EGYPTIAN JOURNAL OF ANAESTHESIA
2023, VOL. 39, NO. 1, 107–113
https://doi.org/10.1080/11101849.2023.2173205

Can statins reduce mortality in critically ill COVID-19 patients? A retrospective cohort study

Heba A. Labib, Rania M. Ali and Ayman I. Tharwat

Department of Anesthesia, Intensive Care, and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: We aimed to investigate the possible association between the continuation of statin treatment and the mortality, length of the ICU stay, and need for mechanical ventilation in critically ill COVID-19 cases.

Methods: This study enrolled 1860 adult patients with laboratory-confirmed COVID-19 who were critically ill. The cases' medical records were categorized into two groups including comorbidities. The statin group included 930 patients who previously received statins and continued this treatment during ICU admission. The non-statin group included 930 patients who previously received statins but stopped taking this treatment during ICU admission. The primary endpoints were mortality and length of ICU stay. Secondary endpoints included the mechanical ventilation's period, subsequent complications, and D-dimer and ferritin serum levels.

Results: The age, sex, comorbidities, and COVID-19 CO-RADS classification showed no significant differences between the studied groups. Among all patients who received statin and among comorbidities subgroups, mortality was significantly reduced, and the length of ICU stay was considerably prolonged in the non-survivors, but it was significantly shortened in the survivors. The duration of mechanical ventilation was prolonged in the non-survivor but shortened in the survivors. The serum ferritin level was significantly reduced among the statin group.

Conclusion: In severely ill COVID-19 cases, continuation of statin therapy during ICU admission reduces the patients' mortality and enhances their survival. Hence, if a patient has a history of statin use, physicians should consider maintaining them on their current medication.

ARTICLE HISTORY
Received 20 November 2022
Revised 17 January 2023
Accepted 20 January 2023

KEYWORDS
COVID-19; statin; mortality; ICU stay; ventilation

1. Introduction

Infection with the COVID-19 is the most recent global catastrophe. Coronavirus 2 is the cause of severe acute respiratory syndrome (SARS-CoV-2). It triggers a powerful systemic hyperinflammatory response known as a cytokine storm or macrophage stimulation syndrome, which is associated with thrombotic consequences [1]. Pulmonary infection is the main clinical manifestation, with acute respiratory distress syndrome (ARDS) being the major cause of high mortality rate [2]. Lung disorders, malignant diseases, cardiac diseases, dyslipidemia, and diabetes are all regarded as high-risk factors for severe morbidity and mortality [3]. Because of the grave nature of this disease, it requires intensive therapy.

Several drugs have been recommended for COVID-19 cases. The main goals of using these medications were to lessen the disease severity and enhance the patients' outcomes [4]. Statins are among the drugs proposed to carry great benefits for COVID-19 cases [5]. Statins are the first-line therapy for dyslipidemia. They are low-cost, well-tolerated drugs with uncommon side effects [6,7]. Statins inhibit the hydroxy methyl glutaryl coenzyme A (HMG-CoA) reductase enzyme, which catalyzes the conversion of HMG-CoA to mevalonate in the cholesterol production pathway [8]. As a result, the cholesterol level decreases, and the cardiovascular system becomes protected from heart attacks and strokes. In addition, statins have antithrombotic, anti-inflammatory, antioxidant, antiviral, and immunomodulatory properties [9]. Hence, statins may help to improve the clinical consequence of COVID-19 [10,11]. However, a few studies noted neither a good nor a negative influence of statin on COVID-19-associated mortality [12,13].

The statins' efficacy in COVID-19 cases remains to be elucidated. The effects of statin discontinuation after hospital admission are not taken into consideration as most documentation of statin medication is dependent mainly on outpatient data. Furthermore, if inpatients are on statins, their therapy may be discontinued if they are going to the ICU [14]. Therefore, the current study was conducted among severely ill COVID-19 cases to explore the correlation between continued statin treatment and mortality, length of the ICU stay, and need for mechanical ventilation.

CONTACT Heba A. Labib drheba@med.asu.edu.eg Department of Anesthesia, Intensive Care, and Pain Management, Faculty of Medicine, Ain Shams University; 38 Abbassia Square, Next to Al-Nour Mosque, Cairo, Egypt

2. Methods

2.1. Ethical considerations

This study obtained approval from the Ethics Committee of the Faculty of Medicine, Ain Shams University, Egypt. We ensured protection of patients' privacy and anonymity, and data were allowed only for the investigators.

2.2. Study design, setting, and duration

This retrospective cohort study was conducted at Ain Shams University Quarantine Hospital and The Obour Specialized Hospital's between April 2020 and September 2021 using the medical files of the confirmed hospitalized COVID-19 patients.

2.3. Participants

Severely ill COVID-19, adult (>18 years), Egyptian cases were included. A nasopharyngeal swab was required for the polymerase chain reaction test to identify COVID-19. We excluded pregnant women and patients whose medications prior to admission were not identified.

Patients were randomized into two groups with comorbidities subgroups. The statin group included 930 participants who were given statins before admission and continued this treatment in the ICU. The non-statin group included 930 patients who received statins prior to admission and did not continue this treatment in the ICU. The patients' demographics, comorbidities, laboratory and radiological data, need for mechanical ventilation and its duration, and clinical outcomes were taken from the patients' medical files.

2.4. Endpoints

The primary outcomes were mortality and the length of ICU stay. The secondary endpoints were the need for mechanical ventilation and its duration as well as the subsequent complications including stroke, angina, renal failure, ARDS, and septic shock. Furthermore, D-dimer and ferritin serum levels were evaluated.

2.5. Study size

Assuming 12% of the COVID-19 cases have received statin and the primary outcome is the ICU hospitalization's length, a sample of at least 1860 cases – with at least 223 statin cases – achieves a power of 80% to determine an effect size of 0.2 using two independent specimens t-test with a level of significance of 0.05.

2.6. Statistical methods

The study was conducted using the Statistical Package for the Social Sciences (SPSS) software for Windows, version 28.0 (IBM Corp., Armonk, NY). The normality of quantitative data was examined utilizing Shapiro-Wilk test. The data were reported as mean ± standard deviation (SD) and compared utilizing the independent samples T-test. The correlations between the analyzed groups were examined using the Chi-square or Fisher's Exact test, and qualitative data were reported as numbers and percentages. A p-value <0.05 was selected to denote statistical significance.

3. Results

In this study, we analyzed the data of 1860 COVID-19 patients' medical records who were stratified into two groups. Statin group included 930 COVID-19 patients with critical condition who received statins before hospital admission and continued this treatment in the ICU. Non-statin group included 930 critically ill COVID-19 cases who underwent statins prior to hospital admission but stop this treatment in the ICU.

The studied groups were comparable as regard age, sex, comorbidities including obesity, hypertension, and diabetes mellitus, and COVID-19 CO-RADS classification (Table 1).

Among all patients who received statins including the comorbidities subgroups, the mortality was significantly reduced compared to those in the non-statin group, while stroke, angina, renal failure, ARDS, and septic shock were less frequent than the non-statin group but did not reach statistical significance (Table 2).

Among the non-survivors of the statin group and the comorbidities subgroups, the duration of ICU stay was significantly longer compared to those in the non-statin group. Meanwhile, among the survivors of the statin group and the comorbidities subgroups, the length of ICU stay was considerably shorter than those in the non-statin group (Table 3).

Furthermore, among the non-survivors of the statin group and the comorbidities subgroups, the period of mechanical ventilation was longer than those in the non-statin group. While, among survivors of the statin group and the comorbidities subgroups, the period of mechanical ventilation was shorter than those in the non-statin group, with no statistically significant differences (Table 4).

The average and maximum D-dimer levels were non significantly lower in all patients of the statin group and comorbidities subgroups compared to those in the non-statin groups. The average and maximum ferritin levels were significantly lower in the statin groups among all cases and among comorbidities subgroups. The statin group showed significant relative

Table 1. Demographic and baseline patients' characteristics.

Variables		Statin, N (%)	No statin, N (%)	p-value
Age (year), Mean ± SD		60.8 ± 14.6	61.3 ± 14.9	0.523
Age categories (year)	20 − 39	99 (10.6%)	95 (10.2%)	0.738
	40 − 59	283 (30.4%)	276 (29.7%)	
	60 − 79	477 (51.3%)	475 (51.1%)	
	≥80	71 (7.6%)	84 (9.0%)	
Sex	Male	544 (58.5%)	556 (59.8%)	0.571
	Female	386 (41.5%)	374 (40.2%)	
Obesity		616 (66.2%)	624 (67.1%)	0.694
Hypertension		409 (44.0%)	420 (45.2%)	0.608
Diabetes mellitus		250 (26.9%)	223 (24.0%)	0.151
Serum cholesterol (mg/dL), (Mean ± SD)		270.4 ± 17.9	271.1 ± 18.4	0.417
CORADS	IV	350 (37.6%)	345 (37.1%)	0.811
	V	580 (62.4%)	585 (62.9%)	

Notes: Data are presented as mean ± SD or number of patients and percentage. P-values are based on the independent-test or chi-square test.
Abbreviations: SD: standard deviation; N: number; CORADS: COVID-19 CO-RADS classification.

Table 2. Stroke, angina, renal failure, acute respiratory distress syndrome, septic shock, the need for ventilator support, and the in-hospital mortality.

Events	Subgroups	Statin, N (%)	No statin, N (%)	p-value	Relative effect RR (95% CI)
Stroke	Obesity	9 (1.5%)	18 (2.9%)	0.086	0.51 (0.23–1.12)
	No obesity	4 (1.3%)	3 (1.0%)	0.999	1.30 (0.29–5.76)
	HTN	7 (1.7%)	9 (2.1%)	0.652	0.80 (0.30–2.12)
	No HTN	6 (1.2%)	12 (2.4%)	0.141	0.49 (0.19–1.29)
	DM	5 (2.0%)	5 (2.2%)	0.552	0.89 (0.26–3.04)
	No DM	8 (1.2%)	16 (2.3%)	0.121	0.52 (0.22–1.21)
	All cases	13 (1.4%)	21 (2.3%)	0.166	0.62 (0.31–1.23)
Angina	Obesity	8 (1.3%)	11 (1.8%)	0.506	0.74 (0.30–1.82)
	No obesity	3 (1.0%)	7 (2.3%)	0.217	0.42 (0.11–1.60)
	HTN	4 (1.0%)	9 (2.1%)	0.177	0.46 (0.14–1.47)
	No HTN	7 (1.3%)	9 (1.8%)	0.623	0.76 (0.29–2.03)
	DM	5 (2.0%)	8 (3.6%)	0.292	0.56 (0.19–1.68)
	No DM	6 (0.9%)	10 (1.4%)	0.354	0.62 (0.23–1.71)
	All cases	11 (1.2%)	18 (1.9%)	0.190	0.61 (0.29–1.29)
Renal failure	Obesity	2 (0.3%)	7 (1.1%)	0.178	0.29 (0.06–1.39)
	No obesity	1 (0.3%)	2 (0.7%)	0.620	0.49 (0.04–5.35)
	HTN	1 (0.2%)	4 (1.0%)	0.374	0.26 (0.03–2.29)
	No HTN	2 (0.4%)	5 (1.0%)	0.244	0.39 (0.08–2.01)
	DM	1 (0.4%)	4 (1.8%)	0.153	0.22 (0.03–1.98)
	No DM	2 (0.3%)	5 (0.7%)	0.453	0.42 (0.08–2.14)
	All cases	3 (0.3%)	9 (1.0%)	0.082	0.33 (0.09–1.23)
Acute respiratory distress syndrome	Obesity	104 (16.9%)	110 (17.6%)	0.728	0.96 (0.75–1.22)
	No obesity	37 (11.8%)	52 (17.0%)	0.064	0.69 (0.47–1.03)
	HTN	69 (16.9%)	78 (18.6%)	0.521	0.91 (0.68–1.22)
	No HTN	72 (13.8%)	84 (16.5%)	0.235	0.84 (0.63–1.12)
	DM	47 (18.8%)	38 (17.0%)	0.619	1.10 (0.75–1.63)
	No DM	94 (13.8%)	124 (17.5%)	0.057	0.79 (0.62–1.01)
	All cases	141 (15.2%)	162 (17.4%)	0.187	0.87 (0.71–1.07)
Septic shock	Obesity	88 (14.3%)	101 (16.2%)	0.352	0.88 (0.68–1.15)
	No obesity	40 (12.7%)	46 (15.0%)	0.409	0.85 (0.57–1.26)
	HTN	63 (15.4%)	73 (17.4%)	0.442	0.89 (0.65–1.21)
	No HTN	65 (12.5%)	74 (14.5%)	0.339	0.86 (0.63–1.17)
	DM	35 (14.0%)	35 (15.7%)	0.604	0.89 (0.58–1.37)
	No DM	93 (13.7%)	112 (15.8%)	0.256	0.86 (0.67–1.11)
	All cases	128 (13.8%)	147 (15.8%)	0.215	0.87 (0.70–1.08)
Need to ventilator support	Obesity	349 (56.7%)	366 (58.7%)	0.476	0.97 (0.88–1.06)
	No obesity	150 (47.8%)	156 (51.0%)	0.424	0.94 (0.80–1.10)
	HTN	246 (60.1%)	266 (63.3%)	0.345	0.95 (0.85–1.06)
	No HTN	253 (48.6%)	256 (50.2%)	0.599	0.97 (0.85–1.09)
	DM	171 (68.4%)	156 (70.0%)	0.715	0.98 (0.87–1.10)
	No DM	328 (48.2%)	366 (51.8%)	0.188	0.93 (0.84–1.04)
	All cases	499 (53.7%)	522 (56.1%)	0.284	0.96 (0.88–1.04)
in-hospital mortality	Obesity	274 (44.5%)	333 (53.4%)	0.002*	0.83 (0.74–0.93)
	No obesity	104 (33.1%)	127 (41.5%)	0.031*	0.80 (0.65–0.98)
	HTN	176 (43.0%)	218 (51.9%)	0.011*	0.83 (0.72–0.96)
	No HTN	202 (38.8%)	242 (47.5%)	0.005*	0.82 (0.71–0.94)
	DM	99 (39.6%)	112 (50.2%)	0.020*	0.79 (0.64–0.96)
	No DM	279 (41.0%)	348 (49.2%)	0.002*	0.83 (0.74–0.94)
	All cases	378 (40.6%)	460 (49.5%)	<0.001*	0.82 (0.74–0.91)

Notes: Data are presented as number and percentage. P-values are based on the Chi square test or Fisher's Exact test. *: Significant at $p < 0.05$.
Abbreviations: DM: diabetes mellitus; HTN: hypertension; RR: relative risk; CI: confidence interval.

Table 3. The length of intensive care unit stay (day).

				Relative effect	
Subgroup	Statin (Mean ± SD)	No statin (Mean ± SD)	p-value	Mean ± SE	95% CI
Non-survivors					
Obesity	11.1 ± 4.2	9.4 ± 6.8	<0.001*	1.7 ± 0.5	0.8–2.6
No obesity	12.0 ± 4.2	10.2 ± 4.0	0.001*	1.8 ± 0.5	0.8–2.9
HTN	11.4 ± 4.1	10.1 ± 7.0	0.022*	1.3 ± 0.6	0.2–2.4
No HTN	11.3 ± 4.3	9.2 ± 5.4	<0.001*	2.1 ± 0.5	1.2–3.1
DM	11.1 ± 4.4	9.0 ± 5.2	0.003*	2.0 ± 0.7	0.7–3.3
No DM	11.5 ± 4.1	9.8 ± 6.5	<0.001*	1.7 ± 0.4	0.8–2.5
All cases	11.4 ± 4.2	9.6 ± 6.2	<0.001*	1.7 ± 0.4	1.0–2.5
Survivors					
Obesity	10.8 ± 6.0	14.5 ± 8.0	<0.001*	−3.8 ± 0.6	−4.9–-2.6
No obesity	10.3 ± 3.9	11.6 ± 5.6	0.008*	−1.3 ± 0.5	−2.2–-0.3
HTN	10.8 ± 4.5	13.5 ± 6.4	<0.001*	−2.7 ± 0.5	−3.7–-1.6
No HTN	10.4 ± 5.8	13.4 ± 8.0	<0.001*	−2.9 ± 0.6	−4.0–-1.8
DM	11.1 ± 6.9	14.4 ± 6.2	<0.001*	−3.3 ± 0.8	−4.9–-1.6
No DM	10.4 ± 4.5	13.1 ± 7.6	<0.001*	−2.7 ± 0.5	−3.6–-1.8
All cases	10.6 ± 5.3	13.4 ± 7.3	<0.001*	−2.8 ± 0.4	−3.6–-2.0

Notes: Data are presented as Mean ± SD. P-values are based on the independent-test *: Significant at $p < 0.05$.
Abbreviations: DM: diabetes mellitus; HTN: hypertension; SD: standard deviation; SE: standard error; CI: confidence interval; ICU: intensive care unit.

Table 4. Duration of mechanical ventilation (day).

				Relative effect	
Subgroup	Statin (Mean ± SD)	No statin (Mean ± SD)	p-value	Mean ± SE	95% CI
Non-survivors					
Obesity	8.6 ± 2.7	8.1 ± 2.9	0.094	0.4 ± 0.2	−0.1–0.9
No obesity	9.2 ± 2.9	9.1 ± 3.0	0.840	0.1 ± 0.4	−0.7–0.9
HTN	8.7 ± 2.7	8.4 ± 3.0	0.204	0.4 ± 0.3	−0.2–1.0
No HTN	8.7 ± 2.8	8.5 ± 3.0	0.485	0.2 ± 0.3	−0.4–0.8
DM	8.7 ± 2.6	8.7 ± 3.1	0.926	0.0 ± 0.4	−0.8–0.9
No DM	8.7 ± 2.8	8.4 ± 2.9	0.127	0.4 ± 0.2	−0.1–0.9
All cases	8.7 ± 2.8	8.43 ± 3.0	0.166	0.3 ± 0.2	−0.1–0.7
Survivors					
Obesity	9.3 ± 2.5	9.8 ± 2.8	0.193	−0.5 ± 0.4	−1.3–0.3
No obesity	10.5 ± 2.6	9.7 ± 2.5	0.161	0.8 ± 0.5	−0.3–1.9
HTN	9.6 ± 2.6	9.9 ± 2.7	0.437	−0.3 ± 0.4	−1.2–0.5
No HTN	9.9 ± 2.6	9.5 ± 2.7	0.468	0.4 ± 0.5	−0.6–1.3
DM	9.2 ± 2.2	9.9 ± 2.8	0.142	−0.7 ± 0.4	−1.6–0.2
No DM	10.2 ± 2.8	9.7 ± 2.6	0.277	0.5 ± 0.5	−0.4–1.4
All cases	9.7 ± 2.6	9.8 ± 2.7	0.889	0.0 ± 0.3	−0.7–0.6

Notes: Data are presented as Mean ± SD. P-values are based on the independent t-test.
Abbreviations: DM: diabetes mellitus; HTN: hypertension; SD: standard deviation; SE: standard error; CI: confidence interval.

effect compared to the non-statin group. The relative effect was calculated with 95% confidence interval (Table 5).

4. Discussion

Statins are common lipid lowering drugs that have been used for COVID-19 treatment. Statin therapy is stopped when the hospitalized COVID-19 patients are admitted to the ICU. The objective of this retrospective cohort study was to assess the effect of continuation of previous statin therapy on mortality, ICU stay, and duration of mechanical ventilation among critically ill, COVID-19 patients.

Comparing all patients who continued statin therapy including the comorbidities subgroups with those who did not stay on this therapy throughout the ICU admission, the age, sex, COVID-19 CO-RADS classification, previous comorbidities, and the subsequent complications were not significantly different. Meanwhile, mortality was significantly decreased in the statin group. The duration of ICU stay was considerably longer among the non-survivors of the statin group and was significantly shorter among the survivors in the statin group. Among the non-survivors, the duration of mechanical ventilation was longer in the statin group, while among the survivors, it was shorter in the statin group but did not reach statistical significance. The D-dimer level was non significantly reduced, meanwhile the serum ferritin level was significantly decreased among the statin group.

Our findings agree with Andrew et al. [15] who analyzed 146,413 hospitalized COVID-19 cases and found that discontinuation of the previously administered atorvastatin is related to deteriorating outcomes. Kuno et al. [16] found that taking statins before and during hospitalization was more advantageous than taking no statins or stopping them. Moreover, in-hospital mortality was lower in the statins-treated patients than those who did not receive statins. This impact may be due to statin rebound effect, which resulted in vascular dysfunction [17]. Daskalopoulou

Table 5. D-dimer and serum ferritin.

				Relative effect	
Subgroup	Statin (Mean ± SD)	No statin (Mean ± SD)	p-value	Mean ± SE	95% CI
Average D-dimer (μg/mL)					
Obesity	0.82 ± 0.33	0.84 ± 0.47	0.177	−0.03 ± 0.02	−0.06–0.01
No obesity	0.81 ± 0.32	0.84 ± 0.48	0.198	−0.03 ± 0.02	−0.08–0.02
HTN	0.83 ± 0.33	0.85 ± 0.45	0.603	−0.02 ± 0.03	−0.08–0.05
No HTN	0.83 ± 0.35	0.87 ± 0.48	0.207	−0.04 ± 0.03	−0.09–0.02
DM	0.81 ± 0.31	0.83 ± 0.46	0.521	−0.02 ± 0.02	−0.06–0.03
No DM	0.79 ± 0.30	0.83 ± 0.48	0.294	−0.04 ± 0.04	−0.11–0.03
All cases	0.83 ± 0.33	0.85 ± 0.47	0.371	−0.02 ± 0.02	−0.06–0.02
Maximum D-dimer (μg/mL)					
Obesity	1.49 ± 0.32	1.51 ± 0.48	0.269	−0.03 ± 0.02	−0.07–0.02
No obesity	1.51 ± 0.33	1.52 ± 0.45	0.698	−0.01 ± 0.03	−0.08–0.05
HTN	1.50 ± 0.35	1.53 ± 0.48	0.286	−0.03 ± 0.03	−0.09–0.03
No HTN	1.49 ± 0.31	1.50 ± 0.46	0.608	−0.01 ± 0.02	−0.06–0.04
DM	1.47 ± 0.30	1.50 ± 0.48	0.437	−0.03 ± 0.04	−0.10–0.04
No DM	1.50 ± 0.33	1.52 ± 0.47	0.429	−0.02 ± 0.02	−0.06–0.03
All cases	1.49 ± 0.33	1.51 ± 0.47	0.262	−0.02 ± 0.02	−0.06–0.02
Average ferritin (ng/mL)					
Obesity	648.1 ± 255.9	700.3 ± 281.4	0.001*	−52.3 ± 15.3	−82.2–-22.3
No obesity	622.0 ± 244.4	678.6 ± 274.0	0.007*	−56.6 ± 20.8	−97.5–-15.7
HTN	666.0 ± 245.6	728.3 ± 284.7	0.001*	−62.3 ± 18.5	−98.5–-26.1
No HTN	618.2 ± 255.6	664.2 ± 271.2	0.005*	−46.0 ± 16.4	−78.2–-13.8
DM	657.6 ± 280.9	733.0 ± 280.4	0.004*	−75.4 ± 25.9	−126.2–-24.6
No DM	632.5 ± 240.7	680.6 ± 277.6	0.001*	−48.1 ± 13.9	−75.5–-20.8
All cases	639.2 ± 252.3	693.2 ± 279.0	<0.001*	−53.9 ± 12.3	−78.1–-29.7
Maximum ferritin (ng/mL)					
Obesity	934.1 ± 235.8	973.6 ± 251.1	0.004*	−39.5 ± 13.8	−66.6–-12.3
No obesity	909.9 ± 226.1	953.3 ± 244.3	0.022*	−43.4 ± 18.9	−80.5–-6.3
HTN	952.8 ± 226.7	998.8 ± 253.7	0.006*	−46.0 ± 16.7	−78.8–-13.2
No HTN	904.8 ± 235.5	940.6 ± 242.0	0.016*	−35.8 ± 14.9	−65.0–-6.6
DM	940.0 ± 257.9	1004.9 ± 251.3	0.006*	−64.9 ± 23.5	−111.1–-18.8
No DM	920.7 ± 222.8	954.9 ± 247.1	0.007*	−34.1 ± 12.6	−58.9–-9.4
All cases	925.9 ± 232.7	966.9 ± 248.9	<0.001*	−41.0 ± 11.2	−62.9–-19.1

Notes: Data are presented as Mean ± SD. P-values are based on the independent-test.*: Significant at $p < 0.05$.
Abbreviations: DM: diabetes mellitus; HTN: hypertension; SD: standard deviation; SE: standard error; CI: confidence interval.

et al. [18] reported that patients who ceased statins use after a myocardial infarction had a greater death rate than those who never used them. Also, Ma et al. [19] found that the use of atorvastatin during surgery had been linked to lower mortality and complications. The American College of Cardiology/American Heart Association recommends maintaining statin therapy to lower the risk of cardiac problems during surgeries [20]. Continuous stain medication may have protective impact because cardiac affection is more common in COVID-19 patients [21]. When statins are discontinued their favourable benefits on the immune system might be quickly lost, and the hazardous effect of statin discontinuation are still unclear. There is currently no proof to recommend the withdrawal of statins in COVID-19 cases, except in the case of significant increase of liver enzymes, rhabdomyolysis, or drug-related risk of death.

The length of ICU stay and period of mechanical ventilation were greater among the non-survivors of the statin groups. These were in accordance with Shen et al. [22], indicating that continued statin use could significantly prolong the survival time and life span. Moreover, serum ferritin was lower among the statin group, which agreed with Gupta et al. [23]. Serum ferritin is one of the proinflammatory biomarkers that predicts the severity and death of COVID-19 cases [24]. Elevated ferritin levels were related mainly to cytokine storm syndrome [25]. Therefore, serum ferritin reduction signifies a decrease in the inflammatory condition and the advantageous role of the continued statin use during COVID-19 infection.

The cytokine storm that results from COVID-19 infection targets endothelial cells, which could also contract the virus. Thus, endothelial cells that are not functioning properly lose their antithrombotic surface characteristics [1]. In fact, the primary causes of cardio-respiratory failure in COVID-19 patients may be endothelial dysfunction with ensuing organ hypoxia [26,27]. Statins have great effects on endothelial function. Statins' capacity to enhance endothelial function may at least partially alleviate the endothelium's prothrombotic condition [28]. The endothelial dysfunction in diabetic patients is complex and is associated with hyperglycemia and insulin resistance [29]. In this regard, statins have been demonstrated to protect the vascular endothelial cells in patients with diabetes by modulating NO availability, suppressing the inflammatory response, preventing endothelial barrier dysfunction, improving plaque stability, and lowering the endothelial cell's thrombogenic potential [30]. Thus, statins may enhance the endothelial function in diabetic cases who get infected with COVID-19.

Additionally, statins can decrease the risk of thrombosis in all vessels [31]. COVID-19 may speed up the atherosclerosis progress during the healing phase and beyond. Thus, it is important to continue statin treatment [32].

Statins may also reduce the development of severe lung injury and ARDS by modulating angiotensin-converting enzyme II expression, cytokine overexpression, and the immunological response. Statins can suppress the inflammatory protein nuclear factor kB (NF-B) [10,33]. Additionally, they can attach with high affinity to the main protease, which enhances viral multiplication and transcription. Hence, they may have anti-SARS-CoV-2 effect by inhibiting viral replication [10,11]. Hence, our findings could be explained by all these statins' actions.

In contrast to our findings, a South Korean cohort analysis of 7,780 COVID-19 participants found no differences in death rates between statin-treated patients and those who did not receive statins [34]. Also, Rey et al. [35] retrospectively analyzed 2,191 COVID-19 patients who were hospitalized and followed-up. The researchers reported that statins were not associated with all-cause mortality. Furthermore, the CORONADO trial discovered that type 2 diabetes patients who were hospitalized with COVID-19 had greater morality while regularly taking statins [36]. However, the mortality risk among both COVID-19 individuals with diabetes and those without can be affected by how hyperglycemia is managed [37]. These differences could be explained by the various statistical techniques employed, the research population size, heterogeneity between studies, and different types of statins.

In addition, the prior statins use with COVID-19 was assessed and demonstrated an improvement in the in-hospital mortality rate. However, there were no differences in mechanical ventilation rate, ICU admission rate, and length of stay [23,38,39].

This retrospective cohort study was a single-center study, lacking control over the confounding variables, with some incomplete medical records. The different types of statins were not identified. Further larger, multicenter studies with identification of the statin types are needed.

In conclusion, continuing statin medication was associated with a significantly lower mortality rate and an enhanced survival for COVID-19 cases. Thus, maintaining statin for severely ill COVID-19 cases with previous use should be considered.

Disclosure statement

The authors report no conflict of interest.

ORCID

Heba A. Labib http://orcid.org/0000-0003-4194-3438

References

[1] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J. 2020;41(32):3038–3044.
[2] Sharma A, Tiwari S, Deb MK, et al. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. Int J Antimicrob Agents. 2020;56(2):106054.
[3] Asselah T, Durantel D, Pasmant E, et al. COVID-19: discovery, diagnostics and drug development. J Hepatol. 2021;74(1):168–184.
[4] Fajgenbaum DC, Khor JS, Gorzewski A, et al. Treatments administered to the first 9152 reported cases of COVID-19: a systematic review. Infect Dis Ther. 2020;9(3):435–449.
[5] Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020;14:1463–1465.
[6] Castiglione V, Chiriacò M, Emdin M, et al. Statin therapy in COVID-19 infection. Eur Heart J Cardiovasc Pharmacother. 2020;6(4):258–259.
[7] Black DM. A general assessment of the safety of HMG CoA reductase inhibitors (statins). Curr Atheroscler Rep. 2002;4(1):34–41.
[8] Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001;292(5519):1160–1164.
[9] Koushki K, Shahbaz SK, Mashayekhi K, et al. Anti-inflammatory action of statins in cardiovascular disease: the role of inflammasome and toll-like receptor pathways. Clin Rev Allergy Immunol. 2021;60(2):175–199.
[10] Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: could an old friend help in the fight against COVID-19? Br J Pharmacol. 2020;177(21):4873–4886.
[11] Reiner Ž, Hatamipour M, Banach M, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci. 2020;16(3):490–496.
[12] Kow CS, Hasan SS. The association between the use of statins and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2022;22(2):167–181.
[13] Hariyanto TI, Kurniawan A. Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020;14(6):1613–1615.
[14] Korani S, Bahrami S, Korani M, et al. Parenteral systems for statin delivery: a review. Lipids Health Dis. 2019;18(1):193.
[15] Andrews L, Goldin L, Shen Y, et al. Discontinuation of atorvastatin use in hospital is associated with increased risk of mortality in COVID-19 patients. J Hosp Med. 2022;17(3):169–175.
[16] Kuno T, So M, Iwagami M, et al. The association of statins use with survival of patients with COVID-19. J Cardiol. 2022;79(4):494–500.
[17] Pineda A, Cubeddu LX. Statin rebound or withdrawal syndrome: does it exist? Curr Atheroscler Rep. 2011;13(1):23–30.
[18] Daskalopoulou SS, Delaney JA, Filion KB, et al. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. Eur Heart J. 2008;29(17):2083–2091.
[19] Ma B, Sun J, Diao S, et al. Effects of perioperative statins on patient outcomes after noncardiac surgery: a meta-analysis. Ann Med. 2018;50(5):402–409.
[20] Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2014;130(24):e278–e333.

[21] Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res. 2017;120 (1):229–243.
[22] Shen L, Qiu L, Wang L, et al. Statin use and in-hospital mortality in patients with COVID-19 and coronary heart disease. Sci Rep. 2021;11(1):23874.
[23] Gupta A, Madhavan MV, Poterucha TJ, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun. 2021;12(1):1325.
[24] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062.
[25] Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. Int J Infect Dis. 2020;95:304–307.
[26] Ganjali S, Bianconi V, Penson PE, et al. Commentary: statins, COVID-19, and coronary artery disease: killing two birds with one stone. Metabolism. 2020;113:154375.
[27] Sahebkar A, Serban C, Ursoniu S, et al. The impact of statin therapy on plasma levels of von Willebrand factor antigen. Systematic review and meta-analysis of randomised placebo-controlled trials. Thromb Haemost. 2016;115(3):520–532.
[28] Masoura C, Pitsavos C, Aznaouridis K, et al. Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins. A systematic review and meta-analysis. Atherosclerosis. 2011;214(1):129–138.
[29] Luscher TF, Creager MA, Beckman JA, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Circulation. 2003;108(13):1655–1661.
[30] Tomizawa A, Hattori Y, Suzuki K, et al. Effects of statins on vascular endothelial function in hypercholesterolemic patients with type 2 diabetes mellitus: fluvastatin vs. rosuvastatin. Int J Cardiol. 2010;144(1):108–109.
[31] Undas A, Brummel-Ziedins KE, Mann KG. Anticoagulant effects of statins and their clinical implications. Thromb Haemost. 2014;111(3):392–400.
[32] Vuorio A, Watts GF, Kovanen PT. Familial hypercholesterolaemia and COVID-19: triggering of increased sustained cardiovascular risk. J Intern Med. 2020;287 (6):746–747.
[33] Tsai PH, Lai WY, Lin YY, et al. Clinical manifestation and disease progression in COVID-19 infection. J Chin Med Assoc. 2021;84(1):3–8.
[34] Oh TK, Song I-A, Jeon Y-T. Statin therapy and the risk of COVID-19: a cohort study of the national health insurance service in South Korea. J Pers Med. 2021;11(2):116.
[35] Rey JR, Merino Llorens JL, Iniesta Manjavacas ÁM, et al. Influence of statin treatment in a cohort of patients admitted for COVID-19. Med Clin. 2022;158 (12):586–595.
[36] Cariou B, Goronflot T, Rimbert A, et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: results from the CORONADO study. Diabetes Metab. 2021;47(2):101202.
[37] Morse J, Gay W, Korwek KM, et al. Hyperglycaemia increases mortality risk in non-diabetic patients with COVID-19 even more than in diabetic patients. Endocrinol Diabetes Metab. 2021;4(4):e00291.
[38] Mitacchione G, Schiavone M, Curnis A, et al. Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. J Clin Lipidol. 2021;15 (1):68–78.
[39] Saeed O, Castagna F, Agalliu I, et al. Statin use and in-hospital mortality in patients with diabetes mellitus and COVID-19. J Am Heart Assoc. 2020;9(24):e018475.