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The Association of Atorvastatin Therapy With COVID-19 Outcomes and Mortality

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Abstract

Background: The world is still witnessing a largely ongoing spread of coronavirus disease 2019 (COVID-19); therefore, the scientific findings in this area need to be shared promptly.

Objectives: This study aimed to assess the usefulness of Atorvastatin treatment in reducing COVID-19 mortality in patients with or without diabetes mellitus (DM) and to correlate them with C-reactive protein (CRP) levels.

Methods: This study consecutively enrolled patients with pneumonia symptoms, positive lung CT scan, and confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on reverse transcription-polymerase chain reaction (RT-PCR). The outcome was defined as intensive care unit (ICU) admission and death. Clinical data and history of atorvastatin administration were evaluated. CRP levels were measured at baseline and repeated after one week in all patients.

Results: A total of 200 patients were included. Their mean age was 60.5 (SD=16.5) years, 113 (56.5%) patients were male, 47 (23.5%) with pre-existing diabetes, and 64 (32%) patients were taking atorvastatin routinely. 68 (34%) required ICU admission of all the studied patients. No gender differences were found in ICU admission and death. The baseline CRP was not significantly different, but the secondary CRP was significantly different between DM and non-DM groups. Secondary CRP also showed a significant reduction in patients receiving atorvastatin ($P=0.017$). The mortality was the same in atorvastatin or non-atorvastatin groups ($P=0.715$).

Conclusion: It seems that taking statin has only some beneficial effects on improving CRP levels in patients with COVID-19. To achieve a reliable result, clinical trials are recommended.

Keywords: Statins, COVID-19, Mortality, C-reactive Protein, Diabetes Mellitus

1. Background

Coronavirus disease-19 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for which there is currently no treatment. It is, therefore, necessary to explore intervention strategies to alleviate morbidity and mortality.[1] This virus typically causes infected people mild to moderate respiratory disease and recovery without requiring particular medications.[2] The leading cause of mortality in the current pandemic of SARS-CoV-2 is acute respiratory distress syndrome (ARDS).[3,4] ARDS is an immunopathologic event, which occurs due to uncontrolled systemic inflammatory response following the release of proinflammatory cytokines and chemokines.[5]

Nonetheless, it is now believed patients with diabetes and high- cholesterol are more likely to experience severe illness during COVID-19 infection.[3,6,7] These comorbidities are two risk factors for clinical exacerbation of SARS-CoV-2 infection and increase the risk of severe complications and lethality.[6-8] In summary, reports from China and Italy show that the overall case fatality rate (CFR) and the number of patients treated in an intensive care unit (ICU) was increased for patients with diabetes.[3,9]

Statins are conventional lipid-lowering agents that act through inhibition of the mevalonate pathway with tolerable side effects.[10] It has been proven that cholesterol promotes viral infection through multiple mechanisms. Consequently, statins and other lipid-lowering drugs are beneficial during viral infections.[6,11] Statins influence several pathways, including the inflammatory, oxidative, and thrombotic processes, besides their main effect as the cholesterol-lowering drugs by the scavenger pathway.[11]

High levels of C-reactive protein (CRP), a prototype inflammatory marker, is associated with increased fatality

risks in COVID-19 patients; along with lung CT scan, it is one of the indicators for confirming positive COVID-19 and can reflect the extent of lung lesions and disease severity.[12-14]

In some studies, co-administration of statins has been suggested as the multipartite combination of potential COVID-19 outcomes mitigation agents.[6] In a retrospective study by Saeed et al,[15] 4252 patients with COVID-19 were recruited, of whom 53% were diabetic. They found that patients with diabetes mellitus (DM) on a statin had lower inflammatory markers (CRP) and reduced cumulative in-hospital mortality than those not on a statin. Moreover, in a review, the significantly reduction of the inflammatory burden and severity of the clinical course of COVID-19 by statins was mentioned.[7]

2. Objectives

We assessed the correlation between atorvastatin remedy, CRP levels, ICU admission, and mortality rate in patients with COVID-19 to provide a reference for clinical intervention.

3. Methods

3.1. Study Design

A cross-sectional study was conducted from 1 March to 30 April 2020. All the patients who were hospitalized in a designated center for COVID-19 (Dr. Shariati hospital) in Tehran, Iran, were investigated.

3.2. Study Population and Sampling

A total of 200 patients with pneumonia symptoms, positive lung CT scan, and confirmed SARS-CoV-2 on real-time reverse transcription-polymerase chain reaction (RT-PCR) were consecutively enrolled in this study till they were recovered or dead. Upper respiratory specimens (throat and/or nasal swabs) were obtained and analyzed by RT-PCR. All the patients in this hospital were diagnosed with COVID-19 according to the Fifth Edition of Diagnosis and Treatment Protocols for SARS-CoV-2 from the Chinese National Health Committee.[16] No exclusion criteria were planned. The patients' demographic information, clinical data and history of atorvastatin administration, vital signs, and laboratory values were studied.

Only the first admission was included for patients with multiple admissions, and all patients' identifiable information had been de-identified before being stored and analyzed.

All blood samples were non-fasting and analyzed at the central laboratory of Dr Shariati hospital. This lab had quality accreditation as the reference laboratory for Iran's ministry of health university hospitals, located in Tehran, Iran. Serum CRP levels were measured at baseline and repeated after one week (Secondary CRP) using HITACHI 7600-020 automated biochemistry analyzer in all patients (reference range: 0.0 to 6.0 mg/L). The outcome was defined as ICU admission, serum CRP ≥ 6 mg/L, and death.

3.3. Statistical Analysis

Considering the SAMPLE guideline,[17] the normally distributed variables were expressed as mean (standard deviation), the variables with skewed distribution were expressed as median and 25th and 75th percentile, and the categorical variables were expressed as number (percentage). Performing the normality tests, the distribution of variables was analysed by both the Shapiro–Wilk/Kolmogorov-Smirnov tests and graphical assessments (histograms, Q–Q plots and box plots). Comparing variables in different groups and investigating the associations between variables, we applied sets of parametric (*t* test, ANOVA tests) and nonparametric (Mann–Whitney U test) statistical tests based on the distribution of the data variables. We performed logistic regression analyses to evaluate the association between our main outcome variables and possible explanatory variables. The effect of atorvastatin was adjusted for age, sex, and diabetes. All p values were reported as two-sided with a significance level of 0.05. All statistical tests were performed in SPSS version 25.0 (IBM, NY, USA). Based on the normal range of CRP and Atorvastatin taking, participants were divided into two groups.

4. Results

The mean duration from the date of hospital admission to the study date was 10 (7–13) days, and the mean duration from ICU admission to the study date was 5 (3–9) days. A total of 370 participants were included in our study at baseline with an initial diagnosis of COVID-19, of which 170 were later excluded because they had missing data in the PCR result, age, and/or atorvastatin taking data. The mean age of the study participants was 60.52 (20-96) years, of which 113 were men and 47 subjects had also diabetes.

CRP values for the subject population ranged from less than 6 to 250.0 mg/L, with an overall mean of 56.71 mg/L (SD: 39.03 mg/L): distribution of primary CRP was normal but secondary CRP was not normal.

As is shown in Table 1, the variables including diabetes, mortality rate, ICU admission, atorvastatin taking, and primary/secondary CRP values were not significantly different between genders.

There was no significant difference in mortality or ICU admission between statin and non-statin groups. A separate reduction trajectory was seen both in primary and secondary CRP levels within atorvastatin-taking subjects, which, however, was only significant in secondary CRP ($P = 0.017$). Data is presented in Table 2.

When the study population was divided by the normal range of CRP, 94% of participants were laid in the CRP group of the above-average range (CRP ≥ 6 mg/L). The median of secondary CRP also remained significantly higher ($P = 0.004$) in subjects with higher primary CRP levels (Table 3).

Among the 56 subjects who were dead within the study, 33 were men, and 14 subjects also had diabetes. There was no relationship between mortality and age ($P = 0.610$),

Table 1. Clinical Characteristics of the Studied Subjects Stratified by Gender

	Gender Groups			*P* Value
	Women No. (%)	Men No. (%)	Total No. (%)	
Qualitative Variables[a]				
Gender	87 (43.5)	113 (56.5)	200 (100)	
Atorvastatin +	25 (39.1)	39 (60.9)	64 (32)	0.385
Atorvastatin -	62 (45.6)	74 (54.4)	136 (68)	
Diabetes +	19 (40.4)	28 (59.6)	47 (23.5)	0.627
Diabetes -	85 (55.6)	68 (44.4)	153 (76.5)	
ICU +	36 (52.9)	32 (47.1)	68 (34)	0.053
ICU -	51 (38.6)	81 (61.4)	132 (66)	
Mortality +	23 (41.1)	33 (58.9)	56 (28)	0.666
Mortality -	80 (55.6)	64 (44.4)	144 (72)	
Quantitative variables				
P-CRP: Mean (SD)**	58.65 2.71)	55.17 (35.99)	56.71 (39.03)	0.809
S-CRP: (Median (P25, P75))***	43.5 (21, 71)	35 (12, 75)	40 (16.5, 74)	0.496

ICU: Intensive care unit; CRP: C-reactive protein
[a] Chi-Square test; [b] Independent sample *t* test; [c] Mann–Whitney U test

gender ($P=0.666$), or diabetes ($P=0.755$). Mean primary serum CRP value was significantly higher ($P=0.001$) among those subjects who were dead during the study (mean of 70.5 mg/L with a standard deviation of 31.6 mg/L; compared to subjects who were alive: mean of 51.1 mg/L with standard deviation 40.4 mg/L), with slightly less variation, as indicated by the lower standard deviation. Despite this difference, the magnitudes of the means and standard deviations of CRP levels are relatively similar in both groups. Most patients showed CRP levels higher than the reference range by a large margin.

Table 3. Clinical Characteristics of the Studied Subjects Stratified by CRP Normal Levels

Qualitative Variables[a]	CRP (mg/L)			*P* Value
	CRP < 6 No. (%)	CRP ≥ 6 No. (%)	Total No. (%)	
Gender-W	5(45.5)	81 (44)	86 (44.1)	0.926
Gender-M	6 (54.5)	103 (56)	109 (55.9)	
Atorvastatin +	4 (36.4)	58 (31.5)	62 (31.8)	0.738
Atorvastatin -	7 (63.6)	126 (68.5)	133 (68.2)	
Diabetes +	5 (45.5)	41 (22.3)	46 (23.6)	0.079
Diabetes -	6 (54.5)	143 (77.7)	149 (76.4)	
ICU +	3 (27.3)	65 (35.3)	68 (34.9)	0.586
ICU -	8 (72.7)	119 (64.7)	127 (65.1)	
Mortality +	2 (18.2)	54 (29.3)	56 (28.7)	0.427
Mortality -	9 (81.8)	130 (70.7)	139 (71.3)	
Quantitative Variables[b]	**CRP mg/L**			***P* Value**
	Median (P25, P75)			
	CRP < 6	**CRP ≥ 6**	**Total**	
S-CRP	5 (3, 5)	40 (17, 74)	40 (16.5, 74)	0.004

W: women; M: Men; ICU: Intensive care unit; CRP: C-reactive protein.
[a] Chi-Square test; [b] Mann–Whitney U test.

The baseline CRP was not significantly different, but the secondary CRP was significantly different between DM and non-DM groups ($P=0.491$ and $P=0.007$, respectively) (Table 4).

By adjusting the age, sex, and diabetes in a logistic regression analysis, atorvastatin from the date before the disease was not associated with the risk of death or increased CRP levels or ICU admission (Table 5).

The results also showed a statistically significant relationship between ICU admission and mortality at a

Table 2. Clinical Characteristics of the Studied Subjects Stratified by Atorvastatin Taking

Qualitative variables[a]	Atorvastatin			*P* Value
	Yes	No	Total	
	No. (%)	No. (%)	No. (%)	
Gender	W: 25 (39.1)	62 (45.6)	87 (43.5)	0.385
	M: 9 (60.9)	74 (54.4)	113 (56.5)	
Diabetes +	30 (46.9)	17 (12.5)	47 (23.5)	<0.001
Diabetes -	34 (53.1)	119 (87.5)	153 (76.5)	
ICU +	25 (39.1)	43 (31.6)	68 (34)	0.330
ICU -	39 (60.9)	93 (68.4)	132 (66)	
Mortality +	19 (29.7)	37 (27.2)	56 (28)	0.715
Mortality -	45 (70.3)	99 (72.8)	144 (72)	
Quantitative variables[b]	**Atorvastatin Status**			***P* Value**
	Yes Median (P25, P75)	**No Median (P25, P75)**	**Total Median (P25, P75)**	
P-CRP	54.00 (25.75, 78.25)	68.00 (20.00, 82.00)	56.71 (39.03)	0.472
S-CRP	20.00 (10.50, 51.00)	53.00 (20.75, 76.00)	40 (16.5, 74)	0.017

W: women; M: Men; ICU: Intensive care unit; CRP: C-reactive protein.
[a] Chi-Square test; [b] Mann–Whitney U test.

Table 4. Comparison of Mean CRP Levels Between Diabetic and Non-diabetic Groups

Variable[a]	Diabetes		*P* Value
	Yes	No	
CRP	53.23 (33.19)	57.78 (40.71)	0.491
S-CRP	29.56 (25.68)	49.23 (31.00)	0.007

CRP: C-reactive protein
Data are presented as mean (standard deviation).
[a] Independent sample *t* test.

Table 5. Logistic Regression Analysis Between Atorvastatin and Mortality or Serum CRP Levels

Outcome[a]	Independent Variable	OR	95% CI OR		*P* Value
			Upper Limit	Lower Limit	
Serum CRP ≥ 6 mg/L	Atorvastatin	0.806	0.227	2.86	0.738
Mortality	Atorvastatin	0.885	0.459	1.79	0.715
Serum CRP ≥ 10 mg/L	Atorvastatin	0.980	0.509	1.91	0.628
ICU admission	Atorvastatin	2.18	0.74	2.57	0.018

ICU: Intensive care unit; CRP: C-reactive protein
[a] Data was adjusted for age, sex, and diabetes.

95% confidence interval. The chance of survival of those who did not go to the ICU was 2.18 times than those of the patients with ICU admission ($P = 0.018$).

5. Discussion

We studied whether the anti-inflammatory action of atorvastatin may be of benefit in Covid-19, a state not well-understood but characterized by inflammation[18] in which high cholesterol is associated with worse outcomes.[7]

In our study, men account for 56.5% of the gender distribution of COVID-19 patients, which is consistent with the previous report.[19, 20] However, disease outcomes, including mortality and high CRP levels, were not affected significantly by gender in our study, which is not following other studies reporting women to seem to be less affected than men by severe/fatal COVID-19 infection, regardless of their age and nationality.[20-22] Although the finding that ICU admission distribution was nearly significant between men and women was consistent with our expectations; our other results were unexpected, which all seem to have arisen from the limited number of patients.

The present results indicated that mortality and ICU admission are not significantly different between atorvastatin users and non-atorvastatin users and seems at odds with the studies showing statin taking is independently associated with lower requirement for ICU admission[23] and also associated with a lower risk of death, and other outcomes in COVID-19 patients.[19,24-26] Rodriguez-Nava et al[24] found a slower progression to death associated with atorvastatin in patients with COVID-19 admitted to ICU. Zhang et al[19] reported that the use of statins in hospitalized subjects with COVID-19 is associated with a lower risk of all-cause mortality compared to non-statin use. On the other hand, our results are following studies which have shown no significant associations between statin use and hospital death or ICU admission in patients with COVID-19.[27,28] On a meta-analysis, they showed that statin use does not improve in-hospital outcomes and mortality from COVID-19 infection.[28] In a retrospective cohort study on 249 hospitalized patients with COVID-19, it was revealed that in a fully adjusted model, statin use was not associated with length of ICU stay or in-hospital death, but it was significantly associated with decreased risk for invasive mechanical ventilation.[27] The same results are also shown by studies on other respiratory disease.[29] There is even some evidence that shows negative effects (including higher IL-18 levels and mortality) of statin treatment on infection-induced ARDS.[30] During their review study, Subir et al[31] stated that de-novo use of statins in COVID-19 should be limited to a clinical trial setting, even though statins have the potential to reduce morbidity and mortality in COVID-19.

Although mortality did not significantly differ between diabetes and non-diabetes groups in our study, in a summary report from China, it has been shown that the overall CFR was augmented from 2.3% to 7.3% for those with pre-existing diabetes.[32] As expected, ICU admission had a statistically significant relationship with mortality which is due to the end-stage of the disease, so more subjects are going to die after ICU admission.[33]

We found that values of primary CRP did not significantly differ between atorvastatin users and non-users. Nonetheless, secondary CRP significantly decreased in the atorvastatin-taking group after taking medication at the hospital, so it seems CRP levels are not under the effects of COVID-19 medication or statin consumption easily. This is in accordance with the literature where results are inconsistent. Voleti and Agrawal [34] investigated the regulation of CRP gene expression to evaluate statin-mediated CRP reduction. The authors have mentioned that the decrease in CRP level following statin treatment does not necessarily attenuate the inflammation. The measurement of serum CRP levels alone in individuals on statin therapy is not as valuable as was supposed. Zhang et al[19] disclosed that the CRP showed a descending trend after hospital admission in both statin and non- statin groups, but with lower levels among the statins users.

The lack of consistent results about the effects of statins on outcomes and mortality in COVID-19 patients can be explained by several proposed reasons. First, there was a risk of channelling bias since patients on statins were more likely to have several comorbid conditions than those without.[23] Second, Statins have some adverse effects which may counter-balanced their beneficial effects, including anti-inflammatory and lipid-lowering properties. Statins may exacerbate compensatory immune signals, increase the expression of ACE2 as the receptor for the virus that causes COVID-19. They may cause myotoxicity in some patients, thus have the potential to exacerbate the pathology of COVID-19.[19,28] Lastly, differences in definitions of what is or is not a COVID-19–related death and outcomes might explain variation in the results from

Research Highlights

What Is Already Known?

Statins influence several pathways, including the inflammatory, oxidative, and thrombotic processes, besides their main effect as cholesterol-lowering drugs by the scavenger pathway

What Does This Study Add?

- Using of statins in hospitalized subjects with COVID-19 is associated with a lower risk of all-cause mortality compared to non-statin use.
- Taking statin has some beneficial effects on the improvement of CRP levels in patients with COVID-19.

studies about statin taking effects. Moreover, the different results from such studies may result from diverse disease conditions and the heterogeneity in the target populations. Thus, randomized controlled trials are needed. Inpatient or outpatient subjects and starting statin therapy during the episode of COVID-19 should also be kept in mind to confirm the actual effect of statins on COVID-19 patients.

5.1. Limitation

However, our study was small, and adverse outcome rates were low. This limitation, along with the observational nature of this study that, may affect the generalizability of results; thus, findings should be taken with caution.

6. Conclusion

It was revealed that taking statin has some beneficial effects on improving CRP levels in patients with COVID-19. To achieve a reliable result, a study of patients with matching clinic characteristics except for statin usage and clinical trials is recommended. Moreover, the exact outcome and effects of statins on COVID-19 patients have yet to be explored in interventional studies, and the underlying mechanisms need to be investigated more in-depth.

Authors' Contributions

HRAM, SZFK and MPS developed the study concept and draft preparation, MA and SA performed data gathering, data analysis and interpretation. All authors revised the manuscript for critical intellectual content and approved the final version of the manuscript.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Ethical Approval

The study was approved by the ethical committee of the Tehran University of Medical Sciences, Tehran, Iran (Approval Number: IR.TUMS.MEDICINE.REC.1400.801). All participants were guaranteed anonymity, and they provided informed consent. The consent form was signed by the participants or their legal guardians of them.

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