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ORIGINAL ARTICLE

The Effect of Statin Use on In-Hospital Mortality in Covid-19 Patients

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ABSTRACT

Objective: Our aim in this study was to determine whether statins with anti-inflammatory and antithrombotic properties reduce in-hospital mortality in Covid-19 patients.

Materials and Methods: 1752 patients hospitalized with the diagnosis of Covid-19 between September and December 2020 were retrospectively analyzed. The patients were grouped according to statin use and their characteristics were compared. The parameters associated with mortality were examined.

Results: For the patients, the median age was 64 years (53-74 interquartile range [IQR]), 804 (45.9%) were over the age of 65, 903 (51.5%) were male, 167 (9.5%) were using statins, and mortality developed in 381 (21.7%) of the patients. The multivariate logistic regression model was applied using statistically significant parameters in the univariate analysis of mortality development. The group using statins was included in the regression model because it was statistically borderline significant (p=0.052). According to this model; increased age (odds ratio (OR) =1.051, 95% confidence interval (CI) 1.039-1.063, p<0.001), male gender (OR=1.002, 95%CI 0.993-1.010, p=0.705), decrease in lymphocyte count (OR=0.452, 95%CI 0.337-0.607, p<0.001) increase in potassium level (OR=1.306, 95%CI 1.025-1.664, p=0.031), increase in aspartate transaminase (AST) level (OR=1.004, 95%CI 1.001-1.007, p=0.003), increase in D-dimer level (OR=1.000, 95%CI 1.000-1.000, p=0.011), increase in procalcitonin level (OR=1.027, 95%CI 1.000-1.053, p=0.046), increase in CRP level (OR=1.007, 95%CI 1.005-1.008, p<0.001), and the development of myocardial injury (OR=3.045, 95%CI 1.864-4.976, p<0.001) was found to be associated with increased mortality. Statin use (OR=1.221, 95% CI 0.759-1.966, p=0.410) was not associated with mortality.

Conclusion: According to our study, statin use was not associated with an increase or decrease in-hospital mortality in patients hospitalized with a diagnosis of Covid-19.

Keywords: Covid-19, in-hospital mortality, statin

INTRODUCTION

The World Health Organization (WHO) recognized Covid-19 diseaseas a pandemic in March 2020, and unfortunately, the disease continues to spread globally at an alarming rate [1].

Acute Respiratory Distress Syndrome (ARDS) and thromboembolism are two major consequences that result in a high fatality rate in hospitalized Covid-19 patients [2,3]. According to current research, fatal consequences of SARS-CoV-2 infection originate from cytokine storm caused by an excessive inflammatory response [4]. SARS-CoV-2 invasion and destruction of epithelial cells in alveoli causes excessive inflammatory response consequently ARDS. Thromboembolism complications occur as a result of the release of inflammatory cytokines, intravascular endothelial dysfunction, thrombin production, and clot accumulation [5-7]. Although statins have traditionally been used to lower serum cholesterol, they show pleiotropic effects with anti-inflammatory, immunomodulatory, and antithrombotic properties [8-10]. This condition makes statins an attractive class of drugs in the adjunct therapy of Covid-19. Statins have been demonstrated to improve outcomes in patients with community-acquired pneumonia in studies [11,12]. However, the use of statins in Covid-19 patients is still contentious as result of several researches [13,14].

Our study aims to examine the effect of statin use on in-hospital mortality in Covid-19 patients.

MATERIALS and METHODS

This study is a retrospective study that included all reverse transcription-polymerase chain reaction (RT-PCR) positive Covid-19 patients hospitalized in our hospital between September and December 2020. The study protocol was approved by the ethics committee of our hospital. Patients older than 18 years were included in the study. Exclusion criteria were as follows; missing medical records, patients hospitalized for more than 28 days (considered decompensated or end-stage of chronic organ failure (e.g. decompensated heart failure, decompensated cirrhosis, or decompensated chronic renal failure), patients with active malignancy or acquired immunodeficiency syndrome (AIDS) or pregnancy. Patients who were prescribed statins for more than 1 month were considered the statin user group.

The demographic information, clinical characteristics, radiological images, and laboratory data of the patients were obtained from the patient files and the hospital digital system. Concomitant diseases such as hypertension, coronary heart disease, heart failure, atrial fibrillation, diabetes mellitus, chronic lung diseases (asthma/chronic obstructive pulmonary disease), cerebrovascular diseases, chronic renal failure, and the medications used by the patients were obtained from the medical history. In-hospital medications and interventions were carried out according to the Covid-19 Guidelines, published by the Ministry of Health of the Republic of Turkey [15]. To protect patient privacy, each patient was given a code before data collection. It was carefully double-checked by experienced physicians to verify the accuracy of the data. Definition of ARDS and septic shock were assessed according to the WHO intermediate guideline [16].

Statistical Analysis

The IBM SPSS software suite was used to conduct all statistical analyses (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The continuous variables were presented given as mean±SD and median interquartile range 25-75% (IQR) in case of non-normal distribution. The categorical variables were expressed as percentages. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Depending on the data distribution, the continuous variables were compared using the Student's t-test or the Mann-Whitney U test. The categorical variables were compared using Chi-square or Fisher's exact tests if appropriate. The non-normally distributed numerical and categorical variables were analyzed with the Mann-Whitney U test in the two groups. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship between statin use and the development of mortality. In stepwise multivariable regression analysis (Backward,

Wald); effect size was adjusted with a univariate significance level of <0.05 for all variables. Adjusted odds ratios (OR) along with the confidence interval (CI) 95% were presented. A 2-tailed p-value<0.05 was considered to be statistically significant.

RESULTS

A total of 1752 patients hospitalized in our hospital with the diagnosis of Covid-19 were included in our study. For the patients, the median age was 64 years (53-74 interquartile range [IQR]), 804 (45.9%) were over the age of 65, 903 (51.5%) were male, 167 (9.5%) were using statins, and mortality developed in 381 (21.7%) of the patients. The characteristics of the study population are summarized in Table 1. In the group using statins; age, systolic blood pressure, and diastolic blood pressure levels were higher (p=0.004, p=0.012, and p=0.002, respectively). In addition, comorbidities such as coronary artery disease, heart failure, hypertension, diabetes mellitus, and asthma were more common (p <0.001, p <0.001, p <0.001, p <0.001, and p=0.031, respectively). While creatinine level and potassium level were higher (p <0.001, and p=0.007) in statin users, AST level was lower (p=0.039). Antiaggregant, ACEI, ARB, beta-blocker, calcium channel blocker, diuretic, oral antidiabetic, and insulin use were more common (p <0.001, p <0.001, p <0.001, p <0.001, p <0.001, p <0.001, p <0.001, and p <0.001, respectively) in the statin user group. Also, mechanical ventilator need and ICU hospitalization rates were higher (p=0.041, and p=0.008) in statin users. Although the mortality rate was higher in the group using statins, it was not statistically significant (p=0.056).

In Table 2, the multivariate logistic regression model was applied using statistically significant parameters in the univariate analysis of mortality development. The group using statins was included in the regression model because it was statistically borderline significant (p=0.052). According to this model; increased age (odds ratio (OR) =1.051, 95% confidence interval (CI) 1.039-1.063, p<0.001), male gender (OR=1.002, 95%CI 0.993-1.010, p=0.705), decrease in lymphocyte count (OR=0.452, 95%CI 0.337-0.607, p<0.001) increase in potassium level (OR=1.306, 95%CI 1.025-1.664, p=0.031), increase in aspartate transaminase (AST) level (OR=1.004, 95%CI 1.001-1.007, p=0.003), increase in D-dimer level (OR=1.000, 95%CI 1.000-1.000, p=0.011), increase in procalcitonin level (OR=1.027, 95%CI 1.000-1.053, p=0.046), increase in CRP level (OR=1.007, 95%CI 1.005-1.008, p<0.001), and the development of myocardial injury (OR=3.045, 95%CI 1.864-4.976, p<0.001) was found to be associated with increased mortality. Statin use (OR=1.221, 95% CI 0.759-1.966, p=0.410) was not associated with mortality.

DISCUSSION

In this study, we found that advanced age, male gender, increased levels of potassium, AST, D-dimer, procalcitonin, CRP, low lymphocyte count, and myocardial damage were associated with increased mortality. We determined that using statins does not affect mortality.

Similar to previous studies [17], we found that advanced age, male gender, increased potassium, AST, D-dimer, procalcitonin or CRP level, low lymphocyte count, and myocardial damage were associated with increased mortality. In our study, the rate of statin use in patients with coronary heart disease was 59.9%. This low rate of statin use may be attributed to the side effects of statins, lack of health insurance, or polypharmacy.

Statins have antiplatelet, anticoagulant, anti-inflammatory, and immunomodulatory properties in addition to reducing the cholesterol level. Statins cause a decrease in platelet activity as a result of an increase in nitric oxide, a potent inhibitor of platelet aggregation. Thrombomodulin (TM) acts as a cofactor of thrombin in the process of activation of activated protein C (APC), which proteolytically inactivates factors V and VIII and acts as an anticoagulant. Statins have been shown to increase the expression of TM and APC [18]. Statins have been reported to have pleiotropic effects on respiratory tract infection and acute lung injury [19,20]. By activating intracellular signaling pathways, it has been demonstrated that statins have a variety of helpful anti-inflammatory and immunomodulatory characteristics [21,22]. In addition, many in vitro and in vivo research results have shown antiviral efficacy of statins against influenza virus [23,24].

Table 1. Characteristics of the study population

Parameters	All patients (n=1752)	Statin users (n=167)	Non Statin users (n=1585)	p value
Age, years	64(53-74)	66(58-73)	64(52-74)	0.004
Gender (male), n (%)	903(51.5)	95(56.9)	808(51.0)	0.146
SBP, mmHg	120.0(110.0-122.8)	120.0(110.0-130.0)	120.0(110.0-120.0)	0.012
DBP, mmHg	70.0(60.0-80.0)	70.0(70.0-80.0)	70.0(60.0-80.0)	0.002
Coronary heart disease, n(%)	280(16.0)	100(59.9)	180(11.4)	<0.001
Chronic heart failure, n (%)	72(4.1)	19(11.4)	53(3.3)	<0.001
Hypertension, n(%)	809(46.2)	134(80.2)	675(42.6)	<0.001
Diabetes mellitus, n(%)	474(27.1)	99(59.3)	375(23.7)	<0.001
COPD, n(%)	106(6.1)	14(8.4)	92(5.8)	0.184
Asthma, n(%)	119(6.8)	18(10.8)	101(6.4)	0.031
Cerebrovascular diseases, n(%)	81(4.6)	8(4.8)	73(4.6)	0.914
Chronic renal diseases, n(%)	68(3.9)	10(6.0)	58(3.7)	0.138
Chronic AF, n(%)	59(3.4)	5(3.0)	54(3.4)	0.778
Neutrophil count, 10^3/uL	5.56(3.80-8.20)	5.41(4.11-7.68)	5.45(3.78-8.23)	0.758
Lymphocyte count, 10^3/uL	1.06(0.74-1.43)	1.10(0.75-1.60)	1.06(0.74-1.41)	0.111
Platelet count, 10^3/uL	210(168-264)	203(159-259)	210(169-265)	0.153
Hemoglobin, g/dl	13.4(12.1-14.5)	13.3(12.0-14.5)	13.4(12.1-14.5)	0.314
Creatinine, mg/dl	0.93(0.79-1.21)	1.03(0.83-1.40)	0.92(0.78-1.19)	<0.001
Potassium, mmol/l	4.18(3.84-4.54)	4.31(3.89-4.73)	4.17(3.84-4.52)	0.007
AST, U/L	33(24-47)	30(23-39)	33(24-48)	0.039
ALT, U/L	25(17-39)	24(16-37)	25(17-40)	0.147
Ferritin, ng/ml	468(236-882)	406(219-730)	474(237-915)	0.065
D-dimer increase, ng/ml	272(177-445)	259(173-436)	272(177-445)	0.936
Procalcitonin, ng/ml	0.11(0.06-0.24)	0.12(0.06-0.29)	0.11(0.06-0.24)	0.505
C-reactive protein, mg/l	83.0(40.2-128.0)	73.1(33.9-117.0)	83.4(40.4-129.4)	0.191
Bilateral lesions, n(%)	1682(96.0)	161(96.4)	1521(96.0)	0.912
Antiaggregant users, n(%)	464(26.5)	124(74.3)	340(21.4)	<0.001
OAC users, n(%)	47(2.7)	3(1.8)	44(2.8)	0.456
ACEI users, n(%)	274(15.6)	65(38.9)	209(13.2)	<0.001
ARB users, n(%)	385(22.0)	58(34.7)	327(20.6)	<0.001
Beta-blocker users, n(%)	357(20.4)	84(50.3)	273(17.2)	<0.001
Calcium channel blocker users, n(%)	395(22.5)	58(34.7)	337(21.3)	<0.001
Diuretic users, n(%)	446(25.5)	65(38.9)	381(24.0)	<0.001
Spironolactone users, n(%)	32(1.8)	4(2.4)	28(1.8)	0.564
Alpha-blocker users, n(%)	36(2.1)	5(3.0)	31(2.0)	0.368
Digoxin users, n(%)	16(0.9)	1(0.6)	15(0.9)	0.653
Oral antidiabetic users, n(%)	367(20.9)	81(48.5)	286(18.0)	<0.001
Insulin users, n(%)	136(7.8)	36(21.6)	100(6.3)	<0.001
Mechanical Ventilation, n(%)	384(21.9)	47(28.1)	337(21.3)	0.041
Septic shock, n(%)	190(10.8)	23(13.8)	167(10.5)	0.201
ARDS, n(%)	332(18.9)	41(24.6)	291(18.4)	0.052
Hospital stays, days	8(6-12)	8(7-11)	8(6-12)	0.191
ICU stays, n(%)	525(30.0)	65(38.9)	460(29.0)	0.008
Myocardial injury, n(%)	106(6.1)	15(9.0)	91(5.7)	0.091
Mortality, n(%)	381(21.7)	46(27.5)	335(21.1)	0.056

Data are shown as % for categorical and as median (interquartile range) for continuous variables. Categorical data were compared using chi-square test and continuous data using Mann-Whitney U test

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ICU, intensive care unit; MV, mechanical ventilation; OAC, oral anticoagulant; SBP, systolic blood pressure

Table 2. Univariate and multivariate logistic regression analysis for in-hospital mortality

Variable	Univariable			Multivariable		
	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age, years	1.060	1.050-1.070	<0.001	1.051	1.039-1.063	<0.001
Gender (male), n (%)	1.434	1.140-1.805	0.002	1.469	1.076-2.005	0.015
SBP, mmHg	1.013	1.005-1.021	0.001	1.002	0.993-1.010	0.705
DBP, mmHg	1.002	0.997-1.008	0.448			
Coronary heart disease, n(%)	1.962	1.482-2.600	<0.001	1.090	0.717-1.656	0.687
Chronic heart failure, n (%)	2.110	1.286-3.461	0.003			
Hypertension	1.839	1.462-2.315	<0.001	1.046	0.690-1.585	0.832
Diabetes mellitus, n(%)	1.385	1.083-1.773	0.010	1.127	0.795-1.598	0.502
COPD, n(%)	2.219	1.470-3.352	<0.001	1.284	0.773-2.132	0.335
Asthma, n(%)	1.116	0.719-1.732	0.625			
Cerebrovascular diseases, n(%)	1.860	1.155-2.996	0.011			
Chronic renal diseases, n(%)	1.643	0.970-2.785	0.065			
Chronic AF, n(%)	2.209	1.287-3.793	0.004			
Neutrophil count, 10^3/uL	1.155	1.123-1.187	<0.001			
Lymphocyte count, 10^3/uL	0.292	0.222-0.383	<0.001	0.452	0.337-0.607	<0.001
Platelet count, 10^3/uL	1.000	0.998-1.001	0.461			
Hemoglobin, g/dl	0.864	0.813-0.917	<0.001	0.950	0.877-1.029	0.210
Creatinine, mg/dl	1.218	1.131-1.312	<0.001	1.003	0.901-1.117	0.955
Potassium, mmol/l	1.650	1.360-2.002	<0.001	1.306	1.025-1.664	0.031
AST, U/L	1.004	1.002-1.006	0.001	1.004	1.001-1.007	0.003
ALT, U/L	1.002	1.000-1.004	0.060			
Ferritin, ng/ml	1.001	1.001-1.001	<0.001			
D-dimer, ng/ml	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	0.011
Procalcitonin, ng/ml	1.065	1.032-1.099	<0.001	1.027	1.000-1.053	0.046
C-reactive protein, mg/l	1.008	1.007-1.010	<0.001	1.007	1.005-1.008	<0.001
Antiaggregant users, n(%)	1.779	1.397-2.267	<0.001	0.777	0.532-1.136	0.193
OAC users, n(%)	1.895	1.025-3.502	0.041			
ACEI users, n(%)	1.144	0.843-1.551	0.388			
ARB users, n(%)	1.431	1.102-1.858	0.007	1.036	0.715-1.500	0.853
Beta-blocker users, n(%)	2.017	1.557-2.613	<0.001	1.478	0.988-2.211	0.057
Calcium channel blocker users, n(%)	1.685	1.305-2.174	<0.001	1.338	0.927-1.930	0.120
Diuretic users, n(%)	1.149	0.890-1.484	0.287			
Spironolactone users, n(%)	1.418	0.651-3.090	0.380			
Alpha-blocker users, n(%)	2.961	1.519-5.772	0.001			
Digoxin users, n(%)	3.654	1.362-9.801	0.010			
Oral antidiabetic users, n(%)	1.198	0.914-1.572	0.191			
Insulin users, n(%)	1.748	1.195-2.558	0.004	1.407	0.828-2.392	0.207
Statin users, n(%)	1.419	0.989-2.034	0.052	1.221	0.759-1.966	0.410
Miyocardial injury, n(%)	6.352	4.223-9.555	<0.001	3.045	1.864-4.976	<0.001

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; OAC, oral anticoagulant; OR, odds ratio; SBP, systolic blood pressure

Statins adjust the antiviral response in human epithelial and bronchial cells, which form the first line of defense against invading pathogens such as H1N1. Significantly reduces the production of proinflammatory cytokines such as TNF-alpha and IL-6 [25,26]. Despite these beneficial effects of statins, it was shown in a study that plasma IL-18 levels were higher in patients using statins and that higher levels of IL-18 were associated with higher mortality in patients with sepsis-induced ARDS [27]. Zhang et al., in a retrospective study involving a total of 13,981 patients, 1219 of whom received statin therapy, a potential reduction in all-cause mortality was determined in Covid-19 patients receiving statin therapy. They found that in-hospital statin use was associated with a 42% reduction in 28-day mortality risk [14]. Although our data may be biased by remaining confounding factors, including patient selection, treatment indication, socioeconomic status, and lack of adjustment for prehospital medication, this controversial finding deserves further investigation. On the other hand, in their study Butt et al. analyzed a total of 4842 patients diagnosed with Covid 19, of which 843 were prescribed a statin at least once in the past 6 months. In this study, there were outpatients and hospitalized patients. The main conclusion of the study was that statin use before Covid-19 diagnosis was not associated with an improvement or worsening in the clinical course of Covid-19 infection [28]. A meta-analysis of 9 studies involving 3449 patients by Hariyanto and Kurniawan showed that the use of statins did not improve the severity and mortality of Covid-19 infection [29]. Oh et al. showed that the probability of developing Covid-19 in the statin treatment group was 35% lower than the control group in their study involving 122040 patients with 22633 statin users, but showed that there was no difference in in-hospital mortality between the statin treatment and control groups [30].

Our results showed that statin use did not result in an increase in-hospital mortality, similar to the results of previous studies. Although statins produce anti-inflammatory and antithrombotic effects, there is no clear evidence that these drugs reduce morbidity and mortality in Covid-19 patients. The use of statins may cause an increase in IL-18 levels and potential detrimental effects may occur [27] and may result in a neutral effect on covid-19, balanced by beneficial effects such as anti-inflammatory and antithrombotic properties.

Limitations

The most important limitation was that our study was a single-center, retrospective study, and the number of patients was small. There was a lack of data from hospital records such as smoking history and body mass index. In addition, since our study was retrospective, an important limitation emerged as there was no data on the doses and drug compliance to prescribed statins.

CONCLUSION

Our study showed that using statins was not associated with an increase or decrease in mortality in Covid-19 patients. Although statins are known to have beneficial effects such as anti-inflammatory and antithrombotic properties, large-scale randomized clinical trials are needed to determine the benefits of statins in Covid-19 patients.

Author contribution

Study conception and design: AA, and BA; data collection: FI, MÇ, İK, ÖA, and Üİ; analysis and interpretation of results: ET, ÖB, and MO; draft manuscript preparation: AA, and MZK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee of SBU Diyarbakır Gazi Yaşargil Education and Research Hospital (Protocol no: 778/29.05.2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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