S, Lee DK. What is the proper way to apply the multiple comparison test? *Korean J Anesthesiol.* Oct 2018;71(5):353-360. doi:10.4097/kja.d.18.00242
17. Tellis GJ, Sood A, Nair S, Sood N. EXPRESS: Lockdown Without Loss? A Natural Experiment of Net Payoffs to Covid Lockdowns. *Journal of Public Policy & Marketing.* 2022;0(ja):07439156221143954. doi:10.1177/07439156221143954
18. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. *J Clin Lipidol.* May-Jun 2020;14(3):297-304. doi:10.1016/j.jacl.2020.04.008

Impact of In-Hospital Statin Use on Mortality

19. De Spiegeleer A, Bronselaer A, Teo JT, et al. The Effects of ARBs, ACEIs, and Statins on Clinical Outcomes of COVID-19 Infection Among Nursing Home Residents. *J Am Med Dir Assoc.* Jul 2020;21(7):909-914 e2. doi:10.1016/j.jamda.2020.06.018
20. Tan WYT, Young BE, Lye DC, Chew DEK, Dalan R. Statin use is associated with lower disease severity in COVID-19 infection. *Sci Rep.* Oct 15 2020;10(1):17458. doi:10.1038/s41598-020-74492-0
21. Lipworth L, Fazio S, Kabagambe EK, et al. A prospective study of statin use and mortality among 67,385 blacks and whites in the Southeastern United States. *Clin Epidemiol.* 2014;6:15-25. doi:10.2147/cep.S53492
22. Yood MU, McCarthy BD, Kempf J, et al. Racial differences in reaching target low-density lipoprotein goal among individuals treated with prescription statin therapy. *Am Heart J.* Oct 2006;152(4):777-84. doi:10.1016/j.ahj.2006.02.036
23. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* Jun 2020;20(6):363-374. doi:10.1038/s41577-020-0311-8
24. Nanna MG, Navar AM, Zakroysky P, et al. Association of Patient Perceptions of Cardiovascular Risk and Beliefs on Statin Drugs With Racial Differences in Statin Use: Insights From the Patient and Provider Assessment of Lipid Management Registry. *JAMA Cardiol.* Aug 1 2018;3(8):739-748. doi:10.1001/jamacardio.2018.1511
25. Sood N, Sangari A, Goyal A, Conway JAS. Predictors of survival for pediatric extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis. *Medicine (Baltimore).* Sep 30 2022;101(39):e30860. doi:10.1097/md.00000000000030860
26. Teixeira L, Temerozo JR, Pereira-Dutra FS, et al. Simvastatin Downregulates the SARS-CoV-2-Induced Inflammatory Response and Impairs Viral Infection Through Disruption of Lipid Rafts. *Front Immunol.* 2022;13:820131. doi:10.3389/fimmu.2022.820131

Table 1. Descriptive Table Comparing Baseline Demographics and Co-Morbidities of Patients with and without In-hospital Statin Use. All binary data are presented as counts (percentages) and continuous data are presented as mean (SE) unless otherwise indicated. P-values were adjusted using the Bonferroni correction.

Variables Examined	No In-hospital statin use (N=549)	In-hospital statin use (N=186)	Total (N=735)	P-value
Age	58.6 (18.1)	66.8 (12.8)	60.6 (17.3)	< 0.001
Sex (Male)	234 (42.6%)	78 (41.9%)	312 (42.4%)	1.000
Race				1.000
African American	463 (84.3%)	153 (82.3%)	616 (83.8%)	
Non-African American	86 (15.7%)	33 (17.7%)	119 (16.2%)	
Obese	206 (37.7%)	80 (43.0%)	286 (39.0%)	1.000
Morbidly Obese	133 (24.3%)	32 (17.2%)	165 (22.5%)	1.000
Hypertension	388 (70.7%)	177 (95.2%)	565 (76.9%)	< 0.001
Diabetes	198 (36.1%)	112 (60.2%)	310 (42.2%)	< 0.001
CAD	40 (7.3%)	27 (14.5%)	67 (9.1%)	0.077
CHF	74 (13.5%)	32 (17.2%)	106 (14.4%)	1.000
COPD	47 (8.6%)	26 (14.0%)	73 (9.9%)	0.819
Renal Disease	74 (13.5%)	42 (22.6%)	116 (15.8%)	0.081
Asthma	58 (10.6%)	27 (14.5%)	85 (11.6%)	1.000
Immunosuppression	24 (4.4%)	8 (4.3%)	32 (4.4%)	1.000
Smoking	93 (16.9%)	41 (22.0%)	134 (18.2%)	1.000
Severe Disease Presentation	272 (49.5%)	83 (44.6%)	355 (48.2%)	1.000

Impact of In-Hospital Statin Use on Mortality

Table 2. Descriptive Table Comparing Secondary Outcomes of Interest by In-hospital Statin Use.

All binary data are presented as counts (percentages) and all continuous data are presented as mean (SE), unless otherwise indicated. P-values were adjusted using the Bonferroni correction.

Outcomes of Interest	No In-hospital statin use (N=549)	In-hospital statin use (N=186)	Total (N=735)	P-value
Mortality	83 (15.1%)	33 (17.7%)	116 (15.8%)	1.000
Need for ICU	134 (24.4%)	55 (29.6%)	189 (25.7%)	1.000
Length of Stay (Days)	9.3 (10.1)	11.7 (12.1)	9.9 (10.7)	0.224
Need for Ventilator	101 (18.4%)	37 (19.9%)	138 (18.8%)	1.000
Length of Intubation (Days)	2.2 (7.0)	2.4 (7.7)	2.3 (7.2)	1.000
Dialysis	32 (5.8%)	17 (9.1%)	49 (6.7%)	1.000

Table 3. Multivariate Logistic Regression Examining the Effect of In-Hospital Statin Use on Mortality

Independent Variables		All variables		Stepwise regression variables	
		OR [95% CI]	P	OR [95% CI]	P
Variables of Interest	In-hospital Statin Use	3.10 [0.46 - 18.92]	0.23	3.03 [0.44 - 19.11]	0.24
	Pre-admission Statin Use	1.46 [0.87 - 2.44]	0.15	1.51 [0.9 - 2.51]	0.11
	Total Statin Duration	0.99 [0.94 - 1.04]	0.80	0.99 [0.94 - 1.04]	0.78
	Statin time from admission	0.83 [0.63 - 1.00]	0.10	0.82 [0.63 - 1.00]	0.09
	Dosage (10mg daily)	1.43 [0.31 - 7.61]	0.65	1.52 [0.34 - 7.85]	0.59
	Dosage (20mg daily)	1.09 [0.25 - 5.47]	0.90	1.16 [0.27 - 5.75]	0.85
	Dosage (40mg daily)	0.97 [0.23 - 4.62]	0.97	1.00 [0.24 - 4.71]	1.00
	Statin duration percentage	0.26 [0.05 - 1.60]	0.14	0.27 [0.05 - 1.63]	0.14
Control Variables	Age	1.05 [1.03 - 1.07]	<0.01	1.05 [1.03 - 1.07]	<0.01
	Sex (Male)	2.34 [1.45 - 3.82]	<0.01	2.25 [1.42 - 3.60]	<0.01
	Race (Non-African American)	1.00 [0.52 - 1.86]	0.99		
	Obese	1.73 [1.02 - 3.00]	0.05	1.75 [1.04 - 2.97]	0.04
	Severe Disease Presentation	5.53 [3.32 - 9.49]	<0.01	5.53 [3.35 - 9.49]	<0.01
	Hypertension	1.38 [0.66 - 3.06]	0.41		
	Diabetes	1.40 [0.87 - 2.27]	0.17	1.52 [0.96 - 2.46]	0.08
	CAD	1.54 [0.73 - 3.13]	0.24	1.68 [0.84 - 3.32]	0.13
	CHF	1.28 [0.70 - 2.32]	0.42		
	COPD	1.00 [0.47 - 2.03]	1		
	Renal Disease	1.27 [0.70 - 2.25]	0.42		
	Asthma	1.23 [0.60 - 2.41]	0.56		
	Immunosuppression	6.17 [2.53 - 15.03]	<0.01	6.11 [2.53 - 14.88]	<0.01
	Smoking	1.01 [0.57 - 1.77]	0.96		

Table 4. Cox Proportional Hazards Model Examining Factors Influencing Time-to-mortality. Significance was determined if $p < 0.05$.

Independent Variables		Hazard Ratio	Significant
Variables of Interest	In-hospital Statin Use	1.34 [0.30 - 5.95]	
	Pre-admission Statin Use	1.78 [1.16 - 2.75]	*
	Total Statin Duration	0.86 [0.81 - 0.91]	*
	Statin time from admission	0.91 [0.75 - 1.09]	
	Dosage (10mg daily)	0.78 [0.22 - 2.77]	
	Dosage (20mg daily)	0.71 [0.21 - 2.47]	
	Dosage (40mg daily)	0.67 [0.20 - 2.21]	
	Statin duration percentage	6.67 [0.34 - 130.04]	
Control Variables	Age	1.03 [1.02 - 1.05]	*
	Sex (Male)	1.78 [1.18 - 2.68]	*
	Race (Non-African American)	1.13 [0.67 - 1.91]	
	Obese	1.40 [0.88 - 2.22]	
	Severe Disease Presentation	2.62 [1.64 - 4.20]	*
	Hypertension	1.25 [0.63 - 2.46]	
	Diabetes	1.20 [0.80 - 1.80]	
	CAD	1.05 [0.59 - 1.88]	
	CHF	1.37 [0.84 - 2.24]	
	COPD	1.10 [0.59 - 2.04]	
	Renal Disease	1.13 [0.70 - 1.82]	
	Asthma	1.13 [0.62 - 2.08]	
	Immunosuppression	3.37 [1.80 - 6.28]	*
	Smoking	0.96 [0.59 - 1.57]	

Conflict of Interest

Declaration: No authors have any conflicts of interest.

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

Journal Pre-proof