Title
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In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19

Highlights
- Statin treatment among 13,981 patients with COVID-19 was retrospectively studied
- Statin use in this cohort was associated with a lower risk of all-cause mortality
- Adding an ACE inhibitor or an ARB did not affect statin-associated outcome in the cohort
- The benefit of statins among this cohort may be due to immunomodulatory benefits

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In Brief
Statins have anti-inflammatory benefits and were suggested as an adjunct therapy for COVID-19. But statins may increase the expression of ACE2, the receptor for SARS-CoV-2. Here, Zhang et al. retrospectively analyzed 13,981 COVID-19 cases and found that in-hospital statin use is associated with a lower risk of all-cause mortality.
Clinical and Translational Report

In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19

Xiao-Jing Zhang,1,2,3,31 Juan-Juan Qin,1,2,31 Xu Cheng,1,2,31 Lijun Shen,1,2,31 Yan-Ci Zhao,1,2,31 Yufeng Yuan,4 Fang Lei,2 Ming-Ming Chen,1,5 Huiliin Yang,1,6 Liangjie Bai,2 Xiaohui Song,2 Lijin Lin,1,2 Meng Xia,2 Feng Zhou,4,3 Jianghua Zhou,1,2 Zhi-Gang She,1,2 Lihua Zhu,1,2 Xinliang Ma,2 Qingbo Xu,2 Ping Ye,2 Guohua Chen,6 Liming Liu,10 Weiming Mao,10 Youqin Yan,11 Bing Xiao,12 Zhigang Lu,13 Gang Peng,14 Mingyu Liu,15 Jun Yang,15 Luyu Yang,17 Changjiang Zhang,1,18

SUMMARY

Statins are lipid-lowering therapeutics with favorable anti-inflammatory profiles and have been proposed as an adjunct therapy for COVID-19. However, statins may increase the risk of SARS-CoV-2 viral entry by inducing ACE2 expression. Here, we performed a retrospective study on 13,981 patients with COVID-19 in Hubei Province, China, among which 1,219 received statins. Based on a mixed-effect Cox model after propensity score-matching, we found that the risk for 28-day all-cause mortality was 5.2% and 9.4% in the matched statin and non-statin groups, respectively, with an adjusted hazard ratio of 0.58. The statin use-associated lower risk of mortality was also observed in the Cox time-varying model and marginal structural model analysis. These results give support for the completion of ongoing prospective studies and randomized controlled trials involving statin treatment for COVID-19, which are needed to further validate the utility of this class of drugs to combat the mortality of this pandemic.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has profoundly affected the health and livelihood of millions of people worldwide at an unprecedented scale and speed. To date, there are no definitive treatments specifically targeted to SARS-CoV-2 infection for COVID-19 therapy or prevention. Moreover, the development of effective vaccines or new therapies for curing...
COVID-19 is time-consuming and likely well off in the future. Thus, repurposing existing approved drugs to mitigate the severity of COVID-19 has been viewed as a more cost-effective and time-sensitive strategy.

Statins are first-line lipid-lowering therapies with well-tolerated side effects, are low in cost, and are broadly available worldwide, including in developing countries. The potent anti-inflammatory and immunomodulatory effects of statins suggest they could be beneficial to counter coronaviral infections, including for SARS-CoV-2 (Castiglione et al., 2020; Dashti-Khazdaki and Khalli, 2020; Fedson et al., 2020). Indeed, observational studies and randomized controlled trials (RCTs) have demonstrated a significant protective effect of statins on improving proinflammatory cytokine release and immune cell functions among individuals with viral and bacterial pneumonia (Fedson, 2013; Papazian et al., 2013; Pertsov et al., 2019; Sapey et al., 2017). A more recent report based on molecular docking analysis showed that statins might inhibit SARS-CoV-2 entry into host cells by directly binding to the main protease of the coronavirus (Reiner et al., 2020). These data led to speculation regarding the potential therapeutic benefits of statins for the treatment of COVID-19 (Arabi et al., 2020; Bifulco and Gazzarro, 2020). However, concerns have been raised regarding whether individuals on statins are at a greater risk for SARS-CoV-2 infection and COVID-19 exacerbation, as this class of drugs has been shown to increase the expression of angiotensin-converting enzyme 2 (ACE2), the receptor for the virus, in lab animals (Hoffmann et al., 2020; Shin et al., 2017; Tikoo et al., 2015; Wang et al., 2020b). Thus, direct clinical evidence is urgently needed to answer the question as to whether statin use is detrimental or beneficial in hospitalized individuals with COVID-19.

In the clinical setting, statins are often prescribed along with renin-angiotensin-aldosterone system (RAAS) blockers, in particular angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), for subjects with hypertension or cardiac pathologies (Ray et al., 2014). Remarkably, clinical applications of ACE inhibitors and ARBs for COVID-19 also share a similar dilemma as a statin treatment regarding the perceived contraindications of increasing ACE2 expression versus anti-inflammation and cardio-protection (South et al., 2020). Our recent research has shown that individuals with COVID-19 on ACE inhibitors or ARBs (ACEi/ARB) are at lower risk of 28-day all-cause mortality than those not treated with ACE inhibitors or ARBs (Zhang et al., 2020). Moreover, combination therapy of statins and ARBs showed encouraging results in improving the survival of Ebola-infected individuals (Fedson et al., 2015). However, the effects of such combination treatment in individuals with COVID-19 have not been studied.
To address these important clinical questions, we conducted one of the largest retrospective cohort studies to date—one involving 13,981 clinically confirmed cases of COVID-19—to determine the association of in-hospital use of statins with clinical outcomes. In the subgroup analysis, we further investigated the additional effects of combining ACEi/ARB with statins on the clinical outcomes of COVID-19. The time-varying Cox model, marginal structure model (MSM), and propensity score-matching analysis consistently showed a lower risk of all-cause mortality of COVID-19 in individuals with statin use versus statin nonuse.

RESULTS AND DISCUSSION

Baseline Characteristics in Participants with and without Statin Treatment

A total of 13,981 cases of confirmed COVID-19 admitted in 21 hospitals from Hubei Province, China, were included in this analysis. Among them, 1,219 had in-hospital use of statins (statin group) and the remaining 12,762 had no statin treatment (non-statin group) (Figure 1). The participants that received statin treatment were older (66.0 versus 57.0 years of age, p < 0.001) and had higher prevalence of chronic medical conditions, including hypertension (81.5% versus 30.3%, p < 0.001), diabetes mellitus (DM) (34.0% versus 14.6%, p < 0.001), coronary heart disease (36.3% versus 5.7%, p < 0.001), cerebrovascular diseases (8.8% versus 2.3%, p < 0.001), and chronic kidney diseases (5.2% versus 3.1%, p < 0.001) than those without statin treatment (Table 1). Chest CT revealed bilateral pulmonary lesions were more common in the statin group compared with that in the non-statin group (89.5% versus 83.7%, p < 0.001) (Table 1). Larger proportions of subjects in the statin group showed increased neutrophil counts, procalcitonin levels, and D-dimer compared with the non-statin group (Table 1). In addition to these inflammatory markers, abnormal serum biochemistry, including increased ALT and AST levels and decreased estimated glomerular filtration rate (eGFR), indicated more prevalent organ impairments in the participants with statin therapy compared to non-statin use (Table 1). The frequencies of individuals with increased low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) levels were higher among the statin group versus the non-statin group at admission. In terms of the whole hospitalization period, lipid profiles were comparable between the two groups (Figure S1). Days from onset of symptom to hospitalization and the median follow-up days were longer in the individuals on statin treatment compared to the non-statin group (Table 1). The absolute values of the median and interquartile range (IQR) of each laboratory examination are shown in Table S1. The laboratory values, including for c-reactive protein (CRP), procalcitonin, D-dimer, LDL-c, TC, and creatine kinase (CK), had different reference ranges for hospitals, which are listed in Table S2.

For subjects enrolled in the propensity score-matching (PSM) model that was conducted to minimize the differences in...
baseline characteristics, 861 participants from the statin group were matched at a 1:4 ratio to 3,444 participants from the non-statin group. The baseline characteristics were comparable between the two groups, except the proportion of individuals with SpO2 < 95% was lower in statin group than the non-statin group (Table S3). Lipid profiles also were comparable during hospitalization between statin and non-statin groups after PSM (Figure S2).

Among the participants on statin therapy, 993 (81.5%) of them had hypertension. Of these participants with hypertension, 319 were also treated with ACE inhibitors or ARB regimen (statin+ACEi/ARB group) for antihypertensive management, while 603 were on nonACEi/ARB antihypertensive drugs (statin+nonACEi/ARB group) for antihypertensive therapy (Figure 1). Age and gender distribution were comparable between the two groups. The systolic blood pressure (SBP)

| Table 1. Characteristics of Patients in Statin and Non-statin Groups |
|--------------------------|-------------------------|------------------|
| Parameters               | Statin (N = 1,219)      | Non-statin (N = 12,762) | p Value* |
| Clinical Characteristics on Admission |
| Age, median (IQR)        | 66.0 (59.0–72.0)        | 57.0 (45.0–67.0)     | <0.001 |
| Male gender, n (%)       | 602 (49.4%)             | 6,228 (48.8%)       | 0.719  |
| Heart rate, median (IQR), bpm | 85.0 (77.0–97.0)     | 84.0 (78.0–96.0)     | 0.744  |
| Respiratory rate, median (IQR), bpm | 20.0 (19.0–21.0)   | 20.0 (19.0–21.0)     | 0.297  |
| SBP, median (IQR), mmHg   | 133.0 (120.0–146.0)     | 128.0 (119.0–139.0)  | <0.001 |
| DBP, median (IQR), mmHg   | 80.0 (72.0–89.0)        | 79.0 (71.0–87.0)     | 0.002  |
| BMI, median (IQR), kg/m²  | 24.3 (22.7–25.6)        | 23.9 (22.3–25.3)     | 0.501  |
| Days from symptom to hospital, median (IQR) | 14.0 (6.0–23.0)     | 11.0 (6.0–20.0)     | <0.001 |
| Days from symptom to medical treatment in hospitalization, median (IQR) | 14.0 (6.0–23.0)     | 11.0 (7.0–20.0)     | <0.001 |
| Follow-up days, median (IQR) | 22.0 (15.0–28.0)   | 17.0 (11.0–25.0)     | <0.001 |
| Comorbidities on Admission |
| COPD, n (%)               | 15 (1.2%)               | 138 (1.1%)           | 0.738  |
| Hypertension, n (%)       | 993 (81.5%)             | 3,867 (30.3%)        | <0.001 |
| Diabetes, n (%)           | 414 (34.0%)             | 1,868 (14.6%)        | <0.001 |
| Coronary heart disease, n (%) | 442 (36.3%)         | 729 (5.7%)           | <0.001 |
| Cerebrovascular disease, n (%) | 107 (8.8%)          | 296 (2.3%)           | <0.001 |
| Chronic liver disease, n (%) | 17 (1.4%)             | 268 (2.1%)           | 0.119  |
| Chronic kidney disease, n (%) | 63 (5.2%)             | 398 (3.1%)           | <0.001 |
| Chest CT on Admission |
| Bilateral lesions, n/N (%) | 1,021/1,141 (89.5%)    | 9,983/11,932 (83.7%) | <0.001 |
| Laboratory Examination on Admission |
| Leukocyte count > 9.5, 10^9/L, n/N (%) | 126/1,182 (10.7%)   | 1,094/11,716 (9.3%)  | 0.153  |
| Neutrophil count > 6.3, 10^9/L, n/N (%) | 201/1,182 (17.0%)   | 1,672/11,706 (14.3%) | 0.013  |
| Lymphocyte count < 1.1, 10^9/L, n/N (%) | 480/1,182 (40.6%)   | 4,708/11,707 (40.2%) | 0.816  |
| C-reactive protein > ULN¹, n/N (%) | 349/717 (48.7%)    | 3,435/6,892 (49.8%)  | 0.579  |
| Procalcitonin > ULN¹, n/N (%) | 487/1,024 (47.6%)   | 3,721/9,358 (39.8%)  | <0.001 |
| ALT > 40 U/L, n/N (%)     | 299/1,178 (25.4%)      | 2,439/11,302 (21.6%) | 0.003  |
| AST > 40 U/L, n/N (%)     | 277/1,178 (23.5%)      | 2,333/11,313 (20.6%) | 0.022  |
| eGFR < 90 mL/min, n/N (%) | 444/1,173 (37.9%)     | 2,878/11,490 (25.1%) | <0.001 |
| D-dimer > ULN², n/N (%)   | 649/1,112 (58.4%)      | 4,721/10,425 (45.3%) | <0.001 |
| LDL-c > ULN², n/N (%)     | 194/1,007 (19.3%)      | 1,147/8,308 (13.8%) | <0.001 |
| TC > ULN³, n/N (%)        | 198/1,093 (18.1%)      | 1,089/9,257 (11.8%)  | <0.001 |
| CK > ULN³, n/N (%)        | 118/1,031 (11.5%)      | 1,037/9,599 (10.8%)  | 0.564  |
| SpO2 < 95%, n/N (%)       | 374/1,219 (30.7%)      | 4,595/12,762 (36.0%) | <0.001 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; CK, creatine kinase; SpO2, oxygen saturation; IQR, interquartile range.

*Upper limit of normal (ULN) was defined according to criteria in each hospital

*P values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher’s exact test or χ² test for categorical variables.
levels and prevalence of DM were higher, while the prevalence of COPD was lower, in individuals on statin+ACEi/ARB, compared to those on the combination of statin and other types of antihypertensive drugs (Table S4). The absolute values of the median (IQR) of each laboratory examination are shown in Table S5. After PSM, 204 individuals in the statin+nonACEi/ARB group were matched at a 1:1 ratio to 204 individuals in the statin+ACEi/ARB group. The baseline characteristics were comparable between the two groups (Tables S5 and S6).

In-Hospital Use of Statins and Combination of Statins and ACEi/ARB

Among the subjects that received statin treatment, atorvastatin was the most frequently prescribed (accounting for 83.2% of all the statins users), followed by rosuvastatin (15.6% of statin users) (Table 2). Statin treatment started at the day of hospital admission. The dose differences among statins were converted to an equivalent dose of atorvastatin according to Hu et al. (2015). The therapeutic duration for individuals in the statin group was 22.0 (14.0–28.0) days, with an atorvastatin equivalent dose of 20.0 (18.9–20.0) mg per day (Table 2). There were 26.2% individuals also treated with ACEi/ARB in the statin group compared to 6.6% for the non-statin group (Table 2). In the PSM cohort, the percentage of individuals on ACEi/ARB treatment was comparable between the statin and non-statin groups (Table 2).

The distributions of different brands of statins, therapeutic duration, and daily equivalent dose of statin were comparable between the individuals in the statin+ACEi/ARB group versus those in the statin+nonACEi/ARB group (Table S8). The median (IQR) day of starting ACEi/ARB treatment was 3.0 (0.0–9.0) days after admission, and the median (IQR) therapeutic duration was 17.0 (9.5–25.0) days (Table S8). In the PSM cohort, the median (IQR) ACEi/ARB starting time was 4.0 (0.0–10.0) days after admission, and the median (IQR) therapeutic duration was 16.0 (9.0–23.3) days (Table S8).

In-Hospital Use of Statins Was Associated with a Lower Risk of All-Cause Mortality

The incidence rate of death during a 28-day follow-up was 0.21 cases 100-person-day in the statin group (the mortality rate at 5.5%) versus 0.27 100-person-day in the non-statin group (the mortality rate at 6.8%) (Table 3). Comparing to the individuals without statin use, the individuals with statin therapy had a lower crude 28-day mortality (incidence rate ratios [IRRs], 0.78; 95% CI, 0.61–0.996; p = 0.046; Table 3). Using a Cox model accounting for statin as a time-varying exposure and with adjustment for baseline differences, statin treatment was associated with lower mortality (adjusted HR [aHR], 0.63, 95% CI, 0.48–0.84; p = 0.001) compared to non-statin users (Table 3).

In the PSM cohort, the crude incidence of death in the statin group (IR, 0.20 cases 100-person-day; death rate 5.2%) was markedly lower than that in the non-statin group (IR, 0.37 100-person-day; death rate 9.4%). Due to the severe symptoms and comorbidities of subjects in the statin group, the matched non-statin group had more severe baseline symptoms and higher proportions of cardiovascular and metabolic comorbidities than the unmatched non-statin group. This might account for the increased death rate in statin nonusers after propensity matching. Using a mixed-effects Cox model without accounting for the time-varying exposures in the PSM cohorts, statin treatment was associated with lower mortality (adjusted HR [aHR], 0.63, 95% CI, 0.48–0.84; p = 0.001) compared to non-statin users (Table 3).
with a lower 28-day mortality (aHR, 0.72; 95% CI, 0.54–0.97; p = 0.032) than individuals with no use of statins (Table 3).

In a sensitivity test, we excluded individuals who were admitted to the ICU or died within 48 h after admission and performed the same analyses for the rest of the individuals. Similar results were observed in the Cox model with time-varying exposure (aHR, 0.74, 95% CI, 0.55–0.99; p = 0.044), the MSM analysis (aHR, 0.73; 95% CI, 0.53–0.99; p = 0.046), and the mixed-effects Cox model in PSM population (aHR, 0.59, 95% CI, 0.44–0.78; p < 0.001) (Table S9). We also conducted E-value analysis and found the point estimate of the primary endpoint was 3.41 in the mixed Cox model. Since the value was larger than the strong 1.2 E-value, we feel comfortable with our results.

A recent retrospective report including 154 COVID-19 cases indicated that statin intake was significantly associated with the asymptomatic status of COVID-19 with an unadjusted OR of 2.91 (De Spiegeleer et al., 2020). Previous observational studies and meta-analyses have shown that statin treatment may be associated with reduced morbidity and mortality in individuals with sepsis-associated ARDS (Mansur et al., 2015). However, large RCTs of individuals with ARDS have shown that neither atorvastatin nor simvastatin provided a significant benefit in overall mortality (McAuley et al., 2014; Truwit et al., 2014; Papazian et al., 2013). The discrepancy in the results between the observational and RCT studies may be due to differences in the heterogeneity of study populations, plausible selection bias, and measured/unmeasured confounders in the observation studies. Further analyses of RCT data have shown the existence of subphenotypes in ARDS and differential response to statin treatment (Caffee et al., 2018; Sinha et al., 2018). For instance, simvastatin was associated with improved survival in the hyper-inflammatory rather than the hypo-inflammatory subgroups, while atorvastatin therapy in the acute phase was not associated with improved survival in patients with sepsis but improved 28-day mortality when pretreated (Kruger et al., 2013). These findings support efforts to examine the effect of statins in targeted subphenotypes of individuals and to pursue the approach to stratify patients in clinical trials.

### Table 3. Incidence Rate Ratios and Hazard Ratios for 28-Day All-Cause Mortality in Statin Group versus Non-statin Group and Statin+ACEI/ARB versus Statin+nonACEI/ARB

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<tr>
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<th>Unmatched</th>
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<th>Matched</th>
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<tbody>
<tr>
<td></td>
<td>Crude Incidence</td>
<td>Cox Model Time-Varying Exposure</td>
<td>Marginal Structural Model</td>
<td>Crude Incidence after PSM</td>
</tr>
<tr>
<td></td>
<td>IR (95%CI)</td>
<td>p Value</td>
<td>aHR (95%CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Statin versus non-statin</td>
<td>0.21 (0.61–0.99)</td>
<td>0.046</td>
<td>0.63 (0.48–0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Statin+ACEI/ARB versus statin+nonACEI/ARB</td>
<td>0.16 (0.34–0.69)</td>
<td>0.119</td>
<td>0.48 (0.21–1.07)</td>
<td>0.074</td>
</tr>
<tr>
<td>Statin+ACEI/ARB versus statin+nonACEI/ARB</td>
<td>0.26 (1.14)</td>
<td>0.26</td>
<td>0.18 (0.12–0.32)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

IR (100-person-day), incidence rate; IRR, incidence rate ratio; aHR, adjusted hazard ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*p values were calculated by R package “fmsb”; the significant probability of the result of null-hypothesis testing.

Adjusted for age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic kidney disease), indicators of disease severity and organ injuries (lesions in chest CT, neutrophil count increase, procalcitonin increase, D-dimer increase, AST increase, creatinine increase, and SpO2), LDL-c increase, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hospitalization.

Adjusted for age, gender, blood pressure (SBP), pre-existing comorbidities (COPD and DM), medications at admission, using invasive mechanical ventilation support covariates, and the number of antihypertensive drugs, with statin and ACEI/ARB therapy as time-varying exposures.

CURB-65 pneumonia severity score, serum ALT levels, and CK levels were considered as time-varying confounders. Additionally, the adjustment factors included age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic kidney disease), indicators of disease severity and organ injuries (lesions in chest CT, neutrophil count increase, procalcitonin increase, D-dimer increase, AST increase, creatinine increase, and SpO2), LDL-c increase, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hospitalization.

CURB-65 pneumonia severity score, serum ALT levels, and creatinine levels were considered as time-varying confounders. Additionally, the adjustment factors included age, gender, pre-existing COPD and DM, medication at admission, use of mechanical ventilation, and the number of antihypertensive drugs.

aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, and SpO2 at admission.

aHR was calculated based on mixed-effect Cox model with adjustment of age, gender, coronary heart disease, CRP increase, D-dimer increase, and LDL-c increase at admission.
Clinical and Translational Report

Despite our extensive efforts to utilize multiple models with rigorous controls, there still could be possible biases that can impact the magnitude of the statin use-associated benefits on all-cause mortality among individuals with COVID-19, thus calling for the need of further validations of our conclusions via RCT studies. Encouragingly, there have been several RCT studies started (NCT04402723, NCT04390074, NCT04348695, NCT04426084, NCT04333407, NCT04380402, and NCT04343001). We are looking forward to the release of those results.

The Combination of Statins and ACEi/ARB Utilization Was Not Significantly Associated with the Risk of All-Cause Mortality among Individuals with COVID-19 and Hypertension

Among the subjects with hypertension, the incidence of 28-day mortality was 0.16 cases 100-person-day versus 0.26 100-person-day in the statin+ACEi/ARB group and the statin+nonACEi/ARB group, respectively, with an IRR of 0.62 (95% CI, 0.34–1.14; p = 0.119) (Table 3). Using a Cox model with statin and ACEi/ARB as time-varying exposures, there was no significant association between ACEi/ARB therapy and 28-day mortality in individuals with hypertension and statin treatment (aHR, 0.48; 95% CI, 0.21–1.07; p = 0.074) (Table 3).

In a sensitivity test, we excluded participants who were admitted to the ICU or died within 48 h after admission and performed the same analyses as described above for the resting subjects. No significant associations were found between statin+ACEi/ARB and all-cause mortality of COVID-19 compared to statin+nonACEi/ARB group using the Cox model with time-varying exposure, the MSM analysis, and the mixed-effects Cox model of the PSM population (Table S9). These results indicated that using ACEi/ARB in combination with statins...
conferred neither additive beneficial nor detrimental effects in 28-day mortality compared to the combined use of non-ACEI/ARB plus statins among subjects with pre-existing hypertension. Although the use of an ACE inhibitor or ARB was once speculated to be potentially harmful in patients with COVID-19 (Fang et al., 2020), numerous observational studies have shown either a protective or neutral effect on mortality (Mancia et al., 2020; Zhang et al., 2020). While more definitive results from RCTs are forthcoming, several professional societies have recommended the continuing use of ACE inhibitors and ARBs in patients with COVID-19 and pre-existing hypertension (ESC, 2020; ISH, 2020). To our knowledge, the results from this study were the first clinical evidence to support the notion that the risk of COVID-19 mortality was not increased by using ACE inhibitors or ARB in combination with statin treatment in individuals with COVID-19.

**In-Hospital Usage of Statins and Combination Usage of Statins and ACE Inhibitors or ARBs Did Not Increase the Risk of Organ Damage and Other Adverse Effects**

In terms of secondary endpoints of COVID-19, we analyzed the association of statin use with incidences of invasive mechanical ventilation, ICU admission, ARDS, septic shock, acute liver injury, acute kidney injury, and acute cardiac injury. After adjusted baseline differences, Cox model analysis showed that statin usage was associated with a lower prevalence of using mechanical ventilation (aHR, 0.37; 95% CI, 0.28–0.53, p < 0.001), ICU admission (aHR, 0.69; 95% CI, 0.56–0.85, p = 0.001), and ARDS (aHR, 0.83; 95% CI, 0.72–0.97, p = 0.015) in individuals with COVID-19 (Table S10). After matching baseline differences in two groups by PSM, the statin group still showed a lower incidence of invasive mechanical ventilation compared to the non-statin group (aHR, 0.51; 95% CI, 0.34–0.78, p = 0.016) (Table 4). Statin therapy was not significantly associated with other secondary outcomes (e.g., acute kidney injury, liver injury, and cardiac injury) and increased serum CK or transaminase levels in the PSM cohort (Table 4).

Among the individuals with COVID-19 and pre-existing hypertension, there were no significant associations between all observed secondary outcomes and statins with or without ACE inhibitors or ARB treatment in unmatched subjects (Table S10). After matching baseline characteristics, the statin group still showed a lower incidence of invasive mechanical ventilation compared to the non-statin group (aHR, 0.51; 95% CI, 0.34–0.78, p = 0.016) (Table 4). Statin therapy was not significantly associated with other secondary outcomes (e.g., acute kidney injury, liver injury, and cardiac injury) and increased serum CK or transaminase levels in the PSM cohort (Table 4).

Table 4. Incidence Rate Ratios and Hazard Ratios for Secondary Outcomes and CK and Transaminase Elevation in Statin Group versus Non-statin Group and Statin+ACEi/ARB versus Statin+nonACEi/ARB after PSM

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>Statin versus Non-statin</th>
<th>Statin+ACEi/ARB versus Statin+nonACEi/ARB</th>
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<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>0.11 versus 0.22</td>
<td>0.50 (0.33–0.76)</td>
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<td>ICU admission</td>
<td>0.29 versus 0.40</td>
<td>0.71 (0.55–0.93)</td>
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<tr>
<td>ARDS</td>
<td>0.65 versus 0.81</td>
<td>0.80 (0.67–0.96)</td>
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<td>Septic shock</td>
<td>0.12 versus 0.13</td>
<td>0.92 (0.60–1.39)</td>
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<td>Acute liver injury</td>
<td>0.30 versus 0.28</td>
<td>1.06 (0.81–1.39)</td>
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<tr>
<td>Acute kidney injury</td>
<td>0.13 versus 0.17</td>
<td>0.78 (0.53–1.16)</td>
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<tr>
<td>Acute cardiac injury</td>
<td>0.51 versus 0.49</td>
<td>1.03 (0.84–1.26)</td>
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CK and Transaminase Elevation

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<tr>
<th>CK &gt; ULN</th>
<th>ALT &gt; 3ULN</th>
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<tbody>
<tr>
<td>0.40 versus 0.46</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>0.23 versus 0.23</td>
<td>1.00 (0.74–1.36)</td>
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IR (100-person-day), incidence rate; IRR, incidence rate ratio; aHR, adjusted hazard ratio; CI, confidence interval; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; CK, creatine kinase; ALT, alanine transaminase; ULN, the upper limit of normal.

aAdjusted HR was calculated based on mixed-effect Cox model adjusted for age, gender, and SpO2 on admission.
bAdjusted HR was calculated based on mixed-effect Cox model.
cAdjusted HR was calculated based on mixed-effect Cox model with adjustment of age, gender, and LDL-c on admission.
dAdjusted HR was calculated based on mixed-effect Cox model with adjustment of age, gender, coronary heart disease, and incidence of increased CRP, D-dimer, and LDL-c on admission.

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Figure 3. Dynamic Change of Inflammatory Factors in Statin and Non-statin Groups during Hospitalization
(A–C) Dynamic profiles of CRP (A), IL-6 (B), and neutrophil count (C) levels during the 28-day follow-up duration in the baseline matched individuals, with 95% confidence interval represented by the shaded regions.
(D–F) Dynamic profiles of CRP (D), IL-6 (E), and neutrophil count (F) levels during the 28-day follow-up duration in the baseline matched survival individuals, with 95% confidence interval represented by shaded regions. The sample sizes for each parameter in each group are labeled in the parentheses of the legends.

An Ameliorated Inflammatory Response Might Underlie Statin-Associated Improved Prognosis of COVID-19

Given the putative anti-inflammatory and immunomodulatory effects of statins (Castiglione et al., 2020; Dashki-Khavidaki and Khalil, 2020; Fedson et al., 2020), we explored the changes of inflammatory markers in statin users with COVID-19. The dynamic changes of inflammatory factors in individuals with COVID-19 with and without statin treatment during the 28-day hospitalization were fitted using a locally weighted regression and smoothing scatterplot (Lowess) model. Circulating CRP, interleukin 6 (IL-6), and neutrophil counts were three inflammation biomarkers selected to represent the overall status of inflammation (Nathan, 2006; Vasileva and Badawi, 2019; Wang et al., 2020a).

In subjects with matched baseline differences, the dynamic trajectories of CRP showed a downward trend after admission in both groups, with lower levels among the statin users for the entire in-hospital duration (Figure 3A). IL-6 in the statin group showed a lower level at admission and had a lower increase than that of the non-statin group for the entire duration of follow-up (Figure 3B). Meanwhile, the dynamic curve of the neutrophil count level showed a more significant downward trend in the statin groups than the non-statin group during hospitalization (Figure 3C). Furthermore, to eliminate any artifacts due to censoring or death, the analysis was also conducted in alive participants. The tendencies were similar when individuals who died during the 28-day follow-up were excluded from each group (Figures 3D–3F).

The dynamic trajectories for circulating CRP, IL-6, and neutrophil counts were also determined in statin users and statin non-users before PSM and found to show similar patterns to those after PSM analysis (Figure S3). Because individuals onstatins were older and had a greater incidence of chronic diseases (Table 1), the benefits of statins in suppressing circulating pro-inflammatory markers were less remarkable as in the matched cohort with comparable baseline characteristics.

Overwhelming inflammation response is a pathological hallmark of COVID-19-associated phenomena and ARDS and contributes to extrapulmonary organ damage (Tay et al., 2020). Statins can reduce inflammation and the progression of lung injury in experimental models (Fan et al., 2018). Mechanistic studies have shown that statins can suppress TLR4/MyD88/NF-κB signaling and cause an immune response shift to an anti-inflammatory status (Gallelli et al., 2014; Yuan et al., 2014). More recent evidence has shown statins have pleiotropic effects on NLRP3 inflammasome activation and cytokine releases in numerous disease conditions (Henriksen et al., 2014; Satoh et al., 2014; Xu et al., 2012). During metabolic dysfunction, factors such as oxidized LDL and advanced glycation end-product, promote NLRP3 inflammasome activation to magnify the inflammatory responses during pathogen infection (Duewell et al., 2010; Sheedy et al., 2013). This response may underlie why patients with the metabolic disorder are prone to more severe complications of COVID-19. The potential benefit of statin on NLRP3 inflammasome might also be associated with improved outcomes in the setting of COVID-19.

Clinical data to date have been inconclusive as to the impact of statins on inflammatory mediators (McAuley et al., 2014; Truwit et al., 2014). Some earlier studies have reported that in bacterial infections or acute lung injury, inflammation mediators (e.g., TNF-α, IL-6, and CRP) were significantly lower either in circulation or in bronchoalveolar lavage among subjects on simvastatin. However, due to a self-control comparison study design and limited sample size, these results need to be interpreted with caution (Craig et al., 2011; Novack et al., 2009). An RCT was conducted among patients from the ICU treated with atorvastatin and found that the plasma level of IL-6 was not significantly affected by atorvastatin therapy (Kruger et al., 2013). Another study designed to explore the
formation of neutrophil extracellular traps (NETs), representing responsiveness of neutrophils to bacterial infection, showed that simvastatin treatment in patients with pneumonia resulted in altered formation. In this study, 4 days of simvastatin adjuvant therapy was associated with improvements in systemic neutrophil altered formation. The different results from such studies may result from diverse disease conditions among the different trials and the heterogeneity in the target populations. Thus, to address these concerns regarding the true effect of statins on inflammatory diseases, RCTs with appropriate patient stratification will be required.

**Conclusion**
The use of statins in hospitalized subjects with COVID-19 was associated with a lower risk of all-cause mortality and a favorable recovery profile. Due to the nature of such retrospective studies, these results should be interpreted with caution; however, these data provide supportive evidence for the safety of statin or combination of a statin with ACEi/ARB for treatment in patients with COVID-19. Further RCTs to prospectively explore the efficacy of statins on COVID-19 outcomes are urgently needed.

**Limitations of Study**
Our study has several limitations. First, the inherent limitation of a retrospective study makes it impossible to infer causality in the association between the use of statins and ACEi/ARB and the ameliorated severity and mortality in COVID-19. Second, even if we used multiple statistical models to adjust for potential bias and performed sensitivity analyses to show that the overall unmeasured confounders were unlikely to undermine our main conclusion, some unforeseen confounders (e.g., prehospital medication and socioeconomic status) may still potentially alter the magnitude of statin effects on all-cause mortality of COVID-19. Third, marginal structural models require the availability of time-varying data on each day surrounding the initiation of statin exposure. The data for time-varying confounders for each day were not fully available, and imputation for days with missing data would also lead to uncertain bias to the conclusion. However, participants started on statin treatment in a very early phase after admission would thus minimize the impact of imputation. Fourth, the BMIs in the statin and non-statin groups were comparable and thus were not adjusted in the following statistical analysis. Moreover, due to the urgent status of the COVID-19 pandemic, BMI was not always measured and has a relatively high missing proportion. This might lead to an uncertainty of the impact of BMI on the associations between statin use and lower risk of all-cause mortality. Fifth, the role of different types of statins on COVID-19 outcomes was not fully analyzed since the majority of the cases were taking atorvastatin and rosuvastatin, while the number of individuals taking other types of statins was relatively small. Sixth, the study population included only hospitalized subjects, so extrapolation of these conclusions to the general population with COVID-19-related complications in the non-hospital setting requires caution.

**STAR+METHODS**
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**SUPPLEMENTAL INFORMATION**
Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2020.06.015.

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**AUTHOR CONTRIBUTIONS**

**DECLARATION OF INTERESTS**
The authors declare no competing interests.

**REFERENCES**


**STAR METHODS**

**KEY RESOURCES TABLE**

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**RESOURCE AVAILABILITY**

**Lead Contact**
Further information and requests for resources and reagents should be directed to the Lead Contact, Hongliang Li (lihl@whu.edu.cn).

**Materials Availability**
The study did not generate any new reagents or materials.

**Data and Code Availability**
The data and codes related to the findings of this study will be available from the corresponding author after publication upon reasonable request. The research team will provide an email address for communication once the data are approved to be shared with others. The proposal with detailed aims, statistical plan, and other information/materials may be required to guarantee the rationality of requirement and the security of the data. The patient-level data, but without names and other identifiers, will be shared after review and approval of the submitted proposal and any related requested materials.
METHOD DETAILS

Study Design and Participants
This retrospective, multi-centered study was conducted in 21 hospitals in Hubei Province, China. A total of 15,649 participants diagnosed with COVID-19 following WHO interim guidance and the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National Health Commission of China were included (National Health Commission of China, 2020; World Health Organization, 2020). Participants were admitted between December 30th, 2019 and April 17th, 2020. The final date of the follow-up was April 25th, 2020. The study protocols were approved by the central ethics committee and were accepted or approved by each collaborating hospital. Patient informed consent was waived by each ethics committee.

Among the original participants with COVID-19, participants with incomplete electronic medical records, aged less than 18 or over 85 years, with pregnancy or severe medical conditions, including acute lethal organ injury (i.e., acute coronary syndrome, acute stroke, and severe acute pancreatitis) were excluded. Individuals with pre-existing hypothyroidism (Fellström et al., 2009; Truwit et al., 2014) or contraindications for statins use including presented serum levels of CK or aminotransferase of more than five times of the upper limit of normal (ULN) at admission were also excluded (Fellström et al., 2009; Truwit et al., 2014). To avoid the confounding effects from non-statin lipid-lowering drugs, participants taking statin combined with other lipid-lowering drugs or those taking non-statin lipid-lowering agents were excluded. The number of participants enrolled in this study from hospitals was listed in Table S11. To explore whether using ACEi/ARB brings additional benefit for individuals with hypertension and taking statins, subjects without hypertension or not taking any antihypertensive medicine during hospitalization were excluded. The flowchart for patient inclusion was illustrated in Figure 1.

Data Collection
Demographic and clinical characteristics, vital sign, laboratory tests, radiological reports, and outcome data were extracted from electronic medical records using a standardized data collection, as described in the previous reports (Lei et al., 2020; Zhang et al., 2020; Zhu et al., 2020). The laboratory data included a routine blood test, serum biochemical markers reflecting liver injury, kidney injury, and cardiac injury, lipid profile, IL-6, CRP, procalcitonin, and D-dimer were collected during hospitalization. In-hospital medication and life support intervention included the classification of the drugs, the dosage, the course of treatment, and using mechanical ventilation were also extracted from medical records. Data were carefully reviewed and confirmed by an experienced physician team and were double-checked to guarantee the accuracy.

Definition
The primary endpoint was defined as 28-day all-cause death. The secondary endpoints were the occurrence of ARDS, septic shock, acute liver injury, acute kidney injury, acute cardiac injury, invasive mechanical ventilation, and intensive care unit admission. ARDS and septic shock were defined according to the WHO interim guideline “Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected.” Acute kidney injury was diagnosed by an elevation in serum creatinine level ≥26.5μmol/L within 48 h (Khwaja, 2012). Acute cardiac injury was defined with serum level of cardiac troponin I/T (cTnI/T) above the ULN (Huang et al., 2020; Yancy et al., 2017). Acute liver injury was defined using serum ALT or alkaline phosphatase above 3 folds of the ULN (Marrone et al., 2018). The adverse effect of statin was determined by CK to increase above ULN or ALT increase above 3-folds of the ULN during follow-up (Truwit et al., 2014).

Association of Statin Use with COVID-19 Mortality
To test the association between in-hospital statin therapy and mortality, three statistical models were applied. One approach was Cox proportional hazards regression model after propensity score-matching for baseline characteristics, but without considering immortal time bias or time-varying confounders; A second approach was Cox proportional hazards regression model accounting for time-varying exposure that adjusted for baseline differences and accounts for immortal time bias (with statin or statin and ACEi/ARB therapy as a time-varying exposure); A third approach was a marginal structural model that adjusts for baseline differences and accounts for indication bias (by examining the impact of time-varying confounders on the daily risk of prescription of statin or ACEi/ARB) and immortal time bias (using statin or statin and ACEi/ARB therapy as a time-varying exposure).

Propensity Score-Matched Analysis
To minimize baseline differences between statin and non-statin groups, we performed propensity score-matched analysis (PSM). Baseline matching variables included age, gender, pre-existing comorbidities (COPD, DM, hypertension, coronary heart disease, cerebrovascular disease, chronic liver disease, and chronic kidney disease), indicators of disease severity and organ injuries (neutrophil counts increase, lymphocyte counts decrease, CRP level increase, ALT increase, creatine kinase [CK] increase, eGFR < 90 mL/min/1.73 m² and LDL-c increase, total cholesterol (TC) increase, and use of ACEi/ARB). Residual imbalance in SpO2 between statin and non-statin group were further adjusted in the Cox regression model.

To match the differences between the individuals with statin combined with ACEi/ARB treatment and statin combined with other types of antihypertensive treatment, we matched variables including age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (COPD, DM, coronary heart disease, cerebrovascular disease, chronic liver disease, and chronic kidney disease), indicators of disease severity and organ injuries (neutrophil counts increase, lymphocyte counts decrease, CRP level increase, eGFR
conditions that could impact clinical decision on initiating ACEi/ARB therapy. The gender, pre-existing COPD and DM, medication
tonia severity score, serum creatinine, and ALT levels were considered as time-varying confounders, which reflected the patient
imputation, ALT and CK levels were standardized through dividing by the upper limit of the reference value of the corresponding
missing values were imputed by the last-observation-carried-forward approach through the linear mixed-effects model. Before
and days from symptom onset to hospitalization were adjusted in the model. ALT level, CK level, and CRUB-65 score in days with
creatine increase, and SpO2), LDL-c increase, TC increase, medications at admission, using invasive mechanical ventilation support,
bidities (DM, hypertension, coronary heart disease, cerebrovascular disease, and chronic kidney disease), indicators of disease
adjusting for age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, ce-
bral arterial disease, and chronic kidney disease), indicators of disease severity and organ injuries (lesions in chest CT, neutrophil
counts increase, procalcitonin increase, D-dimer increase, ALT increase, AST increase, creatinine increase, and SpO2), LDL-c in-
crease, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hos-
pitalization covariates with statin therapy as a time-varying exposure.
When analyzing the association between statin combined with or without ACEi/ARB and mortality accounting for time-varying
exposure, we adjusted for age, gender, pre-existing comorbidities (COPD and DM), SBP, medications at admission, the number of
antihypertensive drugs and using invasive mechanical ventilation support covariates with statin and ACEi/ARB therapy as time-
varying exposures.
Marginal Structural Cox Proportional Hazards Model
Changes in patient conditions influenced the initiation or termination of statin therapy or combined treatment of statin and ACEi/ARB.
We performed a marginal structural model (MSM) analysis with inverse probability of treatment weighting (IPTW) to account for time-
varying confounders. When analyzing the association between statin use and clinical outcomes, age, gender, pre-existing coronary heart disease, 
CRP, LDD-c, and D-dimer were adjusted when analyzing the association between ACEi/ARB treatment and clinical outcomes in sub-
jects with statin treatment. We modeled the site as a random effect in the mixed-effect Cox model. The proportional hazard assump-
tions were verified using correlation testing based on the Schoenfeld residuals.

Mixed-Effects Cox Model
The risk of primary and secondary endpoints and corresponding hazard ratio (HR) were calculated using the Cox proportional hazard
model comparing the statin group versus the non-statin group and the statin+nonACEi/ARB group versus the statin+nonACEi/ARB
group. In the Cox analysis, individuals discharged were treated as “0-at risk” but not censored data for two major reasons. First,
individuals with COVID-19 would not be discharged only if their symptoms significantly relieved with continuous viral PCR negative
two times. Second, individuals discharged from hospitals had another 2-week of quarantine. Any death occurred would be docu-
mented. Thus, discharged individuals were unlikely to die due to COVID-19 and their survival information was still available after
discharge.
Regression adjustment was applied to remove post-PSM residual confounding bias where it included the covariates with a stan-
dardized difference greater than 0.10. Multi-variable adjusted residual imbalances including age, gender, and SpO2 were performed
when analyzing the association between statin treatment and clinical outcomes. Age, gender, pre-existing coronary heart disease, 
CRP, LDD-c, and D-dimer were adjusted when analyzing the association between ACEi/ARB treatment and clinical outcomes in sub-
jects with statin treatment. We modeled the site as a random effect in the mixed-effect Cox model. The proportional hazard assump-
tions were verified using correlation testing based on the Schoenfeld residuals.
Cox Model with Time-Varying Exposure
To examine endpoints as a time to mortality in the statin and the non-statin group, we performed a Cox proportional hazards model
adjusting for age, gender, blood pressure (SBP and DBP), pre-existing comorbidities (DM, hypertension, coronary heart disease, ce-
bral arterial disease, and chronic kidney disease), indicators of disease severity and organ injuries (lesions in chest CT, neutrophil
counts increase, procalcitonin increase, D-dimer increase, ALT increase, AST increase, creatinine increase, and SpO2), LDL-c in-
crease, TC increase, medications at admission, using invasive mechanical ventilation support, and days from symptom onset to hos-
pitalization covariates with statin therapy as a time-varying exposure.
When analyzing the association between statin combined with or without ACEi/ARB and mortality accounting for time-varying
exposure, we adjusted for age, gender, pre-existing comorbidities (COPD and DM), SBP, medications at admission, the number of
antihypertensive drugs and using invasive mechanical ventilation support covariates with statin and ACEi/ARB therapy as time-
varying exposures.
at admission, use of mechanical ventilation and the number of antihypertensive drugs were adjusted in the model. CURB-65 score was assessed every day during hospitalization. Serum creatinine level, ALT level, and CURB-65 score in days were imputed by the last-observation-carried-forward approach.

The treatment selection weights were calculated to evaluate the probability of a patient to receive statin therapy at a specific time \( k \). The weights were updated until the first day of statin therapy and kept constant afterward. The censoring weights were calculated for early patient dropout. The finally stabilized weights were calculated by multiplying the treatment selection weights and the censoring weights. The time-varying intercept was modeled by a smoothing function of time, using restricted cubic splines. Then a generalized additive model was performed to estimate the effect of statin use on results, with age and gender adjusted. The marginal structural Cox proportional hazards model was performed incorporating the stabilized weights to estimate the effect of statin therapy on clinical outcomes and side effects. We modeled the probability of receiving statin therapy with the assumption that once the patient was started on statin therapy the patient will remain on that treatment.

**Sensitivity Analysis**

The E-value analysis was conducted to assess the robustness of the association between statin use and all-cause mortality in the Cox models to address potential unmeasured confounding effect, using the methodology of VanderWeele and Ding (Haneuse et al., 2019; Mathur et al., 2018; VanderWeele and Ding, 2017). The E-value is an alternative approach to sensitivity analyses for unmeasured confounding in our studies that avoids making assumptions that, in turn, require subjective assignment of inputs for some formulas.

Because critically ill patients at admission were less likely to receive statin treatment, this bias could lead to an association between not using statins with poor outcomes. we performed a sensitivity analysis using Cox models with and without time-varying exposure and marginal structural model in patient population not including those who admitted to ICU or died within 48 h after admission. The matched and adjust variables were listed in the footnotes of Table S9.

**Missing Data and Imputation**

Variables were used for matching in propensity-score matched analysis and for adjusting in Cox analysis at admission. To account for the missing data on the laboratory variables, we used non-parametric missing value imputation, based on the missForest procedure in the R (Waljee et al., 2013). A random forest model based on the rest of the variables in the dataset was constructed to predict the missing values with an estimation of the internally cross-validated errors.

**QUANTIFICATION AND STATISTICAL ANALYSIS**

Continuous variables with non-normal distributions were expressed as median [IQR]. Categorical variables were expressed as number and percentage (%). Comparisons between groups were performed with Mann-Whitney U test for nonparametric variables and Fisher’s exact test or \( \chi^2 \) test for categorical variables. Person-time data (Incidence) of two groups with different exposures may be expressed as a difference between incidence rates or as a ratio of incidence rates (IRRs). Person-day is a type of measurement taking both number of subjects and time into account. Mortality rate is the number of new cases of death during follow-up duration divided by the person-day-at-risk, where the person-day is the sum of total days contributed by all subjects. The rate was presented by multiplying both the numerator and denominator by 100. The IRRs of endpoint outcomes were calculated to estimate the incidence difference in absolute change in the incidence of two comparison groups. The cumulative rates of death were compared using the Kaplan-Meier curves. Dynamic changes of inflammatory factors tracking from day 1 to day 28 after admission were depicted using the Lowess model. A two-side \( \alpha \) less than 0.05 was considered to define statistical significance. Data were analyzed in R-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics (version 23.0, IBM, Armonk, NY, USA).