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Effects of Statin Use On Length of Hospital Stay and Clinical Outcome in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

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1. Abstract

The search for effective COVID-19 management strategies continues to evolve. Severity of COVID-19 has been reported to be positively correlated with a concomitant rise in inflammatory cytokine levels (1, 2). Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) are widely used for dyslipidemia for primary and secondary prevention of cardiac and cerebrovascular events. Statins also have anti-inflammatory effects, including reducing C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ) which has been hypothesized in reducing the severity of COVID-19. In this study, we aimed to assess the effects of statin on the length of hospital stay and clinical outcome in patients with COVID-19. This retrospective cohort study found that statin use was not significantly associated with reduced mortality, reduced the need of mechanical ventilation or length of hospital stay among patients hospitalized with COVID-19. This may be due to statin effect on increasing ACE-2 receptor expression along with their advantage in protection against potential coronary endothelial dysfunction due to anti-inflammatory effects. Our study was a retrospective study and there were factors that we couldn't control such as comorbidities that patients with severe disease had, which played roles in severity of COVID infection. It is possible that statin has a more beneficial effect to decrease inflammation, early in the stage of disease and among less sick patients with COVID-19 that do not need to be hospitalized. We believe that our results are of clinical relevance and warrant the need for prospective randomized controlled trials and extensive retrospective studies.

2. Introduction

As the COVID-19 pandemic progresses, the search for effective management strategies continues to evolve. SARS-CoV-2 is capable of producing a devastating viral pneumonia that can progress to adult respiratory distress syndrome and even death [1]. The virus uses the body's angiotensin-converting-enzyme 2 (ACE2) receptor to concentrate in the lungs, enter cells, and replicate. During severe infection, the virus is capable of limiting the expression of ACE2 receptors and poses a challenge to tissue repair mechanisms and clearance [2]. The severity of COVID-19 is positively correlated with a concomitant rise in inflammatory cytokine levels [2,3]. Additionally, it's well documented that those with preexisting medical conditions such as heart disease are at increased risk of severe illness and death from COVID-19 [4]. History of coronary vascular disease specifically, represents the highest odds of adverse outcomes such as need for mechanical ventilation and

death in systematic review of COVID-19 prognosis [5]. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors who's wide use can manage dyslipidemia and prevent primary and secondary cardiac and cerebrovascular events. Statins are also anti-inflammatory, contributing to the reduction of key cytokines including C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFNγ). Reducing proinflammatory cytokines has been hypothesized to reduce the severity of COVID-19 [3, 6]. In a review of statin use in the H1N1 outbreak in the late 2000's, outpatient statin use reduced disease severity for those hospitalized [7]. However, when considering the current COVID-19 pandemic, previous randomized trials and retrospective studies featuring statins as a management tool have been contradictory [6,8]. In this study, we aim to assess the effects of statin use on the length of hospital stay and clinical outcome in patients with COVID-19.

3. Materials and Methods

A retrospective hospital cohort study was performed with patients ≥18-years-old with confirmed reverse transcriptase polymerase chain reaction (rt-PCR) COVID-19 infection during admission. Patients were retrospectively enrolled while admitted to St. Michael's Medical Center in Newark New Jersey between 03/15/2020 and 05/25/2020. Demographics, comorbidities, clinical and laboratory data were reviewed and retrieved from electronic medical records (EMRs). Patients were included in the statin group if they had a history of statin use and home statin medications were continued throughout the admission period or if treating physicians started statin therapy on admission. Statin usage prior to admission was obtained from Home Medication records gathered on admission and the continuation of any home medications was provider dependent. The primary outcomes measured included length of hospital stay and clinical outcome. Length of hospital stay was measured to the nearest full day since admission. Clinical outcome was evaluated on need for mechanical ventilation during admission and discharge status, alive or expired. The study period and length of stay measurement ended with discharge or death. IRB exemption was granted due to the retrospective nature of the

study and all data was de-identified as it was collected. Data was expressed as counts and percentages or mean. Continuous variable analysis was performed with t-test and Mann Whittney test for normal and non-normal distribution and chi-square was used for categorical data analysis. GraphPad Prism v 9.0.2 was used for data analysis. Statistical significance was achieved if the null hypothesis could be rejected at P < 0.05.

4. Results

410 patients were included in the study with 168 of those on statin therapy prior to admission. 87 (51%) of statin users were female and 81 (48%) were male; with an average age of 68. The non-statin group had 242 members, 101 (42%) male and 141 (58%) female; with an average age of 55. Hypertension (63%) was the most common comorbidity, followed by diabetes mellitus (41%) and chronic kidney disease (22%) across all patients. In the statin group, 87 (52%) had diabetes mellitus, 143 (85%) had hypertension, and 52 (31%) had a diagnosis of chronic kidney disease. In the non-statin group, 80 (33%) had diabetes mellitus, 118 (49%) had hypertension, and 40 (17%) had a diagnosis of chronic kidney disease. Average Body mass index (BMI) of the statin group and the non-statin group were 28.9 and 31.7 respectively. The detailed characteristics are shown in Table 1. Across all patients, 93 (23%) received mechanical ventilation and 91 (22%) expired during hospital admission. In the statin group, 31 (18%) patients received mechanical ventilation and 39 (23%) patients expired. For the non-statin group, 62 (26%) patients received mechanical ventilation and 52 (22%) patients expired. When comparing patients in the statin group with those not on statin, there was no statistical significance with predicting the need for mechanical ventilation (p-value=0.0883). For clinical outcome, 129 (76.8%) on statin and 190 (78.5%) not on statin were both discharged alive. There was no statistical significance for predicting a living discharge status (p-value 0.6790). The average length of hospital stay was 7.4 for all patients, 6.7 for statin users, and 7.8 for non-statin users. There was no statistical significance for determining length of hospital for those with COVID-19 on statin therapy (p-value=0.2386). The detailed clinical outcomes of the study population are shown in Table 2.

Table 1: Baseline Characteristics of the study population.

	All (n=410)	Statin (n=168)	No Statin (n=242)	p-value
Age	60.7 ± 15.6	68.3 ± 12.2	55.4 ± 15.5	<0.0001
Gender				
Male	182 (44.4%)	81 (48.2%)	101 (41.7%)	0.1950
Female	228 (55.6%)	87 (51.8%)	141 (58.3%)	
Ethnicities				
Blacks	162 (39.5%)	84 (50%)	78 (32.2%)	0.0892
Latinx	177 (43.2%)	53 (31.5%)	124 (51.2%)	
Whites	38 (9.3%)	17 (10.1%)	21 (8.7%)	
Others	33 (8.0%)	13 (7.7%)	20 (8.3%)	
Comorbidities				
Diabetes Mellitus	167 (40.7%)	87 (51.8%)	80 (33.1%)	0.003
Hypertension	261 (63.7%)	143 (85.1%)	118 (48.8%)	<0.0001
Chronic Kidney Disease	92 (22.4%)	52 (31%)	40 (16.5%)	0.0002
BMI	30.5 ± 8.2	28.9 ± 7.3	31.7 ± 8.5	0.0011

Table 2: Clinical outcomes of the study population.

	All (n=410)	Statin (n=168)	No Statin (n=242)	p-value
Mechanical Ventilation				
Yes	93 (22.7%)	31 (18.4%)	62 (25.6%)	0.0883
No	317 (77.3%)	137 (81.6%)	180 (74.4%)	
Outcome				
Discharged Alive	319 (77.8%)	129 (76.8%)	190 (78.5%)	0.6790
Expired	91 (22.2%)	39 (23.2%)	52 (21.5%)	
Length of Hospital Stay	7.4 ± 9.4	6.7 ± 5.8	7.8 ± 11.3	0.2386

5. Discussion

In this retrospective cohort study of hospitalized COVID-19 patients, statin use was not significantly associated with reduced length of stay or improved clinical outcome. This study did not observe a significant reduction in need for ventilation or death on admission in a statin using cohort when compared to a non-statin cohort. Previous studies highlight the protective benefits of statins for reducing inflammatory markers, preventing thrombosis, and protecting the vascular endothelium [3,6,9]. This study looked to substantiate previous research on statins and investigate their potential for limiting negative outcomes in hospitalized COVID-19 patients. Previous retrospective studies managing COVID-19 patients in Wuhan China, demonstrated lower risk of all-cause in-hospital mortality among statin users compared with non-statin users. The observed benefit in that study was significant among coronary heart disease (CHD) patients and non-CHD patients [6]. However, a more recent randomized controlled trial of atorvastatin compared to placebo by the *INSPIRATION-S Investigators* in 11 Iranian hospitals found that atorvastatin was not associated with a significant reduction in all-cause mortality compared with placebo [8]. Our study's results align more consistently with the INSPIRATION-S trial though it is possible the benefits of statins were missed. First, the statin cohort in our analysis was significantly older than the non-statin cohort. Age plays a significant role in COVID-19 prognosis and could have diluted our results. A previous systematic review and meta-analysis of predictors of adverse prognosis in COVID-19 patients determined that age was the most predictive factor of adverse outcomes for those infected [5]. Additionally, the statin cohort had significantly more reported comorbidities including; diabetes mellitus, hypertension, and chronic kidney disease. The weight of these comorbidities may obscure any perceived benefit from statin therapy for COVID-19 patients. This study looked exclusively at patients hospitalized with COVID-19 but cannot infer the effects of statin use in milder COVID-19 infections. It is possible that the benefits of statins might be observed in less severe COVID-19 infections that do not require hospitalization. Our study had several limitations. First, our patient cohorts were hospitalized in the early part of the pandemic when COVID-19 management strategies were new, varied greatly, and evolved rapidly. Therefore, it is possible that the effect of statins in conjunction with current treatment guidelines may yield different results. Additionally, the retrospective nature of this study and the data collection process limited our knowledge of the statin user group. The duration of statin use before the trial and the reason for statin use was unknown. This study did not investigate statin dosing. Thus, patients on long term statin therapy with high dose may observe different benefits from those with low dose who started therapy on admission, and the dose of statin use was not investigated. Statins are often used to prevent long term mortality but this study was unable to observe potential mortality benefits beyond the initial admission for COVID-19 infection. It is possible that a benefit was observed beyond the admission period that our study missed. Statin safety during severe illness is a concern that this study was unable to investigate. We believe that our results are of clinical relevance and warrant the need for more prospective randomized controlled trials and additional extensive retrospective studies.

6. Conclusion

Among patients hospitalized for COVID-19 treatment, statin therapy did not decrease length of hospital stay or clinical outcome. Patients treated with statins were not more likely to be discharged alive or require mechanical ventilation during hospitalization.

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