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Statin therapy may protect against acute kidney injury in patients hospitalized for interstitial SARS-CoV2 pneumonia

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Abstract *Background and aims:* COVID-19-associated acute kidney injury (AKI) represents an independent risk factor for all-cause in-hospital death in patients with COVID-19. Chronic statin therapy use is highly prevalent in individuals at risk for severe COVID-19. Our aim is to assess whether patients under treatment with statins have a lower risk of AKI and in-hospital mortality during hospitalization for interstitial SARS-CoV2 pneumonia.
Methods and results: Our study is a prospective observational study on 269 consecutive patients admitted for COVID-19 pneumonia at the Internal Medicine Unit of IRCCS Sant'Orsola Hospital in Bologna, Italy. We compared the clinical characteristics between patients receiving statin therapy (n = 65) and patients not treated with statins and we assessed if chronic statin use was associated with a reduced risk for AKI, all-cause mortality, admission to ICU, and disease severity. Statin use was associated with a significant reduction in the risk of developing AKI (OR 0.47, IC 0.23 to 0.95, p 0.036) after adjustment for age, sex, BMI, hypertension, diabetes, and chronic kidney disease (CKD). Additionally, statin use was associated with reduced C-reactive protein (CRP) levels (p 0.048) at hospital admission. No significant impact in risk of all-cause mortality (HR 1.98, IC 0.71 to 5.50, p 0.191) and ICU admission (HR 0.93, IC 0.52 to 1.65, p 0.801) was observed with statin use, after adjustment for age, sex, BMI, hypertension, diabetes, and CKD.
Conclusion: The present study shows a potential beneficial effect of statins in COVID-19-associated AKI. Furthermore, patients treated with statins before hospital admission for COVID-19 may have lower systemic inflammation levels.

1. Introduction

The COVID-19 pandemic represents the most challenging health crisis of the last 100 years. From December 2019 to date thousands of scientific reports, reviews, meta-analyses, and experimental studies have tried to clarify COVID-19 clinical features, risk factors and possible effective treatments [1,2]. Kidney injury has shown to be a common pathological finding in patients with COVID-19 [3]. COVID-19-associated kidney damage has a multifactorial origin [4–6]. In fact, SARS-CoV-2 can directly infect podocytes and proximal tubular cells causing acute tubular necrosis, collapsing glomerulopathy, and minimal change disease [4–6]. On the other hand, SARS-CoV-2-driven immune hyperactivation (including cytokine storm) and systemic endothelial dysfunction and hypercoagulability may be important mechanisms of indirect kidney injury

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[4]. Finally, a reduction in renal oxygen delivery may induce a significant ischemic injury [4–6].

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase used for reducing cholesterol levels in primary and secondary prevention of coronary artery disease [7]. Apart from their cholesterol-lowering properties, statins have multiple other beneficial effects, so called "pleiotropic" effects. These pleiotropic effects include anti-inflammatory, anti-oxidant, antithrombotic, and anti-proliferative properties [8]. It has been proposed that therapy with statins may be beneficial in COVID-19 because of their capacity to protect endothelial cells, to reduce the coagulation cascade activation, and to reverse or inhibit COVID-19-induced cytokine storm [8]. Additionally, statins may exert a protective role towards COVID-19-associated acute kidney injury (AKI). Previous studies have shown that in certain clinical scenarios statins may reduce the incidence and progression of AKI (e.g., contrast-induced AKI, post-surgical AKI) [9]. To our best knowledge only an observational study by Torres-Peña and colleagues have shown that statins may reduce AKI incidence in patients hospitalized for COVID-19 [10].

Our study aims to define the relationships among chronic statin therapy use, COVID-19-associated AKI and COVID-19 severity and in-hospital mortality.

2. Methods

2.1. Data collection

This study was conducted on 286 patients hospitalized for SARS-CoV-2 infection at the Internal Medicine Unit of IRCCS Sant'Orsola Hospital in Bologna, Italy, during the second pandemic outbreak from January 2021 to June 2021. Patients diagnosed with COVID-19 pneumonia were identified by combining clinical, laboratory (nasopharyngeal swab for SARS-CoV2 genome by RT-PCR) and radiological features (high-resolution computed tomography (HRCT)). All patients presented respiratory failure, described by the ratio of arterial oxygen partial pressure (PaO2) and inhaled oxygen fraction (FIO2) (P/F) $<$ 300 mmHg/%. Due to the low specificity of HRCT findings for COVID-19 pneumonia, patients with alternative diagnoses such as acute heart failure, recurrence of obstructive pulmonary disease (COPD or asthma), and chronic kidney disease (CKD) stage IV and end-stage renal disease (ESRD) were excluded. In addition, neoplastic patients with advanced or terminal disease and patients with bacterial infection or suspected or obvious sepsis were excluded from the study. Personal and anthropometric data were collected for each patient as well as their medical history and home medications. The presence of cardiovascular (CV) risk factors such as hypertension, diabetes, dyslipidemia, obesity, smoking habit were also recorded. Clinical and laboratory characteristics were collected from hospital admission to discharge or transfer to the Intensive Care Unit (ICU) and/or death. All laboratory variables were analyzed in line with best medical practice and in the same certified laboratory (Laboratorio Unico Metropolitano (LUM), Bologna, Italy). PaO2 was obtained by hemogasanalysis (PH ABL 90 Flex) from radial artery punction. All patients enrolled in the study were given intravenous dexamethasone and low molecular weight heparin (EBPM) as routinely performed in our Unit. Respiratory support with low-flow oxygen (nasal cannula or Venturi mask) was provided according to the needs of the individual patient and to keep peripheral oxygen saturation above 90%. Progression to severe COVID-19 was defined by the incidence of acute respiratory distress syndrome (P/F $\leq$ 100 mmHg/%, or P/F $\leq$ 150 mmHg/% and respiratory rate $\geq$26/min). AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine by $\geq$ 50% within 7 days or increase in serum creatinine by $\geq$0.3 mg/dL within 48 h or the presence of oliguria (urine output $<$0.5 mL/kg/h) [11].

Patients were codified as having CKD when the estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was under 90 mL/min/1.73 m^2 [12]. As per our Hospital Protocol, all patients with onset of symptoms $\geq$5 days and COVID-19 pneumonia have been treated with methylprednisolone 40 mg/day i.v., with progressive decalage after stable improvement of the gas exchanges. The hydration status of all participants was regularly assessed by physical examination, labs, fluid balance, and ultrasound estimation of inferior vena cava diameter and collapsibility, according to the best clinical practice for acutely ill patients. All our patients received the appropriate infusion of liquids, according to their hydration status and electrolyte balance.

All patients included in the study were over the age of 18 and provided informed consent. The study was approved by the local ethical committee (IRCCS Sant'Orsola Hospital, Bologna, Italy) n°359/2021/Oss/AOUBo in accordance with the declaration of Helsinki.

2.2. Study design

The present study is a prospective cohort study. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for observational studies was followed [13]. The study population of patients hospitalized for COVID-19 intersitial pneumonia has been divided into two cohorts: statin-users and non-statin users. Patients were considered statin-users if any statin was taken at admission and at least one month before, without interruption. All laboratory variables of interest were collected at admission and include: serum creatinine, C-reactive protein (CRP), D-dimer, lactate, lactate dehydrogenase (LDH), and interleukin-6 (IL-6). PaO2 and P/F were collected at admission and at their nadir. The outcomes of the study were the incidence of AKI during hospitalization, all-cause in-hospital mortality, rate of ICU admission, and progression to severe COVID-19.

2.3. Statistical analysis

Continuous variables are presented as mean+/-standard deviation (SD) or as median and interquartile range (IQR)

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Table 1 General characteristics of the population divided according to exposure to statins.

	General population (n = 286)	Statin-users (n = 65)	Non-statin-users (n = 221)	p-Value
Age (years)	64 ± 15	71 ± 13	62 ± 15	<**0.001*****
Sex (females)	113 (39.4%)	25 (38.5%)	88 (39.8%)	0.886
BMI (kg/m^2)	28.7 ± 5.3	29 ± 4.7	28.6 ± 5.4	0.310
Smoking habit	53 (18.5%)	17 (26.1%)	36 (16.3%)	0.081
Hypertension	167 (58.2%)	51 (78.5%)	116 (52.5%)	<**0.001*****
Diabetes mellitus	82 (28.6%)	28 (43.1%)	53 (24%)	**0.004****
History of CV disease (Stroke, CAD, PAD)	42 (14.7%)	23 (43.1%)	19 (8.6%)	<**0.001*****
CKD	2 (0.7%)	0 (0%)	2 (0.9%)	0.309
P/F at admission (mmHg/%)	296 (60)	287 (56)	297 (62)	0.956
PaO2 at admission (mmHg)	63 ± 10	56 ± 9	59 ± 8	0.687
PaCO2 at admission (mmHg)	33 ± 5	33 ± 6	33 ± 4	0.824
Serum creatinine (mg/dl)	0.96 (0.39)	1.0 (0.58)	0.94 (0.36)	0.090
eGFR (ml/min/1.73 m^2)	78 (39)	70 (43)	81 (34)	**0.001****
Lactates (mmol/l)	1.12 (0.60)	1.13 (0.60)	1.12 (0.60)	0.601
d-Dimer (mcg/ml)	0.76 (0.87)	0.89 (0.77)	0.74 (0.96)	0.137
CRP (mg/dl)	7.1 (9)	5.6 (8)	7.45 (9)	0.188
IL-6 (pg/ml)	33.5 (43)	34 (42)	33.5 (44)	0.805
LDH (mU/ml)	302 (138)	300 (191)	302 (121)	0.534
Nadir PaO2 (mmHg)	58 ± 8	57 ± 9	59 ± 9	0.052
Nadir P/F (mmHg/%)	162 (149)	178 (156)	160 (156)	0.928
AKI	84 (29.4%)	15 (23.1%)	69 (31.2%)	0.205
Severe COVID-19	115 (42.1%)	23 (35.4%)	92 (43.2%)	0.501
Death	26 (9.1%)	11 (16.9%)	15 (6.8%)	**0.024***
ICU admission	93 (32.5%)	16 (24.6%)	77 (34.8%)	0.122
Length of hospital stay (days)	11 ± 4	11 ± 4	11 ± 4	0.407

List of abbreviations: AKI, acute kidney injury; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; ICU, Intensive Care Unit; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; PAD, peripheral artery disease. $^{*}p < 0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

based on distribution and skewness, while categorical variables are expressed as numbers and percentages. All continuous variables were tested for normality and log transformation of non-normally distributed variables was performed when appropriate. For the comparisons between groups, Student t test, Chi square test, and U' Mann Whitney test were used according to the variables' type and distribution. Odds Ratios (OR) with 95% confidence intervals (CI) were obtained by adjusted logistic regression models. When time-to-event variable was available Cox-regression models were performed to obtain Hazard Ratios (HR) with 95% CI. Both OR and HR were adjusted for age, sex, BMI, and the presence of hypertension, diabetes, and chronic kidney disease (CKD). All statistical tests were two-tailed, and p-values < 0.05 were considered statistically significant.

The analyses were conducted by SPSS version 23 [SPSS Inc., Chicago, IL, USA], Microsoft Windows version.

3. Results

3.1. Study population: statin-users vs. statin non-users

From January to June 2021, 286 patients were enrolled in the study. Of the 286 patients included in the study, 65 (22.8%) were under chronic treatment with statins. Participants treated with statins were older (71 ± 13 years vs. 62 ± 15 years, $p<0.001$) and had a significant higher prevalence of hypertension, diabetes mellitus, and CV disease ($p = 0.0021$, $p = 0.0027$, and $p<0.001$, respectively). Additionally, participants taking statins had significantly lower eGFR (70 (43) vs. 81 (34), $p = 0.001$) and a higher mortality rate (16.9% vs. 6.8%) compared to non-statin users. The complete characteristics of the two cohorts are summarized in Table 1.

3.2. Cross-sectional analysis: statin use and its associations with clinical and laboratory characteristics

We run logistic regression models adjusted for age, sex, BMI, hypertension, diabetes, and CKD. Statin use was associated with lower CRP and eGFR ($p = 0.048$ and 0.002, respectively) at hospital admission compared to non-statin use. On the contrary, nadir PaO2 inversely associated with statin use ($p = 0.043$). No other significant associations were found (Table 2).

As for study outcomes, statin use was associated with a significantly reduced risk of developing AKI (OR 0.47, IC 0.23 to 0.95, p 0.036) after adjustment for age, sex, BMI, hypertension, diabetes, and CKD. Conversely, statin use was not significantly associated with the severity of COVID-19 (OR 0.718, IC 0.377 to 1.367, p 0.313) (Fig. 1).

3.3. Survival analyses in statin-users vs non-statin users

We performed cox-regression analyses for death and admission to the ICU, after adjustment for age, sex, BMI, hypertension, diabetes, and CKD. Statin use did not significantly impact the risk of death (HR 1.98, IC 0.71 to 5.50, p 0.191) or admission to the ICU (HR 0.93, IC 0.52 to 1.65, p 0.801).

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Table 2 Logistic regression analyses on clinical and laboratory characteristics and statins use Odds Ratios (OR).

	OR	CI	p
P/F at admission (mmHg/%)	1.00	0.99 to 1.01	0.875
PaO2 at admission (mmHg)	0.99	0.97 to 1.02	0.605
PaCO2 at admission (mmHg)	1.02	0.96 to 1.08	0.510
Serum creatinine (mg/dl)	0.38	0.14 to 1.02	0.054
eGFR (ml/min/1.73 m^2)	0.97	0.95 to 0.99	**0.002***
Lactates (mmol/l)	1.13	0.70 to 1.82	0.621
d-Dimer (mcg/ml)	0.97	0.80 to 1.16	0.712
CRP (mg/dl)	0.95	0.89 to 0.99	**0.048***
IL-6 (pg/ml)	0.99	0.99 to 1.00	0.573
LDH (mU/ml)	1.00	0.99 to 1.00	0.240
Nadir PaO2 (mmHg)	0.95	0.90 to 0.99	**0.043***
Nadir P/F (mmHg/%)	1.00	0.99 to 1.01	0.136

List of abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IL-6, Interleukin-6; LDH, lactate dehydrogenase. *p < 0.05, **p < 0.01, ***p<0.001.

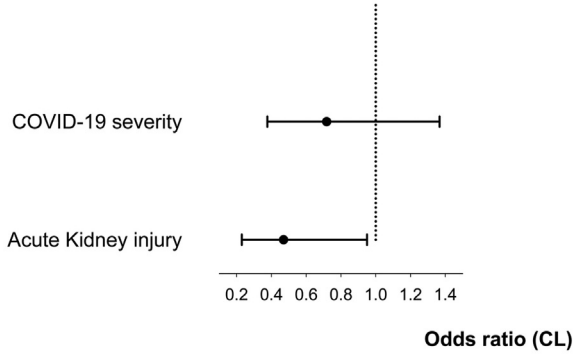

Figure 1 Logistic regression for outcomes associated with statin use. Results are adjusted for age, sex, BMI, hypertension, diabetes, and CKD.

4. Discussion

In our study, patients chronically treated with statins and hospitalized for COVID-19 had reduced levels of inflammation at hospital admission. Additionally, although statin use was associated with reduced eGFR at hospital admission, the risk of developing AKI during the hospitalization was lower in statin-users compared to non-statin users, independently of main confounders. No significant associations between statin use and survival rate and admission to the ICU rate were observed. However, statin use was inversely associated with nadir PaO2 values.

Several large observational studies on patients with COVID-19 reported that statins may reduce the risk of all-causes in-hospital mortality [14–16]. This finding has been confirmed by recent systematic reviews and meta-analyses [17,18]. In our study, although not statistically significant, we observed an increased death rate among patients under statin treatment vs. participants that were not chronically treated with statins. This result may be explained by the severity of COVID-19 in our study population. In fact, all our patients had COVID-19 pneumonia and respiratory failure, with 42.1% of participants experiencing severe acute distress syndrome. Supporting this hypothesis, a recent randomized controlled trial on the role of atorvastatin vs. placebo in the setting of adults with severe COVID-19 admitted to the ICU (INSPIRATION/INSPIRATION-S trial) has shown no benefits of statin over placebo in several outcomes, including in-hospital death [19]. In fact, as the Authors of the INSPIRATION trial hypothesized, it is possible that statins may be beneficial in early COVID-19, before inflammatory irreversible damage occurs. Indeed, statins have anti-inflammatory properties and in our study statin use was associated with decreased levels of CRP. The main anti-inflammatory mechanism of statins has shown to be the dysregulation of the myeloid differentiation primary response protein (MYD) 88 pathway, which has been demonstrated to be involved in several coronavirus infections [20]. To our best knowledge no prior studies have shown that chronic statin use induces a decrease in serum CRP, after adjustment for several possible confounders. However, in the study by Saeed et al. patients chronically treated with statins had lower levels of CRP compared to non-statin users, although no regression analyses were performed [16].

Statin anti-inflammatory effects may also be responsible for the reduction in the risk of AKI that we observed in our study. Indeed, statins have shown to reduce the incidence and progression of AKI in other clinical scenarios like contrast-induced AKI [8,9]. However, to our best knowledge only the study of Torres-Peña and colleagues has shown that statins may reduce AKI incidence in patients hospitalized for COVID-19 [10]. On the contrary, the study by Khalili et al. showed that the use of statins was an independent risk factor for AKI development in patients with diabetes hospitalized for COVID-19 [21]. The conflicting results of studies investigating the role of chronic statin therapy in COVID-19-associated AKI emphasizes the urge for further prospective and randomized studies that better define the role of statins in AKI prevention and/or treatment.

Despite the availability of plenty clinical and pharmacological data, several limitations applied to our research and should be addressed. We did not collect data regarding dosages, and we classified all molecules under the label “statin” with no differentiation. Therefore, we could not measure the effect of the single statin and the impact of their different dosages.

All the analyses were adjusted for several comorbidities and risk factors. Still, we could not exclude that residual confounding might have played a role especially due to the small sample size. The presence of an inverse association between chronic statin exposure and AKI should be considered but we do not know if otherwise healthy people would experience the same benefit. Finally, although excluding patients with advanced CKD attenuates the impact of renal causes of AKI in our analysis, this may represent a selection bias.

In conclusion, the incidence of AKI confers an increased risk of in-hospital death in patients with COVID-19 [22] but unfortunately, there is still a paucity of knowledge on prevention and treatment strategies for COVID-19-associated AKI. Since patients under treatment with

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statins have at least one cardiovascular risk factor that is indeed associated with poor COVID-19 prognosis, it appears evident how a better understanding on the role of statins in COVID-19-associated AKI may be beneficial for a large proportion of patients at risk of severe COVID-19, including AKI development [22,23].

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