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Research Paper

Effect of Statin Treatment on COVID-19 Patients' Outcomes: A Randomized Double-blind Controlled Clinical Trial

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ABSTRACT

Background: Statins may be protective against viral infection and have been suggested for the treatment of coronavirus disease 2019 (COVID-19).

Objective: In this study, we aimed to evaluate the effect of atorvastatin on COVID-19 patients.

Methods: Our study is a randomized double-blind controlled clinical trial that constitutes a population of COVID-19 patients admitted to Bu-Ali Sina Hospital in Qazvin, Iran, from May to August 2021. For the intervention and control groups, in addition to the national standard treatment, atorvastatin 40 mg tablet and placebo were daily administered for 7 days, respectively. A questionnaire including demographic characteristics, history of underlying diseases, vital signs, laboratory and imaging results, and outcome (alive, died) was completed on the first, third, and fifth days of hospitalization. Finally, the obtained data were analyzed by SPSS software, version 25.

Findings: One hundred five patients with COVID-19 (62 females and 43 males, mean age 69 years) were studied. On days 3 and 5 after the intervention, no significant difference was observed between the groups in terms of vital signs, laboratory findings, hospitalization time, and need for intensive care unit hospitalization. However, 5.7% of patients in the atorvastatin group and 0% of patients in the control group died (P=0.243). Among the studied variables, C-reactive protein (P=0.227 vs P=0.002), blood urea nitrogen (P=0.055 vs P<0.001), and creatinine (P=0.598 vs P=0.013) decreased significantly in the statin group (no control group during days 0-5).

Conclusion: There was no evidence about the harm and benefits of statin treatment during COVID-19 hospitalization.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic due to COVID-19 is presently the greatest global threat. Patients of COVID-19 with hypertension, cardiovascular disease, and diabetes mellitus are more often associated with severe or critical diseases. A primary retrospective study on COVID-19 patients in China demonstrated that patients with a history of cardiovascular disease have higher mortality than other COVID-19 patients [1]. During the pandemic, more than 100 drugs have been experimentally used to treat COVID-19 patients [2]. It has been suggested that statins can enhance clinical outcomes in COVID-19 patients. Some mechanisms have been proposed that might explain how such beneficial effects could occur. First, statins, in addition to their cholesterol-lowering role, have several pleiotropic (lipid-independent) effects including modulating the immune response and reducing inflammation [3, 4]. The pleiotropic effects of statins have been described in lung cancer, respiratory infections [5, 6], acute lung injury [7], pulmonary hypertension [8], community-acquired pneumonia [9], and interstitial lung diseases [10]. Thus, they are associated with a reduced risk of acute infections and better outcomes for these infections [3, 4, 11, 12].

Second, the mortality rate of COVID-19 infection in cardiovascular and diabetic patients is much higher than other patients [13, 14], and there is evidence of heart involvement in some COVID-19 patients [15], especially in severe cases [1, 15-24]. It has been hypothesized that statins might prevent or reduce the risk of heart failure and cardiovascular events [3]. Due to the potential protective effects of statins, this drug may prevent myocardial damage and cardiovascular side effects, especially in cardiovascular disease patients [25, 26]. Third, it has also been suggested that by binding to the major protease that causes the virus enters the cell and block severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, they make the virus unable to invade host cells [27]. Several studies have provided valuable insights into the function of statins in SARS-CoV-2 infection. An in-silico study showed that statins may be effective inhibitors of the COVID-19 major protease [27]. In addition, selective statins such as Fluvastatin reduced the entry of SARS-CoV-2 into the human respiratory epithelial cell [28].

Some studies have reported the association of statin treatment with reduced cardiovascular outcomes and mortality in influenza patients. Therefore, it was suggested that COVID-19 patients with damaged lung tissue due to cytokine storm initiate statin therapy for its potential clinical benefits, as its use, even for a short time, may have a positive effect on reducing mortality and secondary complications from infection [29].

An observational study published recently found that in-hospital statin treatment was related to a significant increase in the survival of COVID-19 patients. The authors claimed a 42% reduction in mortality among statin users [30]. A computer-based study also revealed that rosuvastatin may be beneficial in the treatment of COVID-19 infection [2]. However, other observational studies found no benefit from statins in COVID-19 patients [31-33].

In addition, there is extensive clinical experience with statins, and they are generally recognized as safe, inexpensive, and affordable drugs. This manuscript reports the results of the effect of atorvastatin 40 mg orally once daily versus placebo in admitted COVID-19 patients.

2. Materials and Methods

The present study is a randomized double-blind controlled clinical trial that constitutes a population of COVID-19 patients admitted to Bu-Ali Sina Hospital in Qazvin, Iran from May to August 2021. This study was approved by the Ethics Committee of Qazvin University of Medical Sciences, then registered in the Iranian Clinical Trial Center and was obtained informed consent from all participants.

The inclusion criteria include confirmation of COVID-19 infection according to World Health Organization (WHO) diagnostic criteria, such as SARS-CoV-2 ribonucleic acid positive detected by reverse transcription polymerase chain reaction (RT-PCR) on upper respiratory tract samples (nasopharynx, oropharynx), or proved by imaging modalities, chest x-ray, and computed tomography scan. Patients were not admitted to the study if they met any of the following criteria: Any likely infection other than COVID-19 pneumonia, malignancy, or other severe immunosuppression (e.g. use of immunosuppressants), and they were unable to complete the protocol, and they had a history of statin medication or hypersensitivity to this medication. The primary endpoints were survival and length of hospital stay, as well as the necessity for intensive care unit (ICU). Secondary endpoints were respiratory rate, peripheral capillary oxygen saturation, and changes in inflammatory markers.

We calculated that 52 patients were needed in both groups to detect a mean difference of 2 days length of stay (5±1.7 versus 7±1.7 days) between atorvastatin and control groups, with a power of 80%, an alpha level of 0.05, and drop-out rate: 0.1 [34] based on Equation Equation 1.

$$1: \text{the n} \geq \frac{[Z_1 - \frac{a}{Z} + Z_{1-\beta}]^2[\sigma_1^2 + \frac{\sigma_2^2}{r}]}{(\mu_1 - \mu_2)^2}$$

Eligible adult patients were randomly assigned to atorvastatin or matching placebo in a 1:1 ratio (Figure 1). Using the random sequence generator software "Statistics and Sample Size version 1.0," the randomization sequence was generated. This allocation concealment strategy will result in minimal selection and confounding biases. Access to the allocation sequence was concealed from the site clinicians. The study drug and placebo were identical in appearance. Neither the patient nor the investigators conducting the study knew which patients belong to which study arm. The study intervention was atorvastatin 40 mg orally once daily compared with a placebo. The plan was for the study drug to be continued for 7 days from randomization.

The questionnaire included demographic characteristics (age, sex, and body mass index), history of underlying diseases such as coronary artery disease, cerebrovascular accident, chronic obstructive pulmonary disease, DM, and HTN, and vital signs including pulse rate, respiratory rate, O_2 saturation, body temperature, systolic, diastolic and mean arterial blood pressure, and Glasgow Coma Scale scores and laboratory results such as white blood cells, lymphocyte percent, platelets number, C-reactive protein, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, and CURB-65 score and computed tomography scan results, length of hospital stay, need for ICU, and death were recorded. Then, the questionnaire was completed on the first, third, and fifth days of hospitalization. All patients were observed and subsequently asked about all possible side effects. A renal function test was done on days 0, 3, and 5 of hospitalization. All oxygen saturation was measured in breathing room air at rest. A CURB-65 severity score was calculated, and 1 point was given for each feature present (range, 0–4 points) [35, 36].

The investigators had no influence on hospital discharge choices. All patients were treated by the Iranian hospitalized COVID-19 patients management guideline version 5. Heparin prophylaxis was used in conjunction with supplemental O_2 therapy and supportive hydration therapy. To minimize biased estimations of treatment effects, experienced nurses measured and recorded baseline and follow-up clinical and paraclinical data. The investigators did not influence decisions concerning hospital discharge.

Finally, the collected data were analyzed by SPSS software, version 25 (SPSS®, Armonk, NY, USA). The data were summarized as frequencies (percentages) for categorical variables. The normality of the distribution of continuous variables was tested by the one-way Kolmogorov–Smirnov test. The distribution of all variables differed from the normal distribution ($P<0.05$) and was skewed. Hence, descriptive statistics were represented as

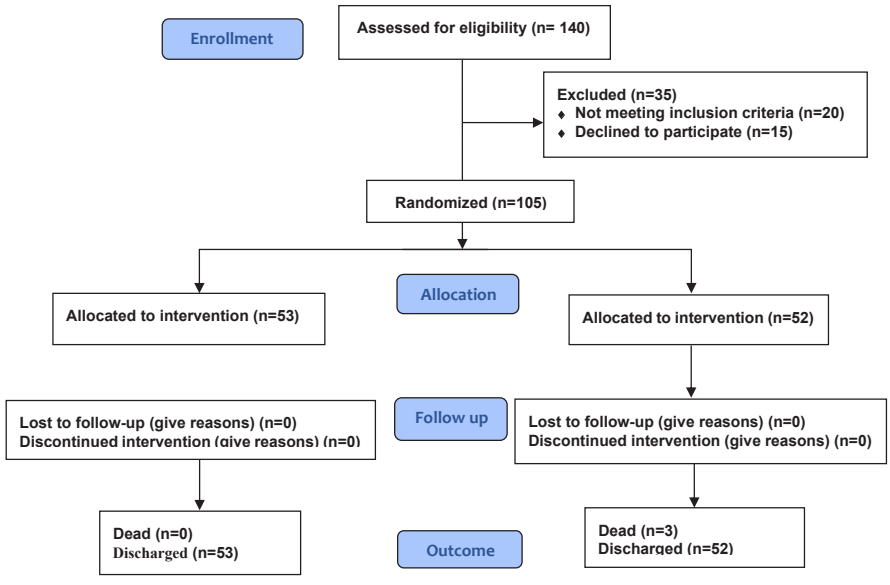

Figure 1. Flow diagram of the study

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medians and interquartile ranges for continuous variables. We compared proportions using the $\chi 2$ test or Fisher's exact test and continuous variables using the Mann-Whitney test. The macro-PROCESS V 3.5 was used to perform moderation analysis. The PROCESS macro generates unstandardized bootstrapped regression output as well as estimates of the effect of the focal predictor variables (duration of hospital and ICU stay, and outcome) for different moderator variable values (i.e. age, DM, and HTN) [37]. $P<0.05$ was considered statistically significant.

3. Results

During 4 months, 105 patients with COVID-19 (62 females and 43 males) were studied; the age of the patients was between 56-77 years and their mean age was 69 years. All of them were hospitalized due to severe COVID-19 at Bu-Ali Sina Hospital in Qazvin. Fifty-two patients were in the placebo group (control group) and 53 patients were in the statin group (intervention group).

The results showed that there was no significant difference between the two groups in terms of demographic information such as gender (P=0.141) and body mass index (P=0.333), but the mean age in the intervention group was higher than the control group (P=0.028).

The highest percentage of underlying disease history in the studied patients was HTN (30.8% in the control group and 11.3% in the intervention group) (P=0.014), however, cerebrovascular accident and chronic obstructive pulmonary diseases were separately observed only in 1% of the studied patients. The comparison of vital signs before the intervention in the two studied groups has been also shown in Table 1. As observed, there was no significant difference between the vital signs except Pulse Rate (P=0.012) and the Glasgow coma scale (P=0.028) between the two groups (P>0.05).

In addition, Table 1 showed that there was no significant difference between the laboratory and CT-Scan findings in the intervention and control groups. Vital signs and laboratory findings of the groups on days 3 and 5 after the intervention showed that there was no significant difference between both groups (Table 2). Only on the fifth-day post-intervention, a significant decrease was observed in mean arterial pressure in the intervention group (91.98, 81.44-95.98) compared to the control group (97.22, 91.92-101.98) (P=028). In addition, in the third-day post-intervention, creatinine levels in the intervention group showed a significant increase (1.1, 0.9-1.5) compared to the control group (0.9, 0.8-1.0) (P=0.032).

Other outcomes such as length of hospital stay were not statistically different between the two groups (P=0.289), as the mean days of hospitalization were 7 and 9 days in the control and intervention groups, respectively. In addition, neither patient in either group needed to be admitted to the ICU. All patients in the control group were discharged without death. However, 94.7% of patients in the intervention group were discharged and 5.7% of patients died (P=0.243). After performing the Hayes PROCESS macro regression to test the moderation effects of HTN and DM (and age as a covariate) on in-hospital clinical outcomes (length of hospital stay, length of ICU stay, and mortality rate), it was shown that DM and HTN is not a significant predictor of length of hospital stay (model 2 Hayes: Y=length of hospital stay, X=group, Covariates=age, W=DM and Z=HTN (P=0.999), length of ICU stay (model 2 Hayes: Y=length of ICU stay, X=group, Covariates=age, W=DM and Z=HTN) (P=0.607), and mortality rate (model 2 Hayes: Y=outcome, X=group, Covariates=age, W=DM and Z=HTN (P=0.486).

Table 3 shows the changes in vital signs and laboratory findings on days 0-3, 3-5, and 0-5 in the control and intervention groups. Among the studied variables, C-reactive protein (P=0.227 vs P=0.002), blood urea nitrogen (P=0.055 vs P<0.001), and creatinine (P=0.598 vs P=0.013) decreased significantly in the statin group (no control group) during days 0-5.

4. Discussion

The present study was designed to determine the effect of atorvastatin on hospitalized COVID-19 patients' outcomes. This experiment did not detect any evidence for the necessity of atorvastatin treatment in the management of COVID-19. No association was observed between statin use during the hospitalization period in terms of length of hospitalization, need for ICU, and mortality risk.

Our findings differ from those of several retrospective cohort and clinical trial research, but they are consistent with the majority of comparable published investigations. While some randomized trials and observational studies have demonstrated that statins can reduce mortality and improve the clinical course of patients with severe infections, particularly viral infections, others have found little benefit [38-42]. Some earlier reports

Table 1. Baseline clinical features and laboratory investigations of patients (day 0)

	Characteristics		No. (%)/Median [interquartile range], Control n=52	Intervention (n=53)	Total (n=105)	P
	Sex	Male	25(48.1)	18(34.0)	43(41.0)	0.141
		Female	27(51.9)	35(66.0)	62(59.0)	
	Age (y)		65 [55-74]	71 [62-80]	69 [56-77]	0.028*
	Body mass index (kg/m^2)		27.34 [23.77-29.22]	26.03 [24.22-28.12]	26.37 [24.17-28.91]	0.333
Underlying disease	Cerebrovascular accident	-	51(98.1)	53(100)	104(99.0)	0.495
		+	1(1.9)	0(0)	1(1.0)	
	Coronary artery disease	-	45(86.5)	46(86.8)	91(86.7)	0.969
		+	7(13.5)	7(13.2)	14(13.3)	
	Chronic obstructive pulmonary disease	-	51(98.1)	53(100)	104(99.0)	0.495
		+	1(1.9)	0(0)	1(1.0)	
	Diabetes mellitus	-	44(84.6)	52(98.1)	96(91.4)	0.016*
		+	8(15.4)	1(1.9)	9(8.6)	
	Hypertension	-	36(69.2)	47(88.7)	83(79.0)	0.014*
		+	16(30.8)	6(11.3)	22(21.0)	
Vital sign	Pulse rate (beats/min)		86 [80-90]	90 [86-93]	88 [83-90]	0.012*
	Respiratory rate (breath/min)		18 [18-20]	18 [18-20]	18 [18-20]	0.995
	Temperature (°C)		36.8 [36.7-37.1]	37.0 [36.8-37.2]	37.0 [36.8-37.1]	0.136
	O_2 saturation (%)		92 [90-93]	91 [90-93]	91 [90-93]	0.437
	Systolic blood pressure (mmHg)		115 [110-120]	110 [110-120]	110 [110-120]	0.206
	Diastolic blood pressure (mmHg)		80 [75-90]	80 [70-85]	80 [70-85]	0.160
	Mean arterial pressure (mmHg)		93.22 [90.33-100.57]	91.98 [86.72-97.99]	92.21 [89.44-98.98]	0.210
	Glasgow coma scale (GCS)		15 [15-15]	15 [15-15]	15 [15-15]	0.028*
Biochemistry	White blood cells (5×10^{10}/mL)		8700 [6350-10600]	7200 [5500-10400]	7600 [5700-10500]	0.698
	Lymphocyte (%)		19 [14-26]	18 [12-23]	19 [13-25]	0.478
	Platelets (5×10^{10}/mL)		190000 [144000-234000]	191000 [151000-245000]	191000 [150000-241000]	0.677
	Erythrocyte sedimentation rate (mm/h)		30 [16-40]	31 [13-56]	30 [13-47]	0.479
	C-reactive protein (mg/dL)		19 [7-37]	19 [7-38]	19 [7-38]	0.972
	Blood urea nitrogen (mg/dL)		19 [14-23]	19 [14-28]	19 [14-23]	0.605
	Creatinine (mg/dL		0.9 [0.7-1.0]	1.0 [0.7-1.5]	0.9 [0.7-1.1]	0.070
	Polymerase chain reaction	negative	40(76.9)	36(67.9)	76(72.4)	0.302
		positive	12(23.1)	17(32.1)	29(27.6)	
	Computed tomography scan	mild	21(41.2)	27(51.9)	48(46.6)	0.288
		moderate	19(37.3)	12(23.1)	31(30.1)	
		severe	11(21.6)	13(25.0)	24(23.3)	
	CURB_65 score		1.0 [0-2.0]	1.0 [1.0-2.0]	1.0 [0-2.0]	0.189

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Table 2. Results of the outcome during the in-hospital stay

Differences		Days	Groups No. (%)/ Median [interquartile range]			P
			Control	Intervention	Total	
	Pulse rate (beats/min)	3	88 [87-90]	89 [87-90]	88 [87-90]	0.989
		5	89 [87-90]	90 [87-91]	90 [87-90]	0.360
	Respiratory rate (breath/min)	3	19 [18-21]	18 [18-21]	18 [18-21]	0.896
		5	18 [18-20]	18 [18-20]	18 [18-20]	0.937
	Temperature (°C)	3	36.9 [36.8-37.0]	37.0 [36.8-37.1]	36.9 [36.8-37.0]	0.182
		5	36.8 [36.8-37.0]	36.8 [36.7-37.0]	36.8 [36.8-37.0]	0.793
	O_2 saturation (%)	3	94 [93-95]	93 [93-94]	94 [93-94]	0.083
		5	94 [94-95]	94 [94-95]	94 [94-95]	0.462
	Mean arterial pressure (mmHg)	3	92.97 [87.91-101.80]	92.04 [89.05-96.97]	92.24 [88.98-98.69]	0.857
		5	97.22 [91.92-101.98]	91.98 [89.44-95.98]	93.10 [90.02-100.73]	0.028*
Laboratory investigations	White blood cells ($\times10^3$/mL)	3	7000 [5600-9500]	6900 [6050-9450]	7000 [5600-9500]	0.747
		5	6950 [4800-9350]	8350 [6500-10600]	7500 [5900-9800]	0.055
	Lymphocyte (%)	3	18 [12-23]	21 [12-25]	19 [12-25]	0.615
		5	20 [12-27]	21 [14-30]	20 [14-28]	0.689
	Platelets ($\times10^{10}$/mL)	3	205000 [141500-221500]	184500 [154000-224000]	194000 [152000-222500]	0.788
		5	220000 [168000-267000]	215000 [198000-271000]	220000 [189000-267000]	0.729
	Erythrocyte sedimentation rate (mm/h)	3	23 [10-40]	40 [20-45]	30 [16-45]	0.094
		5	28 [12-36]	17 [9-27]	20 [10-32]	0.203
	C-reactive protein (mg/dL)	3	20 [6-38]	13 [6-30]	15 [6-30]	0.309
		5	14 [5-30]	12 [6-28]	14 [6-28]	0.939
	Blood urea nitrogen (mg/dL)	3	17 [13-20]	20 [12-27]	18 [13-22]	0.204
		5	15 [12-18]	19 [13-23]	16 [12-21]	0.128
	Creatinine (mg/dL)	3	0.9 [0.8-1.0]	1.1 [0.9-1.5]	1.0 [0.8-1.2]	0.032*
		5	0.9 [0.9-1.0]	1.0 [0.9-1.2]	0.9 [0.9-1.2]	0.266
	Length of intensive care unit stay (days)		0 [0-0]	0 [0-0]	0 [0-0]	0.091
	Length of hospital stay (days)		7 [4-13]	9 [5-13]	7 [4-13]	0.289
	Outcome	expire	0(0)	3(5.7)	3(2.9)	0.243
		discharge	52(100)	50(94.3)	102(97.1)	

Data are presented as numbers (percentages) or the median [interquartile range], * Significant.

contradict our findings. For example, in an observational study based on data from 21 hospitals in China, Zhang et al., demonstrated that in-hospital statin use is associated with improved survival in COVID-19 patients. Specifically, the researchers found a 28-day mortality risk of 5.2% and 9.4% in the statin and non-statin groups, respectively, and in-hospital statin use was associated with a 42% reduction in in-hospital mortality [43]. However, the data may be controversial with patient selection, treatment symptoms, socioeconomic status, and prehospital medications and may need further investigation.

Table 3. Results of the outcome changes in the intervention group during the in-hospital stay (control group vs. intervention group)

Differences	P					
	0 to 3 days		3 to 5 days		0 to 5 days	
	Control	Intervention Group	Control	Intervention Group	Control	Intervention Group
Pulse rate (beats/min)	0.017*	0.237	0.511	0.074	0.023*	0.610
Respiratory rate (breath/min)	0.308	0.243	0.380	0.165	0.806	0.645
Temperature (°C)	0.286	0.119	0.508	0.228	0.432	0.015*
O_2 saturation (%)	<0.001*	<0.001*	0.291	<0.001*	<0.001*	<0.001
Mean arterial pressure (mmHg)	0.320	0.434	0.388	0.600	0.688	0.861
White blood cells ($\times10^3$/mL)	0.002*	0.134	0.981	0.572	0.376	0.894
Lymphocyte (%)	0.963	0.079	0.321	0.001*	0.799	0.024*
Platelets ($\times10^{10}$/mL)	0.444	0.926	0.006*	0.014*	0.009*	0.022*
Erythrocyte sedimentation rate (mm/h)	0.059	<0.001*	0.204	0.005*	0.026*	<0.001*
C-reactive protein (mg/dL)	0.670	<0.001*	0.128	0.100	0.227	0.002*
Blood urea nitrogen (mg/dL)	<0.001*	0.001*	0.077	0.002*	0.055	<0.001*
Creatinine (mg/dL)	0.448	0.398	0.877	<0.001*	0.598	0.013*

Nonparametric tests, Mann-Whitney test, 0: On admission, *Significant.

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In agreement with our study, in a primary meta-analysis, it was reported that statin use did not improve the outcomes of COVID-19 infections in the hospital; this analysis included 9 studies (1 case series and 8 retrospective cohorts). The results showed that the use of the statin did not improve the severity of the outcome [odds ratio=1.64, 95% confidence interval: (0.51–5.23), P=0.41, I2=93%, random-effect modeling] and mortality rate associated with COVID-19 infection [odds ratio=0.78, 95% confidence interval: (0.50–1.21), P=0.26, I2=0%, fixed-effect modeling] [32].

Contrary to the findings of the primary meta-analysis, a recent meta-analysis on retrospective cohort series reports statin use is associated with a better outcome in COVID-19 patients. They identified 32 studies that reported the outcome of all-cause mortality and 15 studies reported the composite endpoint of severe COVID-19 illness between statin users versus non-statin users with COVID-19. This study stated that the use of statins was associated with significantly lower risks of all-cause mortality (HR=0.7 and OR=0.63) and the composite endpoint of severe illness (OR=0.80) in COVID-19 patients, compared to non-use of statins [44]. This finding may be due to the use of different statistical analysis methods. These two studies suggested that the use of statins among COVID-19 patients be investigated in large-scale clinical trials.

In the present study, it was also reported that statin treatment did not pose a direct threat to patients. Even the erythrocyte sedimentation rate in the statin group decreased during the time and may have a mild beneficial effect on the outcome of COVID-19. In a recently published randomized controlled trial on hospitalized COVID-19 patients, the frequency of ICU hospitalization,

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the pulse rate, and the mean hospitalization days were all longer and higher in the intervention group. The hospitalization days in the intervention group were considerably longer and remission occurred 1.7 times sooner in the comparison group. They concluded that adding atorvastatin to the usual regime increased hospitalization days and had a negative impact on symptom recovery in COVID-19 hospitalized patients [34]. Another recent pilot randomized triple-blind placebo-controlled clinical trial reported that atorvastatin significantly reduces supplemental oxygen need, hospitalization duration, and serum hs-CRP level in mild to moderate hospitalized COVID-19 patients [45]. Unfortunately, most clinical trial studies of the statin effect have relied upon small sample sizes.

Overall, the results of our study do not support the routine use of statin in hospitalized COVID-19 patients. Therefore, more studies are needed to determine the role of statins in COVID-19 patients.

There are several limitations of our study. A limitation of our study was that the total cholesterol and low-density lipoprotein levels were not directly assessed. The follow-up period was brief and much longer periods are warranted in COVID-19. Furthermore, while patients were typically discharged when they met the discharge criteria outlined in the national COVID-19 guidelines, numerous concomitant diseases and patients' socioeconomic positions may impact physician decisions.

5. Conclusion

Overall, our study does not provide evidence of the beneficial effect of statins on COVID-19 patients. Further large-scale clinical trials are needed to demonstrate the efficacy and safety of atorvastatin treatment in COVID-19 management.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Qazvin University of Medical Sciences (Approval ID: IR.QUMS.REC.1399.171, Approval Date: 2020-08-15), then registered in the Iranian Clinical Trial Center under the number IRCT20200906048638N1.

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Authors' contributions

Supervision and the project conducting: Abbas Allami; Study design: Seyedeh Azam Nabavi and Abbas Allami; Data collection, investigation, and writing-original draft: Rozita Bahadori; Data interpretation: Seyedeh Azam Nabavi, Samira Dodangeh and Abbas Allami; Data analysis: Samira Dodangeh and Abbas Allami; Revising the manuscript critically: Samira Dodangeh; All authors contributed actively to the discussion of the study results, and approved the final manuscript.

Conflict of interest

The authors declared no conflict of interest.

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