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ORIGINAL RESEARCH ARTICLE

Prior Treatment with Statins is Associated with Improved Outcomes of Patients with COVID-19: Data from the SEMI-COVID-19 Registry

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Abstract

Background The impact of statins on COVID-19 outcomes is important given the high prevalence of their use among individuals at risk for severe COVID-19. Our aim is to assess whether patients receiving chronic statin treatment who are hospitalized with COVID-19 have reduced in-hospital mortality if statin therapy is maintained during hospitalization.

Methods This work is a cross-sectional, observational, retrospective multicenter study that analyzed 2921 patients who required hospital admission at 150 Spanish centers included in the nationwide SEMI-COVID-19 Network. We compared the clinical characteristics and COVID-19 disease outcomes between patients receiving chronic statin therapy who maintained this therapy during hospitalization versus those who did not. Propensity score matching was used to match each statin user whose therapy was maintained during hospitalization to a statin user whose therapy was withdrawn during hospitalization.

Results After propensity score matching, continuation of statin therapy was associated with lower all-cause mortality (OR 0.67, 0.54–0.83, $p < 0.001$); lower incidence of acute kidney injury (AKI) (OR 0.76,0.6–0.97, $p = 0.025$), acute respiratory distress syndrome (ARDS) (OR 0.78, 0.69- 0.89, $p < 0.001$), and sepsis (4.82% vs 9.85%, $p = 0.008$); and less need for invasive mechanical ventilation (IMV) (5.35% vs 8.57, $p < 0.001$) compared to patients whose statin therapy was withdrawn during hospitalization.

Conclusions Patients previously treated with statins who are hospitalized for COVID-19 and maintain statin therapy during hospitalization have a lower mortality rate than those in whom therapy is withdrawn. In addition, statin therapy was associated with a decreased probability that patients with COVID-19 will develop AKI, ARDS, or sepsis and decreases the need for IMV.

Key Points

Prior statin therapy that is maintained during hospitalization is associated with lower mortality rate in patients hospitalized for COVID-19.

Prior statin therapy that is maintained during hospitalization is associated with lower probability of AKI and sepsis rate in patients hospitalized for COVID-19.

Prior statin therapy that is maintained during hospitalization is associated with lower probability of ARDS and IMV rate in patients hospitalized for COVID-19.

José David Torres-Peña, Luis M. Pérez-Belmonte have equal contribution.

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1 Introduction

SARS-Cov-2 (severe acute respiratory syndrome coronavirus 2) infection is a rapidly evolving pandemic with uncertain clinical features. Its true burden on the healthcare system may be underestimated since extrapulmonary manifestations are frequent. Patients with pre-existing cardiovascular disease may develop clinical events early on in the course of the disease and the infection may also have short-, medium-, and long-term implications for cardiovascular health—a finding which has been observed in several patient registries [1–4].

Whether vascular disorders in patients with COVID-19 (coronavirus disease-2019), the disease caused by SARS-CoV-2, are due to direct involvement of the virus on endothelial cells is not currently known. Endothelial dysfunction is a main determinant in the development of arteriosclerotic cardiovascular disease [5, 6]. Microvascular endothelial dysfunction occurs when there is an imbalance between vasoconstriction and vasodilation in favor of vasoconstriction, resulting in organ ischemia, inflammation with edema of the associated tissues, and a procoagulant state. Recent data support the hypothesis of a direct cytotoxic effect of SARS-CoV-2 on endothelial cells and that this contributes to diffuse endothelial inflammation [7]. These findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of inflammation and endothelial cell death. Furthermore, the induction of apoptosis and pyroptosis phenomena may play an important role in endothelial cell injury in patients with COVID-19 [7]. In this sense, severe endothelial damage associated with the presence of intracellular viral particles with rupture of endothelial cell membranes has recently been described in a small series of autopsies in deceased COVID-19 patients, together with histological findings showing thrombosis and microangiopathy [8].

Statins improve endothelial dysfunction by decreasing levels of plasma cholesterol and increasing endothelial nitric oxide (NO) synthesis, stimulating and regulating the action of endothelial NO synthase [9]. They also have anti-inflammatory and immunomodulatory properties, antithrombotic and antiproliferative actions, and reduce the rate of apoptosis [10].

It is known that lipid rafts rich in cholesterol serve as docking SARS-CoV-2 infection. Lipid rafts rich in cholesterol serve as docking sites in SARS-COV-2 infection and for angiotensin-converting enzyme 2 (ACE2) receptors and viral attachment via the S protein sites for ACE2 receptors and viral attachment via the S protein of SARS-CoV-2, and then is taken into the cells by clathrin. Moreover, SARS-COV-2 infection and macrophages can lead to plaque instability and embolization by paracrine pathway. Thus, statins can disrupt lipid rafts and viral binding, modulating viral entry by reducing cholesterol and improving plaque stability, antithrombotic, and anti-inflammatory properties [11]. To sum up, the pharmacological sequestration of cellular or viral cholesterol with statins may significantly blocked both virus attachment and internalization [12]. Antiviral effects of statins has been also proposed, suggesting that statins may have a role in the treatment of viral infections due to their immunomodulatory properties and the inhibition of viral replication acting in different stages of virus cell cycle [13].

For all of these reasons, it would be interesting to know the role of statin therapy in the stabilization process of endothelial cells while viral replication is taking place, especially given their known anti-inflammatory, immunomodulatory, antithrombotic, and antiproliferative properties. Thus, the aim of this work is to assess whether hospitalized patients with COVID-19 in chronic treatment with statins have lower in-hospital mortality and other COVID-19 outcomes if their statin therapy is maintained during the hospitalization.

2 Materials and Methods

2.1 Source of Data

This is a multicenter, retrospective, cohort study based on the SEMI-COVID-19 Registry. This registry includes consecutive patients with COVID-19 infection confirmed via a positive reverse transcription polymerase chain reaction (RT-PCR) test who are hospitalized in 150 Spanish hospitals. Clinical and epidemiological data, laboratory tests upon admission and at 7 days of hospitalization, treatments administered, complications, and their status upon discharge and at 30 days after diagnosis were recorded in electronic medical records and compiled in a secure database. Patients aged < 18 years and patients who did not agree to participate were excluded. The study was approved by the Research Ethics Committee of Málaga (Spain). Further information on the justification, objectives, and methodology of the SEMI-COVID-19 registry has recently been published [4].

2.2 Outcomes

The primary outcome was all-cause in-hospital mortality expressed as the case fatality rate: the proportion of deaths during hospitalization compared to the total number of hospitalized patients with COVID-19. Secondary outcomes were the length of hospital stay and in-hospital complications, including acute respiratory distress syndrome (ARDS), need for invasive mechanical ventilation (IMV), sepsis, and acute kidney injury (AKI).

2.3 Data Analysis

Participants' demographic, clinical, epidemiological, laboratory, and diagnostic imaging data were analyzed. Treatment received, complications, and clinical progress were also examined. Quantitative variables were expressed as means and SD or median and interquartile range. Continuous variables were tested for normal distribution using Kolmogorov–Smirnov. Categorical variables were expressed as absolute frequencies and percentages. *P* values were obtained using the chi-square test, Fisher's exact test, or Mann-Whitney *U* test, when appropriate. Two-tailed p value < 0.05 was considered statistically significant.

2.4 Statistical Analysis

Propensity score matching was performed to account for non-randomized treatment decisions and reduce the effects of confounding variables. Logistic regression was used to determine the probability of having statin treatment and included confounding variables that could have affected treatment choice (age, sex, obesity, hypertension, diabetes, coronary artery disease, dyslipidemia, ischemic stroke, transient ischemic attack, peripheral artery disease, heart failure, treatment with angiotensin-converting enzyme inhibitors, chronic kidney disease; angiotensin II receptor blockers, qSOFA category, C-reactive protein, D-dimer, lymphocyte count, and serum creatinine). The nearest neighbor method with a caliper of 0.1 was used in the propensity score matching and standardized mean differences (SMD) were calculated to evaluate the adequacy of propensity matching.

In order to estimate the association of statin treatment (specifically, in-hospital use of statins during hospitalization vs stopping statin treatment in patients with prior statin treatment) on mortality and other endpoints, both conditional and mixed-effects logistic regressions were performed considering matched pairs as random effects. For the sepsis and IMV endpoints, McNemar test was used to observe differences between the treatments. Statistical analyses were performed using R software, version 3.6.2 (The R Foundation for Statistical Computing, http://www.R-project.org).

2.5 Ethical Aspects

The SEMI-COVID-19 Registry has been approved by the Provincial Research Ethics Committee of Málaga (Spain). Informed consent was obtained from all patients. When it was not possible to obtain informed consent in writing due to biosafety concerns, informed consent was requested verbally and noted on the medical record.

3 Results

3.1 Baseline Clinical Variables

Figure 1 shows the flowchart for patient inclusion. Table 1 shows the baseline demographic characteristics, and complications of all patients included in this sub-analysis. A total of 2921 patients had prior statin therapy at the time of inclusion in the registry and 6669 patients did not. Overall, there were no significant differences between the two groups in the main variables analyzed except for the higher rate of coronary artery disease among statin users.

3.2 Pre- and Post-propensity Score Matching Characteristics in Patient Treated with Statins before Admission

Pre- and post-propensity score matching was used to compare two subgroups of patients within the prior statin use group: those who continued to receive statin therapy during their hospitalization and those who did not. The results of the comparison of their baseline sociodemographic and clinical characteristics are shown in Table 2. After propensity score matching, the subgroups were well-balanced.

3.3 Association between Statin Therapy on Study Outcomes

Tables 3 and 4 show the main clinical outcomes of the study after propensity score matching. Upon analyzing the two subgroups of patients within the prior statin use group (those who continued to receive statin therapy during hospitalization and those who did not), continuation of statin therapy was associated with lower all-cause mortality (OR 0.67, 0.54–0.83, $p < 0.001$), a lower incidence of AKI (OR 0.76, 0.6–0.97, $p = 0.025$), and a lower incidence of ARDS (OR 0.78, 0.69–0.89, $p < 0.001$) (Table 3). In addition, fewer patients in this subgroup required IMV (5.35 % vs 8.57 %, $p < 0.001$) and there was a lower incidence of sepsis (4.82 % vs 9.85 %, $p = 0.008$) compared to patients who did not continue to receive statin therapy during the hospitalization (Table 4).

4 Discussion

This work shows that patients previously treated with statins who develop COVID-19 and continue to receive statins during their hospitalization were associated with a lower mortality rates than those in whom statins were withdrawn. Also, continued in-hospital statin use was associated with a decreased probability of developing other in-hospital

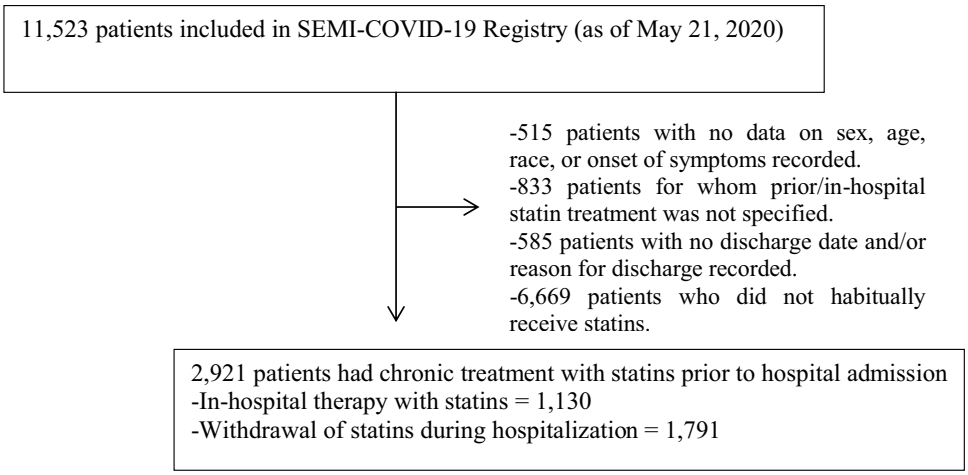

Fig. 1 Patient inclusion flowchart

complications, including ARDS, a need for IMV, sepsis, or AKI. Our results are consistent with other studies that suggest a potential beneficial role of statins in patients with COVID-19.

Recently, a retrospective cohort study by Zhang et al. [14] reported a significantly lower in-hospital death rate among patients with in-hospital statin use compared to a matched non-statin-use control group (5.2 % vs 9.4 %). A meta-analysis that included four studies of nearly 9000 patients with severe COVID-19 [15], including three large-scale studies that adjusted for multiple confounding variables, found that patients taking statins had a 30 % lower risk of death or serious disease when compared to those not taking statins (pooled HR 0.70; 95 % CI 0.53–0.94). Also, work by Daniels et al. [16] showed that among patients hospitalized for COVID-19, statin use prior to admission was associated with a reduced risk of severe disease (death or intensive care unit admission) and a faster recovery time. Specific populations may benefit from the use of statins in the context of COVID-19 [17], thus, an observational study showed that statin therapy was associated with reduced in-hospital mortality from COVID-19 in patients with diabetes. All these findings suggest that statins may favorably modulate COVID-19 disease outcomes.

It has previously been theorized that the use of statins could reduce the probability of complications and mortality in patients with COVID-19; in fact, statins have even been included as a possible anti-COVID-19 therapy in some guidelines [18]. Evidence suggests that statins exert antiviral activity and could block the infectivity of encapsulated viruses [19]. The main protease of SARS-CoV-2 called Mpro—a key enzyme in the coronavirus—has recently come into focus and is a possible pharmacological target. Using a molecular coupling model, it has been shown that statins can be efficient inhibitors of this enzyme [20] and therefore could be used as a potential treatment against SARS-CoV-2.

On the other hand, toll-like receptors (TLR) have been shown to intervene in the immune response mediated by activation of the NF-KB signaling pathway [21]. Activation of TLR and NF-KB by coronaviruses has been observed to trigger both over-expression and under-expression of the MyD88 gene (involved in the expression of myeloid differentiation factors) in experimental mouse models, which has been associated with an increased mortality after MERS-CoV infection [21]. Due to their potential effect of stopping TLR and NF-KB signaling, statins may improve the lung damage associated with SARS-CoV-2 infection through these anti-inflammatory effects. It is important to note that pharmacokinetic characteristics may be relevant in patients who receive statins in the context of COVID-19. Rossi et al. [22] hypothesized that patients taking statins were better protected against mortality than those who do not take statins. Interestingly, they observed that in the group receiving lipophilic statins, mortality was significantly lower compared to patients who did not take statins and those who received hydrophilic statins.

Statins have also been reported to reduce the risk of COVID-19-induced acute coronary syndrome by stabilizing arteriosclerotic plaques and in turn preventing AKI. Given that acute myocardial injury and AKI are predictors of COVID-19-induced mortality [23], statin therapy may prevent these complications and thus increase survival among patients who receive it. This association has also been found in our registry: patients with COVID-19 who were previously receiving chronic statin treatment had a lower risk of developing AKI. Another potential mechanism by which statins may exert these clinical benefits in patients with COVID-19 is through a significant reduction in cholesterol levels. This reduction may suppress coronavirus infection in various ways. In studies on porcine deltacoronavirus and on the coronavirus that produces infectious bronchitis [12], it has been shown that the reduction in cholesterol, as a result of statin therapy, disrupts the lipid core of the viral envelope,

Table 1 Demographics, baseline characteristics, and complications of 2921 patients with habitual statin treatment, from the SEMI-COVID-19 registry

Parameters	In-hospital statin use ($n = 1130$)	Withdrawal of statins ($n = 1791$)	p value
Habitual statin treatment ($n = 2921$)			
Clinical characteristics upon admission			
Age (years) (median ± SD)	72 ± 10	73 ± 11	NS
Sex (male/female) (%)	60.3/39.7	60.3/39.7	NS
SBP (mmHg)	131 ± 21	129 ± 21	NS
DBP (mmHg)	73 ± 13	73 ± 12	NS
Heart rate (bpm)	86 ± 16	87 ± 17	NS
Comorbidities upon admission (%)			
Hypertension	61.8	64	NS
Diabetes	24.2	27.6	NS
Coronary heart disease	9.7	10.2	NS
Cerebrovascular disease	9.3	10.1	NS
Peripheral artery disease	7.5	7.1	NS
Dyslipidemia	60	69	NS
Laboratory values upon admission			
C-reactive protein (mg/L)	85.2 ± 2.6	95 ± 2.2	$p < 0.05$
Procalcitonin (ng/mL)	2.6 ± 0.4	2.10 ± 0.8	NS
D-dimer (ng/mL)	1505 ± 181	1637 ± 119	NS
Neutrophil count ($\times 10^3$ µ/L)	5.23 ± 4.1	5.35 ± 4.01	NS
Lymphocyte count ($\times 10^3$ µ/L)	1.05 ± 25.1	1.06 ± 30.3	NS
LDH (U/L)	338 ± 5.4	372 ± 7.8	NS
Serum creatinine(mg/dL)	1.16 ± 0.31	1.09 ± 0.36	NS
COVID-19 treatment (%)			
Antiviral drug			
Lopinavir/ritonavir	53.8	66.5	$p < 0.05$
Remdesivir	0.3	0.6	NS
Antibiotics			
Beta-lactams	71.4	78.6	$p < 0.05$
Macrolides	63.6	64.5	NS
Quinolones	16.1	16	NS
Corticosteroids	35.7	38.6	NS
Immunoglobulins	0	0.3	NS
Hydroxychloroquine	82.9	85.1	NS
Low-molecular-weight heparin	83.6	87.5	NS

Data are expressed as n (%) or mean ± SEM or SD

DBP diastolic blood pressure, *LDH* lactate dehydrogenase, *NS* not significant, *SBP* systolic blood pressure

P values were calculated using the chi-square test, Fisher's exact test, or Mann-Whitney U test, when appropriate. $p < 0.05$ was considered statistically significant (in bold)

an important element that allows for the binding of the coronavirus to host cells and, consequently, additional infection. Therefore, the action of statins pharmacologically "sequestering" cellular or viral cholesterol served to significantly block virus connection and internalization [12],

All these mechanisms [24] suggest that statins, as anti-inflammatories, play a critical role in inhibiting coronavirus infection due to their effects on the vascular endothelium. For all of these reasons, they can be considered useful drugs to include in the arsenal of anti-COVID-19 therapies.

It is important to highlight that a quarter of our population are patients with type 2 diabetes. The underlying mechanisms involved in endothelial dysfunction when diabetes is present are complex and related to hyperglycemia and insulin resistance [25]. In this context, it is known that statins may exert a protective action on vascular endothelial

Table 2 Pre- and post-propensity score matching of baseline sociodemographic and clinical characteristics of patients with prior statin therapy hospitalized due to COVID-19

	Pre-propensity matching				Post-propensity matching			
	In-hospital use of statins (n =1130)	Withdrawal of statins (n = 1791)	p value	SMD	In-hospital use of statins (n = 934)	Withdrawal of statins (n = 934)	p value	SMD
Age	74(66;81.5)	74 (66;81.5)	0.525	0.022	73 (65;80)	72 (65;80)	0.212	0.065
Male	679 (60.3 %)	1077 (60.3 %)	1	0.081	571 (61.1 %)	580 (62.1 %)	0.703	0.019
Obesity	276 (27.1 %)	432 (26.3 %)	0.675	0.018	249 (26.7 %)	250 (26.8 %)	1	0.002
Hypertension	698 (61.8 %)	1144 (64 %)	0.243	0.045	358 (38.3 %)	353 (37.7 %)	0.565	0.106
Diabetes without target organ damage	181 (16.5 %)	314 (18 %)	0.329	0.039	152 (16.3 %)	165 (17.7 %)	0.460	0.037
Diabetes with target organ damage	86 (7.7 %)	168 (9.5 %)	0.116	0.063	70 (7.4 %)	71 (7.6 %)	1	0.004
Coronary artery disease	110 (9.7 %)	183 (10.2 %)	0.719	0.016	97 (10.4 %)	105 (11.2 %)	0.602	0027
Dyslipidemia	677 (60 %)	1089 (60.9 %)	0.640	0.019	559 (59.9 %)	567 (60.7 %)	0.741	0.017
Ischemic stroke	41 (3.6 %)	65 (3.6 %)	1	0.0001	30 (3.21 %)	30 (3.21 %)	1	0
Transient ischemic attack	62 (5.6 %)	113 (6.4 %)	0.412	0.034	50 (5.35 %)	44 (4.71 %)	0.597	0.029
Peripheral artery disease	83 (7.5 %)	124 (7.1 %)	0.711	0.017	68 (7.28 %)	74 (7.92 %)	0.662	0.024
Heart failure	97 (8.6 %)	129 (7.2 %)	0.203	0.054	77 (8.24 %)	82 (8.78 %)	0.740	0.019
ACEI/ARB treatment	641 (56.9 %)	965 (54.2 %)	0.166	0.054	549 (58.8 %)	550 (58.9 %)	1	0.002
qSOFA (high risk)	81 (7.7 %)	175 (10.4)	0.022	0.018	68(7.3 %)	62(6.6 %)	0.657	0
Serum creatinine(mg/dL)	1.1 (0.7;1.2)	1.09 (0.6;1.1)	0.226	0.133	1.13(0.7;1.2)	1.04(0.7;1.2)	0.205	0.080
C-reactive protein (mg/L)	54 (17.2;127)	66.7 (23;137)	0.004	0.034	54.8(15.9;127)	59.8 (20.8;123)	0.403	0.006
Lymphocyte count (x10^6/L)	920 (660;1290)	900 (670;1200)	0.227	0.017	970(700;1300)	977 (700;1300)	0.795	0
D-dimer (ng/mL)	680 (400;1300)	680 (380;1276)	0.474	0.001	678 (40;1300)	632 (350;1174)	0.051	0.009

Comparisons were made between patients who continued to receive statins versus patients who did not continue to receive statins during hospitalization

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *qSOFA* quick sequential organ failure assessment score

Data are shown as median (interquartile range) or absolute data and percentages. A significant imbalance in the group was defined as a standardized mean difference (SMD) between baseline variables of greater than 10 %. Values were considered to be statistically significant when $p < 0.05$

Table 3 Association between statins, all-cause mortality, acute respiratory distress syndrome and acute kidney injury after propensity score matching

Outcomes	Treatment groups			Conditional logistic regression		Mixed effect logistic regression	
	In-hospital use of statins (n = 934)	Withdrawal of statins (n = 934)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
All-cause mortality	192 (20.6 %)	258 (27.6 %)	< 0.001	0.67 (0.54–0.84)	< 0.001	0.67 (0.54–0.83)	< 0.001
Acute respiratory distress syndrome	333(35.7 %)	407(43.6 %)	0.029	0.72(0.60–0.87)	< 0.001	0.78 (0.69–0.89)	< 0.001
Acute kidney injury	157 (16.8 %)	195 (20.9 %)	0.029	0.76 (0.61–0.97)	0.025	0.76 (0.6–0.97)	0.025

Data are shown as absolute values and percentages

OR odd ratiom *95% CI* 95 % confidence interval

A significant imbalance in the group was defined as a standardized mean difference between baseline variables of greater than 10 %

Values were considered to be statistically significant when $p < 0.05$

cells in patients with diabetes [26] through modulation of NO availability, suppression of inflammatory response, prevention of endothelial barrier dysfunction, improvement of plaque stability, and reduced thrombogenic potential of the endothelial cell [27, 28]. This way, statins may favorably modulate the endothelial function in patients with diabetes and COVID-19 disease.

Table 4 Association between statins, sepsis and invasive mechanical ventilation after propensity matching

Outcomes	Treatment groups		p value
	In-hospital use of statins ($n = 934$)	Withdrawal of statins ($n = 934$)	
Sepsis	45 (4.82 %)	92 (9.85 %)	0.008
Invasive mechanical ventilation.	50 (5.35 %)	92 (8.57 %)	< 0.001

Data are shown as absolute values and percentages. The McNemar test was performed. Values were considered to be statistically significant when $p < 0.05$

Our findings are important because they provide valuable information on the role of statins during hospitalizations on adverse outcomes in patients admitted for COVID-19. Furthermore, data were collected in a large multicenter, nationwide study. Nevertheless, these results should be considered within the context of some limitations. Our study has several limitations. First, it should be noted that although the sample size is large, this is a retrospective study. Thus, it serves to generate hypotheses that must be verified in future research and randomized clinical trials. Second, important information regarding the statin therapy that patients received (drug, doses, duration of therapy or discontinuation of oral treatment in critically ill patients) or lipid profile was not recorded in the registry. It is obvious that the duration of treatment, potency, and type of statin that patients were receiving may influence outcomes and must be considered.

One relevant limitation is that drug-drug interactions may explain why patients stopped statins during hospitalization. Familial Hypercholesterolemia Europe and the International Lipid Expert Panel (ILEP) in a recent brief report recommended that lipid-lowering drugs are generally safe in patients with coronavirus infections and should be continued. When COVID-19 is treated with antiretroviral drugs it is recommended that prescribers discontinue atorvastatin and simvastatin. It is possible to continue therapy with rosuvastatin, with preference for starting at a low dose and titrating up. Moreover, it is possible to continue treatment with pravastatin or fluvastatin. Caution is necessary when treating patients with macrolides. However, there are no data on severe or serious interactions of rosuvastatin and fluvastatin with azithromycin [29]. Finally, we have data on the administration of contrast that may have influenced the development of contrast-induced acute renal injury.

5 Conclusion

This work shows that patients previously treated with statins (chronic treatment) who develop COVID-19 and continue to receive statins during their hospitalization are associated with a lower mortality rate than those in whom statins were withdrawn. Also, continued in-hospital statin use was associated with a decreased probability of developing other in-hospital complications, including ARDS, a need for IMV, sepsis, or AKI. These findings support a potential role of statin therapy in treating COVID-19. Further prospective studies and randomized controlled clinical trials are needed to determine the effects of statin treatment on COVID-19 outcomes and establish the mechanisms through which statins exert these beneficial effects.

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