Association of Statins and 28-Day Mortality in Patients Hospitalized with SARS CoV-2 Infection

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Abbreviations: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Coronavirus disease 2019 (COVID-19), Massachusetts General Hospital (MGH), Angiotensin-converting enzyme-2 (ACE-2), Aspartate Aminotransferase test (AST), Alanine Aminotransferase test (ALT), Intensive Care Unit (ICU), Hazard Ratio (HR), Confidence Interval (CI), acute respiratory distress syndrome (ARDS), Enterprise Data Warehouse (EDW), Body Mass Index (BMI), white blood cell count (WBC), C-reactive protein (CRP), HIV (Human Immunodeficiency Virus), Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), Interquartile range (IQR), Non-alcoholic Fatty Liver Disease (NAFLD), Absolute lymphocyte count (ALC), Creatine Kinase (CK)

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Summary of article:

In our retrospective study evaluating the impact of in-hospital statin usage among 1179 patients with SARS-CoV-2, we found that statin use both in patients who did and did not use statins prior to hospitalization was associated with reduced 28-day mortality.
Abstract

Background: Statins may be protective in SARS-CoV-2 infection. The aim of this study was to evaluate the effect of in-hospital statin use on 28-day mortality and ICU admission among patients with SARS-CoV-2 stratified into 4 groups: those who used statins prior to hospitalization (continued, discontinued) and those who did not (newly initiated, never).

Methods: In a cohort study of 1179 patients with SARS-CoV-2, chart review was used to assess demographics, laboratory measurements, comorbidities, and time from admission to death, ICU admission, or discharge. Using marginal structural Cox models, we estimated hazard ratios for mortality and ICU admission.

Results: Among 1179 patients, 676 (57%) were male, 443 (37%) were at least 65 years old, and 493 (46%) had a BMI ≥30. Inpatient statin use reduced the hazard of death (HR 0.566, P = 0.008). This association held among patients who did and did not use statins prior to hospitalization (HR 0.270, P=0.003; HR 0.493, P=0.038). Statin use was associated with improved time-to-death for patients > 65 years, but not patients ≤ 65 years.

Conclusion: Statin use during hospitalization for SARS-CoV-2 infection was associated with reduced 28-day mortality. Well-designed randomized control trials are needed to better define this relationship.

Key Words: COVID-19, Statins, Mortality, Inpatient Hospitalization, marginal structural model
Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the associated disease (COVID-19) has resulted in millions of deaths (1). During the initial rush for treatments, over 100 off-label drugs were used to treat patients with COVID-19 (2). Off-label statin use was considered early in the pandemic at Massachusetts General Hospital (MGH) for several reasons, including: reports of cardiac complications due to COVID-19 (3, 4) and the cardioprotective effect of statins (5, 6); statins are low cost and generally safe (7); and statins blunt the hyperinflammatory response from infection (8, 9). It was also suggested that statins block SARS-CoV-2 infectivity via binding to the main protease mediating viral entry, inhibiting the virus’ ability to invade cells (10).

The safety and efficacy of statins for the treatment of patients hospitalized with COVID-19 has remained uncertain. Prior to the COVID-19 pandemic, the impact of statins in acute respiratory distress syndrome (ARDS) and sepsis was unclear (11-13), with some trials showing no impact on mortality (14-16), while others found a significant improvement (17-19). Observational studies have similarly yielded mixed results regarding the effects of statins in COVID-19. These investigations have been limited by small sample size (20-23), insufficient adjustments for time varying confounders (20, 24, 25), and lack of a sub-cohort newly initiated on statins for COVID-19 (24, 26-28).

During Spring 2020, physicians at MGH created clinical guidelines that recommended starting statin therapy on patients hospitalized for severe COVID-19 with pre-existing primary indications (29, 30). Clinicians were advised to continue pre-hospital statins and to start atorvastatin 40 mg daily on patients who had an evidence-based indication. Based upon the discretion and clinical judgement of the physician, many patients both with and without pre-existing cardiovascular disease, were started on statin therapy. This placed MGH in a unique position to investigate empirically the impact of starting patients on statin therapy during hospitalization due to COVID-19.
The aim of our study was to evaluate the effect of statins on 28-day time to death in patients hospitalized with COVID-19, using robust models to account for variable timing of statin initiation and competing risks. We further aimed to evaluate the specific effect of new statin initiation on survival.

Methods

Patient Selection

This study utilizes a previously described cohort of patients hospitalized at MGH (31). Inclusion criteria included ≥ 18 years of age confirmed SARS-CoV-2 infection with reverse transcriptase-polymerase chain reaction testing, and hospitalization between March and June 2020. This study was approved by the local Institutional Review Board (IRB # 2020P000829); a waiver of informed consent was granted.

Statin Exposure

Following manual chart review, supplemented by medication orders automatically extracted from electronic health records, patients were categorized into four groups: (A) continued home statin during hospitalization (“continued”), (B) discontinued home statin during hospitalization (“discontinued”), (C) newly initiated statin during hospitalization (“newly initiated”), and (D) did not use statins during or prior to hospitalization (“never”) [Figure 1]. When manual chart review from the patient registry (30) was in conflict with the electronic medication order data, Z.N.M. resolved any conflicts with an additional round of manual chart reviews.
Covariates and Outcomes

Chart abstractors collected information on age, sex, smoking status, medical comorbidities, medications, and date of hospital admission, ICU admission, death, and discharge within 28 days of presentation to care. Laboratory values, self-reported race/ethnicity and body mass index (BMI) were extracted from the electronic health record.

The primary outcome was time to death. Patients discharged to palliative care were classified as deceased on the day of their discharge. The secondary outcome was time to ICU admission or death. For this outcome, a patient must have initiated statins during hospitalization but prior to ICU admission to be categorized as newly initiated or continued.

Statistical Analysis

We examined differences between baseline characteristics among the four statin groups, reporting Fisher’s exact test for categorical variables and Kruskal-Wallis test by ranks for continuous variables.

Analyses that stratify patients by in-hospital statin use are subject to both immortal time bias and time-varying confounding, as a patient’s changing health condition affected when and whether they initiated statins (32). Therefore, we used marginal structural Cox proportional hazards models to evaluate the effect of statins (33). Patients discharged alive or transferred to a non-palliative care facility were categorized together as discharged. To fit the marginal structural Cox model, we fit a pooled multinominal regression to account for discharge as a competing risk, (34) and used inverse-probability weights that were stabilized and trimmed at the 5th and 95th percentiles. If patients did not experience the outcome and were not discharged by 28 days, they were administratively censored. We estimated the hazard ratio of each outcome for initiating statins vs. not initiating statins by the previous day.

The following baseline variables were included as confounders: demographic variables (sex, age>65 years, race, active smoker, BMI>30), comorbidities on admission (coronary artery disease,
congestive heart failure, hypertension, diabetes, dyslipidemia, chronic liver disease, active cancer, pulmonary disease), ACE inhibitor use at presentation to care, number of days from March 1st, 2020 to the date of hospitalization to account for era effect, and prior statin usage. The following time-varying daily lab measurements were included and log-transformed: absolute lymphocyte count, white blood cell count (WBC), aspartate aminotransferase (AST), C-reactive protein (CRP), creatine kinase (CK) and alanine aminotransferase (ALT). To account for missing data, we used multiple imputation with 25 imputations. Peak lab values were calculated for each statin group, defined as the highest lab measurement observed between hospital admission to the end of follow-up.

For the primary outcome of mortality, we also adjusted for ICU admission status each day as a time-varying confounder. 95% confidence intervals and p-values were calculated, accounting for the uncertainty due to estimation of the weighting models (34), and results across imputations were combined using Rubin’s rules (35).

The analysis was repeated for the primary and secondary outcomes on the subset of patients who were not prior users (“Newly initiated” vs. “Never”) and patients who were prior users (“Continued” vs. “Discontinued”). In total, six models were fit. All analyses were conducted in R Version 4.0.2 (36). The nnet package (37) was used to fit the multinomial regression model and the jomo package (38) was used to perform multiple imputation. A Benjamini-Hochberg correction was applied to control the false discovery rate (39).
Sensitivity Analyses

An additional analysis was performed using E-values to assess robustness of the observed results to unmeasured confounding. The E-value assesses how strong an unmeasured confounder would have to be to fully explain away the observed results (40). We also assessed whether the effect of statins differed in patients above and below 65 years of age. First, we fit the marginal structural models including an interaction term between statin initiation and whether a patient was over 65 years old, and then repeated the analysis, stratifying by whether patients were over 65. Finally, we assessed whether exclusion of patients who were admitted to the ICU on the same day of their hospital admission affected the relationship between statin initiation and the primary outcome of mortality.

Results

Baseline Characteristics

Overall, 1179 adult patients with confirmed SARS-CoV-2 were included, after the exclusion of 7 patients who were deceased, discharged, or censored on the day of their hospital admission (Supplementary Table 1). 676 (57%) were male, 443 (38%) were at least 65 years old, and 493 (46%) had a BMI ≥30. Patient characteristics differed by statin group (Table 1). Patients on statins prior to hospitalization (groups A and B) were older (median age 69 vs. 52 years, P < 0.001), and had higher rates of coronary artery disease (29% vs 3%, P < 0.001), congestive heart failure (19% vs. 5%, P < 0.001), hypertension (74% vs. 34%, P< 0.001), type 2 diabetes (56% vs. 17%, P < 0.001), and dyslipidemia (67% vs. 16%, P < 0.001) than those not on statins prior to hospitalization (groups C and D). White/non-Hispanics were more likely to be on statins prior to hospitalization than Hispanics (56% of White/non-Hispanics on statins vs. 33% of Hispanics on statins, P < 0.001).

In total, 777 patients (66%) received a statin during their hospitalization for COVID-19. 274/285 (96%) patients newly initiated statins and 331/434 (76%) patients continued on statins were prescribed atorvastatin. The most common dosage was atorvastatin 40mg daily. Among those continued on statins,
the majority were prescribed statins for more than a year prior to hospitalization (244/466, 52%).

**Supplementary Table 2** contains information on when statins were initiated during hospitalization relative to admission date.

According to first laboratory measurements obtained during hospitalization, patients who discontinued statins at hospitalization had higher erythrocyte sedimentation rate (P = 0.046), CK (P = 0.001), troponin (P < 0.001), and D-dimer (P = 0.002) compared to the other cohorts (**Table 1**).

*Unadjusted Analysis*

In this cohort, 154 (13%) patients died and 841 (71%) were discharged within 28 days. In unadjusted analyses, patients on statins during hospitalization had similar rates of death (108 (14%) vs. 46 (11%), P = 0.273), but higher rates of ongoing hospitalization at 28 days (144 (19%) vs. 40 (10%), P < 0.001) and ICU admission (276 (36%) vs. 85 (21%), P < 0.001) than those not on statins during hospitalization (**Table 2**).

*Peak Laboratory Values*

Unadjusted peak liver biochemistries and inflammatory markers differed across statin groups (**Table 3**), with the highest peaks of AST and ALT in the newly initiated statin group. Patients newly initiated on statins had a lower peak CK than those who discontinued statins (median and interquartile range: 222 [90-636] U/L vs. 374 [89-838] U/L), but higher peak CK than those who continued (178 [85-507] U/L) or were never on statins (173 [78-578] U/L).
Primary Outcome Analysis

The median time to death in each statin group can be found in Table 1. Overall, statin usage during hospitalization decreased the hazard of death (HR 0.566 [95% CI 0.372, 0.862], P=0.008). In the sub-group of patients *not on statin* therapy prior to hospitalization, new statin initiation at hospitalization decreased the hazard of death (HR 0.493 [95% CI 0.253, 0.963], P=0.038). Of the sub-group of patients *on statin* therapy prior to hospitalization, continued statin usage also decreased the hazard of death (HR 0.270 [95% CI 0.114,0.637], P=0.003) (Figure 2). A summary of the distribution of missing laboratory measurements can be found in Supplementary Table 3.

Secondary Outcome Analysis

198 patients were excluded from secondary outcome analyses because they were admitted to the ICU on their day of hospitalization (Supplementary Table 1). Of the 981 patients remaining, 588 (60%) used statins during their hospitalization. Statin use during hospitalization did not change the hazard of the composite outcome of death or ICU admission (HR 0.846 [95% CI 0.600,1.192], P=0.340) (Figure 2 and Supplementary Table 4).

Sensitivity Analyses

For the primary outcome assessing mortality, the point estimate and the upper confidence limit of the E-value associated with statin use during hospitalization are 2.326 and 1.455, respectively. Given that the E-value of 2.326 is much greater than any observed known risk factors examined in the current study (with the exception of age), it is unlikely that an unmeasured confounder exists that would explain away the observed effect in the present analysis. The point estimate and the upper confidence limit of the E-value associated with new initiation of statins are 2.639 and 1.191, respectively. For continuation of statins, these values are 4.305 and 2.073, respectively.
When an interaction term between statin use and being over 65 years old was included in the model, the interaction term was observed to be statistically significant for the primary outcome when including all participants (HR 0.293, P=0.009) and newly initiated vs. never (HR 0.194, P=0.008), which indicated that statins were more protective among patients over 65 years of age (Supplementary Table 5). When analyses were repeated stratifying by whether patients were over 65 years of age, statin use during hospitalization did not change the hazard of death in patients ≤ 65 years (n=736, HR 1.175 [95% CI 0.520, 2.655], P=0.699) (Supplementary Table 6); however, patients > 65 years were found to have a decreased hazard of death with any statin use during hospitalization (n=443, HR 0.477 [95% CI 0.292, 0.78], P=0.003) and within the subgroup of patients newly initiated on statins during hospitalization (HR 0.321 [95% CI 0.137, 0.752], P= 0.009) (Supplementary Table 7).

When patients who were admitted to the ICU the same day as their hospital admission were excluded from analyses of the primary outcome, the protective effect of statins was preserved, whether or not analyses were restricted to patients who had statin usage prior to hospitalization (Supplementary Table 8).

Discussion

In this large cohort from a single tertiary medical center, we found that statin use during hospitalization for COVID-19 was associated with reduced short-term mortality. The survival benefit was seen in both those who continued and those who newly initiated therapy while hospitalized. In sensitivity analyses, statin use was associated with reduced mortality for patients older than 65 years, but not 65 years old or younger. The protective association of statins against mortality was preserved even when patients who were admitted immediately to the ICU were excluded from the analysis.
Our study confirms and expands on prior work. A recent propensity score-matched analysis found that statin use prior to hospitalization reduces the risk of short-term in-hospital mortality from COVID-19 (27). This study probed further, into whether in-hospital statin use had a similar effect on mortality. To investigate the impact of statins administered during hospitalization, we used marginal structural models, which account for both survivorship bias (i.e., patients need to survive long enough to begin statins) and time-varying confounding bias (i.e., patient health status during hospitalization changes over time, affecting the likelihood of initiating treatment). Our study accounted for a wide variety of time-varying confounders, which we believe accurately captures temporal shifts in the likelihood of initiating treatment. We further expanded on prior literature by specifically evaluating the effect of statin initiation during hospitalization without prior use, because 26% of our cohort was newly initiated on statins during COVID-19 hospitalization. Overall, the novel findings presented here are that statin therapy during hospitalization, whether it be a new or continued prescription, was associated with reduced mortality.

The composition of our cohort was similar to other published patient databases of patients with COVID-19 (21, 26, 28). The median age of patients was 60 years old (IQR 47-73 years). Obese patients with a BMI $\geq$30 represented almost half the population (46%), a similar rate to prior studies (21, 26, 41) and consistent with evidence that obesity is a risk factor for hospitalization with COVID-19 (42). Racial and ethnic demographics vary immensely across the literature. However, it is important to note that nationwide, large observational studies have illustrated that underserved communities and people of color are more likely to be hospitalized for COVID-19 (43). This study re-enforces these findings, with the majority of patients identifying with a race or ethnicity other than Caucasian (61%), with Hispanic patients (36.4%) being the most common, followed by Asian and Native American patients (13%), and Black/Non-Hispanic patients (10.8%). This cohort’s mortality rate (13.1%) was similar to the mean published United States hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic (11.8%) among 955 hospitals (44).
Our findings contradict some prior reports. One meta-analysis of 3,449 patients in 9 observational studies found that statin use did not improve severe outcomes or mortality in COVID-19 (45). The majority of these studies were small in size (as few as 50 patients) and most failed to control for potential confounders. Comorbidities such as diabetes, cardiovascular disease and obesity are established risk factors for more severe COVID-19 disease, and patients prescribed statins are more likely to have these comorbidities, highlighting the critical need to control for confounding in this analysis (22). Additionally, most prior work either examined the relationship with antecedent statin usage prior to hospitalization (23, 25-28) or exclusively during hospitalization (20, 22, 24). Our study had several advantages: we investigated the influence of statin use both prior to and during hospitalization, minimized immortal time bias, adjusted for time-varying confounders, and minimized era effect (or the potential changes in COVID-19 care over time). These advantages provide clarity not offered by previous studies.

The duration of statin therapy required to provide mortality benefit in COVID-19 remains unclear. This study suggests that statins do not cause harm and may be associated with a survival benefit even after brief exposure during hospitalization. The reduced hazard of death associated with statin usage was greatest in patients continued on statin therapy, suggesting that the benefit seen with statin exposure may be greater with longer exposure to statins prior to illness. It is important to note that while patients newly started on statins were found to have an associated mortality benefit, this cohort was also found to have higher levels of ICU admission compared to patients continued on antecedent statin usage. As table 1 illustrates, patients newly initiated on statins were found to have higher levels of inflammatory markers compared to the antecedent statin usage group, CRP (85, (48-152)), ESR (49 (35-84)), and D-dimer (1554 (826-6580)). While our data does not prove this, it is theoretically possible that statin usage prior to viral infection may blunt the inflammatory response caused by both the virus and the immune system. For instance, in a prior phase-2 randomized, placebo-controlled, multicenter trial investigating the impact of atorvastatin on severe sepsis, the investigators found that prior statin use decreased interleukin-6 levels and reduced mortality, however, this was not seen in statin naïve patients receiving in-hospital statin
exposure only (11). Further insight is needed on a possible dose and duration effect. Interestingly, in a recent Cochrane systematic review that assessed the effects of early administered statins on patients with acute coronary syndrome, they found no significant reduced risk of death, non-fatal myocardial ischemia or stroke at 1 month (46). Further study is needed on the main therapeutic mechanism of action of statins on patients infected with SARS-COV-2 and how this may differ from the benefits seen in cardiovascular disease. Given the association between COVID-19 infection and a hyperinflammatory response that provokes end organ damage (6), it is possible that new initiation of statins even for a short duration could have provided a positive impact on both mortality and secondary complications.

Another proposed explanation for statins’ mechanism of action in COVID-19 is the drug’s ability to inhibit hydroxymethylglutaryl-coenzyme A reductase, which may interfere with the virus’ invasion into cells by compromising the lipid-rich membrane required for SARS-CoV-2 to interact with the cellular receptor angiotensin-converting enzyme 2 (47). If statins improve COVID-19 outcomes by inhibiting viral cell invasion, the benefit may be enhanced when statins are prescribed before infection.

In this study, we found an association with mortality benefit with statin use in adults over 65 years old but not in patients 65 years or younger. Given these findings were generated from a sensitivity analysis, we hesitate to provide age cut-offs for statin initiation for the treatment of COVID-19, but do not believe that age should be a contraindication to statin use during COVID-19 hospitalization.

Liver biochemistries are frequently elevated in severe COVID-19 disease and are associated with worse clinical outcomes (48). Separately, statins are known to increase liver biochemistries in certain patients (42). In our study, newly initiated statin use was associated with higher levels of peak AST and ALT throughout hospitalization; however, only 16% of patients on statins developed an ALT level greater than 5 times the upper limit of normal, which is a similar rate compared other cohorts with severe COVID (49). These findings are limited in that peak levels could have occurred before or after statin initiation and
were unadjusted for confounding. Despite these limitations, there is no clear evidence that statin exposure during infection is associated with clinically important hepatotoxicity.

Myotoxicity is a known, albeit rare, complication of statins. In the context of COVID-19, where creatinine kinase elevations are prevalent, there is concern that statins could increase myotoxicity and subsequent creatinine kinase-induced nephrotoxicity. This was not seen among individuals newly initiated on statins or continued on statin therapy, with creatinine kinase peak levels never reaching three times the upper limit of normal, considered the threshold for acute kidney injury due to pigment associated nephropathy (50).

Our findings must be interpreted in the context of study design. Although we utilized two data sources to confirm demographics, medications, laboratory data and clinical outcomes, misclassification errors are possible. We limited this error rate by employing physician review of discrepant data. Additionally, we were unable to account for patients who had dose escalations in their statin usage or who had their statin temporarily held during hospitalization. Finally, patients who were on statin therapy prior to hospitalization but had the medication discontinued during hospitalization, presumably due to organ dysfunction, are a unique sub-cohort of patients that warrant further exploration, and there may be additional unmeasured time-varying factors that explain their poorer outcomes. Given the safety and availability of statins worldwide, a randomized controlled trial of statins in COVID-19 should be considered.
Figure 1. Definition of Statin Treatment Groups

Figure 2: Marginal Structural Model Outputs for Primary and Secondary Outcomes.

Estimates were obtained from fitting marginal structural Cox models adjusted for the following baseline covariates: sex, age $\geq$ 65 years, race, active smoker, BMI $\geq$ 30, comorbidities on admission (coronary artery disease, congestive heart failure, hypertension, diabetes, dyslipidemia, chronic liver disease, active cancer, pulmonary disease), ACE inhibitor use, number of days since March 1st, 2020, and prior statin usage. The following time-varying covariates were adjusted for as well: ALC, WBC, AST, CRP, CK, ALT, and ICU admission status. Models were fit accounting for immortal time bias, time-varying confounding, and discharge as a competing risk. Applying a Benjamini-Hochberg correction to the primary outcome analysis, the three calculated p-values all fall below the corrected significance thresholds: 0.003 < 0.017, 0.008 < 0.033, and 0.038 < 0.05.
References:

1. United States COVID-19 Cases and Deaths by State [Internet]. U.S. Department of Health & Human Services. 2020. Available from: https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days.

2. Fajgenbaum DC, Khor JS, Gorzewski A, Tamakloe MA, Powers V, Kakkis JJ, et al. Treatments Administered to the First 9152 Reported Cases of COVID-19: A Systematic Review. Infect Dis Ther. 2020;9(3):435-49. Epub 2020/05/27. doi: 10.1007/s40121-020-00303-8. PubMed PMID: 32462545; PubMed Central PMCID: PMC7251321.

3. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020;141(20):1648-55. Epub 2020/03/21. doi: 10.1161/CIRCULATIONAHA.120.046941. PubMed PMID: 32200663.

4. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, et al. The Variety of Cardiovascular Presentations of COVID-19. Circulation. 2020;141(23):1930-6. Epub 2020/04/03. doi: 10.1161/CIRCULATIONAHA.120.047164. PubMed PMID: 32243205; PubMed Central PMCID: PMC7314498.

5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10. doi: 10.1001/jamacardio.2020.0950. PubMed PMID: 32211816; PubMed Central PMCID: PMC7097841.

6. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. J Am Coll Cardiol. 2020. Epub 2020/06/05. doi: 10.1016/j.jacc.2020.06.007. PubMed PMID: 32517963; PubMed Central PMCID: PMC7279721.

7. Salami JA, Warraich H, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, et al. National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013: Insights From the Medical Expenditure Panel Survey. JAMA Cardiol. 2017;2(1):56-65. doi: 10.1001/jamacardio.2016.4700. PubMed PMID: 27842171.

8. Sapey E, Patel JM, Greenwood H, Walton GM, Grudzinska F, Parekh D, et al. Simvastatin Improves Neutrophil Function and Clinical Outcomes in Pneumonia. A Pilot Randomized Controlled Clinical Trial. Am J Respir Crit Care Med. 2019;200(10):1282-93. doi: 10.1164/rccm.201812-2328OC. PubMed PMID: 31206313; PubMed Central PMCID: PMC6857486.

9. Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. Nat Rev Immunol. 2019;19(2):104-17. doi: 10.1038/s41577-018-0094-3. PubMed PMID: 30487528.
10. Reiner Ž, Hatamipour M, Banach M, Pirro M, Al-Rasadi K, Jamialahmadi T, et al. Statins and the COVID-19 main protease. Arch Med Sci. 2020;16(3):490-6. Epub 2020/04/25. doi: 10.5114/aoms.2020.94655. PubMed PMID: 32399094; PubMed Central PMCID: PMC7212226.
11. Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med. 2013;187(7):743-50. doi: 10.1164/rccm.201209-1718OC. PubMed PMID: 23348980.
12. Kopterides P, Falagas ME. Statins for sepsis: a critical and updated review. Clin Microbiol Infect. 2009;15(4):325-34. doi: 10.1111/j.1469-0691.2009.02750.x. PubMed PMID: 19416304.
13. Chalmers JD, Short PM, Mandal P, Akram AR, Hill AT. Statins in community acquired pneumonia: Evidence from experimental and clinical studies. Respir Med. 2010;104(8):1081-91. Epub 2010/05/05. doi: 10.1016/j.rmed.2010.04.005. PubMed PMID: 20447815.
14. Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med. 2014;370(23):2191-200. Epub 2014/05/18. doi: 10.1056/NEJMoa1401520. PubMed PMID: 24835849; PubMed Central PMCID: PMC4241052.
15. McCauley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, et al. Simvastatin in the acute respiratory distress syndrome. N Engl J Med. 2014;371(18):1695-703. Epub 2014/09/30. doi: 10.1056/NEJMoa1403285. PubMed PMID: 25268516.
16. Deshpande A, Pasupuleti V, Rothenberg MB. Statin therapy and mortality from sepsis: a meta-analysis of randomized trials. Am J Med. 2015;128(4):410-7.e1. Epub 20141217. doi: 10.1016/j.amjmed.2014.10.057. PubMed PMID: 25526798.
17. Frost FJ, Petersen H, Tollestrup K, Skruper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007;131(4):1006-12. doi: 10.1378/chest.06-1997. PubMed PMID: 17426203.
18. Vandermeer ML, Thomas AR, Kamimoto L, Reingold A, Gershman K, Meek J, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis. 2012;205(1):13-9. Epub 2011/12/13. doi: 10.1093/infdis/jir695. PubMed PMID: 22170954.
19. Patel JM, Snaith C, Thickett DR, Lintervort L, Melody T, Hawkey P, et al. Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). Crit Care. 2012;16(6):R231. Epub 20121211. doi: 10.1186/cc11895. PubMed PMID: 23232151; PubMed Central PMCID: PMC3672620.
20. 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. 2020;24(1):429. Epub 2020/07/14. doi: 10.1186/s13054-020-03154-4. PubMed PMID: 32664990; PubMed Central PMCID: PMC7358561.
21. Song SL, Hays SB, Panton CE, Mylona EK, Kalligeros M, Shehadeh F, et al. Statin Use Is Associated with Decreased Risk of Invasive Mechanical Ventilation in COVID-19 Patients: A Preliminary Study. Pathogens. 2020;9(9). Epub 2020/09/17. doi: 10.3390/pathogens9090759. PubMed PMID: 32957539; PubMed Central PMCID: PMC7559887.
22. Tan WYT, Young BE, Lye DC, Chew DEK, Dalan R. Statin use is associated with lower disease severity in COVID-19 infection. Sci Rep. 2020;10(1):17458. Epub 2020/10/15. doi:
23. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L, 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. 2020;21(7):909-14.e2. Epub 2020/06/15. doi: 10.1016/j.jamda.2020.06.018. PubMed PMID: 32674818; PubMed Central PMCID: PMC7294267.

24. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. Cell Metab. 2020. Epub 2020/06/24. doi: 10.1016/j.cmet.2020.06.015. PubMed PMID: 32592657.

25. Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, et al. Role of Drugs Used for Chronic Disease Management on Susceptibility and Severity of COVID-19: A Large Case-Control Study. Clin Pharmacol Ther. 2020;108(6):1185-94. Epub 2020/10/05. doi: 10.1002/cpt.2047. PubMed PMID: 32910830.

26. Daniels LB, Sitapati AM, Zhang J, Zou J, Bui QM, Ren J, et al. Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients. Am J Cardiol. 2020. Epub 2020/09/16. doi: 10.1016/j.amjcard.2020.09.012. PubMed PMID: 32946859; PubMed Central PMCID: PMC7492151.

27. Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun. 2021;12(1):1325. Epub 2021/02/26. doi: 10.1038/s41467-021-21553-1. PubMed PMID: 33637713; PubMed Central PMCID: PMC7910606.

28. Butt JH, Gerds TA, Schou M, Kragholm K, Phelps M, Havers-Borgersen E, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. BMJ Open. 2020;10(12):e044421. Epub 2020/12/04. doi: 10.1136/bmjopen-2020-044421. PubMed PMID: 33277291; PubMed Central PMCID: PMC7722358.

29. Hospital MG. Rationale for Consideration of Statins for COVID-19 Patients: The General Hospital Corporation; 2020. Available from: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/rationale-for-consideration-of-statins-for-COVID-19-patient.pdf.

30. McCarthy CP, Murphy S, Jones-O’Connor M, Olshan DS, Khababati JR, Rehman S, et al. Early clinical and sociodemographic experience with patients hospitalized with COVID-19 at a large American healthcare system. EClinicalMedicine. 2020;26:100504. Epub 2020/08/19. doi: 10.1016/j.eclinm.2020.100504. PubMed PMID: 32838244; PubMed Central PMCID: PMC7434634.

31. Bassett IV, Triant VA, Bunda BA, Selvaggi CA, Shinnick DJ, He W, et al. Massachusetts general hospital Covid-19 registry reveals two distinct populations of hospitalized patients by race and ethnicity. PLoS One. 2020;15(12):e0244270. Epub 2020/12/22. doi: 10.1371/journal.pone.0244270. PubMed PMID: 33351826; PubMed Central PMCID: PMC7755195.

32. Wolkewitz M, Lambert J, von Cube M, Bugiera L, Grodd M, Hazard D, et al. Statistical Analysis of Clinical COVID-19 Data: A Concise Overview of Lessons Learned, Common Errors and
33. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 2000;11(5):561-70. doi: 10.1097/00001648-200009000-00012. PubMed PMID: 10955409.

34. Moodie EE, Stephens DA, Klein MB. A marginal structural model for multiple-outcome survival data: assessing the impact of injection drug use on several causes of death in the Canadian Co-infection Cohort. Stat Med. 2014;33(8):1409-25. Epub 2013/11/25. doi: 10.1002/sim.6043. PubMed PMID: 24272681.

35. Little RJ, Tchetgen EJT, Troxel AB. University of Pennsylvania 11th annual conference on statistical issues in clinical trials: Estimands, missing data and sensitivity analysis (afternoon panel session). Clin Trials. 2019;16(4):381-90. Epub 2019/06/27. doi: 10.1177/1740774519853565. PubMed PMID: 31244326; PubMed Central PMCID: PMC6661711.

36. Team RC. R: A language and environment for statistical computing. Vienna, Austria 2020. p. R Foundation for Statistical Computing.

37. Venables W, BD R. Modern Applied Statistics with S. Fourth edition ed. New York: Springer; 2002.

38. Quartagno M, Grund S, Carpenter J. Jomo: a flexible package for two-level joint modelling multiple imputation. R Journal 9.1; 2019.

39. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society: Series B; 1995. p. 289-300.

40. Ding P, VanderWeele TJ. Sensitivity Analysis Without Assumptions. Epidemiology. 2016;27(3):368-77. doi: 10.1097/EDE.0000000000000457. PubMed PMID: 26841057; PubMed Central PMCID: PMC4820664.

41. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966. Epub 2020/05/22. doi: 10.1136/bmj.m1966. PubMed PMID: 32444366; PubMed Central PMCID: PMC7243801.

42. Fresán U, Guevara M, Elía F, Albéniz E, Burgui C, Castilla J, et al. Independent Role of Severe Obesity as a Risk Factor for COVID-19 Hospitalization: A Spanish Population-Based Cohort Study. Obesity (Silver Spring). 2021;29(1):29-37. Epub 2020/12/06. doi: 10.1002/oby.23029. PubMed PMID: 32885905.

43. Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States. Clin Infect Dis. 2021;72(4):703-6. doi: 10.1093/cid/ciaa815. PubMed PMID: 32562416; PubMed Central PMCID: PMC7337626.

44. Asch DA, Sheils NE, Islam MN, Chen Y, Werner RM, Buresh J, et al. Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic. JAMA Intern Med. 2020. Epub 2020/12/22. doi: 10.1001/jamainternmed.2020.8193. PubMed PMID: 33351068; PubMed Central PMCID: PMC7756246.

45. Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020;14(6):1613-5. Epub
46. Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F, et al. Statins for acute coronary syndrome. Cochrane Database Syst Rev. 2014(9):CD006870. Epub 2014/09/01. doi: 10.1002/14651858.CD006870.pub3. PubMed PMID: 25178118.
47. Lu Y, Liu DX, Tam JP. Lipid rafts are involved in SARS-CoV entry into Vero E6 cells. Biochem Biophys Res Commun. 2008;369(2):344-9. Epub 2008/02/13. doi: 10.1016/j.bbrc.2008.02.023. PubMed PMID: 18279660; PubMed Central PMCID: PMC7092920.
48. Mishra K, Naffouj S, Gorgis S, Ibrahim H, Gill S, Fadel R, et al. Liver Injury as a Surrogate for Inflammation and Predictor of Outcomes in COVID-19. Hepatol Commun. 2021;5(1):24-32. Epub 2020/10/06. doi: 10.1002/hep4.1586. PubMed PMID: 33437898; PubMed Central PMCID: PMC7789831.
49. Z F, L C, J L, C T, Y Z, S H. Clinical Features of COVID-19 Related Liver Damage. 2020.
50. Sakthirajan R, Dhanapriya J, Varghese A, Saravanakumar K, Dineshkumar T, Balasubramaniyan T, et al. Clinical profile and outcome of pigment-induced nephropathy. Clin Kidney J. 2018;11(3):348-52. Epub 2017/11/06. doi: 10.1093/ckj/sfx121. PubMed PMID: 29942498; PubMed Central PMCID: PMC6007272.
Table 1: Patient Characteristics at Hospitalization for COVID-19.

Stratified by (A) continued statin during hospitalization (Continued), (B) discontinued statin during hospitalization (Discontinued), (C) newly initiated statin during hospitalization (Newly Initiated), and (D) no statin prior to admission nor during hospitalization (Never).

| Demographics                  | Total 1,179 subjects | (A) Continued (n=466) | (B) Discontinued (n=42) | (C) Newly Initiated (n=311) | (D) Never (n=360) | p-value^a |
|-------------------------------|----------------------|-----------------------|-------------------------|-----------------------------|-------------------|-----------|
| **Demographics**              |                      |                       |                         |                             |                   |           |
| Male sex, n/N (%)             | 298/466 (63.9%)      | 26/42 (61.9%)         | 173/311 (55.6%)        | 179/360 (49.7%)             |                   | 0.001     |
| Age, median (IQR)             | 68 (59-78) [n=466]   | 70 (58-78) [n=42]    | 55 (43-66) [n=311]     | 48 (35-62) [n=360]          |                   | <0.001    |
| Age > 65, n/N (%)             | 265/466 (56.9%)      | 24/42 (57.1%)        | 83/311 (26.7%)         | 71/360 (19.7%)              |                   | <0.001    |
| Race/Ethnicity, n/N (%)       |                      |                       |                         |                             |                   |           |
| 1. White                      | 233/457 (51%)        | 23/42 (54.8%)        | 84/301 (27.9%)         | 114/355 (32.1%)             |                   |           |
| 2. Black or African American | 40/457 (8.8%)        | 7/42 (16.7%)         | 43/301 (14.3%)         | 37/355 (10.4%)              |                   |           |
| 3. Hispanic                   | 131/457 (28.7%)      | 10/42 (23.8%)        | 129/301 (42.9%)        | 159/355 (44.8%)             |                   | <0.001    |
| 4. Other (American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, others) | 53/457 (11.6%) | 2/42 (4.8%) | 45/301 (15%) | 45/355 (12.7%) |                   |           |
| Active smoker, n/N (%)        | 24/442 (5.4%)        | 7/37 (18.9%)         | 15/275 (5.5%)          | 39/330 (11.8%)              |                   | <0.001    |
| BMI, median (IQR)             | 29 (26-34) [n=430]   | 29 (25-32) [n=38]    | 30 (26-34) [n=290]     | 29 (25-34) [n=316]          |                   | 0.735     |
| BMI >= 30, n/N (%)            | 192/430 (44.7%)      | 14/38 (36.8%)        | 141/290 (48.6%)        | 146/316 (46.2%)             |                   | 0.500     |
| Comorbidities on Admission, n/N (%) |
|-------------------------------------|
| **Coronary Artery Disease** |
| 140/466 (30%) | 6/42 (14.3%) | 9/311 (2.9%) | 12/360 (3.3%) | <0.001 |
| **Congestive Heart Failure** |
| 90/466 (19.3%) | 6/42 (14.3%) | 15/311 (4.8%) | 19/360 (5.3%) | <0.001 |
| **Hypertension** |
| 349/466 (74.9%) | 29/42 (69%) | 130/311 (41.8%) | 100/360 (27.8%) | <0.001 |
| **Diabetes** |
| 261/466 (56%) | 24/42 (57.1%) | 76/311 (24.4%) | 42/360 (11.7%) | <0.001 |
| **Dyslipidemia** |
| 320/466 (68.7%) | 19/42 (45.2%) | 59/311 (19%) | 46/360 (12.8%) | <0.001 |
| **Chronic kidney disease** |
| 121/458 (26.4%) | 9/41 (22%) | 31/299 (10.4%) | 32/356 (9%) | <0.001 |
| **Dialysis** |
| 18/458 (3.9%) | 1/41 (2.4%) | 7/299 (2.3%) | 6/356 (1.7%) | 0.238 |
| **Chronic liver Disease** |
| 37/458 (8.1%) | 5/41 (12.2%) | 30/299 (10%) | 36/353 (10.2%) | 0.567 |
| **Alcohol-related Cirrhosis** |
| 4/458 (0.9%) | 2/41 (4.9%) | 5/299 (1.7%) | 4/353 (1.1%) | 0.161 |
| **NAFLD** |
| 22/458 (4.8%) | 0/41 (0%) | 16/299 (5.4%) | 14/353 (4%) | 0.499 |
| **Current Viral Hepatitis** |
| 18/466 (3.9%) | 1/42 (2.4%) | 11/311 (3.5%) | 25/360 (6.9%) | 0.125 |
| **HIV** |
| 6/413 (1.5%) | 0/40 (0%) | 4/283 (1.4%) | 6/329 (1.8%) | 0.947 |
| **History of Cancer** |
| 88/459 (19.2%) | 10/42 (23.8%) | 43/298 (14.4%) | 32/354 (9%) | <0.001 |
| **Pulmonary Disease** |
| 167/461 (36.2%) | 14/41 (34.1%) | 76/301 (25.2%) | 91/357 (25.5%) | 0.001 |
| **COPD** |
| 71/461 (15.4%) | 6/41 (14.6%) | 20/301 (6.6%) | 23/357 (6.4%) | <0.001 |
| **Asthma** |
| 60/461 (13%) | 7/41 (17.1%) | 37/301 (12.3%) | 55/357 (15.4%) | 0.548 |
| **ILD** |
| 3/461 (0.7%) | 0/41 (0%) | 3/301 (1%) | 3/357 (0.8%) | 0.938 |
| **Home oxygen supplementation** |
| 14/461 (3%) | 1/41 (2.4%) | 3/301 (1%) | 3/357 (0.8%) | 0.065 |
| **Obstructive Sleep Apnea (OSA)** |
| 46/466 (9.9%) | 4/42 (9.5%) | 16/311 (5.1%) | 12/360 (3.3%) | 0.001 |
| **History of organ transplant** |
| 13/462 (2.8%) | 2/41 (4.9%) | 6/301 (2%) | 7/356 (2%) | 0.480 |
| **Treatment with immunosuppressing agent in the past 6 months** |
| 36/448 (8%) | 4/38 (10.5%) | 16/295 (5.4%) | 22/353 (6.2%) | 0.366 |
| **Medications at Presentation to Care, n/N (%)** |
| **Type and dose of statin (at PTC)** |
| 309/458 (67.5%) | 28/41 (68.3%) | 95/309 (30.7%) | 7/28 (25%) | 0.358 |
| **Atorvastatin 10mg-20mg** |
| 116/309 (37.5%) | 12/28 (42.9%) | 85/309 (27.5%) | 7/28 (25%) |
| **Atorvastatin 80mg** |
| 13/309 (4.2%) | 2/28 (7.1%) | 1/41 (2.4%) | 0.018 |

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### Type and dose of statin (during hospitalization)

| Statin               | n/N (%)         | n/N (%)         | p-value |
|----------------------|-----------------|-----------------|---------|
| Atorvastatin         | 331/434 (76.3%) | 274/285 (96.1%) | <0.001  |
| 10mg-20mg            | 76/331 (23%)    | 53/274 (19.3%)  |         |
| 40mg-60mg            | 138/331 (41.7%) | 147/274 (53.6%) |         |
| 80mg                 | 117/331 (35.3%) | 74/274 (27%)    |         |
| Unknown Dosage       | 0/331 (0%)      | 0/274 (0%)      |         |
| Rosuvastatin         | 33/434 (7.6%)   | 6/285 (2.1%)    |         |
| Other Statins        | 70/434 (16.1%)  | 5/285 (1.8%)    |         |

### Duration of pre-admission statin use at PTC

| Statin               | <= 1 year n/N (%)  | >1 year n/N (%)  | Unknown n/N (%)  | p-value |
|----------------------|---------------------|------------------|------------------|---------|
| Atorvastatin         | 54/466 (11.6%)      | 244/466 (52.4%)  | 168/466 (36.1%)  | 0.973   |
| Azithromycin         | 17/457 (3.7%)       | 4/42 (4.8%)      | 15/42 (35.7%)    |         |
| Immunosuppressants   | 42/466 (9%)         | 3/42 (7.1%)      | 10/311 (3.2%)    | 0.326   |
| Oral Steroid         | 29/466 (6.2%)       | 3/42 (7.1%)      | 8/360 (2.2%)     | 0.598   |
| Cytokines            | 13/466 (2.8%)       | 2/42 (4.8%)      | 8/360 (2.2%)     | 1.000   |
| Hydroxychloroquine   | 4/466 (0.9%)        | 0/42 (0%)        | 3/360 (0.8%)     |         |

### Presentation to Care, n/N (%)

| Symptomatic (yes/no) | 439/462 (95%) | 36/40 (90%) | 305/309 (98.7%) | 333/357 (93.3%) | p-value |
|----------------------|---------------|-------------|-----------------|-----------------|---------|

### First Available Labs, median (IQR)

| Laboratory Parameter | Value ([n]) | Value ([n]) | Value ([n]) | Value ([n]) | p-value |
|----------------------|-------------|-------------|-------------|-------------|---------|
| White blood cell count /µL | 6.5 (4.9-8.3) | 7.1 (5.2-10.5) | 6.8 (5.2-9.2) | 6.7 (4.9-9.2) | 0.152   |
| Aspartate aminotransferase, U/L | 40 (28-56) | 58 (30-121) | 44 (31-65) | 48 (30-72) | <0.001  |
| Alanine aminotransferase, U/L | 27 (18-42) | 34 (23-62) | 34 (21-58) | 34 (21-66) | <0.001  |
| Total bilirubin, mg/dL | 0.5 (0.4-0.7) | 0.5 (0.4-0.8) | 0.5 (0.4-0.7) | 0.5 (0.3-0.6) | 0.125   |
| Alkaline phosphatase, U/L | 86 (67-108) | 91 (69-127) | 75 (59-95) | 80 (62-108) | <0.001  |
| Troponin, ng/L | 17 (8-39) | 39 (14-90) | 8 (6-17) | 7 (6-18) | <0.001  |
| C-reactive protein, mg/L | 74 (33-142) | 85 (48-152) | 89 (49-152) | 68 (31-136) | 0.001   |
| Erythrocyte sedimentation rate, mm/h | 114 (63-217) | 298 (82-702) | 114 (67-223) | 132 (65-349) | 0.003   |
|                            | D-dimer, ng/mL | Absolute lymphocyte count, K/µL |
|---------------------------|----------------|---------------------------------|
|                           | 1063 (695-1812) | 1 (0.6-1.3)                     |
|                           | [n=455]        | [n=466]                         |
| 1554 (826-6580)           | 1 (0.6-1.5)    |                                 |
|                           | [n=37]         | [n=40]                          |
| 1074 (693-1770)           | 1 (0.7-1.3)    |                                 |
|                           | [n=305]        | [n=311]                         |
| 949 (608-1661)            | 1 (0.7-1.4)    |                                 |
|                           | [n=329]        | [n=341]                         |
|                           | 0.002          | 0.132                           |

**Calendar Days Since 03/01/2020, median (IQR)**

|                            | Number of days from 03/01/2020 to hospital admission date |
|---------------------------|----------------------------------------------------------|
|                           | 43 (33-52)                                               |
|                           | [n=466]                                                  |
|                           | 50 (41-56)                                               |
|                           | [n=42]                                                   |
|                           | 37 (30-44)                                               |
|                           | [n=311]                                                  |
|                           | 46 (40-54)                                               |
|                           | [n=360]                                                  |
|                           | <0.001                                                   |

* a p-values were calculated comparing all 4 groups using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables.

* b Unknown and other chronic liver disease not presented in the table

* c Note that this is first available lab result following admission

Non-alcoholic Fatty Liver Disease (NAFLD), HIV (Human Immunodeficiency Virus), ILD (interstitial lung disease), COPD (chronic obstructive pulmonary disease)
Table 2: Unadjusted Patient Outcomes at 28 Days

| Total 1,179 subjects | (A) Continued (n=466) | (B) Discontinued (n=42) | (C) Newly Initiated (n=311) | (D) Never (n=360) | p-value<sup>a</sup> |
|----------------------|-----------------------|------------------------|-----------------------------|-------------------|-------------------|
| **Patient status at 28 days, n (%)** |                       |                        |                             |                   |                   |
| Deceased<sup>b</sup> | 78/466 (16.7%)         | 14/42 (33.3%)          | 30/311 (9.6%)               | 32/360 (8.9%)     | <0.001            |
| Discharged alive     | 252/466 (54.1%)        | 20/42 (47.6%)          | 176/311 (56.6%)             | 257/360 (71.4%)   |                   |
| Transfer to other facility (non-palliative care) | 61/466 (13.1%) | 4/42 (9.5%) | 36/311 (11.6%) | 35/360 (9.7%) |                   |
| Still hospitalized at 28 days after presentation to care | 75/466 (16.1%) | 4/42 (9.5%) | 69/311 (22.2%) | 36/360 (10.0%) |                   |
| Days from hospital admission to death, median (IQR) | 10 (6-15) [n=78] | 3 (1-4) [n=14] | 12 (7-16) [n=30] | 6 (3-13) [n=32] | <0.001            |
| Days from hospital admission to discharge or transfer to non-palliative facility, median (IQR) | 7 (4-10) [n=313] | 4 (1-6) [n=24] | 7 (4-10) [n=212] | 5 (3-8) [n=292] | <0.001            |
| **Patient events during 28 days of follow-up, n (%)** |                       |                        |                             |                   |                   |
| ICU admission        | 145/466 (31.1%)        | 8/42 (19.0%)           | 131/311 (42.1%)             | 77/360 (21.4%)    | <0.001            |
| Invasive intubation  | 122/466 (26.2%)        | 6/42 (14.3%)           | 110/311 (35.4%)             | 65/360 (18.1%)    | <0.001            |
| Bacterial Pneumonia  | 132/466 (28.3%)        | 9/42 (21.4%)           | 106/311 (34.1%)             | 71/360 (19.7%)    | <0.001            |
| Acute Respiratory Distress Syndrome | 112/466 (24.0%) | 5/42 (11.9%) | 105/311 (33.8%) | 61/360 (16.9%) | <0.001            |
| Stroke / Cerebrovascular accident | 3/466 (0.6%) | 1/42 (2.4%) | 3/311 (1.0%) | 2/360 (0.6%) | 0.390  |
| Cardiac arrest       | 2/466 (0.4%)           | 1/42 (2.4%)           | 2/311 (0.6%)                | 2/360 (0.6%)      | 0.390  |
| Rhabdomyolysis/myositis | 18/466 (3.9%) | 2/42 (4.8%) | 18/311 (5.8%) | 21/360 (5.8%) | 0.499  |
| Liver dysfunction    | 80/466 (17.2%)         | 11/42 (26.2%)          | 71/311 (22.8%)              | 64/360 (17.8%)    | 0.123  |

IQR (Interquartile range)

<sup>a</sup>p-values were calculated comparing all 4 groups using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables.

<sup>b</sup>deceased includes 3 patients who were discharged to hospice care.
Table 3: Unadjusted Peak Laboratory Values by Statin Group.

| Peak Labs, median (IQR) | (A) Continued (n=466) | (B) Discontinued (n=42) | (C) Newly Initiated (n=311) | (D) Never (n=360) | p-value* |
|-------------------------|-----------------------|-------------------------|-----------------------------|-------------------|---------|
| White blood cell count, /µL | 8.7 (6.6-12.5) [n=466] | 7.9 (6.3-16) [n=40] | 9.9 (7.1-15.2) [n=311] | 8.3 (6.2-12.1) [n=349] | 0.001 |
| Aspartate aminotransferase, U/L | 65 (40-119) [n=463] | 60 (32-208) [n=38] | 84 (45-150) [n=311] | 66 (35-127) [n=338] | 0.008 |
| Alanine aminotransferase, U/L | 46 (26-85) [n=463] | 47 (23-121) [n=38] | 68 (31-120) [n=311] | 57 (26-118) [n=338] | <0.001 |
| Total bilirubin, mg/dL | 0.7 (0.5-1.1) [n=463] | 0.5 (0.4-0.8) [n=38] | 0.6 (0.5-1) [n=311] | 0.6 (0.4-0.9) [n=338] | 0.11 |
| Alkaline phosphatase, U/L | 105 (79-166) [n=463] | 101 (77-155) [n=38] | 97 (72-156) [n=311] | 96 (72-140) [n=338] | 0.017 |
| Troponin, ng/L | 23 (10-52) [n=451] | 40 (14-90) [n=38] | 12 (6-29) [n=305] | 8 (6-23) [n=322] | <0.001 |
| C-reactive protein, mg/L | 145 (69-252) [n=459] | 141 (50-231) [n=38] | 151 (82-283) [n=311] | 117 (52-175) [n=330] | <0.001 |
| Erythrocyte sedimentation rate, mm/h | 57 (36-104) [n=426] | 68 (36-90) [n=32] | 72 (41-114) [n=297] | 44 (26-74) [n=295] | <0.001 |
| Creatine kinase, U/L | 178 (85-507) [n=461] | 374 (89-838) [n=36] | 222 (90-636) [n=310] | 173 (78-578) [n=331] | 0.028 |
| D-dimer, ng/mL | 1863 (986-3596) [n=455] | 1944 (1075-7380) [n=37] | 2090 (1038-5098) [n=305] | 1241 (713-3270) [n=329] | <0.001 |
| Absolute lymphocyte count, K/µL | 1.6 (1.1-2.2) [n=466] | 1.5 (1-2.5) [n=40] | 1.9 (1.4-2.4) [n=311] | 1.7 (1.3-2.3) [n=341] | <0.001 |

*p-values were calculated comparing all 4 groups using the Kruskal-Wallis test for continuous variables and Fisher’s exact test for categorical variables.
Figure 1

| Statin prior to the admission | Statin during the hospitalization |
|------------------------------|----------------------------------|
| Yes                          | Yes (A) Continued | No (B) Discontinued |
| No                           | Yes (C) Newly Initiated | No (D) Never |

Figure 2

Primary outcome: time to death
- Statin during hospitalization (A & C) vs. No statin during hospitalization (B & D)
- Newly initiated (C) vs. Never (D)
- Continued (A) vs. Discontinued (B)

Secondary outcome: time to death or ICU admission

P-value
- Primary outcome: 0.008
- Secondary outcome: 0.340

Hazard Ratio (95% CI)
- Statin during hospitalization: 0.586 (0.372, 0.862)
- No statin during hospitalization: 0.493 (0.253, 0.963)
- Newly initiated: 0.270 (0.114, 0.637)
- Never: 1.052 (0.473, 1.643)
- Continued: 0.846 (0.600, 1.192)
- Discontinued: 0.592 (0.306, 1.146)

P-value
- Primary outcome: 0.038
- Secondary outcome: 0.825
- Primary outcome: 0.003
- Secondary outcome: 0.120