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The impact of statin therapy in the COVID-19 patients with very high cardiovascular risk

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Abstract

Antithrombotic and anti-inflammatory impacts of statins have been studied in viral pneumonia. However, the clinical benefits of statins have not been fully explored in high-risk patients with coronavirus disease 2019 (COVID-19). Therefore, the present study assessed the effect of statin use in hospitalized COVID-19 patients with very high cardiovascular risk. Consecutive COVID-19 patients admitted from June 1 to December 31, 2020, were analysed retrospectively. Propensity score-matched analysis was used for creating a 1:1 matched cohort. COVID-19 patients with and without statin use were compared for demographic data, comorbidities, treatments, laboratory findings and in-hospital outcomes. 707 patients (56±9.3 years old; 37% female) were included. Among those, 24.6% (n=174) received statin therapy. A propensity-matched group of 342 patients (171 receiving statins and 171 not receiving statins) was demarcated. The present study demonstrated that statin use significantly reduced in-hospital mortality within 30 days (primary end-point) in univariate (OR=0.314, 95% CI: 0.195 to 0.507) and multivariable-adjusted analysis (OR=0.348, 95% CI: 0.187 to 0.648). Among hospitalized COVID-19 patients with very high cardiovascular risk, statin use was found to be significantly associated with reduced in-hospital 30-days mortality.

Keywords: COVID-19, coronavirus, high cardiovascular risk, pandemic, statin therapy

Introduction

Since the first case in 2019, the Coronavirus Disease 2019 (COVID-19) contaminated more than 260 million people. More than 5 million people died due to this disease. With newly emerging mutations, the pandemic continues to be a leading cause of mortality and morbidity worldwide.

SARS-CoV-2 mainly uses angiotensin-converting enzyme 2 (ACE2) to get into cells and triggers an intense inflammatory host response [1]. This excessive inflammatory response is known to have a negative effect in the development of acute

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respiratory distress syndrome (ARDS) [2] and in particular in the case of COVID-19. The reducing effect of anti-inflammatory drugs on the hyperinflammatory response of COVID-19 have been studied. Animal studies have indicated that inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase could modulate a number of underlying mechanisms involved in the occurrence of ARDS [3]. As an HMG-CoA reductase inhibitor, statins are postulated to be protective in the treatment of COVID-19 in consequence of their immunomodulatory properties. Early studies have demonstrated that pre- and in-hospital statin use may be associated with decreased mortality in COVID-19 patients [4].

The efficacy of statin is more prominent in patients with higher cardiovascular risk. However, its efficacy has not been examined among high-risk patients in the COVID-19 setting. Therefore, in the current retrospective study, the efficacy of statin therapy was studied among patients hospitalized for COVID-19 with very high cardiovascular risk.

Material and Methods

Study population

The patients hospitalized in the intensive care unit of Antalya due to SARS-CoV-2 infection from January 1, 2020 to December 31, 2020 were included in the study retrospectively. Among the consecutive patients hospitalized in the intensive care unit with the diagnosis of SARS-CoV-2 infection, 707 patients with very high cardiovascular risk were analyzed. This study conforms with the tenets of the Declaration of Helsinki and was approved by the ethics committee of Antalya training and research center (2021-059).

Demographic, clinical, and laboratory information of the patients were obtained from the electronic medical record system. Patients were classified according to the HeartScore high-risk countries risk chart [5]. The patients were divided into two groups as those who received and did not receive statin therapy before hospitalization The patients <40 years old were excluded from the study. Patients identified in the very high cardiovascular risk group were included in the analysis. The study population consisted of two groups: patients receiving statin therapy vs. those who did not receive statin therapy before the hospitalization. In-hospital mortality during the follow-up period was the primary outcome.

Statistical analysis

Medians with interquartile ranges or means with standard deviations for continuous variables and percentages for categorical variables were used for the presentation of summary statistics. The two-sided independent t-test and chi-squared test were used, as appropriate for the analysis of the differences in clinical and demographic characteristics and outpatient medications stratified by statin use.

With the objective of minimizing the influence of confounding by indication, a propensity-score matching was used to balance out the clinical characteristics of the two groups. In order to perform the matching, a 1:1 matching protocol without replacement was used, with a caliper width equal to 0.02 of the standard deviation of the propensity score's logit. The following variables were used for adjustment: age, sex, history of atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cancer, chronic kidney disease, chronic obstructive pulmonary disease, smoking, and corticosteroid treatment. We performed descriptive analyses for all baseline variables in the overall cohort and the propensity-matched cohort.

To identify potential predictors of mortality, we initially performed a univariate logistic regression in the overall cohort. Covariables with $p < 0.20$ were selected for entry into the multivariable model, and covariables with $p > 0.05$ were removed from the final model. Similarly, both univariable and multivariable logistic regression was performed in the propensity-score matched cohort. All the analyses were performed with the assistance of the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall, 707 patients (56±9.3 years old; 37% female) were included in the study. Hypertension (HTN; 69%), diabetes mellitus (DM; 49%), and coronary artery disease (CAD; 21%) were highly prevalent comorbidities. In addition, 46 % of patients were smokers (Table I). Within all patients, 24.6% (n=174) were chronic statin users. The patients receiving statins were younger [68.8±8.5 vs. 72.3±9.3 years, $p<0.001$] and we found no significant difference in sex between two groups ($p = 0.37$). There were significant differences between patients receiving and not receiving statins in regard of HT (86.8% vs. 62.9%), DM (66.7% vs. 43.2%), CAD (52.9% vs. 10.9%), heart failure (8.0% vs. 2.1%) ($p<0.001$ for all), and chronic kidney disease (9.8% vs. 5.8%) ($p=0.07$) respectively. Although the mean LDL value was lower in the patient group receiving statin therapy, no statistically significant difference was found between two groups (101.4±35.1 vs 105.9±53.8, $p=0.31$). No significant differences in chronic obstructive pulmonary disease (COPD) and atrial fibrillation were detected between the two groups ($p=0.84$ and 0.35 respectively). Compared to patients not on statins, those using statins were considerably more likely on ACEi (36.8% vs. 11.6%), clopidogrel (23.0% vs. 7.1%), ($p<0.001$ for all) and oral anticoagulant therapies (8.0% vs. 3.4 % p:0.01)

The mortality ratio in the patients included in the study was 47.5% (n:336). While the mortality ratio of the patients receiving statin therapy was 20.1% (n:35), it was found 56.5% (n:301) in the patients not receiving statin therapy ($p<0.001$). A total of 169 patients required mechanic ventilation. This ratio was 18.5% (n:32) in the patient group receiving statin therapy, whereas 25.7% (n:137) of the patients required mechanical ventilation in the group of patients not receiving statin therapy ($p=0.054$). A total of 167 patients received inotropic support therapy. This

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ratio was 17.8% (n:31) in the statin treatment group, while it was found 25.5% (n:136) in the group not receiving statin therapy (p=0.038).

Propensity-matched cohort characteristics

A total of 707 patients (171 patients receiving statins, 171 patients not receiving statins) were retained using 1:1 propensity score matching. There were significant differences in terms of CAD, congestive heart failure (CHF), and ACE inhibitor medication, whereas the other demographic factors remained in

Table 1. Patient characteristics by statin use in unmatched and matched cohorts

Variable	Unmatched			Matched		
	Statin use(N=174)	No statin use(N=533)	p-value	Statin use(N=171)	No statin use(N=171)	p-value
Age	68.8±8.5	72.3±9.3	<0.001	68.8±8.5	69.0±8.5	0.84
Male	115(66.1)	332(62.3)	0.37	114(66.7)	105(61.4)	0.31
Smoking	84(48.6)	242(45.4)	0.47	83(48.5)	79(46.2)	0.66
Comorbidities						
Atrial fibrillation	5(2.9)	24(4.5)	0.35	5(2.9)	4(2.3)	0.74
Cancer	3(1.7)	33(6.2)	0.020	3(1.8)	4(2.3)	0.70
Chronic kidney disease	17(9.8)	31(5.8)	0.07	17(9.9)	9(5.3)	0.10
Chronic obstructive pulmonary disease	18(10.3)	58(10.9)	0.84	18(10.5)	12(7.0)	0.25
Congestive heart failure	14(8.0)	11(2.1)	<0.001	13(7.6)	0(0.0)	<0.001
Coronary artery disease	92(52.9)	58(10.9)	<0.001	91(53.2)	39(22.8)	<0.001
Diabetes mellitus	116(66.7)	230(43.2)	<0.001	113(66.1)	105(61.4)	0.37
Hypertension	151(86.8)	335(62.9)	<0.001	148(86.5)	140(81.9)	0.24
Medications						
ACE inhibitors	64(36.8)	62(11.6)	<0.001	64(37.4)	25(14.6)	<0.001
ARBs	34(19.5)	125(23.5)	0.28	33(19.3)	44(25.7)	0.15
Aspirin	73(42.0)	99(18.6)	<0.001	73(42.7)	52(30.4)	0.018
Clopidogrel	40(23.0)	38(7.1)	<0.001	40(23.4)	21(12.3)	0.007
Other antiplatelet agents	2(1.1)	3(0.6)	0.42	2(1.2)	3(1.8)	0.65
Oral anticoagulants	14(8.0)	18(3.4)	0.010	14(8.2)	3(1.8)	0.006
Corticosteroids	100(58.1)	314(59.0)	0.84	99(57.9)	98(57.3)	0.91
Lipid profile						
Total cholesterol	173±44.1	174.4±42.3	0.71	172.5±44.1	174.8±41.4	0.62
Low-density lipoprotein cholesterol	101.4±35.1	105.9±53.8	0.31	101.0±35.1	103.9±33.0	0.42
High-density lipoprotein cholesterol	44.9±8.4	42.5±15.5	0.05	44.8±8.4	40.8±13.0	<.001
Triglycerides	148.3±99.4	144.3±57.2	0.51	148.6±100.2	152.3±66.9	0.69
Laboratory results						
Hemoglobin	12.6±1.8	12.2±1.9	0.05	12.6±1.8	12.4±1.8	0.35
Platelet	216.4±89.8	220.9±97.9	0.59	217.2±90.3	216.5±89.1	0.95
White blood cell	8.2±3.9	8.9±5.4	0.10	8.2±3.9	8.4±4.1	0.75
Neutrophil	6.4±3.7	7.0±4.9	0.14	6.4±3.7	6.5±3.9	0.78
Lymphocyte	1.4±1.4	1.5±3.3	0.53	1.4±1.4	1.4±1.4	0.98
Neutrophil-lymphocyte ratio [median (IQR)]	4.96(3.23-7.45)	5.06(3.07–10.3)	0.43	7.3±8.0	9.0±21.1	0.11
C-reactive protein [median (IQR)]	72(25–114)	88(37-156)	0.006*	87.5±82.6	106.7±88.3	0.039
D-dimer [median (IQR)]	313(181-565)	380(211-715)	0.024*	313.0(180-555)	290(201-637)	0.042
Troponin [median (IQR)]	20.0(10.0-51.0)	17.0(9.0–36.0)	0.28	20.5±(10-51)	14(9-41)	0.17

* P with Non parametric Mann-Whitney U test

ARB: Angiotensin receptor blocker. ACE: Angiotensin converting enzyme. IQR. interquartile range

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the propensity-matched cohort were similar (Table 1).

Clinical outcomes of a propensity-matched cohort

Statin use significantly reduced in-hospital mortality within 30 days (primary end point) in univariate (OR 0.314, 95% CI: 0.195 to 0.507) and multivariable-adjusted analysis (OR 0.348 95% CI: 0.187 to 0.648) (Table 2). Age, smoking, ACEI use and high CRP

Table 2. Univariable and multivariable analysis in unmatched and matched cohorts

Variable	Unmatched				Matched			
	Univariable		Multivariable		Univariable		OR (95% CI)	p-value
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	0.348 (0.187 to 0.648)	0.001
Statin	0.194 (0.129 to 0.292)	<0.001	0.191 (0.115 to 0.320)	<0.001	0.314 (0.195 to 0.507)	<0.001	1.082 (1.041 to 1.125)	<0.001
Age (per 1 years)	1.060 (1.042 to 1.079)	<0.001	1.052 (1.027 to 1.077)	<0.001	1.056 (1.027 to 1.085)	0.001	3.453 (1.794 to 6.647)	<0.001
Smoking	1.730 (1.283 to 2.332)	<0.001	2.572 (1.747 to 3.786)	<0.001	2.115 (1.335 to 3.351)	0.001	-	-
Atrial fibrillation	0.567 (0.260 to 1.237)	0.154	-	-	0.250 (0.031 to 2.024)	0.194	–	–
Cancer	1.107 (0.566 to 2.165)	0.766	–	–	0.336 (0.040 to 2.828)	0.316	–	–
Chronic kidney disease	0.847 (0.469 to 1.528)	0.581	–	–	1.311 (0.575 to 2.991)	0.519	-	-
Chronic obstructive pulmonary disease	0.880 (0.545 to 1.419)	0.599	–	–	0.291 (0.099 to 0.854)	0.024	–	–
Congestive heart failure	0.930 (0.411 to 2.104)	0.861	–	–	0.606 (0.163 to 2.246)	0.453	-	-
Coronary artery disease	0.663 (0.459 to 0.957)	0.028	1.728 (1.022 to 2.923)	0.041	1.354 (0.853 to 2.147)	0.198	–	–
Diabetes mellitus	0.325 (0.239 to 0.442)	<0.001	0.513 (0.357 to 0.736)	<0.001	0.526 (0.331 to 0.836)	0.007	–	–
Hypertension	0.694 (0.504 to 0.955)	0.025	–	–	1.474 (0.765 to 2.839)	0.247	0.448 (0.209 to 0.960)	0.039
ACE inhibitors	0.446 (0.297 to 0.672)	<0.001	–	–	0.467 (0.265 to 0.824)	0.009	–	–
ARBs	0.978 (0.687 to 1.394)	0.903	–	–	1.325 (0.781 to 2.249)	0.297	–	–
Aspirin	0.518 (0.363 to 0.739)	<0.001	0.474 (0.305 to 0.737)	<0.001	1.190 (0.747 to 1.897)	0.464	–	–
Clopidogrel	0.582 (0.357 to 0.948)	0.029	–	–	0.833 (0.455 to 1.523)	0.552	–	–
Other antiplatelet agents	4.446 (0.494 to 39.97)	0.183	–	–	8.477 (0.937 to 76.73)	0.057	–	–
Oral anticoagulants	0.850 (0.416 to 1.737)	0.656	–	–	0.849 (0.292 to 2.471)	0.764	2.312 (1.142 to 4.684)	0.020
C-reactive protein (≥37.2)	2.480 (1.751 to 3.511)	<0.001	1.981 (1.325 to 2.961)	<0.001	3.236 (1.830 to 5.723)	<0.001	–	–
D-dimer (≥521)	1.907 (1.374 to 2.647)	<0.001	–	–	2.133 (1.297 to 3.508)	0.003		
Troponin (≥15)	2.131 (1.572 to 2.888)	<0.0001	1.625 (1.101 to 2.398)	0.014	2.657 (1.671 to 4.226)	<0.001		

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and troponin levels were the other factors related with increased rates of the primary endpoint.

Discussion

In this study of hospitalized COVID-19 patients with very high cardiovascular risk, the principal findings are: [1] use of statin therapy was common (24.6%) in the overall cohort; [2] patients receiving statin therapy was slightly younger but with a higher burden of cardiovascular morbidity including CHF, CAD, DM, and HTN; and [3] statin use reduced in-hospital mortality in both the overall cohort and the propensity score-matched cohort after multivariable adjustment.

In a recent meta-analysis of COVID-19 patients, it was revealed that while no significant reductions in intensive care unit admissions and mortality by statins were experienced, there was in fact a significant decrease in all-cause mortality in the subset of patients with cardiovascular disease [4]. However, the observed association still needs to be confirmed due to the limited number of included studies. The current study is the first to confirm the survival benefit of receiving statin therapy among hospitalized COVID-19 patients with very high CV risk.

Prior to the event of COVID-19, some studies had revealed that hospitalized pneumonia patients taking statins had a lower mortality rate in comparison to those not taking statins, and also correlation between continuous use of statins and decreased risk of mortality or intubation in patients with COPD was demonstrated [6,7]. As expected, the effects of statins on the disease were also investigated during the COVID-19 period. Several studies demonstrated favorable outcomes with statins in patients with COVID-19 [8-10]. In general, meta-analyses have also supported the efficacy of statins. Zein et al. found that in the meta-analysis of propensity score-matched cohorts with multivariable-adjusted analysis, statin decreased mortality risk in patients with COVID-19 [11]. In a meta-analysis of retrospective observational studies on hospitalized COVID-19 patients performed by Kolias et al., the authors revealed a 35% decrease in the adjusted risk of mortality with statin therapy [12]. In contrast, certain studies did not show a relation between statin use and reduced mortality, but demonstrated increased risk of severe COVID-19 infection [13]. The main reason for conflicting results between the studies and meta-analyses could be related to the cardiovascular profile of the studied patients. Given the proven benefits of statins in various and despite the mixed evidence, pursuance of statin therapy continues to be generally recommended in COVID-19 patients with increased cardiovascular risk [14].

Favorable characteristics of statins are plaque stabilization and anti-thrombotic properties [15]. It was shown in studies consisting of COVID-19 patients that there is a relation between pre-existing cardiovascular disease and worse clinical outcomes [16]. Therefore, it is possible that statin therapy confers benefit by preventing thrombotic events and myocardial injury, which are the key contributors of mortality in this population. In addition, there is a strong evidence indicating statins' anti-inflammatory properties of statins in various clinical contexts. In this regard, patients on statin therapy were shown to have lower levels of CRP and D-dimer than those who did not receive statins. In the current study there was no significant difference in the mean LDL values of the two groups. This suggests that the beneficial effect of statin therapy is not associated with low LDL value, but may be due to its anti-inflammatory effect.

Several important limitations should be considered. First, although propensity score matching and multivariable analysis were performed, there could still be unmeasured confounding factors in this retrospective study. Especially, the difference in ACEi therapy between the two groups is confusing. It should be tested in prospective studies. Second, the duration and adherence of statin could not be verified in the study. Third, patients who received statin therapy may have undergone more intense surveillance and care due to comorbidities, which may have affected the in-hospital mortality. Finally, our sample size was relatively limited and the study method was retrospective.

Conclusion

This study has revealed that there indeed exists an association between statin use and reduced in-hospital mortality, in hospitalized COVID-19 patients presenting a very high cardiovascular risk. The results require to be validated by large-scale prospective studies.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study conforms with the tenets of the Declaration of Helsinki and was approved by the ethics committee of Antalya training and research center (2021-059).

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