INTRODUCTION

The COVID-19 pandemic is still growing around the world and more than 90 million cases around the world with over 2 million deaths have been identified. Immune dysregulation and cytokine release associated with SARS-COV-2 infection are considered as an important cause of mortality in this population and it could induce hyper-inflammatory state, vasculitis and cardiovascular events.

In previous studies, the anti-inflammatory role of statins in the reduction in cytokines, in some conditions other than infectious diseases, has been confirmed. Also, studies have shown that patients who have received atorvastatin had a better prognosis in viral and bacterial pneumonia. In some studies, it is hypothesised that decreasing the synthesis of cholesterol by statins and depletion of cell membrane cholesterol content could disturb the entry of the virus into the cells. SARS-COV-2 also generates multi-proinflammatory cytokines by activating Toll-like receptors (TLRs) on T lymphocytes. This TLR-MYD88-NFκB pathway promotes cytokine release. Statins also block this pathway; inhibit T-cell activation and proliferation, so they have immunomodulatory effects.

Abstract

Purpose: Considering the anti-inflammatory effect of atorvastatin and the role of medical comorbidities such as hypertension and coronary artery disease on the prognosis of the COVID-19 patients, we aimed to assess the effect of atorvastatin add-on therapy on mortality caused by COVID-19.

Methods: We conducted a retrospective cohort study, including patients who were hospitalised with confirmed diagnosis of severe COVID-19. Baseline characteristics and related clinical data of patients were recorded. Clinical outcomes consist of in-hospital mortality, need for invasive mechanical ventilation and hospital length of stay. COX regression analysis models were used to assess the association of independent factors to outcomes.

Results: Atorvastatin was administered for 421 of 991 patients. The mean age was 61.640 ± 17.003 years. Older age, higher prevalence of hypertension and coronary artery disease reported in patients who received atorvastatin. These patients have shorter hospital length of stay (P = .001). Based on COX proportional hazard model, in-hospital use of atorvastatin was associated with decrease in mortality (HR = 0.679, P = .005) and lower need for invasive mechanical ventilation (HR = 0.602, P = .014).

Conclusions: Atorvastatin add-on therapy in patient with severe COVID-19 was associated with lower in-hospital mortality and reduced the risk of need for invasive mechanical ventilation which supports to continue the prescription of the medication.
Furthermore, this class of medication is linked to a rise in IL-18 levels and mortality in patients with acute respiratory distress syndrome which could be harmful in this population and deteriorate the condition of the patients.\textsuperscript{12}

By considering the effect of underlying conditions such as hypertension, diabetes, cardiovascular diseases and hyperinflammation associated with COVID-19, statins could affect the prognosis of the patients who have been hospitalised because of COVID-19.\textsuperscript{13-15} Therefore, we aimed to assess the effect of atorvastatin use in the outcomes of the patients with severe-to-critical COVID-19.

2 | PATIENTS AND METHODS

2.1 | Study design and patient selection

In this retrospective cohort study, all adult patients (age $\geq$18 years old) who were hospitalised because of severe-to-critical COVID-19, from March 2020 to July 2020, in the Imam Hossein medical centre affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, were evaluated.\textsuperscript{16} Patients without positive reverse transcriptase-polymerase chain reaction (RT-PCR) results were excluded and data from patients with a diagnosis of COVID-19 based on RT-PCR were included. The study was conducted based on the declaration of Helsinki and the institutional review board committee approved the study.

2.2 | Data collection

For each patient, demographic and laboratory data including past medical and drug history, outcomes, baseline complete blood count and inflammatory markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin and lactate dehydrogenase (LDH) and liver function tests were recorded. Also, vital signs on admission and selected pharmacotherapy for management of COVID-19, besides the administration of atorvastatin and other cardiovascular medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers, were documented. Atorvastatin use was defined as the administration of the medication on first day of admission and the medication continued during the hospitalisation period if no contraindication was present.

2.3 | Outcomes

In hospital mortality was defined as the primary outcome for the study. The need for invasive mechanical ventilation including ventilation via endotracheal or tracheostomy tubes and length of hospital stay are considered as the secondary outcomes.

What’s known

Previous studies showed that patients who used statins may have decreased rate of mortality caused by COVID-19. Results about the effect of statins on other outcomes including need for mechanical ventilation and hospital length of stay were inconsistent.

What’s new

In our large-scale retrospective cohort study, we examined the effect of atorvastatin, as a lipophilic statin, on outcomes of patients with severe-to-critical form of COVID-19. In addition to decrease in mortality, we observed lower risk of need of invasive mechanical ventilation associated with atorvastatin administration and also shorter hospital length of stay in patients who received atorvastatin.

2.4 | Statistical analysis

Statistical analysis was performed by STATA software version 14 (StataCorp). All included patients stratified as they received atorvastatin or not during hospitalisation. The parametric or non-parametric distribution of the quantitative data was analysed using the Kolmogorov-Smirnov test. Data description of parametric quantitative variables was reported as means $\pm$ standard deviation and non-normally distributed data reported as median (interquartile range = IQR). Qualitative variables were reported as frequency (percentage). Continues variables were compared using independent t test or Mann-Whitney U-test for normally and non-normally distributed data in bivariate analysis respectively. Categorical variables were analysed using chi-square or Fisher’s exact test (in the situation in which more than 25% of the categories had frequencies below five). A P-value of less than .05 is considered significant.

The crude association between atorvastatin administration and occurrence of outcomes including the need for invasive mechanical ventilation and in-hospital mortality was performed using the univariable COX proportional hazards regression model. For the selection of the best predictors, variables with a P-value of less than .2 are were considered to be analysed in multivariable COX regression analysis using a stepwise selection approach. Confounders were selected based on the recommendation of previously published epidemiological studies that reported the probable prognostic value of underlying conditions and also medications that were being used.\textsuperscript{17} This included age, gender, body mass index (BMI) in demographics, hypertension, diabetes mellitus, coronary artery disease, chronic respiratory conditions, malignancies, immunocompromised and chronic kidney disease in comorbidities. Also, we adjusted the model for using beta-blockers and ACEIs or ARBs.\textsuperscript{18,19} The model was adjusted for the medications which were used to treat COVID-19. Patients with negative time to event were removed from the analysis. A
| Characteristics | Total (n = 991) | Received atorvastatin (n = 421) | Not received atorvastatin (n = 570) | P-value |
|-----------------|----------------|---------------------------------|-----------------------------------|---------|
| Age (y)         | 61.640 ± 17.003 | 65.46 ± 14.94                  | 58.82 ± 17.88                     | <.001   |
| Gender          |                |                                 |                                   |         |
| Male (%)        | 544 (54.89)    | 225 (53.44)                     | 319 (55.97)                       | .431    |
| Female (%)      | 447 (45.11)    | 196 (46.56)                     | 251 (44.03)                       |         |
| Body mass index (kg/m²) | 27.051 ± 4.854 | 27.34 ± 26.49                  | 26.81 ± 4.74                      | .119    |
| Vital signs     |                |                                 |                                   |         |
| Systolic blood pressure (mmHg) | 117.59 ± 20.71 | 118.55 ± 19.65                  | 116.95 ± 21.49                     | .219    |
| Diastolic blood pressure (mmHg) | 74.69 ± 27.19 | 74.70 ± 11.76                   | 74.71 ± 34.58                      | .985    |
| Pulse rate (beats/min) | 89.55 ± 15.71 | 89.01 ± 15.83                   | 89.94 ± 15.41                      | .538    |
| Respiratory rate (breath/min) | 20.64 ± 7.92 | 20.80 ± 10.69                   | 20.51 ± 5.06                       | .670    |
| O₂ saturation (%) | 88.29 ± 7.82 | 88.35 ± 7.04                    | 88.25 ± 8.38                       | .924    |
| Comorbidities   |                |                                 |                                   |         |
| Hypertension (%)| 407 (41.07)    | 233 (55.34)                     | 174 (30.53)                       | <.001   |
| Diabetes (%)    | 303 (30.58)    | 117 (27.79)                     | 186 (32.81)                       | <.001   |
| Coronary artery disease (%) | 194 (19.58) | 133 (46.08)                     | 61 (10.70)                        | <.001   |
| Chronic kidney disease (%) | 102 (10.29) | 37 (8.79)                       | 65 (11.40)                        | <.001   |
| Malignancy (%)  | 42 (4.24)      | 32 (7.60)                       | 10 (1.75)                         | .012    |
| COPD/asthma     | 87 (8.78)      | 38 (9.03)                       | 49 (8.60)                         | .813    |
| Baseline laboratory data |        |                                 |                                   |         |
| WBC (cell/µL)  | 6.90 (4.63)    | 7.20 (4.80)                     | 6.60 (4.40)                       | .020    |
| Lymphocyte (cell/µL) | 821.75 (1588.10) | 828.00 (1596.00)              | 821.50 (1587.20)                   | .780    |
| Haemoglobin (g/dL) | 12.41 ± 2.08  | 12.30 ± 2.17                    | 12.28 ± 2.14                      | .898    |
| INR             | 1.20 ± 0.48    | 1.22 ± 0.52                     | 1.08 ± 0.20                       | .239    |
| PT              | 13.09 ± 5.09   | 13.26 ± 5.30                    | 12.94 ± 4.96                      | .415    |
| PTT             | 28.25 ± 12.79  | 27.39 ± 10.87                   | 28.93 ± 14.22                     | .126    |
| Lactate dehydrogenase | 645.00 (403.00) | 643.00 (404.00)                | 659.00 (525.25)                    | .282    |
| Ferritin        | 621.30 (964.00) | 579.10 (812.10)                | 750.95 (1134.40)                   | .508    |
| C-reactive protein | 54.00 (53.10)  | 55.30 (53.30)                   | 51.50 (51.65)                      | .040    |
| Erythrocyte sedimentation rate | 52.74 ± 28.41 | 48.20 ± 29.01                   | 60.17 ± 26.12                     | .021    |
| Creatine phosphokinase | 130.00 (211.00) | 130.00 (206.00)              | 136.00 (264.00)                    | .203    |
| Serum creatinine | 1.40 (1.20)   | 1.40 (1.20)                     | 1.45 (1.08)                       | <.001   |
| Serum creatinine | 50.00 (45.00)  | 48.20 (41.90)                   | 52.30 (55.88)                      | <.001   |
| Procalcitonin   | 0.73 (1.85)    | 0.49 (1.31)                     | 1.16 (2.41)                       | .873    |
| D-dimer         | 799.20 (2434.00) | 709.00 (1257.00)            | 1712.50 (3756.75)                  | .365    |
| Aspartate aminotransferase | 26.00 (27.00)  | 25.00 (25.40)                   | 29.60 (38.13)                      | .470    |
| Alanine aminotransferase | 37.00 (29.50) | 40.00 (26.40)                   | 34.40 (39.78)                      | .490    |
| Medication used to treat COVID-19 |        |                                 |                                   |         |
| Hydroxychloroquine | 553 (55.80)  | 213 (89.67)                     | 340 (59.65)                       | .005    |
| Lopinavir/ritonavir | 557 (56.21)  | 236 (56.06)                     | 321 (56.32)                       | .935    |
| Corticosterone  | 287 (28.96)    | 141 (33.49)                     | 146 (25.61)                       | .007    |
| Interferon beta-1a | 372 (37.54)  | 170 (40.38)                     | 202 (35.44)                       | .112    |
| Remdesivir      | 46 (4.64)      | 21 (4.99)                       | 25 (4.39)                         | .656    |
| Favipiravir     | 40 (4.04)      | 23 (5.46)                       | 17 (2.98)                         | .050    |
atorvastatin is associated with reduced risk of in-hospital mortality.

COX regression proportional hazard ratio analysis revealed that and need for mechanical ventilation (0.709 [0.486-1.034]). Stepwise associated with a decreased in-hospital mortality (0.820 [0.639-1.054]) for primary and secondary outcomes are represented in Table 2.

Data are presented in Table 1.

Regarding demographics, patients who received atorvastatin were older (P < .001), but no significant differences were observed in gender distribution and BMI between the two groups. Considering comorbidities, except for diabetes and CKD, which were more prevalent in patients who did not receive atorvastatin (P < .001), and others including hypertension (P < .001), coronary artery disease (P < .001) and malignancy (P = .012) were significantly higher in the group of patients who received atorvastatin. From laboratory data collected at baseline, CRP was significantly higher in the group of patients who received atorvastatin (P = .040). Patients who did not receive atorvastatin had a higher baseline ESR, serum creatinine and urea levels compared with those who did not. Except for hydroxychloroquine (P = .005) and corticosteroids (P = .007), there were no significant differences between the two groups in medications used to treat COVID-19. Baseline demographics, clinical and laboratory data are presented in Table 1.

Based on the crude analysis, no significant differences were observed in mortality rate between two groups (26.84% vs 25.09%, P = .221). Patients who received atorvastatin have a significantly lower hospital length of stay (P < .001). Also, this group had a lower but non-significant need for mechanical ventilation (P = .563). Results for primary and secondary outcomes are represented in Table 2.

In unadjusted COX proportional analysis, atorvastatin was associated with a decreased in-hospital mortality (0.820 [0.639-1.054]) and need for mechanical ventilation (0.709 [0.486-1.034]). Stepwise COX regression proportional hazard ration analysis revealed that atorvastatin is associated with reduced risk of in-hospital mortality (0.679 [0.517-0.890]) and the need for mechanical ventilation (0.602 [0.401-0.903]). Independently. From demographics, age, obesity, coronary heart disease and malignancy were included in the multivariable analysis to evaluate the need for invasive mechanical ventilation. Also, utilisation of beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine and lopinavir/ritonavir were analysed. In the stepwise model for the analysis of survival, age, hypertension, coronary heart disease, malignancy and medication, ie beta-blockers, ACEIs/ARB, atorvastatin, corticosteroid, hydroxychloroquine and lopinavir/ritonavir, remained in the multivariable model. The association of factors with mortality and the need for invasive mechanical ventilation in COX proportional analysis is represented in Table 3.

3 RESULTS

Nine hundred and ninety-one patients were included in the study. The mean age was 61.640 ± 17.003, and 544 (54.89%) and 447 (45.11%) of the patients were men and women respectively. Four hundred and twenty-one patients (42.48%) received atorvastatin, whereas five hundred and seventy (57.52%) did not. Of those who received atorvastatin, 169 (40.14%) were taking the medication prior to hospital admission and atorvastatin was initiated for the rest of the patients on the first day of hospital admission.

Regarding demographics, patients who received atorvastatin were older (P < .001), but no significant differences were observed in gender distribution and BMI between the two groups. Considering comorbidities, except for diabetes and CKD, which were more prevalent in patients who did not receive atorvastatin (P < .001), and others including hypertension (P < .001), coronary artery disease (P < .001) and malignancy (P = .012) were significantly higher in the group of patients who received atorvastatin. From laboratory data collected at baseline, CRP was significantly higher in the group of patients who received atorvastatin (P = .040). Patients who did not receive atorvastatin had a higher baseline ESR, serum creatinine and urea levels compared with those who did not. Except for hydroxychloroquine (P = .005) and corticosteroids (P = .007), there were no significant differences between the two groups in medications used to treat COVID-19. Baseline demographics, clinical and laboratory data are presented in Table 1.

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4 DISCUSSION

In our retrospective cohort study, among 991 patients suffering from severe-to-critical COVID-19, atorvastatin which was administered for 421 of the patients was associated with a significant decrease in mortality (HR = 0.679), the need for mechanical ventilation (HR = 0.602) and hospital length of stay. Very little was found in the literature about the role of statins in the management of patients with COVID 19. In line with our study, data from the largest cohort study from China by Zhang et al demonstrated that in-hospital use of statins improved survival among COVID-19 patients (HR = 0.58).

In this retrospective study, which included 1219 patients who used a statin, 28-day all-cause mortality risk was 5.2% and 9.4% in the statin and non-statin users respectively.20 The lower mortality rate in this study compared with our results could be as a result of including moderate cases in the study by Zhang et al which were not included in our study. Another study enrolled 71 patients with a preexisting chronic cardiovascular disease, and in accordance with our findings, the mortality rate of patients who received statins was lower compared with the group of patients without statins (21.4% vs 34.5%; P < .05), and in their subgroup analysis, it is reported as a significant reduction in mortality in the patients who were taking atorvastatin compared with non-statin users and patients who were taking other statins (P = .025).21 In another retrospective cohort study, which compared intensive care unit (ICU) admission, invasive mechanical ventilation rate and death between statin users and non-statin users, ICU admission was lower in the statin group but other outcomes were not different between the two groups.22 Another

| Variable                  | Total (n = 991) | Received atorvastatin (n = 421) | Not-received atorvastatin (n = 570) | P-value |
|---------------------------|----------------|--------------------------------|------------------------------------|---------|
| Need for mechanical ventilation (%) | 144 (14.53) | 58 (13.78) | 86 (15.09) | .563 |
| Hospital length of stay (days) [range] | 6.00 (6.00) [1-80] | 6.00 (5.00) | 7.00 (6.00) | <.001 |
| In-hospital outcome (%) |                  |                                |                                    |         |
| Death                     | 256 (25.83) | 113 (26.84) | 143 (25.09) | .221 |
| Recovery                  | 735 (74.17) | 308 (73.16) | 427 (74.91) |         |
### TABLE 3  Association of factors with outcomes in COX proportional hazard regression model

| Variable                                      | Crude HR, 95% CI     | P-value | Adjusted HR, 95% CI   | P-value |
|------------------------------------------------|----------------------|---------|-----------------------|---------|
| **In hospital mortality**                      |                      |         |                       |         |
| Age (y)                                        | 1.034 [1.025-1.043]  | <.001   | 1.036 [1.026-1.045]   | <.001   |
| Gender                                         | 1.197 [0.930-1.541]  | .162    |                       |         |
| Obesity                                        | 0.982 [0.957-1.009]  | .188    |                       |         |
| Hypertension                                   | 1.535 [1.199-1.965]  | .001    | 1.227 [0.916-1.644]   | .170    |
| Diabetes                                       | 0.982 [0.755-1.277]  | .890    |                       |         |
| Coronary heart disease                         | 1.331 [1.004-1.764]  | .047    | 0.980 [0.719-1.337]   | .901    |
| Chronic kidney disease                         | 1.002 [0.688-1.459]  | .992    |                       |         |
| Malignancy                                     | 1.370 [0.784-2.396]  | .269    | 1.706 [0.961-3.031]   | .068    |
| Chronic respiratory disease                    | 1.194 [0.962-1.482]  | .107    |                       |         |
| Immunosuppressive disorders                    | 1.205 [0.674-2.152]  | .530    |                       |         |
| Smoking                                        | 0.932 [0.667-1.302]  | .679    |                       |         |
| Beta-blocker                                   | 1.375 [1.052-1.794]  | .020    | 1.327 [0.981-1.795]   | .066    |
| ACEIs/ARB                                      | 1.067 [0.808-1.407]  | .647    | 0.754 [0.553-1.029]   | .075    |
| Atorvastatin                                   | 0.820 [0.639-1.054]  | .121    | 0.679 [0.517-0.890]   | .005    |
| Corticosteroid                                 | 1.205 [0.930-1.561]  | .159    | 1.245 [0.941-1.649]   | .125    |
| Hydroxychloroquine                             | 0.814 [0.635-1.045]  | .106    | 0.813 [0.629-1.051]   | .113    |
| Lopinavir/ritonavir                            | 1.220 [0.945-1.574]  | .128    | 1.250 [0.951-1.641]   | .110    |
| Remdesivir                                     | 0.815 [0.456-1.457]  | .489    |                       |         |
| Favipiravir                                    | 0.739 [0.430-1.273]  | .276    |                       |         |
| **Mechanical ventilation**                     |                      |         |                       |         |
| Age (y)                                        | 1.019 [1.007-1.028]  | .001    | 1.026 [1.014-1.038]   | <.001   |
| Gender                                         | 1.259 [0.868-1.825]  | .225    |                       |         |
| Obesity                                        | 0.994 [0.969-1.029]  | .744    | 1.390 [0.903-2.140]   | .134    |
| Hypertension                                   | 1.190 [0.781-1.811]  | .418    |                       |         |
| Diabetes                                       | 1.141 [0.779-1.672]  | .499    |                       |         |
| Coronary heart disease                         | 1.115 [0.750-1.657]  | .592    | 0.704 [0.422-1.174]   | .179    |
| Chronic kidney disease                         | 0.750 [0.405-1.390]  | .361    |                       |         |
| Malignancy                                     | 1.652 [0.768-3.352]  | .199    | 1.963 [0.894-4.312]   | .093    |
| Chronic respiratory disease                    | 1.470 [0.838-2.577]  | .179    |                       |         |
| Immunosuppressive disorders                    | 0.924 [0.340-2.508]  | .877    |                       |         |
| Smoking                                        | 1.008 [0.624-1.629]  | .972    |                       |         |
| Beta-blocker                                   | 1.639 [1.110-2.418]  | .013    | 2.071 [1.334-3.217]   | .001    |
| ACEIs/ARB                                      | 0.823 [0.545-1.242]  | .252    | 0.670 [0.426-1.054]   | .084    |
| Atorvastatin                                   | 0.709 [0.486-1.034]  | .074    | 0.602 [0.401-0.903]   | .014    |
| Corticosteroid                                 | 1.507 [1.034-2.196]  | .033    | 1.445 [0.962-2.170]   | .076    |
| Hydroxychloroquine                             | 0.711 [0.489-1.033]  | .073    | 0.707 [0.482-1.036]   | .076    |
| Lopinavir/ritonavir                             | 1.367 [0.934-2.000]  | .108    | 1.357 [0.904-2.037]   | .141    |
| Remdesivir                                     | 0.944 [0.414-2.152]  | .892    |                       |         |
| Favipiravir                                    | 1.577 [0.859-2.893]  | .141    |                       |         |

Note: The model was fitted based on the Schoenfeld residual test for the evaluation of the proportional hazard assumption with $P = .253$ and $P = .218$ respectively.

Abbreviation: HR, hazard ratio.
retrospective multi-centre cohort study showed a significant association between statin intake in 31 subjects and the absence of symptoms during COVID-19 with an odds ratio of 2.91; nevertheless, there were no effects on serious clinical outcomes.23

Based on the result from our study, which is in accordance with the previously performed studies, reduced need for mechanical ventilation as two important measures for pulmonary function, we could say that atorvastatin administration strongly reduces the disease severity by inhibition of the inflammatory process during the disease course. Also, these effects alongside to reduction in mortality rate, which was statistically significant, make the medication an important choice of add-on therapy. Based on the significance of the mechanisms involved in the beneficial effect of the atorvastatin in the course of COVID-19, and the clinically proven efficacy, we could consider it in the treatment of patients who suffer from a severe form of the disease. It is important to note that we studied the effect of the atorvastatin on the outcome of the patients as add-on therapy and we should not forget about the importance of early antiviral agents administration as potent inhibitors of the viral replication which could reduce the hospital length of stay,24 and the role of potent anti-inflammatory agents such as corticosteroids and interleukin pathways inhibitors on mortality and severity in the treatment of the COVID-19.25-28 As an important pharmacokinetic consideration in the administration of atorvastatin, antiviral agents such as lopinavir/ritonavir and remdesivir could increase serum level of atorvastatin and increase the probability of adverse reactions such as myopathy.29,30

By considering the result of the study, we should be aware of the limitation we are facing in this study. First, this study was performed by a retrospective method which complicates control of all confounders and makes further randomised controlled trials emerge. Second, we could not evaluate the possible adverse effects of atorvastatin and also the relation between statin dose and duration with the effect and side effects of the drug. Finally, extrapolation of the results to non-hospitalised patients with moderate disease severity may not be possible as we included data related to severe form of the disease.

5 | CONCLUSION

In conclusion, we found that atorvastatin therapy has positive effects on the course of hospitalisation in patients with severe COVID-19. Mostly, these effects were seen in important outcomes of these patients, i.e. mortality rate, duration of hospitalisation and needs for mechanical ventilation caused by COVID-19. Prospective randomised, controlled trials are to be recommended to confirm the effect of statins on patients with viral infections, especially severe COVID-19.

DISCLOSURES

The authors declare no conflict of interest.
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